Volume 31 Number 2 (Supplement 1) May 2004

CALGARY, ALBERTA
JUNE 8-12, 2004

39th MEETING OF THE CANADIAN CONGRESS OF NEUROLOGICAL SCIENCES

CANADIAN CONGRESS OF NEUROLOGICAL SCIENCES
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Calgary, AB Canada T2H 2K6
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PROGRAM AND
ABSTRACTS

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The Canadian Neurosurgical Society
La Société Canadienne de Neurochirurgie

The Canadian Society of Clinical Neurophysiologists
La Société Canadienne de Neurophysiologie Clinique

The Canadian Association of Child Neurology
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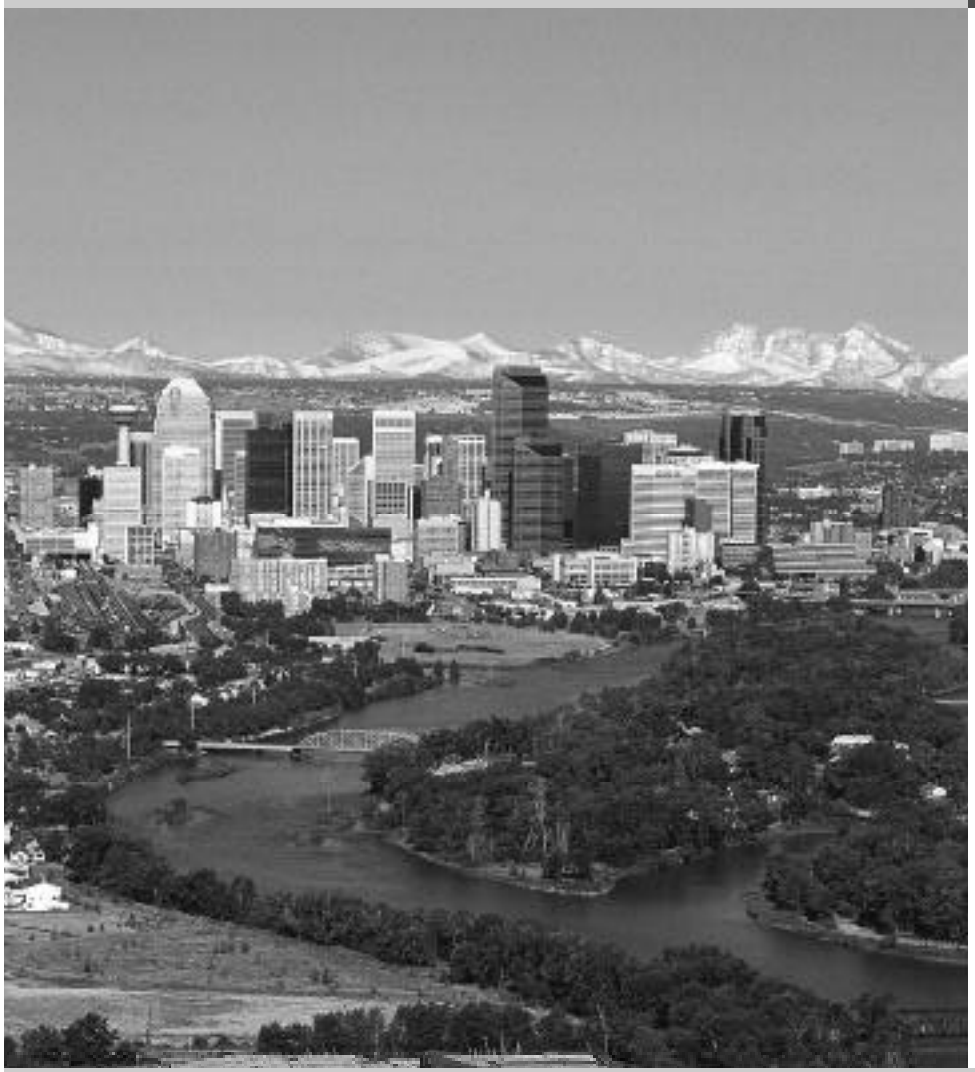
PROGRAM



39th

meeting of the

Canadian Congress of Neurological Sciences

Calgary

CCNS • CCSN

June 8-12 juin 2004

Tuesday June 8, 2004

Pre-Congress Courses

08:00-17:30 Neurobiology Review Course
09:00-16:00 ALS-Strategies for Quality Life/Quality Care
18:00-21:00 Movement Disorders Video Session
18:00-21:00 Headache

Wednesday, June 9, 2004

08:00-17:30 Spinal Course
08:00-12:00 Brain Tumour Course
08:00-12:00 Epilepsy
08:00-12:00 EMG – Update on Electromyography and its Clinical Applications
13:30-17:30 Alzheimer's Disease
13:30-17:30 Radiosurgery Course – Current Role in Neurosurgical Practice
13:30-17:30 Movement Disorders
13:30-17:30 EEG
18:00-20:00 Welcome Reception

Thursday, June 10, 2004

08:30-10:30 Plenary Session I: Neurology and Neurosurgery in the Developing World
11:00-13:00 Platform Session
13:00-14:30 Poster Session
14:30-16:00 Platform Session
16:00-17:30 Grand Rounds
17:30-19:00 Poster Tours

Friday, June 11, 2004

08:30-10:30 Plenary Session II: New Directions in the Neurosciences
11:00-13:00 Platform Session
13:00-14:30 Poster Session
14:30-16:30 Plenary Session III: Risk Reduction in the Clinical Neurosciences
18:00 Social Night

Saturday, June 12, 2004

08:00-10:00 Neurocritical Care Mini-symposium
08:00-10:00 What's New in Neurology? Mini-symposium
08:00-10:00 How I do it … Neurosurgery. Mini-symposium
08:00-17:30 Child Neurology Day
10:30-17:00 Stroke
10:30-17:30 Multiple Sclerosis

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ABSTRACTS

SOCIETY PRIZE PRESENTATIONS

Canadian Neurological Society – Frances McNaughton Memorial Prize
Canadian Association of Child Neurology – President's Prize
Canadian Society of Clinical Neurophysiologists – Herbert Jasper Prize
Canadian Neurosurgical Society – K.G. McKenzie Prize in Basic Neuroscience Research
Canadian Neurological Society – Andre Barbeau Prize

PLATFORM PRESENTATIONS

Thursday June 10, 2004

Friday June 11, 2004

POSTER PRESENTATIONS

Thursday June 10, 2004 and Friday June 11, 2004

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2004 Society Prize Papers

The President's Prize – Canadian Association of Child Neurology

How to quantify motor learning in the cerebellum

M Salman (Toronto), JA Sharpe (Toronto), M Elzenman (Toronto), L Lillakas (Toronto), M Dennis (Toronto), C Westall (Toronto), M Steinback (Toronto)*

Background: Saccades are fast orienting eye movements. Saccadic adaptation (SA), an unconscious corrective change in the amplitude of saccades, provides a method for studying motor learning. The cerebellum is a major participant in SA. The aims of the study were to ascertain whether SA occurs in children and quantify its magnitude in typically developing children. *Methods:* Horizontal saccades were measured with an infrared eye tracker. Thirty-nine children (21 males), aged 8-19 years (mean 13.7, SD 3.5) completed the study. Visual targets stepped 12 degrees horizontally, then during the primary saccade to the target, they stepped 3 degrees backwards, requiring a corrective reduction of the amplitudes of the primary saccades. The adaptive learning task consisted of 200 target steps with intra-saccadic back-steps. *Results:* SA was achieved in 67% of participants ($p<0.05$). The mean amplitudes of their primary saccades decreased by 9.3%. Regression analyses revealed no effects of gender or of age on saccadic adaptation. *Conclusions:* SAoccurs in typically developing healthy children as young as 8 years. Children in this age group have mature functions of the cerebellar circuits responsible for the motor learning required for saccadic adaptation.

Frances McNaughton Memorial Prize – Canadian Neurological Society

Physiotherapy coupled with dextroamphetamine for motor rehabilitation after hemiparetic stroke: a randomized, double-blind, placebo-controlled trial

DJ Gladstone (Toronto), CJ Danells (Toronto), A Armesto (Toronto), WE McIlroy (Toronto), WR Staines (Toronto), SJ Graham (Toronto), N Herrmann (Toronto), JP Szalai (Toronto), SE Black (Toronto)*

Background: Hemiparesis is the commonest disabling deficit caused by stroke. In animals, dextroamphetamine (AMPH) paired with training enhances motor recovery, but its clinical efficacy is uncertain. *Methods:* In a randomized, double-blind, placebo-controlled trial, 71 stroke patients were stratified by hemiparesis severity and randomly assigned to 10 sessions of physiotherapy coupled with either AMPH 10mg or placebo. Study treatments were administered by one physiotherapist, beginning 5-10 days poststroke and continuing twice/week for 5 weeks. Outcomes were assessed by one physiotherapist at baseline, after each treatment, 6 weeks, and 3 months. The primary outcome was motor recovery (impairment level) on the Fugl-Meyer (FM) scale. Secondary outcomes assessed mobility/ambulation, arm/hand function, and independence in activities of daily living. *Results:* Baseline hemiparesis was severe overall (mean FM score: 27.7 ± 20.0). Motor scores improved in both groups (mean change, baseline to 3 months: 29.5 ± 16.6). Repeated measures ANOVA revealed no significant differences in recovery between the treatment groups for the entire cohort (n=67), or for subgroups with severe hemiparesis (n=43), moderate hemiparesis (n=24), or cortically-based stroke (n=26). In the moderate subgroup, there was a significant drug x time interaction for upper extremity recovery ($F=5.14$, $p<0.001$). *Interpretation:* In stroke patients with a severe motor deficit, AMPH 10mg coupled with physiotherapy twice/week for 5 weeks provided no additional benefit in motor or functional recovery compared to physiotherapy alone. Patients with moderate severity hemiparesis deserve further investigation. Increased intensity and longer duration drug/therapy dosing regimens should be explored targeting the upper and lower limbs separately.

Herbert Jasper Prize – Canadian Society of Clinical Neurophysiologists

Treatment of refractory status epilepticus with inhalational anesthetic agents: isoflurane and desflurane

Seyed M Mirsattari (London), Michael D Sharpe (London), G Bryan Young (London)*

Background: Refractory status epilepticus (RSE) is defined as continued seizures after two or three antiepileptic drugs (AEDs) have failed. Several intravenous agents have been utilized for RSE, however, problems occur with their toxicity and/or effectiveness. We report our experience with inhalational anesthetics (IAs) in patients who were refractory to other AEDs. *Methods:* Retrospective review over a four year period of patients with RSE treated with isoflurane and/or desflurane. *Results:* Seven patients (four males) aged 17-71 years received 7-15 (mean 10) AEDs in addition to IAs. IAs were initiated after 1-103 (mean 19) days of RSE and were used for 11±8.9 days. All patients received isoflurane and one patient in addition received desflurane anesthesia 21 days after the onset of RSE for a total of 19 days. Regardless of seizure type, isoflurane and desflurane consistently stopped epileptic discharges with adequate, sustained EEG burst-suppression within minutes of initiating IA therapy. Four patients had good outcomes, three died (one of acute hemorrhagic leukoencephalitis, one of bowel infarction and one with toxic encephalopathy who remained in a persistent vegetative state until death five and a half months after the onset of seizures. Complications during IA therapy included hypotension (7/7), atelectasis (7/7), infections (5/7), paralytic ileus (3/7) and deep venous thrombosis (2/7 patients). No patient developed renal or hepatic dysfunction. *Conclusions:* Isoflurane and desflurane adequately suppressed RSE in all cases. Complications were common but mortality and long-term morbidity related to the

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2004 Society Prize Papers

underlying disease and duration of RSE. Prolonged use of isoflurane and desflurane is well-tolerated.

K.G. McKenzie Prizes in Basic Neuroscience Research – Canadian Neurosurgical Society

Downregulation of potassium channels after subarachnoid hemorrhage contributes to cerebral vasospasm

BS Jahromi (Toronto), Y Aihara (Chicago), M Agbaje-Williams (Chicago), E Nikitina (Chicago), GW Weyer (Chicago), D Ryan (Chicago), R Yassari (Chicago), RL Macdonald (Chicago)*

Introduction: Vascular myocyte membrane potential and tone are primarily regulated by potassium (K^+) channels. Reduced K^+ channel function may thus contribute to vasospasm by impairing cell membrane hyperpolarization, thereby promoting calcium (Ca^{2+}) entry and arterial contraction. *Methods:* Dogs were randomly assigned to control or to undergo subarachnoid hemorrhage using the standard double-hemorrhage model. K^+ channel function was compared using molecular (quantitative real-time RT-PCR, western blotting), electrophysiological (perforated and whole-cell patch-clamp, single channel analysis), immunohistochemical and isometric tension techniques. *Results:* Basilar artery diameter was reduced by 58±2% on angiography 7 days after SAH. Two predominant types of K^+ channels were observed in basilar artery myocytes: the large conductance Ca^{2+}-activated K^+ (BK) channel and the voltage-gated K^+ channel Kv2.2. BK channels were unchanged after SAH whereas Kv current density was reduced by 49% and vasospastic myocytes were depolarized by 9.5mV. Pharmacological block of Kv currents reproduced this depolarization in control cells and contracted basilar artery rings under isometric tension. Kv2.2 mRNA and protein were significantly diminished and Kv2.2 immunostaining was decreased after SAH. *Conclusions:* The decrease in Kv2.2 channel function after SAH can lead to smooth muscle cell depolarization and arterial constriction. This novel mechanism may be involved in the pathogenesis of vasospasm.

Andre Barbeau Memorial Prize – Canadian Neurological Society

RAGE in the nervous system: insights into a new pathophysiological relationship to diabetic complications within the central and peripheral nervous system

C Toth (Calgary), AM Schmidt (New York), U Tuor (Calgary), V Brussee (Calgary), J Kaur (Calgary), D Zochodne (Calgary)*

Background: Central nervous system (CNS) and peripheral nervous system (PNS) complications of diabetes are numerous and remain incompletely understood. In the cerebrum, white matter abnormalities (WMA) and brain atrophy are related to cognitive decline and risk of stroke. In the PNS, peripheral neuropathy with changes in the dorsal root ganglion (DRG) is a major cause of pathology and disability. *Objective:* To determine the possible association of receptors for advanced glycosylation end products (RAGE) in nervous tissue of mice with long term experimental diabetes. *Methods:* A long-term (8 month) streptozotocin-induced diabetic mouse model with characteristic pathological changes was subjected to magnetic resonance imaging (MRI) of the brain. Parameters for diabetes were monitored throughout life, including nerve conduction studies (NCS). RAGE immunohistochemistry was used to examine RAGE expression in the cerebrum, DRG, and peripheral nerve. *Results:* MRI detected WMA to occur in the cerebrum over regions for which abnormalities of myelination were found and these coincided with increased expression of RAGE. Increased RAGE expression was also noted in cerebral neurons. Diabetic peripheral nerves demonstrated electrophysiological deficits with NCS and morphological changes. Diabetic peripheral nerve and DRG demonstrated increased RAGE expression relative to controls. Epidermal foot pad biopsies demonstrated loss of end neurites in diabetes, but diabetic end neurites and end bulbs also had a rise in expression of RAGE relative to controls. *Conclusions:* RAGE expression is significantly increased over regions of myelination deficit and is present in neurons in the diabetic CNS, as well as in peripheral nerve, DRG, and epidermal nerve fibers. Accumulation of advanced glycosylation end products in these tissues may stimulate upregulation of RAGE expression and contribute to the pathogenesis of diabetic complications within the nervous system.

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PLATFORM PRESENTATIONS

CEREBROVASCULAR SURGERY

A-01

Treatment of ischemic brain damage by uncoupling NMDA receptor-PSD-95 protein interactions.

*M Tymianski**

Royal College of Physicians and Surgeons of Canada Gold Medallist in Surgery (2003) winner.

A-02

Wound hematomas after carotid endarterectomy

D Steven (London), E Claus (New Haven), M Eliasziw (Calgary), G Ferguson (London)*

Background: Wound hematomas are potentially lethal events that complicate 2-7% of carotid endarterectomies. Without prompt recognition and surgical intervention they may lead to airway compromise, cerebral ischemia and death. *Methods:* The preoperative, intraoperative and postoperative data of 2670 patients who underwent carotid endarterectomy in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and Aspirin in Carotid Endarterectomy (ACE) trial were analyzed. Using a logistic regression model, multiple variables were examined as potential risk factors for the development of wound hematomas. *Results:* Of the 2670 symptomatic patients who underwent carotid endarterectomy in NASCET and ACE, 180 (6.7%) suffered a postoperative wound hematoma. One hundred and twelve of the hematomas were classified as mild, 63 as moderate and 5 as severe. A multivariate analysis revealed nonreversal of heparin with protamine as the only avoidable risk factor for a clinically significant (moderate or severe) wound hematoma. Contrary to previous reports, the use of protamine was not associated with an increased risk of fatal or nonfatal strokes; however, an association was identified between the use of protamine and a small number of deaths related to cardiac ischemia. *Conclusions:* The administration of protamine sulfate reduces the risk of wound hematoma formation without an increased risk of fatal or nonfatal strokes. This practice may be associated with a higher risk of complications related to cardiac ischemia.

A-03

Adverse events in the early management of subarachnoid hemorrhage.

N Limaye (Halifax), I Fleetwood (Halifax)*

Background: Early complications of subarachnoid hemorrhage (SAH) can lead to devastating clinical outcomes. We investigated the sources of delay in patient management leading to such complications. *Methods:* We reviewed the charts of 174 patients identified from our prospective database diagnosed with SAH from January 1999 to December 2002. Patients referred from outside Nova Scotia were excluded. We recorded all clinical events and management details from onset of SAH to time of aneurysm treatment, focusing on time intervals between onset and subsequent finite points in management. The primary outcome measures were rebleeding, hydrocephalus, seizure or other neurological deterioration such as cranial neuropathy or altered consciousness. *Results:* Of 160 Nova Scotian patients seen at our institution, 62 suffered adverse events prior to definitive aneurysm management. Twelve experienced rebleeding, 6 experienced seizures, 19 experienced other neurological deteriorations and 24 developed hydrocephalus. At least 71% of adverse events occurred within 24 hours of SAH onset. Of those who rebled, 6 didn't seek or reach medical attention in time, 2 were not diagnosed at initial presentation and 4 had other delays in management. *Conclusions:* Improvements in public education, emergency room diagnosis and expedited referral centre management may reduce the risk of adverse events soon after SAH.

A-04

eClips technology: a novel approach for endovascular treatment of intracranial aneurysms

T Gunnarsson (Toronto), G Bourne (Vancouver), T Marotta (Toronto)*

Background: Many coiled aneurysms are partially treated leaving a residual aneurysm that may grow and pose a future threat. A more effective and safer endovascular treatment is needed. *Methods:* eClips (endovascular clip systems), is a new stent-like device with an anchoring section and a leaf section. The leaf section is covered with an impermeable biocompatible membrane. A delivery system that allows for fluoroscopic orientation is used to place the leaf accurately over the opening of the aneurysm excluding it from the circulation. Bench testing in the Levy model and cadaver testing were performed to evaluate the ability to orient and to access the human cerebral vasculature with eClips. The device was also tested in a porcine aneurysm model. *Results:* Cadaver access demonstrated eClips superior to most stents currently used in the cerebral vasculature and near to that of a standard microcatheter. All ten aneurysms were successfully excluded or near closed in the porcine model. *Conclusions:* eClips is a new endovascular device to close aneurysms at the neck without having to enter the aneurysm. It may prove to be an effective way to treat even wide neck aneurysms. Further animal testing is required to evaluate the long term efficacy.

A-05

Early surgical complications after aneurysm clipping. Analysis of etiologies and patient outcome

N McLaughlin (Montreal), MW Bojanowski (Montreal)*

Background: Most series on ruptured intracranial aneurysm report the occurrence of selected intra-operative complications. However, the understanding of all surgical complications might guide towards improvement of surgical procedures and enrich discussions concerning alternative management which are not exempt of complications and aneurysmal recurrence. *Methods:*

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Retrospective study of 143 consecutive patients with subarachnoid hemorrhage (SAH) surgically treated over a 3-year period. A surgical complication was considered on a clinical and/or radiological basis in the absence of confounding factors such as initial SAH ictus, vasospasm, hydrocephalus, septic status. Functional outcome was assessed at 3 months using the GOS. *Results:* Surgical complication were diagnosed in 20.3% (29/143) of patients. Brain tissue injury including cerebral edema and hemorrhagic contusions was diagnosed in 6.3%, unpredicted residual aneurysm neck in 5.3%, and cranial nerve deficit in 2.8%. GOS was good in 75.9% (22/29) of patients with surgical complications. Surgical complication mortality was 0.7% (1/143). *Conclusions:* Surgical complications are more prevalent than previously thought. They might have been overlooked because of the low morbidity and mortality in this group. A proposed classification of procedure-related surgical complication could guide the identification of these complications. This analysis may stimulate research of solutions to better surgical treatment of aneurysmal SAH.

A-06

Complications after endovascular occlusion of unruptured aneurysms. Implications for early discharge

G Redekop (Vancouver), D Graeb (Vancouver)*

Background: Endovascular aneurysm occlusion is believed to be associated with lower rates of complications and shorter lengths of stay in comparison to microsurgery. A series of unruptured aneurysms is reported, emphasizing frequency and time course of procedural complications and impact on length of stay. *Methods:* 107 endovascular coil occlusion procedures for unruptured intracranial aneurysms were performed. A prospective database was created, including patient and aneurysm details, outcomes, complications, and length of stay. *Results:* Morbidity occurred in 19 cases (17.8%). There was no mortality. In 14 cases complications were minor but resulted in increased length of stay (asymptomatic coil protrusion into parent artery in 3, groin hematomas in 6, intraluminal thrombus in 4, TIA in 1). Intracranial hemorrhage occurred in 5 cases (4.7%). Three patients experienced minor bleeding due to artery perforation from a guidewire, without neurological symptoms. Two patients (1.9%) had serious morbidity from vessel or aneurysm rupture. In the last 80 cases the average length of stay was 2.2 days. Thirty-two of these patients (40%) had a length of stay less than 24 hours. Complications occurred in two distinct time frames, either during the procedure or within 4 hours of femoral sheath removal. There were no delayed complications and no patients required readmission after discharge. *Conclusions:* Endovascular repair of unruptured intracranial aneurysms can be accomplished with low rates of serious complication and brief hospitalization.

A-07

Endovascular coiling of intracranial aneurysms: rates and outcomes of incomplete occlusion

G Pickett (London), M Kole (London), D Pelz (London), S Lownie (London)*

Objective: The long-term durability of endovascular coiling for intracranial aneurysms is unknown. We investigated the procedural risk and clinical and angiographic outcomes of coiling, and the natural history of incompletely coiled aneurysms. *Methods:* We retrospectively reviewed all patients with intracranial aneurysms treated by endovascular coils, without balloon remodeling or stent-assisted techniques, at our centre from 1995 to 2003. *Results:* 142 aneurysms in 139 patients were treated, ranging in diameter from 2-34mm. 76% of aneurysms had ruptured. 30% were located in the posterior circulation. Median neck size was 4mm, and 54% were classified as complex aneurysms. Mean packing density was 17%. Failure of coil detachment occurred in 3.5% of cases. Periprocedural risk of death and permanent stroke was 2.8% and 8% respectively. Good or excellent clinical results were obtained in 73% of patients. Follow-up angiography revealed complete occlusion or stable remnants in 46%, but 36% required retreatment or possessed unstable remnants. Of remnants, 31% thrombosed or remained stable, 46% were unstable, while 23% were considered indeterminate risk. Annual rebleeding risk was 1.2%. *Conclusions:* While most patients had good clinical outcomes, a significant proportion demonstrated incomplete aneurysmal occlusion. Nearly half of aneurysm remnants were unstable in average follow-up of 2 years.

A-08

Comparison of monitoring methodologies for intraoperative cerebral ischemia

D Rowed (Toronto), D Houlden (Toronto), A Bethune (Toronto), M Nolan (Toronto)*

Background: There is an extensive literature on intraoperative monitoring for cerebral ischemia but none of the previous reports have documented direct, simultaneous comparison of all commonly employed monitoring modalities correlated with clinical outcomes. *Methods:* Median nerve somatosensory evoked potentials (SSEP), electroencephalogram (EEG), and middle cerebral artery (MCA) mean flow velocity (VMCA) and frequency of emboli, from transcranial Doppler ultrasound (TCD) were recorded simultaneously before, during and after internal carotid artery (ICA) occlusion under general anesthesia in 171 consecutive patients. *Results:* SSEP was the most accurate predictor of waking neurological deficit (sensitivity, specificity, positive and negative predictive values all =1) Duration of SSEP change as brief as 16 minutes was associated with waking deficit. Variations in collateral cerebral blood flow (CBF) led to apparent confounding results detected by different monitoring modalities. *Conclusions:* Comparative studies like the present report, by simplifying methodology for detection of ischemia, reduce confusion and lead to more widespread use of monitoring with improved patient safety.

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SPINAL DISORDERS I

B-01

A comparison of percutaneous and open lumbar surgical techniques

S Marzouk (Detroit), M Abdulhak (Detroit), F Schreiber (Detroit), D Nerenz (Detroit)*

Background: Back pain is one of the most prevalent medical problems in adults. Surgeries that result in shorter recovery periods and hospital stays benefit the patient, physician and health care system. This study is designed to compare the results of patients undergoing percutaneous lumbar discectomies, laminotomies/ foraminotomies (nonfusion), or pedicle screw fixation with lumbar interbody fusion (270 fusion), to patients undergoing these surgeries using a traditional open technique. *Methods:* Patients are enrolled in a prospective randomized trial and their outcomes surveyed using the SF-36v2, and Oswestry disability and patient satisfaction questionnaires. In addition, factors such as return to work, fusion rate, complications, technical difficulty, OR time, blood loss, length of stay and cost are analyzed. If percutaneous patients decline participation in randomization, these variables are studied through a case registry. *Results:* There are currently 150 patients who have completed surgery in our study. Statistical significance ($p<0.05$) was found in these areas: blood loss, hospital stay and costs, and operative time. Statistical significance was also found in the social functioning category of the SF36V2 data, and strong clinical trends in the categories of physical role, vitality, mental health, and health transition. *Conclusions:* Our data suggest that percutaneous spine techniques will lead to better patient outcomes.

B-02

Synchrotron-supported imaging of the rat spinal column and spinal cord: a feasibility study in an animal model

M Kelly (Saskatoon), E Schultke (Saskatoon), C Beavis (Saskatoon), D Fourney (Saskatoon), R Griebel (Saskatoon), D Chapman (Saskatoon)*

Background: Synchrotron-supported imaging methods such as diffraction enhanced imaging (DEI) are currently under development for clinical use. This study represents the first attempt to image the spinal cord and the spinal column using DEI. *Materials and Methods:* The spinal columns of 4 male Wistar rats were studied: 2 animals underwent laminectomies (T6 or L2) and 2 served as controls. An additional 23 animals underwent T6 laminectomy and spinal cord injury as per the Tator aneurysm clip model. The spinal cords were removed. The specimens were imaged with DEI and conventional absorption radiography. *Results:* DEI provided superior contrast compared to conventional radiography, allowing identification of the bone, intervertebral discs, interspinous ligaments and facet joint capsules. DEI showed precise determination of the sites of bony removal. Post-surgical disruption of facet joint capsules was also evident. None of the 23 isolated spinal cords could be seen with DEI at 40 keV. *Conclusions:* DEI represents a novel imaging modality for the spinal column that allows for excellent discrimination between the bone and ligamentous anatomy. Further work is needed to develop this technique for imaging the spinal cord.

B-03

Spinal cord injuries and the relationship to the APOE allele: a cytogenetic analysis of traumatic spinal cord injury

BD Toyota (Vancouver), R Sahjpaul (Vancouver)*

The APOE allele has been found to be a reliable genetic marker of neurologic susceptibility to injury. This has been shown to be true in brain injury as well as hemorrhagic stroke. The association between the presence of the APOE allele and spinal cord injury has never been analyzed. We have initiated a pilot project to determine if polymorphisms involving the apolipoprotein E gene influence recovery from an incomplete spinal cord injury. The clinical data regarding the spinal cord injury and the degree of recovery is reviewed and compared to the presence of the APOE allele on each patient. We will discuss the potential of this result in terms of future directions and its implications for spinal cord injury management. It also leads to both pragmatic considerations in terms of rehabilitation as well as thoughts about the pathophysiology of traumatic spinal cord injury and, therefore, potential molecular strategies for treatment.

B-04

Minocycline opening the door for new therapies to treat acute spinal cord injury

J Wells (Calgary), RJ Hurlbert (Calgary), VW Yong (Calgary)*

Background: Treatment options for reducing damage after acute SCI are limited. Recently, as minocycline has displayed neuroprotective properties, we explored the efficacy of minocycline in SCI. *Methods:* CD1 mice were subjected to SCI at the level of T3/T4. Minocycline was injected ip at 50 mg/kg at 1 and 24h and subsequently at 25mg/kg daily for 5 days. Behavioural assessments using the Basso Beattie Bresnahan Locomotor rating scale and inclined plane task were conducted throughout the study. Evoked potentials were recorded from somatosensory and cerebellar cortices 28 days post-injury. Retrograde labeling of red nucleus neurons was performed in order to determine the integrity of axons of the rubrospinal tract (major locomotor pathway in rodents). *Results:* Mice treated with minocycline demonstrate improved recovery of hindlimb function ($p<0.05$) and strength ($p<0.05$) compared to vehicle (saline) treated controls. This can be correlated to the partial preservation of cerebellar evoked potentials ($p<0.01$) as well as spared axonal integrity of the rubrospinal tract. Microarray and differential display techniques are being employed to elucidate potential mechanisms. *Conclusions:* Minocycline treatment spares tissue, preserves physiological function, and enables significant recovery in locomotor ability. Minocycline may be of therapeutic benefit in acute SCI in humans.

B-05

Vertebral artery ectasia and posterior C1-C2 transarticular screw fixation: real or perceived limitations?

J-F Chevalier (Calgary), S Casha (Calgary), J Bouchard (Calgary), RK Cho (Calgary), P Salo (Calgary), SJ Du Plessis (Calgary), RJ Hurlbert (Calgary)*

Background: Posterior C1-C2 transarticular screw fixation is an effective method for atlanto-axial arthrodesis. However, reports

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suggest restriction of screw insertion due to vertebral artery ectasia (VAE) in 15-20% of trauma patients and in up to 50% patients with rheumatoid arthritis (RA), arguing for intraoperative navigation. We review our experience in light of these observations. *Methods:* Retrospective case series. Patients undergoing isolated C1-C2 arthrodesis between 1996 and 2003 at our institution were identified and their charts reviewed. *Results:* Eighty-seven patients underwent C1-C2 arthrodesis over the 7 year period (n=23 RA, n=64 non-RA). Indications for surgery included ligamentous laxity and post-traumatic or congenital instability. In the RA group, 44 of 46 possible C1-C2 transarticular screws were placed uneventfully (96%). One screw was not attempted because of pre-operatively defined VAE; one was removed secondary to malposition. In the non-RA group, 124 of 128 possible screws were inserted uneventfully (97%). Two screws could not be inserted because of marked kyphosis, one was removed because of malposition, and one fractured the pars interarticularis without clinical consequence. There were no excluded attempts due to VAE among non-RA patients, nor known vertebral artery lacerations. *Conclusions:* Surgeons may be overly sensitive to perceived VAE. In our experience, safe bilateral transarticular screw fixation is possible in over 95% of RA and in up to 100% of non-RA patients without vertebral artery laceration or the need for intra-operative navigation.

B-06

Assessment of neurological status and prediction of neurological outcome after acute traumatic spinal cord injury (SCI) using quantitative assessment of canal stenosis by CT scan and MRI

J Furlan (Toronto), E Massicotte (Toronto), M Fehlings (Toronto)*

Background: Maximum canal compromise (MCC) and maximum spinal cord compression (MSCC) may be a valuable tool for assessing neurological status and predicting neurological outcomes in individuals with acute SCI (Fehlings et al., Spine, 1999). This study examines this issue in a consecutive series of SCI patients. *Methods:* All consecutive individuals with acute traumatic SCI who underwent MRI and CT scan at admission between 1998-2000 were neurologically assessed (ASIAscore) at admission and at discharge from outpatient clinic. Data were analyzed using ANOVA and linear regression. *Results:* There were 22 individuals (6F, 16M; ages 17-82 years; mean=53) who were surgically (50%) or conservatively treated for different degrees of SCI (ASIA A1/B2/7C/8D/4E). CT-MCC (p=0.044), MRI-MCC (p=0.004), and MRI-MSCC (p=0.021) were correlated with baseline ASIA scores. Individuals with more severe SCI had larger MRI-MCC (p=0.01) and there was a trend for similar association with MRI-MSCC (p=0.064). There were no significant differences for CT-MCC measurements among individuals with different ASIA scores (p=0.392). Neurological outcome, after a mean follow-up of 10.2 months, was correlated with MRI-MCC (p=0.003) and MRI-MSCC (p=0.011), but not CT-MCC measurements (p=0.848). *Conclusions:* All three radiologic parameters correlated significantly with admission ASIAscores. However, only MRI-MCC and MRI-MSCC demonstrated an association between the severity of canal stenosis or cord compression and outcome after SCI. In conclusion, MRI-MCC and MRI-MSCC measurements at admission are predictors for neurological outcomes after SCI.

B-07

Optimizing transoral odontoid resection with intraoperative magnetic resonance imaging and neuronavigation

J Kelly (Calgary), S Casha (Calgary), S DuPlessis (Calgary), G Sutherland (Calgary), R Hurlbert (Calgary)*

Background: The confined surgical corridor of the transoral approach to the anterior craniocervical junction and C1-C2 complex (O-C1-C2) offers limited exposure and surgical orientation. We have used intraoperative magnetic resonance imaging (iMRI) and neuronavigation to overcome these limitations. *Methods:* Retrospective review of 10 cases that underwent transoral odontoidectomy using iMRI, 7 with neuronavigation. *Results:* Pathologic conditions of the craniocervical junction treated include a synovial cyst of C2, basilar invagination (degenerative, rheumatoid arthritis), chordoma, plasmacytoma and metastasis. Preoperative MR imaging used for navigation was useful for retractor placement and planning the surgical trajectory. Inter-dissection images were obtained to assess the decompression, confirm anatomic orientation and to update the navigation system. Postoperative imaging was performed to confirm adequate decompression/resection and to rule-out complications. An immediate benefit to iMRI was obtained in 3 of 10 cases which required further resection and decompression. Postoperative imaging demonstrated complete resection in all cases and confirmed one complication, a high cervical spinal cord injury. *Conclusions:* iMRI and neuronavigation in the transoral approach to O-C1-C2 facilitates retractor placement, maximizes the surgical corridor, evaluates the extent of resection intra-operatively and allows navigation system updating.

B-08

Percutaneous vertebroplasty for the treatment of osteoporotic compression fractures

C Lum (Ottawa), T Nguyen (Ottawa), E Belanger (Ottawa), W Miller (Ottawa), J Prasad (Ottawa), M Goyal (Ottawa)*

Purpose: To investigate the safety and efficacy of percutaneous vertebroplasty (PV) for treatment of symptomatic vertebral compression fractures. *Patients and Methods:* A total of 33 consecutive patients who were referred to our service for PV were studied. Patients were directly examined under fluoroscopy. Selection criteria included significant pain correlated to the level of fracture at fluoroscopic evaluation. Pre-procedure CT scans and, in some cases, MRI were performed. PV was performed via a uni- or bipedicular approach. Post-procedure CT scans were performed. Clinical follow-up was performed via phone interview. A 4-point decrease in subjective pain score was judged as significant improvement. The rationale for procedure refusal was also recorded. *Results:* Twenty patients had PV performed at 33 vertebral body levels. Nineteen patients had osteoporotic fractures, one had PV for stabilization of a thoracic level involved by tumor. Follow-up was available in 17 patients, of which 14 (82%) reported significant pain relief. One patient sustained rib fractures from treatment of a thoracic compression fracture. No other procedure-related complications. Two patients had recurrent pain which was from fractures at sites adjacent to treated levels. Thirteen patients had procedures refused,

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of which 8 (62%) had insignificant or poorly localized pain. Five patients who had procedures refused were found by our service to have other significant findings previously unsuspected, including: large lytic tumor, spinous process fracture, cauda equina syndrome, discitis/osteomyelitis and migrated herniated disc. *Conclusions:* Percutaneous vertebroplasty is effective in providing significant pain relief in patients with symptomatic osteoporotic compression fractures. It can be performed safely with a very low complication rate. The frequency of fractures at other adjacent levels is comparable to the literature. Our protocol can help identify other significant causes for the patients pain.

General Neurosurgery

C-01

RAGE in the nervous system: insights into a new pathophysiological relationship to diabetic complications within the central and peripheral nervous system

C Toth (Calgary), AM Schmidt (New York), U Tuor (Calgary), V Brussee (Calgary), J Kaur (Calgary), D Zochodne (Calgary)*

Andre Barbeau Memorial Prize winner (see page 8)

C-02

ALS with cognitive impairment: a novel tauopathy

M Strong (London), W Yang (London), W Strong (London)*

Background: In order understand abnormal tau protein deposition in ALSci, and how this differs from both normal aging and ALS without cognitive impairment, we compared the neuropathological and neurochemical characteristics of tau protein aggregation in ALS, ALSci and age-matched controls. *Methods:* We used archival paraffin-embedded frontal and hippocampal tissue from 90 neurologically and neuropathologically normal cases (10 per decade, age 0-90 years) to characterize tau deposition as a function of aging and contrasted this to both ALS and ALSci (n=6 each). Both soluble and insoluble tau protein, isolated from frontal grey and subcortical white matter and from hippocampus, was examined by Western blot analysis. *Results:* We observed a normal age-dependent pattern of neuronal and extraneuronal tau deposition. Tau immunoreactive intraneuronal and astrocytic aggregates and extraneuronal neuropil tau was unique to ALS prior to the 7th decade of life. ALSci patients demonstrated the greatest load of tau deposition. All ALSci cases demonstrated insoluble tau protein while none was observed in controls, with a heterogeneous expression in ALS without cognitive impairment. *Conclusions:* We have observed that ALSci is a unique tauopathy that can be differentiated on neuropathological and neurochemical grounds from the age-dependant deposition of tau.

C-03

The effect of different stimulator positions on transcranial motor evoked potentials

D Houlden (Toronto), L Burkholder (Toronto), A Taylor (Toronto), D Suchon (Toronto)*

Background: Motor evoked potentials (MEPs) are used to intraoperatively monitor motor pathways. The effect of different stimulating positions on MEP recruitment has not been fully investigated. *Methods:* Intraoperative transcranial electric stimulation was performed using 2 different stimulus orientations; a) C3 anode - C4 cathode b) C4 anode C3 cathode (International 10-20 system). MEPs were concomitantly recorded from wrist extensors, hypothenar, tibialis anterior and plantar foot muscles bilaterally. Stimulus intensity was gradually increased from threshold (T: minimum intensity to produce MEP in any muscle) up to T + 400V for each stimulus orientation. *Results:* 103 patients undergoing spinal surgery were studied. MEPs contralateral to the anode were recruited at lower stimulus intensities than MEPs ipsilateral to the anode ($p < 0.01$). High intensity C3 anodal stimulation (T + 400V) produced bilateral upper and lower limb MEPs in more patients (74% and 78% of patients respectively) than C4 anodal stimulation did (63% and 63% of patients respectively). C3 anodal stimulation (T + 400V) recruited MEPs from more muscles than C4 anodal stimulation ($p < 0.01$). Stimulus intensities above T + 250V rarely recruited more MEPs, regardless of stimulus orientation. *Conclusions:* C3 (left scalp) anodal stimulation was better than C4 (right scalp) anodal stimulation at recruiting MEPs during spinal surgery.

C-04

Variant Creutzfeldt Jacob disease: association with anti-gliadin antibodies

C Voll (Saskatoon), J Scott (Saskatoon), C Robinson (Saskatoon), C Bergeron (Ottawa)*

Background: Variant Creutzfeldt Jacob disease (vCJD) has only rarely been reported in countries outside of the United Kingdom (UK). *Methods:* We report the first confirmed case of vCJD in Canada, and the second in North America. *Results:* An unusual finding in this patient was the presence of anti-gliadin antibodies in the absence of biopsy features of gluten enteropathy. *Conclusions:* We speculate that this may have occurred as a consequence of the presence of prion protein within the GI tract in this patient. Since prion protein is present within the gastrointestinal mucosa in vCJD, this raises the possibility that prion protein elicits enterocyte mucosal alterations which may immunogenic resulting in the elaboration of anti-gliadin antibodies. This may have diagnostic and pathophysiological implications and requires study in other vCJD patients.

C-05

Characterizing beta-amyloid producing enzymes in the lysosome.

S Pasternak (London), J Callahan (Toronto), D Mahuran (Toronto)*

Background: Beta-amyloid is produced by the sequential proteolytic cleavage of the amyloid precursor protein (APP), first by a beta-secretase and then by a gamma-secretase. Although many lines of evidence suggest that beta-amyloid is produced in the endosomal/lysosomal system, the relative contribution of these compartments to total beta-amyloid production remains controversial. Furthermore, the enzymes responsible for endosomal/lysosomal beta-amyloid are poorly characterized. *Methods:* Using

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the tritosome technique, we have produced highly purified lysosomes from the rat liver. We examined beta- and gamma-secretase proteins and activity in this preparation using western blotting and *in vitro* enzyme assays. *Results:* We have previously demonstrated that gamma-secretase proteins and activity are highly enriched in the lysosome. Here we show that although BACE-1 and 2 are not enriched in the lysosome, beta-secretase activity is highly enriched in the lysosome, as is the resulting beta-cleaved APP. Pharmacologically, this activity appears to be due to the BACE-1 enzyme, as well as a combination with other aspartyl and non-aspartly proteases. *Conclusions:* Taken together, our work demonstrates that lysosomes are highly enriched in the enzyme activities required for the production of beta amyloid. Lysosomes may therefore play an important role in the pathogenesis of AD.

C-06

Magnetization transfer imaging in post-poliomyelitis syndrome

MC Tartaglia (London), DL Arnold (Montreal), DA Trojan (Montreal)*

Background: Post-poliomyelitis syndrome (PPS) is believed to be a motor unit disorder, but the presence of CNS pathology whether resulting from acute encephalitis or a degenerative process is questioned. Brain magnetization transfer (MT) imaging is sensitive to pathological changes in myelin and axons and can assess structural changes that may be responsible for some of the symptoms seen in PPS patients. Decreases in MTR have been reported in a number of conditions, including multiple sclerosis and stroke. *Objective:* To assess whether PPS patients displayed low MTR in the midbrain or more generally in the centrum semiovale (CS). *Methods:* The mean MTR from the CS and the central part of the midbrain were calculated in eight normal controls and sixteen PPS patients. *Results:* The controls midbrain mean MTR 32.45 ± 0.8 was nonsignificantly higher than the PPS patients 31.74 ± 1.2 (p=0.120). The CS mean MTR was similar in both groups (34.82 ± 0.8 in controls and 34.78 ± 1.1 in PPS; p greater than 0.999). *Conclusions:* In this preliminary study, we found a trend toward a lower MTR in the midbrain of PPS patients but not in the CS, thus arguing for the possibility of a focal central nervous system pathology in PPS.

C-07

Successful treatment of migraine with prolonged aura: does a label of HaNDL syndrome help?

GM Klein (Calgary), JA Pettersen (Calgary)*

Background: The combination of headache, neurological deficit and cerebrospinal fluid (CSF) lymphocytosis is called HaNDL syndrome or pseudomigraine. It is regarded as a distinct benign headache syndrome. The medical literature contains numerous case reports and small series, but does not offer many clues to either etiology or preferred therapies. Some patients have received high dose steroids on an empiric basis. *Methods:* Case report. *Results:* A 33-year-old man presented to the emergency room with a one-month history of headache. Seven days prior to presentation, he had developed intermittent left-sided numbness and severe right-sided headache. MRI and CT scans were normal. CSF studies revealed 76 white blood cells (95% lymphocytes). He was treated with high-dose steroids. All symptoms resolved in 24 hours. *Conclusions:* CSF pleocytosis is well-described in both complicated and uncomplicated migraine, and CSF abnormalities in between migraine attacks have also been reported. The concept of HaNDL syndrome was first created in 1995. The use of high dose steroids in these patients is logical, as there appears to be sterile inflammation in the CSF. The creation of a new syndrome distinct from migraine appears redundant unless a specific cause is identified.

C-08

Canadian neurological survey

S Warren (Edmonton), P Bailey (Saint John)*

Canadian human resources survey. *Background:* The Canadian Neurological Society commissioned a manpower survey in 2002 to assess demographics, distribution, speciality interests, working conditions, job satisfaction and future plans of neurologists across the country. *Methods:* A survey was developed to assess the above objectives. It was mailed to all known Canadian neurologists on 2 separate occasions. Further encouragement by telephone contact was undertaken. 371 of 694 neurologists complied with the survey for a 54% response rate. Resultswere coded and collated at the University of Alberta. *Results:* The demographic profile concludes that the mean age of neurologists is 51 years with only 14% being women. The distribution ranges from 1 per 33, 000 residents in Quebec to 1 per 74, 000 in the Prairies. Approximately 55% of neurologists are community based. 277 out of 364 neurologists designated a subspecialty interest. On average neurologists work 55 hours per week and the majority have significant on-call commitments. Job satisfaction is greater in Academic than in Community Neurology and greater in men than women. Older neurologists enjoy their work more than younger neurologists. Significant attrition in the neurological work force is a concern as 20% of neurologists plan retirement in the next 5 years and between 10 to 20 % wish to cut back their practice substantially. *Conclusions:* This survey highlights significant concerns facing Canadian neurology over the next 5 years. Major efforts to retain existing expertise and enhance residency training will be required to simply maintain the present quality of neurological care in Canada.

MULTIPLE SCLEROSIS

D-01

The epidemiology of multiple sclerosis in Newfoundland and Labrador

S Sloka (St John's), W Pryse-Phillips (St John's), M Stefanelli (Chamberlains)*

Background: The incidence, prevalence, and natural history of MS in Newfoundland and Labrador (NL) was studied. *Methods:* Case searches through patient files of neurologists in NL were conducted. A complete list of patients billed for MS in NL between 1996 and 2003 was obtained and all cases were confirmed via chart review. A survey was mailed to all living patients requesting place of birth, subsequent places of residence, and relatives with MS. *Results:* 491 living MS patients yielded a prevalence of 94.1/100, 000. 265 had RRMS, 74 had SPMS, 57 had PPMS and 95 had

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unspecified MS. Female to male ratio was 2.7:1. Significant delays between first symptoms and final diagnosis were common. 72% of mail outs were returned. A high birth incidence was noted for a small, remote community and a low birth incidence was noted for an entire region. Unusually low birth incidence was noted for the quinquennium 1956-1960. A significant shift in incidence to a different region where first symptoms were experienced from the birth region was noted. *Conclusions:* Newfoundland and Labrador, with its strong founder effect and low in-migration rate, presents an excellent opportunity to study etiology of complex diseases such as MS.

D-02

Indicators of quality health care: the impact of population-based MS clinic care on use of disease modifying therapy in multiple sclerosis

LM Metz (Calgary), CA Stoian (Calgary), GR Currie (Calgary), LW Svenson (Edmonton), ML Myles (Edmonton), I Heinrichs (Red Deer), Jennifer Rodgers (Edmonton), Colleen J Harris (Calgary), Scott B Patten (Calgary)*

Background: Use of disease modifying therapy (DMT) is recommended for people with active relapsing multiple sclerosis (MS). All Albertans have equal access to government funding, but systems of care differ regionally. We used DMT utilization as an indicator of quality of MS care delivery. *Methods:* Anonymous administrative data describing DMT utilization were analyzed by region: Calgary, Edmonton, southern and northern Alberta. MS cases in each region were estimated using 2001 Census and 1999 MS prevalence data. Descriptive analysis and odds ratios (OR) were performed. *Results:* Characteristics of the 606 treated patients were similar across regions: mean age 39.0 years, 74.8% women, median disease duration 6.9 years, and median EDSS 2.5. The patient distribution was Calgary 45.9%, Edmonton 27.9%, southern Alberta 17.9% and northern Alberta 8.4%. Calgary patients had 1.6 times the odds of being treated compared to Edmonton patients. Northern Albertans had 0.6 times the odds of being treated than those in Edmonton. Southern Albertans were more likely to be treated than northern Albertans (OR=1.9) or Edmonton (OR=1.2) but less likely than Calgary patients (OR=0.7). *Conclusions:* Proximity to neurological care and receiving care from a multidisciplinary MS clinic (Calgary) were associated with a greater chance of being treated with DMT.

D-03

Comparison of the quality of life in relapsing-remitting multiple sclerosis undergoing treatment with Betaseron, Copaxone and Rebif

W Hader (Saskatoon), L Carroll (Edmonton), JD Cassidy (Toronto)*

Background: Quality of life (QOL) has been reported to be drastically reduced in early stages of multiple sclerosis, and improvements on immunomodulatory drugs have been reported. *Objective:* To compare the quality of life of MS patients undergoing disease modifying therapy treatments, interferon-beta 1b (Betaseron), glatimer acetate (Copaxone), and interferon-beta 1a (Rebif), using the SF-36 Health Survey, a standard assessment instrument for health outcomes. *Methods:* QOL was assessed in 261 consecutive patients in an open label independent study over three years. They self-completed a baseline questionnaire, and were telephone interviewed quarterly. QOL was determined and compared with historical controls. *Results:* The baseline scores were reduced as compared to a normal population. 224/261 continued interviews, 170/261 remained on the original prescription, 54 discontinued, 37 switched. There is a significant difference ($p<.001$) of the role-emotional scale between the baseline and the first year of treatment. There were no other significant differences in the seven remaining SF-36 scales and the physical and mental summary scores. No significant decline or improvement was observed. *Conclusions:* The three therapies appear to enhance the role-emotional scale during the first year and maintain the same quality of life in MS patients over three years of treatment.

D-04

Multiple Sclerosis: a neurodegenerative disease induced by inflammation

F Giuliani (Calgary), A Bar-Or (Montreal), VW Yong (Calgary)*

Background: MS lesions are characterized by infiltration of inflammatory cells, axonal loss and neuronal degeneration. We seek 1) to determine whether leukocytes can kill neurons, 2) whether Th1 and Th2 polarized T cells have different capacity for neurodegeneration. *Methods:* We used a co-culture system of human neurons and T cells. Neurons were incubated with activated T cells or antigen-specific T cell lines that were either Th1 or Th2 polarized. EAE was induced in C57/BL6 mice for spinal cord histology. *Results:* When added to neurons, activated T lymphocytes aggregated around neuronal elements and death ensued. By 3h of co-culture, the number of neurons was reduced by 50% when compared to controls. Th1 cells were toxic to neurons whereas Th2 were not. Finally, co-localization of inflammation and axonal loss was shown in the spinal cord of EAE mice ($r = 0.9$, $p < 0.001$). *Conclusions:* These data demonstrate that activated Th1 cells can kill human neurons *in vitro* and that axonal loss occurs in EAE in areas of T cell inflammation. We suggest that activated T cells can traffic into the CNS to cause neurodegeneration. The shift of T cells towards a Th2 phenotype decreases their potential toxicity.

D-05

Abnormal profile of B cell regulatory cytokines in MS – potential target of therapy

A Bar-Or (Montreal), S Hebert (Montreal), F Adatia (Montreal), M Duddy (Montreal), M Niino (Montreal)*

Objectives: We identified a novel human B cell regulatory cytokine network and examined whether it is dysregulated in patients with multiple sclerosis (MS). *Background:* Traditionally, B cells are thought to contribute to adaptive immune responses based on their potential to differentiate into plasma cells and elaborate antigen-specific antibodies following cognate interaction with T cells. In general, B cells have been viewed as passive recipients of T cell help during the germinal center reaction. Our lab has recently identified a novel human B cell effector cytokine network, that points to the ability of B cells to actively enhance or suppress immune responses depending on the context of their stimulation.

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Methods: Ex vivo purified B cells (MACS, Miltenyi Biotec) were isolated from patients with relapsing remitting MS and from matched normal individuals (n=9). B cells were stimulated by either: (1) sequential engagement of their B cell receptor (BCR) to simulate antigen binding, and of CD40 to simulate T cell help. This paradigm mimics the appropriate context for antigen-driven B cell activation. (2) engagement of CD40 alone – mimicking bystander activation of a B cell that happened across an activated T cell with a different antigenic specificity. The same was repeated for 6 patients with MS during therapy with Mitoxantrone, a recently approved therapy for MS patients with aggressive and/or progressive disease. *Results:* In normal individuals, sequential stimulation via BCR and CD40 resulted in B cell secretion of high levels of lymphotoxin (LT) and TNFa. These proinflammatory cytokines would actively contribute to the desired development of a germinal center reaction. In contrast, 'Bystander activated'B cells (CD40 engagement alone) secreted IL-10 and no LT or TNFa. This B cell IL-10 would serve to suppress an undesired immune response. Compared to normal B cells, MS patient B cells produced similar amounts of the pro-inflammatory cytokines LT and TNFa but had a significant defect in their ability to produce IL-10 ($p < 0.02$). We further found that treatment with mitoxantrone significantly suppressed the B cell production of LT and TNFa ($p < 0.03$), while significantly enhancing B cell IL-10 production ($p < 0.02$). *Conclusions:* We propose that, in the normal state, B cell IL-10 serves to down-regulate undesired immune responses, as one mechanism whereby peripheral tolerance to self-antigens is maintained. Indeed, this postulate is supported by emerging animal model studies that have implicated B cell IL-10 in the regulation of autoimmune colitis as well as of experimental autoimmune encephalomyelitis, the commonly used model of MS. Our findings point to an abnormality in this novel B cell regulatory cytokine network in patients with MS and identify this network as a potential target for therapy.

D-06

Results of testing for antibodies to interferon in clinical situations – the UBC experience

J Oger (Vancouver), E Gibbs (Vancouver)*

Background: We regularly receive serum samples of interferon beta (IFN beta) -treated multiple sclerosis (MS) patients from MS clinics all over the province of British Columbia and test them for anti-interferon beta antibodies. We have reviewed our experience. *Methods:* We have assayed single serum samples from 256 patients (111 Betaseron®-treated, 126 Rebif®-treated, 19 Avonex®-treated) using an ELISAfor binding antibodies (BABs) as a screening. Only positive samples are referred for neutralizing antibodies (NAB) assay by CPE to Dr. S. Grossbergs lab (Milwaukee). *Results:* The 256 patients were treated for 41 ± 27 months (average ± sd). 131 patients (51.2%) tested positive for BABs and 125 (48.8%) tested negative. The 131 BAB-positive patients could be broken down as follows: 81 were positive among 111 Betaseron®-treated (73%), 47 were positive among the 126 Rebif®-treated (37.3%) and only 3 were positive among the 19 Avonex®-treated (15.8%). Overall, there was a significant difference (Pearson $c2=40.3$, $p<0.001$) in the number of BAB-positive patients between the different treatment groups. Presently we have received results on 58 patients BAB positive samples, only 12 (20.7%) tested positive for NAB and 44 (79.3%) negative: 7 out of 24 Betaseron®-treated tested positive (29%), 5 out of 29 Rebif®-treated (17%) and 0 out of 3 (0%) Avonex®-treated. We extrapolate that only 15% of Betaseron-treated patients and 6% of Rebif-treated patients are exposed to a possible reduction of interferon effect due to eliciting NABs. *Conclusions:* The frequency with which NAB positive samples are found in an unselected population of treated MS patients is relatively small even among the most immunogenic drugs.

D-07

Hydroxychloroquine: a novel microglia modulator?

R Zabad (Calgary), R Lewkonia (Calgary), L Metz (Calgary), V Yong (Calgary)*

Background: Hydroxychloroquine (HQ), an anti-malarial agent, is used as an immunomodulator in lupus and rheumatoid arthritis. It interferes with antigen processing and inhibits cytokine production by peripheral blood mononuclear cells. We studied the effect of HQ on activated microglia, thought to be crucial to the pathogenesis of multiple sclerosis. *Methods:* HQ was studied *in vitro* using human fetal and adult microglia and the U937 line. Cells were pretreated for 2 hours with HQ followed by lipopolysaccharide (LPS), a monocytoid activator, overnight. The culture medium was subjected to TNF-a and IL-10 measurement using ELISA. HQ was also compared to minocycline, a microglia modulator. The effect of HQ on transcripts encoding matrix-metalloproteinases (MMPs) was evaluated using Taqman PCR. *Results:* HQ (3-15 μM) significantly decreased TNF-a and IL-10 levels and was superior to minocycline in inhibiting TNF-a production. HQ reduced the mRNAfor MMP-1, 9 and 12 which are incriminated in the pathogenesis of MS and its animal model, experimental autoimmune encephalomyelitis (EAE). *Conclusions:* To our knowledge this is the first study to test HQ as a microglia modulator. By interfering with microglia activity and MMPs, HQ deserves to be tested further as a disease modifying therapy in EAE and MS.

D-08

Temporal texture analysis of normal appearing white matter in multiple sclerosis

H Zhu (Calgary), X Wei (Calgary), Y Zhang (Calgary), LM Metz (Calgary), JR Mitchell (Calgary)*

Background: Detecting abnormalities in normal appearing white matter (NAWM) may help reveal subtle pathological changes in multiple sclerosis (MS). We hypothesize that as white matter (WM) becomes abnormal, its underlying magnetic resonance (MR) texture will change. We developed a novel texture analysis technique and applied it to analyze NAWM on serial T1-weighted (T1-w) gadolinium-enhanced MRI. Our goal is to detect subtle textural changes within NAWM, particularly to investigate whether those subtle changes predict subsequent MS lesion formation. *Methods:* One patient with relapsing-remitting MS was examined monthly over a 2-month period on a 3 Tesla MR scanner. In each examination, cross-sectional T1-w pre-/post-contrast and T2-w images were acquired. Two types of regions within NAWM on T1-w post-contrast MRI were selected for texture analysis: regions with no lesions over days 0-60 and regions with a new enhancing lesion

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first evident at day 60. *Results:* Serial texture analysis demonstrated that significant textural differences exist between NAWM and active lesions. We also detected early textural changes prior to the appearance of a new lesion in terms of focal contrast-enhancement. *Conclusions:* Our findings suggest that our texture analysis technique may provide an early indication of MRI intensity changes in NAWM in MS.

Spinal Disorders II

E-01

Anterior cervical fusion for posterior element instability

D Serletis (Calgary), S Casha (Calgary), R Cho (Calgary), RJ Hurlbert (Calgary)*

Background: Anterior cervical discectomy and fusion (ACDF) is an alternative to posterior fusion for traumatic posterior element disruption. *Methods:* Retrospective review of 72 patients with facet fracture and/or dislocation treated by ACDF (65 single level, 7 multilevel). *Results:* Seventeen females, 55 males, mean age 41. 64% had neurological injury (29 radiculopathy, 17 spinal cord injury). 61% had neck pain. Mean follow-up was 16 months. Fusion occurred in 97%. Asymptomatic spinal deformity was seen in 5 patients (2 kyphosis, scoliosis, anterolisthesis, retrolisthesis). There were 5 complications (esophageal fistula, iliac fracture, 2 laryngeal nerve injury and hypoglossal nerve injury). Hardware failure occurred in 3 patients (plate fracture, graft extrusion, screw back-out). Three patients underwent re-operation (nonunion, hardware failure, adjacent level disease, dislocated ilioplasty). Eight patients with spinal cord injury improved neurologically, 6 were unchanged. Twenty-five radiculopathic patients improved, 3 were unchanged. None were worse postoperatively. At last follow-up, 34 patients denied pain, 27 had mild pain and 8 had moderate or severe pain. Nine patients were independent but restricting activities, 5 patients required assistance for daily living. *Conclusions:* After comparison with previous publications, ACDF for traumatic posterior element instability exhibits better fusion rates and fewer complications than posterior fusion techniques.

E-02

Transoral cervical decompression using intraoperative neuro-navigation

D Rabin (London), N Duggal (London)*

Background: The transoral approach to the occipito-atlanto-axial complex for the purpose of safe and effective anterior decompression of the cervical spinal cord requires adequate surgical exposure. We describe the application of MR-based image-guided surgery for this procedure. *Methods:* The patient was placed in a halo-thoracic vest prior to undergoing a pre-operative MRI. Localizing fiducials were placed on bony landmarks on the face and forehead. The field of view for the pre-operative MRI encompassed the anterior cranial fossa rostrally and C4 caudally. Following intra-operative registration of the fiducials, the MRI-based neuro-navigation system (Stealth, Sofamor Danek) was used for the transoral approach and removal of a retro-odontoid mass. *Results:* The introduction of neuro-navigation to this procedure increased surgery time by approximately one hour. The neuro-navigation system accurately identified anatomic structures and facilitated an extensive removal of the retro-odontoid mass. *Conclusions:* The application of MR-based image-guided surgery to transoral surgery represents a potential solution to precise intraoperative localization of soft-tissue anatomic structures and pathological lesions in the upper cervical spine. The proximity of the occipito-atlanto-axial complex to the skull base allows for successful application of cranial neuro-navigation techniques to the anterior subaxial cervical spine.

E-03

Improved functional recovery with matrix supplemented hydrogel channels

E Tsai (Toronto), L Lukas (Toronto), P Dalton (Aachen), M Shoichet (Toronto)*

Background: Although we have demonstrated hydrogel channels composed of poly (2-hydroxymethyl methaxcrylate) (PHEMA) without an implanted matrix can promote axonal regeneration after complete spinal cord transection, there was no significant functional recovery. We then sought to determine whether PHEMA channels supplemented with a matrix could improve the extent of locomotor recovery. *Methods:* Adult, female Sprague Dawley (n=7-8/group) rats underwent complete spinal cord transection at T8 and implantation of PHEMA channels alone or channels filled with one of the following: collagen, fibrin glue, Matrigel, methylcellulose, or four smaller PHEMA channels. Controls underwent transection without channel implantation. Functional recovery was assessed weekly using the Basso, Beattie, Bresnahan Locomotor (BBB) scoring system for 8 weeks. *Results:* The mean BBB scores of the collagen, fibrin glue, and the four smaller channel groups were significantly increased (two way ANOVA, $p<0.001$, Tukey test: p, 0.05) compared to the empty tube group and controls. The best BBB scores at 7 weeks in the collagen, fibrin glue, four smaller channel and controls groups were 9, 7, 7, and 2. *Conclusions:* Matrix supplemented PHEMA channels can improve functional recovery after complete spinal cord transection. Analysis of axonal regeneration is ongoing.

E-04

Early results and complications with an artificial cervical disc

GE Pickett (London), N Duggal (London)*

Introduction: An increasing number of Canadian spinal surgeons are adopting arthroplasty techniques for the management of degenerative conditions of the spine. Although disc replacement may potentially become the next standard of care for cervical disc disease, this new technology must be studied rigorously to ensure safety and long-term efficacy. We report our early experience, including complications, with the Bryan Cervical Disc Prosthesis. *Methods:* We prospectively analyzed clinical and radiographic outcomes in over 20 insertions of the Bryan disc for cervical radiculopathy and/or myelopathy. Operative data and perioperative complications were recorded. The Neck Disability Index, McGill Pain Questionnaire, and SF-36 were assessed preoperatively and at regular intervals following surgery. *Results:* Radiographs confirmed preserved motion of the operated spinal segments, up to 24 months following surgery. All outcome measures showed marked improvement. The end-plate angle of the operated disc space

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demonstrated varying degrees of kyphosis compared with pre-operative studies. *Conclusions:* Insertion of the Bryan disc following cervical discectomy appears to be safe and provides good clinical results in early follow-up. Postoperative kyphosis, a previously unreported finding, may be a risk factor for neck pain. Long-term assessment is required to determine whether use of the prosthesis reduces the incidence of adjacent segment disease.

E-05

Occipito-cervico-thoracic fusions in patients with extensive cervical involvement from rheumatoid arthritis

G Swamy (Calgary), RJ Hurlbert (Calgary)*

Background: A minority of patients with rheumatoid arthritis experience severe cervical involvement with atlanto-axial subluxation, basilar invagination and subaxial subluxation. We have been performing occipito-cervico-thoracic (OCT) fusions in these patients using a combined anterior/posterior approach, in an attempt to treat all three pathologies definitively. *Methods:* We reviewed the hospital records and office charts of patients undergoing OCTfusion at our institution from 1997-2003. Seven patients were identified, all with severe rheumatoid arthritis. Mean follow-up was 24 months. Pre-operatively two patients were classified as Ranawat I neurologic status, 2 patients were Ranawat II; and 3 were Ranawat IIIb. The indications for surgery were progressive neurologic deterioration in 5 and intractable neck pain in 2. *Results:* Surgery involved a staged anterior and posterior approach in all seven patients. The mean total operative time was 18 hours, with a mean ICU stay of 8 days (range 0-18). Postoperatively 3 patients were Ranawat I neurologic status, 1 was Ranawat II and 2 remained Ranawat IIIb. Serious complications included CHF, pneumonia, airway obstruction, esophageal dysfunction, DVT, renal insufficiency, and temporary weakness. All patients experienced significant pain relief. One patient with nonunion died from multi-organ failure following revisional surgery 1 year after the index OCT fusion. Thoracic adjacent segment disease with myelopathy was seen in one patient, requiring extensive additional thoracolumbar decompression and fusion. *Conclusions:* OCT fusion is an effective method to definitively treat extensive cervical involvement from rheumatoid arthritis, but surgeons and patients should be aware of the high complication rate in this difficult population.

E-06 (Now being presented as Poster P-214. See page 84)

Time course and effect of methylprednisolone on lipid peroxidation levels after acute spinal cord injury in rats

SD Christie (Halifax), I Mendez (Halifax)*

Background: Oxidative stress leading to lipid peroxidation is a significant cause of secondary injury following spinal cord trauma. The objectives of this project were to determine the duration of lipid peroxidation following acute spinal cord injury (SCI) and the effect of both short- and long-term administration of methylprednisolone (MP). *Methods:* 226 female Wistar rats received a clip compression SCI. Animals naïve to treatment were sacrificed at various time points between 0 and 10 days. Treated animals received clinical doses of either MP or saline for either 24 hours or 7 days and were sacrificed between 0 and 7 days. Spinal cord tissue was assayed colorimetrically for malondialdehyde (MDA) as a marker for lipid peroxidation. *Results:* MDA levels initially peaked 4 hours post injury. By 12 hours, MDAlevels returned to baseline. A second rise was observed from 24 hours to 5 days. Both peak values differed statistically from the trough values ($p<0.008$). MP reduced MDA levels ($p<0.04$) within 12 hours of injury. No effect was seen at 24 hours or beyond. *Conclusions:* Oxidative stress persists for five days following SCI in rats. MP reduces MDA levels within the first 12 hours but had no effect from 24 hours to 5 days.

NEUROCRITICAL CARE

F-01

Mechanisms underlying serum sodium control after acute cervical spinal cord injury (SCI): clinical, neuroanatomical, and molecular evidence for autonomic dysfunction and loss of descending renal inhibitory control

J Furlan (Toronto), M Fehlings (Toronto)*

Background: Autonomic dysfunction is common after acute SCI and may underlie abnormalities in electrolyte balance. This study was undertaken to evaluate (1) incidence of hyponatremia in early stage (2 weeks) after cervical SCI, (2) association of hyponatremia with severity of SCI, (3) localisation of descending renal sympathetic (inhibitory) pathways (DRSPs), and (4) effects of DRSPs destruction on serum sodium concentration (sSC). *Methods:* All individuals with acute cervical SCI admitted to a university hospital between 1998-2000 were reviewed. Also, postmortem spinal cord sections from cervical SCI individuals (below injury) and control cases (intact CNS) were evaluated for area of demyelination (LFB) and axonal preservation (NF200) within descending vasomotor pathways (DVPs), 3mm ventrolateral from dorsolateral sulcus (3mm-area), corticospinal tracts (CST), and dorsal column (DC). *Results:* There were 21 SCI individuals (6F, 15M; ages 17-83 years, mean=57.1) who mostly suffered mild SCI (ASIA 10C/4D). Hyponatremia occurred in 85.7%. Postmortem analysis included 5 control cases (3M, 2F; ages 30-73 years, mean=51.4) and 6 individuals (2F, 4M; ages 31-82 years, mean=59.2) with severe SCI (ASIA 4A/2B) of whom 50% developed hyponatremia. Number of preserved axons within CST, DVPs and 3mm-area was significantly reduced after SCI. Mean and lowest sSC were directly correlated with area of demyelination and inversely correlated with number of preserved axons within 3mm-area (not DVPs). Normonatremic SCI individuals showed more preserved axons within 3mm-area (not DVPs) than hyponatremic SCI individuals. *Conclusions:* Hyponatremia is frequent and is associated with the severity of acute SCI. Of note, the extent of destruction of DRSPs (3mm-area) is inversely correlated with post-SCI hyponatremia and this may reflect autonomic renal dysfunction in volume regulation.

F-02

Treatment of agitation following traumatic brain injury: a review of the literature

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Background: Agitation, restlessness, and aggression are frequent neurobehavioural sequelae in the early stages of recovery from

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traumatic brain injury. These behavioural symptoms disrupt patient care and impede rehabilitation efforts. However, no consensus exists on the pharmacological treatment of agitation in traumatic brain injury patients in the acute and chronic settings. *Methods:* A review of the relevant published literature was undertaken. The Medline and CINAHL databases from 1985 onwards were searched using terms focusing on types of pharmacological agents, cross-referenced with traumatic brain injury, agitation, delirium, and aggression. The Criteria for Level of Evidence Assignment from the Canadian Network for Mood and Anxiety Treatments (CANMAT) was used to grade the articles and their contents. *Results:* A total of 58 papers were found and reviewed. Twenty-five pharmacological agents were evaluated for their effectiveness in reducing agitation in this population, and mechanisms of action and potential adverse effects were summarized. *Conclusions:* Review of the literature suggests that there is limited evidence to accurately guide clinicians in the management of this patient population.

F-03

Gender differences in encephalopathy and mortality in sepsis

B Young (London), J Wilson (London), Z Husain (London), Z Hutchinson (London)*

Background: Septic encephalopathy is thought be due to multiple mechanisms, one of which is oxidative injury produced by free radicals. Since estrogens have an anti-oxidant effect, we explored whether bacteremia was associated with reduced morbidity and mortality in premenopausal adult women than in adult, age-matched males. *Methods:* From the microbiology data bank we retrieved cases of positive blood cultures with Gram-negative organisms for 1997-2002 and obtained the hospital charts for women and men between 15 and 40 years. With HMRI data we examined in-hospital mortality rates for both groups. We also examined the EEG classifications in a subgroup of bacteremic patients. We excluded cases with Gram-positive blood cultures or cultures thought to be false positives. *Results:* There were no statistically significant differences in mortality or EEG classifications between 126 men and women who met our criteria. *Discussion:* We found no evidence of difference in severity of encephalopathy (as reflected in EEG classification) or in-hospital mortality between men and women and thus no evidence for a protective effect of estrogens in sepsis.

F-04

Uncoupling of glial and neuronal metabolism following traumatic brain injury

CN Gallagher (Calgary), RL Tyson (Calgary), GR Sutherland (Calgary)*

Background: In Canada approximately 20, 000 people suffer traumatic brain injury (TBI) per annum and represent 12% of all injury hospitalizations. As most of these patients are young, employed adult males (65%), the direct and indirect costs to society are staggering. In this study we use 13C substrates in combination with MR spectroscopy to study cerebral metabolism in the setting of TBI. *Methods:* Male Sprague-Dawley rats underwent traumatic brain injury, induced using a weight drop model. Each animal received an infusion of either [2-13C]acetate or [1-13C]glucose. 1H MR spectroscopic analysis and 1H{13C} Spin-echo difference (SED) MR spectroscopy was used to analyze cerebral metabolites. *Results:* In animals infused with [2-13C]acetate in a control and immediately following head trauma, incorporation of label into the C-4 position of glutamate is greatly reduced, while for C-4 glutamine the labeling remains unaltered. Animals infused with [1-13C]glucose show incorporation of label into the C-4 position of both glutamate and glutamine is reduced by about 30% following head trauma. *Conclusions:* We show here that significant alterations in TCAcycle labeling of metabolites associated with the TCAcycle occur and that metabolic trafficking between neurons and glia is uncoupled during the first 24 hr following TBI.

F-05

Brain oxygenation ($PbtO_2$) monitoring in acute nontraumatic neurologic illnesses: Delayed brain hypoxia, APACHE II scores and outcome

V Puri (Omaha), P Narotam (Omaha)*

Background: Patients with acute neurologic illnesses are susceptible to secondary injury due to cerebral hypoxia and ischemia. We hypothesize that $PbtO_2$ monitoring predicts outcome and is a monitor of success of interventions. *Methods:* Thirty patients were admitted for acute nontraumatic neurological disorders; aneurysmal SAH (n = 17), hypertensive bleed (n = 9), others (n = 4). All underwent twist drill craniostomy for placement of Licox trademark bolt for $PbtO_2$, brain temperature and ICP monitoring. A critical care algorithm was used to direct ventilation, fluid resuscitation, transfusions etc. APACHE II scores, GCS, $PbtO_2$ and ICP were correlated to outcome. *Results:* Cerebral hypoxia was seen in 48 percent patients one week after starting therapy. The mean 1-week $PbtO_2$ was significantly higher in survivors vs. mortalities (27.74 ± 5.07 vs. 10.95 ± 3.89 mm Hg, $p < 0.0001$, t test). The 1-week APACHE II scores were also significantly different in these two groups. A low $PbtO_2$ at 1 week was strongly correlated with high APACHE scores (r = minus 0.74, $p < 0.05$). Further, high $PbtO_2$ and low APACHE II scores correlated with good Glasgow outcome scores. *Conclusions:* $PbtO_2$ monitoring detects delayed hypoxia in acute nontraumatic neurologic disorders, allowing interventions to minimize secondary injury, and correlates with APACHE II scores and outcome.

F-06

DVT prophylaxis in traumatic intracranial hemorrhage: a decision analysis

J Riva-Cambrin (Toronto), D Scales (Toronto), A Detsky (Toronto)*

Introduction: Though evidence exists to support the routine use of anticoagulation for TE prophylaxis in trauma patients, this therapy is often considered to be absolutely contraindicated in patients with traumatic intracranial hemorrhage (ICH) because of concerns that it might lead to progression of the bleeding injury. We sought to answer the question: should patients with traumatic brain injury be given low-molecular weight heparin (LMWH) at 24 hours for TE prophylaxis? *Methods:* Using decision analysis modeling techniques, we developed a model for trauma patients with documented ICH. The only decision node involved the choice to administer or to withhold TE prophylaxis at 24 hours. Advantages of withholding therapy were decreased risk of ICH progression (death,

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disabling neurologic deficit, nondisabling neurologic deficit), and decreased risk of systemic bleeding complications (death, massive bleed). The associated disadvantage was greater risk of developing TE complications (DVT, PE, death). Probabilities for each outcome were derived from natural history studies and randomized controlled trials when available *Results:* The expected value of the no TE prophylaxis arm was 0.896 compared to 0.886 for the LMWH strategy. This negligible difference represents a toss up; neither treatment strategy appeared to be advantageous to the other. In our 1-way sensitivity analysis only two threshold values were encountered. If the effectiveness of LMWH at preventing DVT/PE reached 0.8 (range from literature 0.33-0.82), our model clearly favored this therapy. Similarly, the model demonstrated a benefit to LMWH if the risk of ICH progression with this therapy was only increased by 5% above the baseline risk. *Conclusions:* Based on current medical knowledge, our model shows that the decision to use LMWH for TE prophylaxis in patients with traumatic ICH has completely balanced risks of bleeding versus clotting. Therefore, a randomized controlled trial can be ethically conducted to definitively answer this clinical question.

STROKE/NEUROLOGY

G-01

Physiotherapy Coupled with Dextroamphetamine for Motor Rehabilitation After Hemiparetic Stroke: A Randomized, Double-Blind, Placebo-Controlled Trial

DJ Gladstone (Toronto), CJ Danells (Toronto), A Armesto (Toronto), WE McIlroy (Toronto), WR Staines (Toronto), SJ Graham (Toronto), N Herrmann (Toronto), JP Szalai (Toronto), SE Black (Toronto)*

Frances McNaughton Memorial Prize – Canadian Neurological Society (See page 7)

G-02

Stroke mortality: enumerating the dead is not as easy as it looks.

S Phillips (Halifax), G Gubitz (Halifax), C Christian (Halifax), J Jarrett (Halifax)*

Background: The June 2003 issue of MacLeans Fifth Annual Health Care Ranking reported that the Halifax / Dartmouth region placed 32nd out of 37 for 30-day in-hospital stroke mortality rate (26%, cf. national average 19%). We sought to understand this. *Methods:* MacLeans used 1998-2001 data from CIHI, which adjusted crude 30-day mortality rates (obtained from local ICD-9 codes) using a logistic regression model. We duplicated these methods using data from our Health Region administration, and compared the results to the CIHI data, and to data from our local prospective stroke registry. We scrutinized hospital records of the dead to determine discrepancies. *Results:* Unadjusted in-hospital 30 day death rate using local ICD-9 data = 27% (182/ 679 strokes); using local registry data = 14% (119/858 strokes). Chart review found 40 cases of stroke with ICD-9 codes not included in CIHI stroke definition; 139 cases of stroke were not captured by the ICD-9 coding system. *Discussion:* Despite the potential utility of 30-day in-hospital stroke mortality as a process indicator for stroke care, it is difficult to obtain reliable data on even this simple outcome measure. Our findings may help plan modifications to hospital separation data collection to make the data more informative.

G-03

Preliminary assessment of rapid evaluation of CT perfusion images in acute stroke

MJ Hogan (Ottawa), A Srinivasan (Ottawa), M Sharma (Ottawa), C Lum (Ottawa), M Goyal (Ottawa)*

Background: Thrombolytic therapy is of benefit within the first 3 hours of ischemic stroke although it is possible that some individuals may benefit at later times. CT perfusion imaging measures cerebral blood volume (CBV) and cerebral blood flow (CBF) and may identify the infarct core and ischemic penumbra. To be useful in acute stroke management rapid evaluation of these imaging data is required. *Methods:* Acute stroke patients undergoing a CT cerebral perfusion study within 6 hours of stroke onset were reviewed. Eight patients with subsequent brain imaging studies were identified. CBV and CBF images were reconstructed following a standard protocol and displayed using standardized color scales. These images were assessed visually by an experienced observer and partitioned, based on appearance only, into regions of interest (ROI) showing severe or moderate reduction, no change or an increase in regional CBV and CBF. The most closely aligned CT image from a follow-up examination showing the extent of ischemic injury was partitioned into ROI showing infarct. A quantitative analysis based on these ROI was performed and the overlap between perfusion parameter changes and infarct determined. *Results:* Mean CBV and CBF measurements within ROI with appearance consistent with severe or moderately reduced, normal or increased values were 0.3 ± 0.1, 1.1 ± 0.3, 1.8 ± 0.5 and 2.1 ± 0.9 ml/100g for CBV and 4.5 ± 0.9, 17.4 ± 5.6 and 34.4 ± 7.7 ml/100g/min for CBF. Hyperperfusion was not identified. Severe reduction of CBV and CBF was associated with cerebral infarct in 83% of ROI and 69% of ROI respectively. Moderate CBF reduction was associated with infarct in 35% of ROI. Infarct was observed in 3% of ROI with normal indices. *Conclusions:* Rapid visual partitioning of perfusion images based on the appearance of CBV or CBF change correlated with the quantitative measurements of these parameters. Severe reduction of CBV or CBF was associated with cerebral infarction. The outcome of ROI showing moderate reduction in these parameters was uncertain.

G-04

Hyperperfusion on perfusion CT following early revascularization for acute stroke: report of four cases and review of the literature

T Nguyen (Ottawa), C Lum (Ottawa), J Eastwood (Durham), P Stys (Ottawa), M Hogan (Ottawa), M Goyal (Ottawa)*

Background: Reperfusion of areas of cerebral ischemia has been observed to occur at variable times after a stroke due to an occlusion of the middle cerebral artery. This could lead to hyperperfusion which is an increase in cerebral blood flow above the level of the normal contralateral hemisphere. The clinical significance of hyperperfusion following a stroke remain unclear. *Methods:* We

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retrospectively analyzed the CT perfusion maps of 14 patients who presented with an acute anterior circulation stroke and who underwent a therapeutic recanalization. Cerebral blood volume (CBV) and cerebral blood flow (CBF) maps were compared between the affected territory and the normal contralateral hemisphere. *Results:* Four patients had some hyperperfusion in the affected territory (mean CBV=3.6 ± 2.0 ml/100g, mean CBF= 39 ± 25 ml/100g/min) compared to the normal side (mean CBV=2.7 ± 2.1 ml/100g, mean CBF= 27 ± 23 ml/100g/min). There was no intracranial hemorrhage in the hyperperfused territories. At follow-up CT, some hyperperfused brain areas progressed to infarction while others retained normal white to gray matter differentiation. *Conclusions:* These findings suggest that hyperperfusion is due to recanalization and loss of vasoautoregulation and is not a primary predictor of tissue survival or demise.

G-05

Transcranial Doppler criteria for predicting proximal arterial occlusion that require rescue ia therapy

M Saqqur (Edmonton), J Roy (calgary), N Akhtar (Edmonton), A Salam (Edmonton), A Shuaib (Edmonton), A Demchuk (Calgary)*

Background: Combined therapy using iv and intra-arterial (ia) tPA has potential to enhance recanalization rates and improve outcome when compared to iv tPA alone. Only some patients require rescue ia lysis because occlusion has recanalized or moved distally with iv tPA alone. TCD offers monitoring capability to assess whether a proximal occlusion persists requiring further ia intervention. We examined the clinical utility of TCD flow findings in patients considered for combined iv/ia lytic treatment. *Method:* All stroke patients at 3 centres who received iv tPA and/or were considered for rescue ia lysis by emergent angiography were included. Patients received iv/ia tPA (0.6-0.9 mg/kg iv and up to 0.3 mg / kg ia tPA) in less than 3 hours or ia tPA therapy in less than 6 hours and underwent urgent TCD performed prior to ia tPA were included. TCD flow findings were analyzed to identify which findings correctly predicted an arterial occlusion proximal enough that ia was attempted in the anterior circulation internal carotid artery, M1 or M2 middle cerebral artery (MCA). *Results:* 38 patients identified with angiography, 28 received iv/ia combined therapy, 5 iv alone, 1 ia alone, and 4 angiogram but no ia lysis. (mean age 61 ±15years, M:F, 24:10, baseline median NIHSS:17). No temporal windows were found in 3 patients (9%). Median time to TCD test from stroke onset is 125 minutes. Median time to cerebral angiography from stroke onset is 171 minutes. The affected MCA mean flow velocity (MFV) / unaffected MCA MFV ratio<0.5 had sensitivity 96.3% (95%CI: 85.3-96.4); specificity 100 % (95% CI: 55.5 -100); PPV 98.1% (88.5 100%); NPV 81.3% (48.6 87.5%) for identifying patients with ia lytic requiring occlusion in the anterior circulation (mean ratio ia lysis lesion present vs absent; 0.218 ± 0.04 vs 0.89 ± 0.09, p<0.001). Clinical outcome correlated with mean MCAMFV(patients with 3 months Rankin 3-6: 2.8 ± 1.9 cm/sec vs. Rankin 0-2: 25.1 ± 5.5 cm/sec; p=0.001). *Conclusions:* TCD has significant potential as a screening tool for iv/ia or ia lysis protocols. The ratio of affected MCA MFV/unaffected MCA MFV <0.5 appears to be highly sensitive and specific for identifying arterial occlusions that require additional ia intervention. MCAMFV on the affected side appears to predict clinical outcome.

G-06

Therapeutic hypothermia in comatose survivors of cardiac arrest: a feasability study

B Young (London), O Al-Muslim (London), M Sharpe (London)*

Background: Hypothermia reduces mortality and morbidity in patients resuscitated from cardiac arrest. We reviewed our experience and examined prognostically relevant factors. *Methods:* Data collected by chart review included age, type of cardiac arrest, ischemic time, initial neurologic exam, time to achieve the target temperature, neurologic outcome and mortality. *Results:* Sixteen patients were treated with induced hypothermia. Average age was 59 years. Eight patients had ventricular fibrillation (VF). Mean time for restoration of spontaneous circulation was 20 minutes. About three hours elapsed before the initiation of hypothermia. Time to attain the target temperature was 3 hours. Five (63%) VF arrest patients and two (25%) non-VF arrest patients had good neurologic outcomes. Initial neurologic exam (GCS and light reflex) was not helpful in predicting outcomes. *Conclusions:* This pilot study confirmed the feasibility of the guideline. Patients characteristics, the time to attain the target temperature and the outcomes data were comparable to the results of the clinical trials. Prospective studies are essential to confirm these results and to evaluate the predictors of good neurologic outcomes.

EPILEPSY/EEG

H-01

Treatment of Refractory Status Epilepticus with Inhalational Anesthetic agents: Isoflurane and Desflurane

Seyed M Mirsattari (London), Michael D Sharpe (London), G Bryan Young (London)*

Herbert Jasper Prize winner – Canadian Society of Clinical Neurophysiologists (See page 7)

H-02

Do acetylcholine receptor antibodies in myasthenia gravis place the patient at greater risk for systemic disease?

Cory Toth (Calgary), David McDonald (Ottawa), Keith Brownell (Calgary)*

Introduction: In myasthenia gravis (MG), the presence of acetylcholine receptor antibodies (AchRAbs) appears to lead to a distinctive phenotype when compared to seronegative MG (without AchRAbs). *Background:* Myasthenia gravis may or may not be associated with the presence of AchRAbs. Along with features of MG, AchRAb positivity has also been speculated to relate to other immune-mediated diseases. *Methods:* A retrospective evaluation of MG patients was performed, with patients separated into AchRAb positive (seropositive) and AchRAb negative (seronegative) groups. The prevalence of other immune-mediated disorders, as well as the epidemiology, sensitivity of diagnostic testing, and thymic pathology, was compared between the two MG groups. *Results:* A total of 101 MG patients, 66% seropositive, were identified. Presence of AchRAb in MG was associated with greater likelihood

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of significant repetitive stimulation decrement, presence of thymic pathology, and presence of thyroid disease. The only patients with diagnoses of diabetes (either insulin-dependent or steroid-induced) were AchRAb positive. *Conclusions:* The presence of AchRAbs in MG imparts not only a distinctive clinical phenotype of MG, but also is associated with greater likelihood of electrophysiological neuromuscular deficit, thymic pathology, and presence of both thyroid disease and diabetes.

H-03

Optimizing outcome after selective amygdalo-hippocampectomy for intractable mesial temporal lobe epilepsy with intraoperative MRI

J Kelly (Calgary), GR Sutherland (Calgary), ST Myles (Calgary), W Hader (Calgary)*

Background: The extent of resection of mesial temporal structures has previously been recognized as an important predictor of postoperative seizure outcome in patients undergoing temporal lobectomy. We evaluate our experience with high field intraoperative MRI in patients undergoing selective amygdalo-hippocampectomy for intractable mesial temporal lobe epilepsy (MTLE). *Methods:* A retrospective study of patients who underwent selective amygdalo-hippocampectomy for intractable MTLE, from 2000-2003, in the setting of a high field (1.5T), mobile intraoperative magnetic resonance imaging (iMRI) system, was completed. Interdissection MR images were performed to assess the extent of removal of mesial temporal lobe structures. Seizure outcome was according to Engel. *Results:* Twenty-seven patients, 15 females and 12 males, were identified. Mesial temporal sclerosis was present on surgical planning MR images in 21 of 27 patients. Interdissection MR images identified residual mesial temporal structures in 12 (44%) patients which was subsequently resected. Histopathology demonstrated mesial temporal sclerosis in 17 of 27 patients. Twenty (78 %) patients were seizure free (Engel class I) at last follow-up while 5 patients (18.5%) had persistent or recurrent seizures. One patient suffered a postoperative retraction hemiparesis. *Conclusions:* Intraoperative MRI ensures the complete resection of mesial temporal lobe structures in patients undergoing selective amygdalo-hippocampectomy and allows the greatest chance of long term postoperative seizure freedom.

H-04

Intra-occipital localisation of intractable occipital epilepsies: clinical, neuroimaging and subdural electroencephalographic correlates

W Blume (London), L Tapsell (London), S Wiebe (London)*

Background: Whether ictal semiology or clinical examination can distinguish mesial occipital and lateral occipital originating seizures was sought. *Methods:* We included patients whose seizures arose from either the mesial occipital or lateral-inferior occipital surface, determined by subdural recordings or those with an occipital lesion whose removal improved seizures by over 90%. *Results:* Seizures arose on the mesial surface in 20 patients and the lateral surface in 11. Unformed and formed visual phenomena each failed to distinguish such origins. Dyscognitive (85%, 82%) and GTC (75%, 91%) likewise failed to distinguish these epileptogenic surfaces. All 8 patients with a preoperative visual field deficit had seizures arising from the mesial surface as compared to 11 patients with mesial and 10 patients with lateral occipital origins and normal Goldmann visual fields. *Conclusions:* Ictal semiology failed to identify which occipital surface was epileptogenic. Visual field abnormalities appeared only with mesial occipital originating seizures.

H-05

Functional MRI analysis of the pre-ictal state.

P Federico (Calgary), R Briellmann (Melbourne), D Abbott (Melbourne), G Jackson (Melbourne)*

Rationale: The transition from interictal to ictal discharges is poorly understood. One possibility involves the brain changing into a facilitating state promoting seizures. Nonlinear mathematical analysis of EEG has confirmed the presence of a pre-ictal state, however, spatial resolution was limited. We report on fMRI analysis of the pre-ictal state in three patients with focal epilepsy. *Patients and Methods:* We studied three patients with frequent complex partial seizures originating from the left face sensory area (patient #1), right superior frontal gyrus (patient #2), and right supplementary sensorimotor area (patient #3). All subjects had typical complex partial seizures in the scanner while continuous BOLD fMRI whole brain images were being acquired at 3 T. The preictal changes in BOLD contrast were analysed by comparing BOLD signals for the one minute prior to seizure onset (task) to a span of one minute beginning five minutes prior to seizure onset (rest). *Results:* One typical complex partial seizure was captured in each patient. In patient #1, a striking pre-ictal BOLD signal increase was seen over the left (ipsilateral to seizure focus) frontocentral region, maximal at the seizure focus. Patient #2 showed a robust pre-ictal BOLD increase over the left (contralateral) posterior frontal region. Patient #3 showed a pre-ictal BOLD increase in the left (contralateral) premotor area. *Conclusions:* Highly significant BOLD fMRI signal changes occur minutes before the onset of seizures. These can be localised to the site of seizure onset, as well as to normal brain regions. We presume that the neuronal changes that occur pre-ictally are a combination of excitation and inhibition as the normal parts of the brain try to suppress the biochemical and electrical cascade that leads to seizures. fMRI analysis of pre-ictal BOLD signal changes supports the presence of a pre-ictal state.

H-06

A comparison of sevoflurane and methohexital for activation of epileptiform activity during intraoperative electrocorticography (ECoG) during epilepsy surgery

T Sankar (Edmonton), BM Wheatley (Edmonton), DW Gross (Edmonton), N Ahmed (Edmonton)*

Background: Methohexital (brevital) has been used as an intravenous agent for inducing epileptiform activity during intraoperative electrocorticography (ECoG). Over the last decade, the availability of methohexital has been variable. This prompted our search for other agents capable of inducing epileptiform activity during ECoG for epilepsy surgery. *Methods:* We describe our results comparing methohexital to sevoflurane in three patients who had epilepsy surgery and intraoperative ECoG. Methohexital (20-40mg

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intravenous) and sevoflurane (2-3 percent inhalational anesthetic) were administered successively while under general endotracheal anesthesia. The second agent was administered after a washout period of 10 minutes. The ECoG was reviewed by two epileptologists (DWG and NA). *Results:* One patient had a parietal resection (gliosis), one patient had a temporal resection (MTS and cavernous malformation) and one patient had a temporal and parietal resection (cortical dysplasia). Two patients had interictal epileptiform activity prior to the administration of either agent. In both patients methohexital and sevoflurane broadened the epileptic field but did not induce *de novo* epileptic activity. The third patient (parietal resection) had no activation with methohexital but had focal activation of the presumptive epileptogenic focus with sevoflurane. This epileptiform activity was concordant with presurgical surface EEG. *Conclusions:* Sevoflurane may be useful in inducing epileptiform activity as an alternative to methohexital and when methohexital is not effective.

NEURO-ONCOLOGY

I-01

Concomitant and adjuvant temozolomide and radiotherapy for newly diagnosed glioblastoma multiforme: results of a randomized controlled clinical trial by the EORTC and the NCIC clinical trials group.-

R Stupp (Lausanne, Switzerland)*

I-02

A randomized prospective controlled clinical trial of photodynamic therapy [PDT] in the treatment of newly diagnosed malignant supratentorial gliomas using porfimer sodium [Photofrin]

P Muller (Toronto), B Wilson (Toronto), L Lilge (Toronto), H Hetzel (Denver), T Fullagar (Denver), J Abrams (Detroit)*

Background and Objective: We are presenting the preliminary survival results of a prospective trial of PDT in the treatment of malignant gliomas. [NIH 5PO1CAS043892-13] *Methods:* Only patients with pathologically confirmed glioblastoma multiforme are included in this study cohort. Patients were randomly assigned to the control [surgical resection + postoperative radiotherapy + chemotherapy] or to the experimental arm [surgical resection + intraoperative PDT + postoperative radiotherapy + chemotherapy]. The PDT arm received 2 mg/kg Photofrin iv 12-36 hours prior to resection and 110-130 J/cm^2 photo-illumination]. A total of 101 participants have been enrolled [47 at Toronto and 54 at Denver]. A total of 77 individuals, 39 from Toronto and 38 from Denver met the eligibility criteria and accepted their assigned treatment. *Results:* There were no clinically or statistically significant differences in demographic characteristics or baseline neurological measures between treatment arms. The median survival was 8 mos. (95% CI 3 mos., 10 mos.) for patients receiving surgery alone and 11 months (95% CI 6 mos., 14 mos.) for patients on the PDT+surgery arm. The curves crossed at approximately 15 months, and when treatment is the only predictor in the model there was evidence of nonproportional hazards (p=0.04). *Conclusions:* The median survival of patients with GBM was extended by 3 months in the PDT arm. The preliminary analysis of the primary end-point [crude survival] has not reached statistical significance.

I-03

Introduction of Gamma Knife surgery in Canada

A Kaufmann (Winnipeg), M West (Winnipeg)*

Introduction: The Gamma Knife (GK) is being utilized to treat a growing proportion of neurosurgical patients at centres worldwide. In Canada, however, no GK has been available and few patients were referred out of the country to receive this treatment. Our feasibility analysis supported the installation of a GK in Winnipeg. We report here our initial experience with GK surgery in Canada. *Methods:* The Winnipeg Centre for Gamma Knife Surgery commenced operations on November 3rd, 2003, with projections of treating 240 patients annually. Referrals have been accepted from within our province (population approximately 1 million) as well as all other Canadian provinces (total population approximately 30 million). *Results:* In the first two months of operations, 52 patients were treated and another 69 patients were deemed appropriate GK candidates, with future surgery dates scheduled. Among the total 111 patients, local referrals accounted for 63 (57%) and out-of-province referrals accounted for 48 (43%). Fifty-eight (52%) GK patients were referred by medical doctors, including 92% of local cases but only 20% of out-of-province cases. Self-directed referrals initiated by patients were common (48%). *Conclusions:* Our initial GK feasibility projections underestimated the number of patients we have treated and scheduled in the first two months of operation. The local medical community has incorporated GK surgery into their management strategy, while most referrals from other Canadian regions have been patient initiated. We anticipate an increase in GK referrals, as the medical community adopts radiosurgery into their existing management strategies.

I-04

Combinatorial benefit of inhibition of epidermal growth factor receptor and mammalian target of rapamycin (mTOR) in the treatment of malignant glioma xenografts

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Background: Activation of the epidermal growth factor receptor (EGFR) pathway is present in the majority of patients with malignant glioma and is associated with a poorer prognosis. AEE788 is an EGFR tyrosine kinase inhibitor, and RAD001 is a potent inhibitor of the mammalian target of rapamycin (mTOR). We hypothesized that combined inhibition of these two related pathways would result in greater anti-tumor activity. *Methods:* We examined the effect of these two inhibitors on human glioma cell lines and on subcutaneous and intracranial xenografts. *Results:* Treatment with the EGFR inhibitor AEE reduced the phosphorylation of the EGF receptor and of ERK1/2. The mTOR inhibitor RAD001 decreased the activation of S6 and 4E-BP1. Orally administered AEE788 and RAD001 in combination were well-tolerated by athymic nude mice. The combination of AEE788 (100 mg/kg/day t.i.w.) and RAD001 (5 mg/kg/day) administered orally to athymic mice bearing established human glioblastoma tumor xenografts produced inhibition of

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subcutaneous tumor growth and increased survival in mice with intracranial tumors that was greater than either agent as monotherapy. *Conclusions:* These preclinical data show that the combination of EGFR inhibition and mTOR inhibition is a potentially effective new therapy for malignant glioma. Preliminary results of a clinical study will be presented.

I-05

PDT with porfimer sodium associated LDL and vinorelbine exert synergistic microtubule depolymerization, antiangiogenicity and induction of D2 apoptosis in chemoresistant glioblastoma overexpressing bcl-2 and MDR-1 (Pgp)

John Giannios (Athens)*

Introduction: Glioblastoma expressing bcl-2 and MDR-1 is incurable due to chemoresistance. *Materials and Methods:* Glioblastoma overexpressing MDR-1 and bcl-2 was treated with vinorelbine and porfimer sodium entrapped into the lipophilic core of LDL targeting the tumor proliferating cell surface which possess an enhanced number of LDL receptors. The tumor was treated photodynamically with laser light at a wavelength of 630 nm. With high density cDNA array technology, we detected expression changes of various genes pre and post treatment. *Results:* Post treatment, LDL facilitated porfimer sodium access into tumor cells via receptor mechanisms. Laser irradiation induced microtubule depolymerization in tumor and endothelial cells according to immunofluorescence microscopy using b-tubulin antibody. Enhancement in intracellular calcium resulted in microtubule depolymerization which acted synergistically with vinorelbine. Flow cytometry exhibited cell cycle arrest at G2/M. There was overexpression of bcl-2. Vinorelbine caused downregulation of bcl-2 and upregulated Bax circumventing resistance to chemotherapy and photocytotoxicity. Singlet oxygen induces c-fos and c-jun and activates p38 which phosphorylates transcription factors ATF-2 and Elk-1. Oxidative stress downregulated MDR-1 and VEGF while it induced c-myc and WAF1/CIP1/p21 causing cell cycle arrest in tumor cells through inhibition of cdk2, cdk6, cyclinD1 and cyclinE. Apoptosis was confirmed with TdT and TUNEL. D2 apoptotic signs were exhibited with electron microscopy. *Conclusions:* We eradicated chemoresistant glioblastoma by combined PDT and chemotherapy after downregulating bcl-2, MDR-1 and VEGF.

I-06

Human dendritic cells primed with glioma or malignant melanoma naturally processed tumour peptides induce cytotoxic antitumour response *in vitro*

R Kerr (Edmonton), H Chen (Edmonton), M Protti (Milan), K Petruk (Edmonton)*

Introduction: Glioblastomas and melanomas have evolved complex methods to avoid recognition and effective response by the immune system. Dendritic cells (DCs) are antigen presenting cells capable of strong antigen presentation in the context of MHC and co-stimulatory molecules. We hypothesize that autologous or HLA A2 matched DCs primed with naturally processed tumour peptides from malignant gliomas or melanomas can induce CD8+ lymphocyte lysis of target tumour cells *in vitro*. *Methods:* Autologous or HLA-A2 matched DCs were generated from CD14+ monocytes and primed with naturally processed tumour peptides extracted from early explant tumour cultures. Primed DCs were co-cultured with matched CD8+ lymphocytes. CTLs were evaluated for proliferation, IFN gamma secretion, and target cell lysis. *Results:* CTLs demonstrated prolific clonal expansion by 48 hours. One week after admixture, IFN gamma concentrations for autologous experiments for Ed276Bt, Ed326Bt, and Ed343Mel were 477, 301.5, and 3, 593 pg/ml respectively. 51Cr CTL assays using HLA-A2 matched DCs and CTLs against SK24Mel and Ed276Bt at a 1:20 target/effector cell ratio resulted in 38% and 58% target cell lysis respectively at 4 hours. *Conclusions:* Autologous or HLA-A2 matched DCs primed with glioma or melanoma peptide extracts induce CD8+ lymphocyte proliferation, activation, and cytotoxic lysis of glioma and melanoma cells *in vitro.*

I-07

***In vitro* studies of a novel drug delivery system for malignant glioma**

M Loubani (London), K Walsh (London), R Hammond (London), J Megyesi (London), I McLennan (Lansing)*

Introduction: One of the challenges to chemotherapy in cases of malignant glioma has been overcoming the blood brain barrier. Achieving therapeutic intratumoral concentrations using systemic chemotherapy has often been limited by adverse systemic reactions. In the present study, we describe a novel sugar-polymer nanosphere, which has been used to successfully encapsulate carmustine (BCNU) and doxorubicin (Dox). The encapsulated nanospheres have the potential to overcome the adverse effects of systemic drug delivery by intratumoral implantation. *Methods:* Nanospheres 130-170 nm in diameter were produced from polysaccharides using a high shear method. These nanospheres form stable dispersions in saline up to 40 percent (w to w). Nanospheres were then used to encapsulate either BCNU or Dox, which were assayed for loading efficiency and then tested against free BCNU or free Dox to determine their relative cytotoxicities on U-251 and U-87 glioma cell lines. *Results:* Dox and BCNU encapsulated nanospheres were produced with a loading efficiency of 1 percent (w to w). Both nanosphere types showed cytotoxicities comparable to the free BCNU or free Dox. The mechanism of cytotoxicity was found to be apoptotic as determined by immunohistochemistry using caspase-3. LDH assays showed no release of LDH with BCNU encapsulated, Dox encapsulated, or control nanospheres tested against U-251 and U-87. *Conclusions:* The encapsulation of BCNU or Dox was carried out successfully in polysaccharide-based nanospheres, while preserving the cytotoxicities of both drugs. Supported by NCI FLAIR Grant R43 CA92817.

I-08

Size, genes and surgical resectability of oligodendrogliomas and mixed oligo-astrocytomas

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Background: Complete surgical resection of glial tumors is difficult to attain due to their invasiveness, size, and location.

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Methods: We retrospectively reviewed charts and images of patients diagnosed with oligodendrogliomas and mixed oligo-astrocytomas to assess the role of age, sex, clinical presentation, tumor size, location, and 1p/19q loss of heterozygosity (LOH) on surgical resectability. *Results:* Forty-six patients were included in this study. Twelve patients (26%) had complete resection (CR) defined as >95% (stereotactic biopsies excluded), 34 (74%) patients had partial resection (PR). Mean age was 40.6 years. The mean maximum diameter for all tumors was 5.7cm (3.3cm in totally resected and 6.7cm in partially resected tumors). Of tumors < 5 cm in maximum diameter, 63% had CR. No tumors > 5cm had CR. Tumors with 1p/19q LOH were < 5cm in 75% of cases and 78% of those had CR. Tumors with no 1p/19q LOH were < 5cm in 29% of cases and only 50% of these had CR. Nine (20%) tumors involved deep structures, all had PR. *Conclusion:* In this study (1) tumor size played the strongest role in surgical resectability of oligodendrogliomas and mixed oligo-astrocytomas. (2) tumors that had 1p/19q LOH became symptomatic at a smaller size and were more surgically resectable when compared to tumors that had no 1p/19q LOH.

PEDIATRICS

J-01

How to quantify motor learning in the cerebellum

M Salman (Toronto), JA Sharpe (Toronto), M Elzenman (Toronto), L Lillakas (Toronto), M Dennis (Toronto), C Westall (Toronto), M Steinback (Toronto)*

The President's Prize winner – Canadian Association of Child Neurology (See page 7)

J-02

Posterior resection for childhood epilepsy

D Barry Sinclair (Edmonton), M Wheatley (Edmonton), T Snyder (Edmonton), D Gross (Edmonton)*

Background: There are now several reports on temporal lobectomy for intractable childhood epilepsy. There are few reports on epilepsy surgery outside the temporal lobe. We reviewed our experience with posterior resection for intractable childhood epilepsy. *Methods:* We retrospectively reviewed all children with posterior resection (parietal and occipital lobe) operated on by the Comprehensive Epilepsy Program at the University of Alberta Hospital between the years 1990-2002. The patients had preoperative and postoperative seizure history charts, neurological examination, EEG, long term video EEG (LTV EEG), MRI, and neuropsychological assessments. Patients were followed and reassessed in the Pediatric Epilepsy Clinic at 3 months, 6 months, and then yearly following surgery. *Results:* Fifteen patients, 6 males and 9 females, were studied. Age of surgery was 18 months to 16 years. Nine patients had a parietal resection and 6 patients had an occipital resection. Surgical outcome was variable. Nine patients had an excellent outcome (Engel Class I), 2 patients had a poor outcome (Engel Class III), and 2 patients had a very poor outcome (Engel Class IV). Pathology at surgery included focal cortical dysplasias (4), brain tumors (4), tubers of tuberous sclerosis (2), cerebrovascular accidents (2), porencephalic cysts (1), and normal pathology (2). Complications included visual field loss in the occipital lobe patients (4/6). *Conclusions:* Posterior resection can be successful for children with intractable epilepsy originating in the parietal and occipital lobes. The best results are seen in those patients with discreet lesions on MRI followed by lesionectomy. Invasive monitoring is necessary in some patients to establish the extent of the epileptic zone prior to surgery. A good surgical outcome is dependent on the presence of a circumscribed lesion and ability to surgically remove all the pathology. Visual abnormalities are an expected complication of surgery in the occipital lobe, but may improve over time.

J-03

Near infrared spectroscopy discloses the cerebrovascular and metabolic consequences of neonatal seizures

C Hahn (Boston), J Riviello (Boston), H Bassan (Boston), J Soul (Boston), G Walter (Boston), A du Plessis (Boston)*

Background: The extent to which neonatal seizures may compromise cerebrovascular hemodynamics and oxygenation remains poorly understood. *Methods:* A 27-week gestational age female infant was monitored during the first five days of life by continuous bedside recording of mean arterial pressure (MAP) and near infrared spectroscopy measurements of cerebral total hemoglobin (HbT), oxygenated hemoglobin (HbO_2), deoxygenated hemoglobin (Hb), oxy- minus deoxyhemoglobin (HbD), and oxidized cytochrome oxidase ($CytO_2$). *Results:* Four generalized tonic seizures were recorded. Each seizure was associated with similar changes in MAP and NIRS signals. Seizures began with an acute rise in MAP lasting approximately 10 seconds, accompanied by a rapid rise in HbT, HbO_2 and Hb. Over the next 20 seconds, MAP and HbT returned to baseline, whereas HbO_2 and HbD dropped to below baseline, and Hb remained constant. Over the ensuing 1-2 minutes, while MAPand HbT remained constant, HbO_2 and HbD declined further, whereas Hb rose slightly. Over the next 2-3 minutes, all NIRS signals gradually returned to their baseline values. $CytO_2$ remained unchanged throughout. *Conclusions:* Following an initial adaptive increase in MAP and cerebral blood flow (HbT), tonic seizures in this infant were associated with sustained cerebrovascular oxygen desaturation attributable to increased tissue oxygen extraction.

J-04

Neonatal seizures in Saskatchewan: incidence, etiology, clinical features and outcome by gestational age.

E Leung (Saskatoon), M Moodley (Saskatoon), N Lowry (Saskatoon)*

Background: Among perinatal risk factors, gestational age, seizures and intracranial hemorrhage are the strongest independent discriminators between the child who will be neurologically impaired and controls. However, information on epidemiology, etiology, short and long term prognosis for neonatal seizures are sparse in preterm infants and limited in term infants. Only 1 publication in 1997 reviews Canada's specific data on neonatal seizures. *Methods:* A retrospective review of all infants with neonatal seizures admitted to the neonatal intensive care unit at the Royal University Hospital in Saskatoon, between January 1996 to

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December 2002. *Results:* During the 7 year period, 81 patients with neonatal seizures were identified, of which 73% were male, 7% were premature, 49% had clonic seizures, 19% tonic, 18% myoclonic, 14% subtle. Hypoxic ischemic cerebral injury was the principle etiology in term babies accounting for 32% while intraventricular hemorrhage was the principal etiology in preterms accounting for 19%. Seizures manifested earlier in preterm babies overall compared to term infants. EEGs were abnormal in 77% and CT brain scans were abnormal in 58%. Six patients died and of those who survived, 96% were seizure free at the time of discharge *Conclusions:* Gestational age exerts a considerable influence on the incidence, onset, etiology and prognosis of neonatal seizures.

J-05

Diabetic neuropathy in children with type 1 diabetes

J Mah (Calgary), C Adams (Victoria), H Darwish (Calgary), D Huggard-Nelson (Calgary), S Hui (Calgary), D Pacaud (Calgary)*

Background: Neuropathy is a serious diabetic complication. Early detection is important for treatment planning and secondary prevention. *Objectives:* 1) To determine the prevalence of neuropathy in diabetic children followed at the Alberta Children's Hospital, 2) To examine the clinical factors associated with diabetic neuropathy, 3) To explore the utility of a diabetic neuropathy symptoms questionnaire. *Methods:* Children with five years or longer history of diabetes underwent detailed clinical and neurophysiologic testing. Descriptive statistics and logistic regression were used for analysis. *Results:* Seventy-three children (mean age 13 years) had diabetes for at least 5 years (range 5-15). Three patients experienced regular symptoms on the diabetic neuropathy questionnaire. Forty-two (57%) children had diabetic neuropathy based on nerve conduction criteria, of which 20/42 (47%) patients had distal sensory loss and/or diminished reflexes. Patients age, height, HbA1c level, and abnormal neurological exam were significantly associated with the presence of diabetic neuropathy (p=0.0001). Total score on the diabetic neuropathy symptoms questionnaire was not predictive of diabetic neuropathy in children. *Conclusions:* Neuropathy was common among study participants. The diabetic symptoms questionnaire is not a useful screening tool in children due to their lack of symptoms. Careful clinical assessment may identify patients at risk for diabetic neuropathy.

J-06

"Fast-sequence" magnetic resonance imaging (MRI) in evaluating pediatric hydrocephalus: no sedation, no radiation and no fuss

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Background: Evaluation of pediatric hydrocephalus often involves computed tomography (CT). Within the scientific community, an understanding of the potential danger of frequent pediatric CTscanning has developed. An ideal test would be one that could quickly assess ventricular size, avoid radiation exposure and eliminate sedation. *Methods:* We retrospectively reviewed our experience in the last eighteen months with fifty cases of children with shunted hydrocephalus. Fast-sequence MRI involves a FISP sequence that requires 6.4 seconds to acquire and eliminates sedation. Images were reviewed by two radiologists and two neurosurgeons to assess how well the shunt, ventricle, and subdural space were visualized. The parents of these children were also surveyed to assess their experience. *Results:* Preliminary results demonstrate that this technique allows rapid assessment of the ventricular size however shunt visualization may be difficult. In addition preliminary results from the parents point to a high degree of satisfaction. Parent satisfaction appears related to image acquisition, lack of radiation, anatomical detail and the belief the children are receiving a better test. *Conclusions:* Fast-sequence MRI appears to be a useful test in the assessment of ventricular size and is associated with high parent satisfaction. The lack of radiation exposure and sedation are important features that we have found valuable in daily practice.

J-07

Hip joint changes after selective dorsal rhizotomy for spastic cerebral palsy

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Background: The effects of selective dorsal rhizotomies (SDR) on the hip joints of patients with spastic cerebral palsy (CP) are not well-described. This study was performed to determine the impact of SDR on hip subluxation. *Methods:* Pre- and postoperative hip radiographs done as part of a prospective protocol in children with spastic CP and SDR were reviewed retrospectively. Femoral head center edge (CE) angle, acetabular index (AI), and femoral neck shaft (NS) angle were recorded. *Results:* The study group comprised 82 patients (164 hip joints) with mean follow-up of 3.9 years (1 - 12.1). Mean age at SDR was 5.2 (±2.4) years. Pre- and postoperative values respectively were: right CE angle mean 14.12º versus 17.2º; left CE angle mean 13.6º versus 15.1º; right AI mean 21º versus 19.3º; left AI mean 21º versus 19.8º; right NSA mean 155.5º versus 153.2º; left NSA mean 155º versus 152º. Using > 5º of CE angle change as clinically significant, 72 hips (43.5%) remained unchanged, 63 (38.4%) improved, and 29 (17.7%) worsened. *Conclusions:* SDR is more likely to have a positive or no effect on hip joint subluxation, than a negative effect.

J-08

Radioisotope shuntograms at the Children's Hospital of Eastern Ontario

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Background: Nuclear medicine shuntograms using the radiotracer 99mTc-DTPA have been utilized for many years as an additional method to assess shunt patency and performance. *Methods:* The medical records of all children who had shuntograms performed at the Children's Hospital of Eastern Ontario CHEO between January 13, 2000 and January 10, 2003 were retrospectively reviewed. There were a total of 68 procedures in 56

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patients with an average age of 9 years, 3 months. During the same time period there were 123 shunt revisions. *Results:* Forty-two shuntograms were reported as normal. Of these, ten were identified to be false-negative. Two children with fractured shunts had shuntograms performed in order to assess for CSF flow patency; the shuntograms were identified to be normal, confirming shunt-dependence, and the shunt replaced. Twenty-six shuntograms were reported as abnormal; seventeen went on to have surgery and the shunt malfunction was confirmed. Seven patents did not require surgery: five were declared shunt independent, two patients clinically improved after severe constipation was treated. *Conclusions:* Approximately one-fourth of all shuntograms reported as normal are not (false-negative rate= 25%). Review of five other major studies between 1980 and 2003 have reported false-negative rates between 2-36%, which may be explained by variations in shuntogram protocols. A standardized method is proposed.

General Neurology

K-01

Downregulation of potassium channels after subarachnoid hemorrhage contributes to cerebral vasospasm.

BS Jahromi (Toronto), Y Aihara (Chicago), M Agbaje-Williams (Chicago), E Nikitina (Chicago), GW Weyer (Chicago), D Ryan (Chicago), R Yassari (Chicago), RL Macdonald (Chicago)*

The K.G. McKenzie Prize in Basic Neuroscience Research winner – Canadian Neurosurgical Society (See page 8)

K-02

Porcine intestinal submucosa (DURASIS) as a novel dural substitute: a prospective multicenter study.

G Bejjani (Pittsburgh), J Maroon (Pittsburgh), J Zabramski (Phoenix), F Barranco (Phoenix), K Smith (Phoenix), A Levi (Miami)*

Introduction: Small intestinal submucosa (SIS) is a naturally occurring extracellular matrix extracted from porcine small intestine. It has been used as a wound matrix (OASIS) and for many types of herniorraphy (SURGISIS). It has numerous properties including promoting new vessel growth, remodeling by host tissue, and is a high strength biomaterial. DURASIS is a SIS-based device designed for use as a dural substitute. We report the results of a prospective multicenter study on DURASIS. *Methods:* The IDE study was carried out in 5 centers: the University of Pittsburgh, the Barrow Neurological Institute, the University of Miami, Wayne State University and Methodist Hospital of Indianapolis. Patients older than 18 years requiring spinal or cranial dural graft substitute were recruited. Clinical information was recorded preoperatively, intraoperatively, 7-10 days, 1 month, 3 month and 6 months postoperatively. Postoperative imaging was analyzed. Endpoints for analysis were incidence of complications and device performance. *Results:* The results reported are on 51 patients, with a mean age of 47 years and a 3/1 female/male ratio. Average follow-up duration was 6.5 months. The pathologies included: Chiari malformation (29), tumors (14), aneurysm (3), tethered cord (2), pseudo-meningocele (1), epilepsy (1), and benign cyst (1). Three patients (6%) had a spinal graft. Seventy-two percent of cases were infratentorial. There was one case of CSF leak (2%) which resolved within one month post-op, and one case of wound infection (2%) noted at 9 days post-op. In this case the wound was re-explored and the graft found to be intact, and the infection was resolved 10 days later. There was no evidence of brain or spinal cord adverse reaction attributed to DURASIS on imaging. No device failures were recorded. Various handling characteristics of the device ranged from 3.96/4 to 4/4. *Conclusions:* The results obtained in this multicenter study are encouraging. The incidence of CSF leak was low (2%) considering the fact that 78% of the grafts were used in the posterior fossa or spine. There was no evidence of rejection, inflammatory reaction, or loss of barrier to the infection in the single case of wound infection. DURASIS seems promising as a dural graft substitute with excellent handling characteristics and a potential to resist infection.

K-03

Endoscopic versus microsurgical resection of third ventricle colloid cysts: a cohort study

RT Grondin (Calgary), WJ Hader (Calgary), MG Hamilton (Calgary)*

Background: Endoscopic resection of colloid cysts has been performed as an alternative to microsurgical resection since 1982. To date, there are no published studies adequately comparing the two procedures. We present the largest series of endoscopic procedures addressing this issue. *Method:* Retrospective chart review of all patients presenting with colloid cysts from 1992-2003. *Results:* Thirty-two patients were identified. Twenty-three endoscopic and 9 microsurgical procedures were performed. Two patients underwent a cerebral spinal fluid diversion procedure only. Complete resection was achieved in 18 of 23 procedures in the endoscopic group, compared with 8 of 9 procedures in the microsurgical group. Both the length of operative time and length of hospital stay were significantly reduced in the endoscopic group. One patient in the endoscopic group had a complication (hemiparesis). By contrast, 4 patients in the microsurgical group had complications (permanent memory deficit, disconnection syndrome, ventriculitis/bone flap infection, and transient memory deficit). There was one cyst recurrence requiring further intervention in each group. *Conclusions:* Endoscopic resection of colloid cysts can be performed with significantly lower risk of complication than microsurgical resection and with equivalent surgical success. Furthermore, operative time and length of hospital stay are both significantly reduced with endoscopic resection.

K-04

Motor cortex stimulation for central and peripheral deafferentation pain.

R Garcia (Halifax), R Brownstone (Halifax), I Beauprie (Halifax), P Gaudet (Halifax)*

Background: The used of epidural motor cortex stimulation (MCS) for the treatment of refractory deafferentation pain, is a less invasive alternative treatment. The area providing strong pain inhibition appeared to correspond to the motor cortex area. We report the early clinical course of our firsts 6 patients to receive epidural implantation for MCS. *Methods:* Retrospective and

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descriptive study. Six patients with central and peripheral deafferentation pain were treated with MCS. Indications for the procedure included atypical facial pain, brachial plexus injury, phantom limb pain and complex regional pain syndrome (CRPS). Each patient was evaluated with Visual Analogue Scale and McGill Pain Questionnaire. These patients underwent imaging-guided epidural MCS. *Results:* Age of patients was 32 to 49 years, average 40 years. The intensity of the pain was 8.5 average before surgery and 4 after the surgery. In five (83 %) of the 6 patients, good pain control was obtained. Only one patient did not respond favorably to this therapy and was considered fair result. Stimulation was performed for 10 minutes on and 2 hours off. Minor complications that include intra-operative seizures were presented in one case. Major complications include tissue infection occurred in another patient. *Conclusions:* Our results indicated that motor cortex stimulation could be safe and effective for peripheral and central deafferentation pain. Prospective and double blind studies will help to clarify the full benefit of this technique.

K-05

Wrong-side / wrong-level neurosurgery. A survey of Canadian neurosurgeons

B Jhawar (London), D Rabin (London), J Kellar (London), D Mitsis (London), N Duggal (London)*

Introduction: Perhaps the single greatest error that a neurosurgeon hopes to avoid is operating at the wrong site. Despite the seriousness of this mistake, there exists virtually no information on the topic. In this report we set out to measure the incidence and possible determinants of incorrect site surgery (ICSS) among Canadian neurosurgeons. *Methods:* In December 2003, we asked all Canadian neurosurgeons to participate in our anonymous survey.We asked these surgeons to report the number of craniotomies, lumbar and cervical discectomies performed during 2003 as well as whether or not ICSS had occurred. We also asked detailed questions on potential determinants of ICSS. *Results:* As of January 1, 2004, 66 neurosurgeons responded to our first mailed questionnaire; three declined to participate. In 2003, participating neurosurgeons performed 2, 210 lumbar and 1, 466 cervical discectomies; during the same year they performed 4, 383 craniotomies. Based on this self-report, we estimated the incidence of wrong-level lumbar surgery to be 4.5 occurrences per 10, 000 operations. The corresponding counts per 10, 000 cervical discectomies and craniotomies were 6.8 and 2.2 respectively. Neurosurgeons recognized fatigue, unusual time-pressure and emergency operating as contributing factors. For spine surgery in particular, unusual patient anatomy and lack of the use of intra-operative imaging was also commonly reported. *Conclusions:* Incorrect site surgery occurs in Canada. Prevention of such errors will require recognizing risk factors and increased use of intra-operative imaging.

K-06

Development of a multi-disciplinary stereotactic radiosurgery program in Alberta

ZHT Kiss (Calgary), D Choi (Calgary), R Manthey (Calgary), J Wong (Calgary), D Spencer (Calgary), A Chan (Calgary)*

Background: Stereotactic radiosurgery (SRS) is a required therapy for many neurosurgical conditions. Its use in Canada has been limited by availability of the technology and the interest of stereotactic neurosurgeons at individual centres. Our aim with this report is two-fold: (i) to describe the development of a multi-disciplinary SRS program from initiation as a tool for radiation oncology treating only malignant disease to its present broad scope, and (ii) to report our preliminary results. *Methods:* The Alberta SRS program was initiated by the radiation oncology group at the Tom Baker Cancer Centre in 2000. An audit of all referrals, case mix, the protocols and obstacles encountered till December 2003 was undertaken. All consecutive patients undergoing single and fractionated SRS were studied with respect to radiation doses, adverse effects and outcomes. *Results:* A total of 171 patients have been referred and discussed at biweekly multi-disciplinary rounds. Sixty patients have received SRS and another 15 benign skull base tumours have received fractionation. Whereas 14% of cases treated in 2000-2001 were benign lesions, in the recent 2 years, 43% have been benign (10 AVMs, 7 acoustics, 3 meningiomas, 1 choroid plexus papilloma, 1 glomus jugulare tumour). Three major obstacles for expansion were encountered: (i) limited access to a shared LINAC; (ii) a Heritage-funded health services report emphasizing the lack of Class I evidence; and (iii) referral bias. *Conclusions:* Despite obstacles, we have developed a multi-disciplinary SRS program in Calgary. As neurosurgical involvement in rounds increased and clinics were established where patients are seen by both radiation oncology and neurosurgical staff, the case mix has evolved to encompass more benign neurosurgical disease. The obstacle that remains the most difficult to overcome is the limited Class I evidence for this treatment; therefore Canadian centres should be encouraged to develop and collaborate on such clinical trials.

K-07

Unexplored clinical and operative predictors of facial nerve outcome during translabyrinthine resection of acoustic neuromas

M Shamji (Ottawa), B Benoit (Ottawa), J Cole (Ottawa)*

Background: Translabyrinthine acoustic neuroma resection affords maximum exposure to dissect the facial nerve with anatomic preservation in 95% of cases. Positive outcome (House-Brackman I/II) in asymptomatic patients ranges from 64% to 90%, and transient postoperative deterioration commonly occurs. *Methods:* This study retrospectively examined 128 consecutive patients to identify new clinical and operative indicators of facial nerve outcome and improvement in those experiencing early postoperative deficit. *Results:* Consistent with literature, 65% of asymptomatic patients had good result with function preserved in 82% of lesions less than 20 mm and in 50% of tumours greater than 22 mm. Among all patients, size (p=0.001) and preoperative House-Brackman score (p=0.003) independently predicted outcome. For those with antecedent paresis, nerve recovery or no change was observed in those with short symptom duration of 24 days (p=0.02) and hypoacusis of 20 days (p=0.01). House-Brackman I patients with preoperative tinnitus (p=0.03), short hearing loss duration (p=0.001), intraoperative nerve stimulation less than 0.10 mA (p=0.003), and tumour nonadherence to the facial nerve (p=0.02) experienced positive outcome and recovery of early deficit. *Conclusions:* Previously unestablished outcome predictors in

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asymptomatic patients include tinnitus and duration of facial paresis and hypoacusis. We reaffirm the long-term predictive value of intraoperative nerve stimulation.

K-08

The use of intraoperative image guidance to optimize cranioplasty for complex skull defects

C DeSilva (London), J Megyesi (London)*

Background: The repair of large, complex skull defects may be difficult. The challenge lies in the accurate reproduction of difficult anatomical contours inherent in large cranial defects. We present a relatively simple method, using intraoperative image guidance, to optimize the fabrication of large complex cranioplasties. *Methods:* Patients must have neuroimaging (MRI or CT) available from the time of their initial surgery that shows the intact skull. Prior to the cranioplasty operation fiducial markers are placed on the head and a CT scan is obtained. These CT images are fused with the images from the initial surgery. The image guidance probe is then used intraoperatively to guide the fabrication of the cranioplasty flap to make it coincide with the contours provided by the initial images of the intact skull. The blend feature on the image guidance computer (Stealth) allows the surgeon to alter the ratio between the initial and current images throughout the operation. *Results:* The method has been successfully used in two patients. Cranioplasties are both functional and cosmetically satisfactory. Pre- and postoperative neuroimaging and intraoperative photographs will be shown. *Conclusions:* Intraoperative image guidance to optimize cranioplasty for large complex skull defects is both simple and effective.

Movement Disorders

L-01

DBS for torticollis: preliminary results from the multicentre Canadian pilot study

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Background: Deep brain stimulation (DBS) of the globus pallidus (GPi) is beneficial for generalized dystonia. It has also been proposed for cervical dystonia, but only anecdotal reports on its efficacy are available. Therefore, the CNSS Stereotactic-Functional and Canadian Movement Disorders Groups designed this pilot project. We proposed that in patients refractory to medical management, bilateral GPi-DBS will reduce the severity of cervical dystonia at 1 year follow-up. *Methods:* Ten patients with refractory isolated cervical dystonia for at least 5 years will be enrolled in a prospective study of bilateral GPi-DBS surgery with blinded outcome measures. The primary outcome is the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) subscore for severity. Secondary outcomes are the pain and disability TWSTRS subscores, SF-36, Beck depression inventory and adverse events. Pre-operative videotapes, questionnaires, neuropsychology and swallowing assessments are performed and repeated at 6 months and 1 year after surgery. Neurosurgeons use their usual techniques for brain mapping and DBS implant and MR imaging will be reviewed at the lead centre. At the completion of the study, all videotapes will be randomized and 2 neurologists blinded to patient state will score the severity of the dystonia. *Results:* Two patients have undergone surgery in Calgary, and other sites are starting to enroll patients. The first patient (8 month follow-up) had an immediate significant improvement in severity and pain, whereas the second patient (3 month follow-up) has yet to experience any change in severity, although his pain has improved. No adverse effects have occurred at this preliminary time point. Further follow-up and data on more patients will be available in the coming months. *Conclusions:* The intent of this pilot project is two-fold: not only to determine the results of DBS surgery for torticollis, but also to assess the feasibility of a multicentre Canadian trial. Therefore the success of this trial will be judged not only on its results, but its ability to foster cooperation between functional neurosurgery centres and develop larger randomized controlled trials in the future.

L-02

STN-DBS outcomes: the Calgary experience

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Background: Subthalamic nucleus deep brain stimulation (STN-DBS) is the biggest advance that has occurred in the past decade to treat advanced Parkinson's disease (PD). Whereas several groups have reported their early results, long term outcome data are still limited. Our aim was to examine the outcomes over time of STN-DBS in patients in whom both surgery and follow-up was performed in Calgary. *Methods:* All consecutive patients undergoing bilateral STN-DBS were studied with a battery of motor and quality of life tests before and after surgery at the 6 month, then yearly postoperative time points. The battery of tests were the Unified PD Rating Scales (UPDRS), dyskinesia rating scales, time spent in each motor state, medication doses, timed walk, Perdue pegboard and PDQ-39. One-way repeated measures ANOVA was used to compare scores over time, ON and OFF medication states. *Results:* Nineteen patients have had STN-DBS surgery with a mean follow-up of 24 months (range 2-57) in Calgary. Significant improvements in UPDRS motor scores were found between pre-op OFF meds (42.1 ± 12.5) and post-op OFF meds/ON stim states at 6 months (29.2 ±14.1, N=15, P=0.002) and 1 year (31.3 ± 14.5, N=12, P<0.001), as well as between ON and OFF stim states at each time point. There was no significant difference between pre-op and post-op ON meds-ON stim UPDRS scores, but patients were worse in the OFF-stim states, likely related to significant reduction in medication doses (1504 ± 723 mg levodopa equivalent pre-op vs. 866 ± 645 mg at 1 y, N=10, P=0.03). Patients went from 5.3 (±3.4) waking hours in the ON state pre-operatively to 10.9 (±1.5) h ON at 2 y (P=0.023) without dyskinesia. *Conclusions:* Our results are consistent with those reported by the Grenoble group and with the general understanding of degree of benefit expected for STN-DBS surgery. In well-selected patients, stimulation improves motor function in the OFF medication state, increasing apparent hours spent in the well-functioning ON motor state. STN-DBS allows Parkinson's patients to reduce their medication by about half.

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L-03

Episodic ataxia type 2: A novel mutation in the CACNA1A gene and its impact on calcium channel function

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Objective: To describe a novel EA2 mutation in the CACNA1A gene and its impact on the P/Q type channel properties. *Background:* EA2 is characterized by episodes of ataxia and nystagmus which result from mutations in the CACNA1Agene, encoding the alpha1A subunit of the P/Q type calcium channel. To date, EA2 gene mutations have resulted in nonfunctional channels when expressed in mammalian systems. *Design/Methods:* A patient with EA2 was identified and the CACNA1A gene was screened for mutations. In-vitro mutagenesis was employed and the newly identified mutation was subsequently transfected into HEK cells. The biophysical properties were determined by patch clamp analysis. *Results:* We have identified a novel missense mutation (H1736) in the CACNA1A gene. The biophysical properties of this mutation demonstrate reduced expression density, increased inactivation kinetics and a shift of the V50 activation kinetics to more positive values when compared to wild type. Activation kinetics, deactivation kinetics and V50 inactivation kinetics are unaltered. *Conclusions:* We have identified a novel H1736L mutation in the CACNA1Agene associated with the EA2 phenotype. This mutation results in a functional channel and analysis of the biophysical properties have demonstrated that this mutation results in a loss of channel function.

L-04

A second locus for paroxysmal dystonic choreoathetosis

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Background: Paroxysmal dystonic choreoathetosis (PDC) is an autosomal dominantly inherited episodic movement disorder characterized by dystonia or chorea. The locus for PDC has previously been mapped to a region on Chr 2q32-36 in several families from diverse geographic locations. A locus for paroxysmal choreoathetosis/spasticity (CSE), a similar yet clinically distinct condition, has been mapped to a region on Chr 1p34-32. *Design/Methods:* Linkage analysis was performed on 14 individuals from a three-generation Canadian family. The affected phenotype was characterized by idiopathic episodes of dystonia in a limb lasting up to five minutes in duration. Attacks were not triggered by sudden movement. Linkage to Chr 2q32-36 and Chr 1p34-32 was sought using microsatellite markers. *Results:* Multipoint linkage analysis data for both the Chr 2q32-36 region and the Chr 1p34-32 region generated LOD scores of less than 2.65. *Conclusions:* These results exclude the Chr 2q32-36 and Chr 1p34-32 loci as the locus containing the gene responsible for PDC in this Canadian family. Our results indicate that the gene responsible for PDC in this family is at a novel locus, implying genetic heterogeneity for this condition. A genome wide linkage search is currently underway.

L-05

SCA6 channelopathy or cytopathy? Functional analysis of the trinucleotide repeat expansion (CAG) 22 in the human alpha1Acalcium channel

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Objective: To examine the impact of the SCA6 trinucleotide repeat expansion on the biophysical properties of the ±1Asubunit of the P/Q type calcium channel. *Background:* Spinocerebellar ataxia type 6 (SCA6) is characterized by progressive cerebellar ataxia, dysarthria, and nystagmus. It results from a CAG expansion (20 to 33 repeats) in the CACNA1A gene which codes for the alpha1A subunit of the P/Q type calcium channel. Pathologically there is cytoplasmic aggregation of the alpha1A protein. Two other conditions result from mutations in the CACNA1A gene, EA2 and FHM, both of which are channelopathies. It is unknown whether SCA6 results from disruption of the channel function (channelopathy) or a result of intracytoplasmic inclusions (cytopathy). *Methods:* Utilizing patch clamp analysis of transfected HEK cells the properties of the wild type (WT) CAG12 and CAG22 channels were determined. *Results:* There was no significant difference in voltage-dependant activation, steady state inactivation, activation and deactivation kinetics, and current density with the CAG22 mutant when compared to WT. *Conclusions:* CAG22 is the most common pathological allele expansion seen in SCA6. This pathological allele size does not appear to directly affect the biophysical properties of the channel, suggesting that SCA6 is a cytopathy rather than a channelopathy.

L-06

COMT alleles and levodopa complications in Parkinson's disease

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Background: The cause of Parkinson's disease (PD) remains unknown. Levodopa (LD) remains the most effective medication. However, motor complications, including wearing-off (WO) and dyskinesias (DK) develop in many patients and can be problematic. Catechol-O-methyltransferase (COMT) inactivates catecholamines by methylation. Inhibition of peripheral COMTactivity allows more LD to be available centrally for conversion to dopamine. COMT inhibitors treat WO but may worsen DK. COMT activity has trimodal distribution determined by paired autosomal dominant alleles: low (LL), intermediate (HL), and high (HH). *Methods:* 43 cases with autopsy verified PD were included. Motor fluctuations were recorded prospectively in the medical record, and all cases were clinically assessed by a single neurologist (AHR). Genetic analysis was done by standard PCR based methods from frozen half brain sample. *Results:* Of the 43 cases, 12 had WO and DK, 7 had only WO, and 9 had only DK. WO was associated with COMT genotype; those with HH genotype were less likely to have wearing off (chi-square = 4.00, $p<0.05$) (OR=0.13, 95% CI 0.00-1.28). DK were not associated with COMT genotype. *Conclusions:* COMT high activity (HH) genotype is associated with reduced frequency of WO. The mechanism for this is uncertain.

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L-07

Clinical and quantitative evaluation of tremor-suppressing action of topiramate

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Background: Few drugs are effective in attenuating essential tremor. A recent study identified the anti-epileptic topiramate as a possible treatment. Accordingly, we evaluated topiramate quantitatively in 8 individuals with essential tremor. Finger tremor was quantified for seven motor function tests as well as for 24-hour periods of daily activity. *Methods:* Tremor was evaluated before, during and after drug treatment (range 12.5-100 mg twice daily) in 4 men and 4 women. Qualitative measures: blinded clinical ratings of videotapes of motor function tests. Quantitative measures: 1) mean time (Tm) of spiral drawing and pegboard tests; 2) 24-hour continuous monitoring of tremor amplitude with a 3-axis accelerometer, from which we derived Ti, the total time per day that tremor amplitude exceeded levels impairing tasks of daily life; 3) Mean tremor amplitudes (Am) in motor tests. *Results:* Topiramate reduced tremor by about 50% in 7/8 subjects, typically halving Ti. Tm was reduced by 34% (spiral drawing) and 20% (pegboard). Am was reduced by 41% across seven motor tests. Our study revealed systematic differences between raters in interpreting the Bain et al (1993) tremor severity scale. *Conclusions:* Topiramate significantly attenuates essential tremor. Quantification is useful in calibrating and thus standardizing clinical ratings.

L-08

Ataxia and the role of antiglidin antibodies

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Background: Sporadic ataxias are a common neurological disorder. Gluten sensitivity relates to an immunological hyper-responsiveness to gluten. It has been reported that gluten sensitivity, can present with isolated neurological dysfunction, most commonly ataxia and can be associated with elevated IgG and IgA antigliadin antibodies. Some research groups have reported elevated antigliadin antibodies in 68% of sporadic ataxic patients, whereas others have found no association. *Methods:* Patients with a diagnosis of ataxia were recruited through UBC by way of a chart review. An equal number of control subjects were recruited. Serum samples were obtained from participating individuals and measured for IgG and IgA antigliadin antibodies using an ELISA test. *Results:* 59 ataxic patients and 59 controls were recruited. Of the ataxic patients, 34/59 were weakly positive for IgG antigliadin antibodies and 5 were strongly positive compared to controls of whom 36 were weakly positive and 3 were strongly positive. In the ataxic group, 32/59 were weakly positive for IgA antigliadin antibodies and 2 were strongly positive compared to the control group in whom 23/59 were weakly positive and 2 were strongly positive. *Conclusions:* These results do not support an association between IgG or IgAantigliadin antibodies and ataxia.

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POSTER PRESENTATIONS

CEREBROVASCULAR DISEASE

P-001

Hypomelanosis of Ito and moyamoya syndrome

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Introduction: Moyamoya disease, a cerebrovascular disease, featuring stenosis of the internal carotid arteries and proximal anterior and middle cerebral arteries, is considered a syndrome when it presents with other conditions. An association between moyamoya and some of the neurocutaneous syndromes such as neurofibromatosis, tuberous sclerosis, and incontinentia pigmenti has been well-described in literature. Hypomelanosis of Ito (HI), another rare neurocutaneous syndrome, is characterized by macular hypopigmented skin whorls and variable neurological involvement. An association between HI and moyamoya syndrome to the best of our knowledge, has been reported only once in the literature. *Methods:* Retrospective chart review of a 17-year-old girl presented to our clinic. *Results:* We report a second patient that describes the coexistence of moyamoya with HI. Our patient presented with intractable seizures, progressive left hemiparesis and skin manifestations of HI. Her angiography showed bilateral stenosis of proximal branches of internal carotid artery, characteristic of moyamoya disease. Bilateral EDAS resulted in gradual improvement of hemiparesis and seizures but remains with significant cognitive impairment. *Conclusions:* Although one might consider a coincidental association, a second case points to a real association between the two disorders. Detailed neuroimaging, in particular angiography, should be considered in children with HI and neurologic presentations

P-002

Use of recombinant factor VIIa in neurosurgery: 2 cases, a review and some hope.

M Al-Otibi (Toronto), MD Cusimano (Toronto), BJ Jhawaral (Toronto)*

Background: Postoperative and coagulopathy induced intracranial hemorrhage is a well-known cause of morbidity and mortality in the neurosurgical patient. Complications from the evacuation of postoperative hematoma, particularly in deep surgical beds can potentially lead to further disability or be fatal. In other fields of medicine, recombinant factor VIIa has been promising as an agent to control bleeding without subjecting the patient to surgical intervention. The purpose of this report is to highlight the potential uses of Factor VIIa in the neurosurgical patient and to demonstrate the use in two patients. *Method:* A review of the literature on Factor VIIa in surgical patients was performed. Our own cases thus far include a 50-year-old female who underwent craniotomy for recurrent malignant glioma who developed a postoperative left sided hemiparesis and tumor bed hematoma which was shown to be progressive on serial scans and clinically. The second patient was a 27-year-old man who suffered violent head trauma, a squamous temporal fracture, epidural hematoma and brain contusion. Each patient received 90 micrograms of Factor VIIa per kilogram body weight. *Results:* A total of 10 papers met our inclusion and exclusion criteria. The results of this review will be presented. Neither of our patients showed progression of bleeding on serial CT and both stabilized and ultimately improved clinically. Neither patient required subsequent surgery to control bleeding. Neither patient suffered thrombotic complication. *Conclusions:* Factor VIIa is an inducer of hemostasis that holds tremendous promise in many aspects of neurosurgery-related indications for hemostasis. Further studies and well-controlled placebo-controlled clinical trials to assess the use of factor VIIa in neurosurgery are needed to establish efficacy and cost-effectiveness.

P-003

Changing patterns of hypoxic-ischemic brain injury in term newborns (1985-2003)

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Background: Two principal patterns of hypoxic-ischemic (HI) brain injury occur in term newborns: injury to cortex and white matter following prolonged, partial insult, and central injury involving brainstem, thalami, basal ganglia after acute, near-total insult. The objective of this study was to identify changes in frequency of these patterns between 1985 and 2003. *Methods:* Term newborns with HI encephalopathy (HIE) who had acute neuroimaging were entered into a database. Neuroimaging and clinical data were reviewed (blinded to year of birth). *Results:* 479 infants had CTscans; 79 also had MRIs. Imaging was normal in 234. The incidence of abnormal scans increased from 33% before 1994 to 54% after that time. Central injury accounted for 16% of abnormal cases before 1994 but 54% subsequently. The proportion of cortical and combined injury decreased by 50% after 1994. These observations are not explained by changes in pattern recognition on neuroimaging or altered referral patterns. *Conclusions:* A significant change has occurred in the patterns of HI brain injury in term newborns between 1985 and 2003. This presumably corresponds to change in the principal underlying insult from a prolonged, partial to an acute, near-total type, which, in turn, may relate to improved obstetric management.

P-004

Recurrent lobar intracerebral hemorrhage and cerebral amyloid angiopathy: case report

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Background: Cerebral amyloid angiopathy (CAA) is responsible for 10% of intracerebral hemorrhages (ICH). Although a few cases of recurrent CAA-ICH have been previously reported in the literature, more than 2 recurrences have never been reported. *Methods:* This report describes one case and reviews the relevant

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literature on recurrent CAA-ICH and ApoE genotype. *Results:* The patient was a 66-year-old female who presented with severe headache and left homonymous hemianopsia. CThead scan revealed a 3.5 cm right occipital ICH, and cerebral angiogram revealed no vascular abnormality. Patient was discharged home with an uneventful stay, but returned 4 weeks later with another lobar ICH just anterior to the first. Ten days after the second ICH, the patient presented with the following sequential lobar hemorrhages: right fronto-parietal ICH, then 3 weeks later a right anterior frontal ICH, then 7 days later a left anterior frontal ICH, and finally 2 weeks later a left fronto-parietal ICH which took the patients life. Brain biopsy done during the craniectomy after the third ICH revealed CAAwith DNA analysis confirming the ApoE genotype Epsilon-2/Epsilon-3. *Conclusions:* Although the Epsilon-4 ApoE allele is associated with the highest recurrence rates in CAA-ICH, we report a unique case of a patient who was heterozygote for the ApoE gene (not an Epsilon4 carrier) with 6 lobar ICH within 3 months all in different anatomical locations. Further study is warranted into cases of CAA with such malignant clinical behaviour.

P-005

Calcium channel blockers and stroke recovery

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NMDA receptors and calcium channels may have differential effects on cell survival, depending on their regional expression on neurons; synaptic NMDAreceptors appear to play a neuroprotective role, whereas extra synaptic NMDAreceptor stimulation contributes to cell death. Furthermore, neurite outgrowth requires activation of calcium channels and NMDA receptors. Since the stroke recovery process may require neurite outgrowth and calcium signaling, we chose to assess the effect of interventions that target calcium conduction following ischemic cerebral injury. Specifically, we chose to assess the effect of calcium channel blockade on long-term recovery in patients with stroke. Using the Registry of the Canadian Stroke Network, we identified a cohort of 1545 consenting patients admitted to Canadian institutions with nonhemorrhagic stroke. Using the Stroke Impact Scale-16 and Health Utilities Index-3, we are assessing functional outcome of patients 6 months post-discharge based on their exposure to calcium channel blockers. Included in our analysis are potential confounding variables such as stroke severity (Canadian Neurological Score), prior medical history, and concurrent medication use. We hope this information will help guide the medical management of patients following the acute phase of stroke.

P-006

Delayed brainstem short-circumferential infarct after negative angiography extended perimesencephalic subarachnoid hemorrhage: new evidence for a ruptured perforating artery mechanism in nonaneurysmal subarachnoid hemorrhage

A Gagnon (Calgary), J Wong (Calgary), A Demchuk (Calgary)*

Background: Rupture of a small superficial artery with subsequent lacunar infarct as an etiology of nonaneurysmal subarachnoid hemorrhage was first reported in 1974. Cases of acute lacunar stroke in association with angiogram-negative subarachnoid hemorrhage were subsequently reported. We described a case of delayed pontine short-circumferential infarct happening on day 16 after negative angiography extended perimesencephalic subarachnoid hemorrhage. *Case report:* A 57-year-old man with a long history of hypertension and hypercholesterolemia presented with a sudden severe headache without localizing symptoms. Brain CT scan revealed extended perimensephalic subarachnoid hemorrhage. Investigation consisting of two cerebral angiograms and brain and cervical spine MRI were normal without obvious cause or vasospasm. After transient ischemic symptoms on day 2, the patient develop a lacunar syndrome on day 16, confirmed on MRI by a new right pontine infarct in a short circumferential artery territory. Deficits seemed to initially improved but return a few days later. Gradually symptoms resolved over several weeks with no residual functional deficit. *Conclusions:* Our case report and review of the literature support a ruptured small vessel artery as a mechanism of nonaneurysmal hemorrhage. Subsequent infarct may happen secondarily to progressive thrombosis of the vessel.

P-007

Lack of association between microbleeds and subsequent hemorrhagic transformation after acute ischemic stroke

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Background:: Microbleeds (MB) on T2*-weighted imaging have been seen in up to 68% of patients with prior ischemic stroke. We prospectively examined the association between MB detected on initial T2*-EPI and hemorrhagic transformation on a 1-month MRI scan. *Methods:* Patients presenting with stroke or transient ischemic attack (TIA) were imaged within 24 hours of symptoms and again at 1-month, using 3 T MRI. MB were defined as hypointensities on the first T2* PWI images prior to bolus arrival. Hemorrhagic transformation (petechiae or hematoma) was defined as hypointensities on T2-weighted images. *Results:* A total of 105 patients had MRI performed at a median of 5.8 hours from symptom onset. At the 1-month follow-up, 10 of 18 (55.6%) patients with MB had hemorrhagic transformation, compared with 20 of 87 (23.0 %) patients without MB (unadjusted relative risk=2.4 (95% CI: 1.4 to 4.2, p-value=0.008). After adjusting for demographic and clinical variables in a logistic regression model, hemorrhagic transformation was no longer related to the presence of MB and the adjusted relative risk was almost unity (adjusted relative risk=1.1, 95% CI: 0.4 to 2.9, p-value=0.91). *Conclusions:* Subsequent hemorrhagic transformation is not related to MB, after accounting for other coincidental demographic and clinical risk factors.

P-008

Cardiac arrest survivors: are diagnostic tests being utilized?

MS Hussain (Edmonton), AM Hussain (Edmonton), A Shuaib (Edmonton)*

Background: Many studies have assessed neurological outcome after cardiac arrest, mainly focusing on clinical factors. More recent studies have looked at diagnostic tests, some of which show promise. However, factors such as patient stability may make the use of these techniques unfeasible. Overall, the benefit of these tests is unclear. *Methods:* A retrospective chart review of 68 cardiac arrest

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patients at the University Hospital in Edmonton, Canada. *Results:* The patients surviving to discharge had significant differences in clinical parameters at 24 hours as compared to those patients who died. The majority of patients in both groups had no investigations performed. The remaining patients had either CTor EEG performed. These investigations were done in patients who presented an unclear clinical picture. *Conclusions:* The assessment of neurological outcome remains a clinical one. The majority of decisions are made without diagnostic tests. This approach to management is important, as interventions, such as hypothermia, should not be delayed for diagnostic testing. In patients with an unclear clinical picture, diagnostic tests may be considered, but often remain inconclusive. Other diagnostic tests, such as evoked potentials, may provide more useful information and may be more beneficial to the long term care of patients.

P-009

Spinal cord transient ischemic attacks treated with abciximab

MS Hussain (Edmonton), Z Siddiqi (Edmonton)*

Background: Spinal cord TIAs are described in the setting of aortic dissection or occlusion. No guidelines exist for management. We report a case of spinal cord TIAs secondary to aortic occlusion, successfully treated with abciximab and anticoagulation. *Case presentation:* A 53-year-old man presented with transient episodes of bilateral leg weakness, bladder incontinence, and saddle anesthesia. Spinal cord MRI was unremarkable. Abdominal CTscan and aortography revealed marked aortic atherosclerosis with an occluding sub-acute thrombus. Spinal MRA showed the artery of Adamkewicz originated proximal to the occlusion. Due to worsening TIAs, he was treated with abciximab and heparin infusion. Although the repeat CT scan was unchanged, his TIAs improved significantly. Over the next 72 hours, he became asymptomatic. He was discharged 7 days later on warfarin, with no further episodes reported. Aorto-bifemoral bypass done 6 months later was uncomplicated. *Discussion:* Our patient presented with spinal cord TIAs. Abciximab likely improved the microcirculation and blood flow to the patients conus medullaris. The anticoagulation prevented further thrombus propagation. Over time, the patient likely re-established collateral circulation, mainly from the intact artery of Adamkewicz. Our report suggests a role for abciximab and anticoagulation in treating spinal cord TIAs secondary to aorto-occlusive disease.

P-010

Stroke in a 23-year-old taking Diane 35™

Thomas Jeerakathil (Edmonton), Nasser Rizvi (Edmonton)*

Background: Diane 35™, a combination of the anti-androgen cyproterone acetate and ethinyl estradiol, may be associated with an increased risk for venous thrombotic events compared to low dose OCP but we are aware of no association with stroke. *Methods:* A fit 23-year-old female was taking Diane 35™ for acne but had no other medical history and no family history of thrombotic events. She developed acute nonfluent aphasia and facial droop. CT head was normal and she received thrombolysis with intravenous tPA with full clinical recovery. *Results:* Brain MRI showed a small, patchy, left frontal cortical infarct. Cerebral angiogram, TEE, holter monitor and TCD bubble study showed no source of embolism and lipid profile, fasting blood sugar, homocysteine, and hypercoagulable battery were normal. *Conclusions:* Given that an extensive work-up showed no etiology for stroke in this previously healthy 23-year-old it is likely that Diane 35™ was a contributing factor. Given the lack of reports in the literature the occurrence of stroke with use of Diane 35™ must be infrequent but the risk should be quantified with prospective study and the medication should probably not be prescribed outside of its current narrow indications.

P-011

Carotid artery occlusion and hemispheric infarction secondary to Takayasu arteritis in an infant.

A Kirton (Calgary), J Harder (Calgary), J Scott (Calgary), J Mah (Calgary)*

Introduction: Takayasu arteritis is a medium-large vessel vasculitis rarely encountered in young children. Neurological complications may be related to proximal cerebral vascular disease. *Methods:* Case report. *Results:* A 5-month old boy presented with recurrent high fevers, fatigue, skin rash, and right-sided partial seizures. His initial head CT was normal. He was diagnosed with atypical Kawasakis disease due to the presence of multiple coronary aneurysms. Treatment with IVIG, anticoagulants, and anticonvulsants was initiated. After improving, the child returned 3 months later with renal artery stenosis, malignant hypertension, and suffered a myocardial infarction that was treated with urokinase. He returned to neurology care at 10 years of age in good health with only a mild spastic right hemiparesis and recurrence of left-sided partial seizures. Cerebral MRI/MRA demonstrated large watershed infarction of the left hemisphere and complete occlusion of the ipsilateral internal carotid artery. The finding of multiple large vessel vasculitis with aneurysmal dilatation was suggestive of Takayasu arteritis. *Conclusions:* Systemic vasculidities affecting the nervous system in small children can be difficult to diagnose. Diseases such as Takayasus arteritis may have multiple neurological complications including carotid artery occlusion and hemispheric stroke. MRA/MRI is helpful in establishing the diagnosis and monitoring disease activity over time.

P-012

Diffusion weighted imaging of post-coronary artery bypass graft (CABG) encephalopathy

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Post-CABG encephalopathy (PCE) is defined as delirium, coma, or seizures after the first 24 hours following CABG surgery. Studies of PCE have primarily focused on predictive factors only. We propose the use of MR imaging to assess structural changes in the brain parenchyma as it relates to the severity of PCE and relate these changes to morbidity/mortality. *Methods:* MR DWI scans will be obtained of all post-CABG encephalopathy patients to assess for ischemic micro-infarction as a possible underlying etiology. Encephalopathy will be defined as a positive Confusion Assessment Method for the Intensive Care Unit (JAMA 2001;286:2703-2710). MR DWI will be reviewed by a neuroradiologist and correlated with the clinical outcome. *Results:* Since study initiation, one patient has

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met inclusion criteria. This patient with no focal neurological findings was encephalopathic for 6 days following double CABG. MR DWI revealed pinpoint areas of signal change in the left hemisphere consistent with micro-infarction. *Discussion:* This descriptive case series will present structural evidence by MR DWI of micro-infarction secondary to micro-emboli as an etiology of post-CABG encephalopathy. It will also attempt to correlate severity of PCE with a quantitative analysis of the demonstrated structural lesions and the impact on PCE on morbidity/mortality.

P-013

Variability of middle cerebral artery blood velocity waveforms in young and postmenopausal women.

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Background: We characterized middle cerebral artery (MCA) blood flow velocity waveforms measured by transcranial Doppler ultrasound in young women (n=12), and in postmenopausal women who did (n=6) and did not (n=7) take hormone replacement therapy (PM-HRT and PM-noHRT, respectively). We hypothesized that MCA waveform feature points would show significant difference between young and postmenopausal women. *Methods:* A dynamic end-tidal forcing system was used to maintain end-tidal PO_2 ($PETO_2$) at euoxia (88 mmHg) and end-tidal PCO_2 ($PETCO_2$) at 1.5 mmHg above eucapnic values. Doppler data for the velocity spectral outline (VP) were collected every 10 ms. Waveform features were identified over each cardiac cycle, and included the average VP (VCYC), maximum acceleration (Amax), and the ratio of the velocity at the reflected wave and the velocity at peak systole (VR:Vmax). *Results:* VCYC was unchanged between young, PM-HRT and PM-noHRT (69.1±9.3, 67.4±12.9, 67.6±9.6 cm/s). Amax was significantly higher ($p=0.007$) in young compared with PM-HRT and PM-noHRT (1124.6±308.6, 877.0±89.0, 831.1±143.6 cm/s^2). VR:Vmax was significantly smaller ($p<0.001$) in young (0.88±0.09) compared to PM-HRT (1.13±0.07) and PM-noHRT women (1.08±0.05). *Conclusions:* In postmenopausal women, the acceleration was reduced and the reflected wave was higher than Vmax, suggesting the presence of a reflected shoulder in the MCA waveform.

P-014

Balloon angioplasty of clot in acute anterior circulation stroke: a preliminary study

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Purpose: This is a preliminary investigation studying the safety and efficacy of rapid recanalization of clot causing acute stroke symptoms in the anterior circulation using a soft silicone balloon after a limited trial of intra-arterial tPA. This study evaluates our experience with balloon angioplasty of embolic clot in acute stroke using CT perfusion. *Patients and Methods:* Nine patients who had balloon angioplasty in the MCA/ICA for acute stroke were studied. All had a nonenhanced CT, followed by CT angiography and CT perfusion. Maps of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) were generated. Thrombolysis was attempted with intra-arterial tPA (ia-tPA). Resistant clot was angioplastied with a soft silicone balloon. Recanalization was graded using the TIMI scale. Follow-up CT scans were performed. Clinical outcome was evaluated using the modified Rankin scale (mRS) and Barthel indices (BI). Good outcomes were assigned a mRS < 2 and BI > 90. *Results:* Between Mar/02-Mar/03, 9 patients had attempted angioplasty of acute clot. In seven cases, CT perfusion showed a significant penumbra. 3 patients had ICA, and 6 patients had MCA clot. TIMI 2 or 3 flow was achieved in 8 patients (89%). The average time from CT to recanalization was 2.1 hrs, from symptom onset to recanalization was 4.1 hrs. One patient had an asymptomatic bleed. There were no procedure-related complications and no cases of symptomatic intra-cranial hemorrhage. Five patients had good outcomes, four of which were excellent (mRS<1), none died. 3 patients had moderate to severe disability, one had mild to moderate disability. *Conclusions:* This pilot study suggests that balloon angioplasty can be a safe, effective procedure in well-selected patients and can be an effective complimentary procedure in patients with tPA resistant clot. A short CT to recanalization time is critical to maintain tissue viability and is a valuable indicator to help document and compare the efficacy of interventional neuroradiology services and their tools. A larger scale study would be ideal to evaluate the efficacy of this combined treatment.

P-015

Arterial occlusion due to distal emboli during aneurysm clipping: c**ase series**

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Background: Although microembolization is a common phenomenon in aneurysmal SAH, clinically eloquent embolic events resulting from ruptured aneurysms have been infrequently reported. In surgical complication studies, arterial occlusion is most often due to aneurysm clips. Rarely does distal emboli occur during aneurysmal surgery. The management in this circumstance is not well-defined. *Methods:* Case series. *Results:* Two patients presented with aneurysmal subarachnoid hemorrhage and one patient with transient ischemic attack due to an unruptured aneurysm. Aneurysmal clipping was performed in all cases. In early postoperative period, all patients presented a new neurological deficit. Vascular embolic occlusions were documented by angiography in all cases. In one patient thrombolysis brought significant improvement of cerebral blood flow and neurological deficit. *Conclusions:* Although microemboli is reported to be common in aneurysmal SAH, arterial occlusion by distal macroemboli is an infrequent vascular surgical complication. Minimal manipulation of vessels and aneurysm during surgical intervention might contribute to reduce the occurrence of this potentially devastating complication. The suspicion of this event is essential to orient the appropriate management.

P-016

Intraoperative assessment of carotid endarterectomy with digital subtraction angiography (DSA)

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Background: In order to prevent postoperative stroke, we attempted to detect complications of endarterectomy with the intra-operative DSA (IDSA). *Methods:* We performed IDSA in 157

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consecutive patients undergoing carotid endarterectomy. After the completion of the endarterectomy, subtraction images of the carotid bifurcation were obtained by injecting contrast into the common carotid artery. *Results:* No complication related to the IDSA occurred. Seven patients required intervention based on the result of the IDSA. Three patients required re-opening of the arteriotomy and removal of the residual plaque. One of them underwent patch graft as well. In two patients, separate arteriotomy was made distal to the initial one and residual plaque was removed. In two other patients, kinking of the ICA origin was causing significant narrowing. The artery was mobilized to correct the course of artery. In all, the second IDSA confirmed patency of the artery. None of the 157 patients experienced major stroke or stroke-related death. Four patients experienced worsening of the neurological status postoperatively, but resolved within a week. *Conclusions:* Occlusion of the endarterectomy site is a major, preventable cause of postoperative stroke. Although this is not a controlled study, the results suggest IDSAis an important adjunct for safer carotid endarterectomy.

P-017

CT angiography for the evaluation of carotid artery stenosis in patients undergoing endovascular stenting

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Background: Although digital subtraction angiography (DSA) is the current gold standard in carotid imaging, CTAngiography (CTA) is growing in popularity as a second, less invasive investigation after carotid ultrasound. The purpose of this study is to determine if CTA accurately quantifies carotid stenosis. *Methods:* A retrospective chart and film review of patients undergoing carotid stenting was carried out. We examined this population since, in addition to frequently receiving CTA during their diagnostic work-up, they also receive DSA at the time of stenting. Measurements were made using the NASCET method, and CTA was compared to DSA in terms of sensitivity and specificity of detecting severe stenoses. Their ability to detect calcifications and ulcerations was also compared. *Results:* Agreement on category of stenosis between CTA and DSA was found in 30 of 36 carotid arteries studied. CTA was 83% sensitive and 83% specific for the detection of severe stenosis. DSA was better for the detection of ulcerations, while CTA more readily detected calcifications. *Conclusions:* CTA is both sensitive and specific for the detection of severe stenosis compared with the gold standard. The lower cost, invasiveness, and risk of complications compared with DSA, however, comes at the expense of possible diagnostic errors.

P-018

Clasmatodendrosis likely represents astrocytic response to chronic ischemia

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Background: Leukoaraiosis refers to regions of white matter hypodensity on CT, considered analogous to white matter signal hyperintensity on MRI, and often correlating with ischemic changes and demyelination postmortem. A newly recognized correlate is clasmatodendrosis, coined by Alzheimer to describe swollen astrocytes with broken, stunted dendrites and proposed to represent a pathological astrocytic response to ischemia, distinguishable from astrocytic gliosis, in which reactive astrocytes proliferate and exhibit robust, branching dendrites. *Methods:* Autopsy cases exhibiting clasmatodendrosis between July 2000 and January 2003 were prospectively divided into mild, moderate, and severe groups. A retrospective chart review identified the clinical characteristics. *Results:* 22/150 cases of clasmatodendrosis were identified, in which severe cases were associated with more severe atherosclerosis ($p=0.03$). The likelihood of co-existing Alzheimer's disease changes was equal across groups. Analysis of clinical records available in 18 cases revealed an association with cerebrovascular risk factors ($p=0.02$) and clinical manifestations of atherosclerosis ($p=0.02$) in the most severely affected group. Neuroimaging available in 10 patients did not reflect differences in the degree of leukoaraiosis between groups. *Conclusions:* The severity of clasmatodendrosis correlates with the severity of clinical indicators and neuropathological changes of atherosclerosis, and supports an ischemic etiology.

P-019

Development of a finite element analysis model of intracerebral hematoma

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Background: Finite element analysis is a mathematical technique used to model the behaviour of complex structures. We aimed to develop a finite element model of the human brain, and to model the pressures surrounding an intracerebral hematoma (ICH). *Methods:* A 3-dimensional model of the human brain was created using a normal magnetic resonance scan of a 72-year-old man and previously validated material constants. An ICH was introduced, and tissue displacements and stresses analysed. *Results:* The tissue pressures in three selected zones surrounding the ICH are 125 mmHg, 67 mmHg, and 39 mmHg. This corresponds to a cerebral blood flow of 0ml/100mg/min in zone 1, 10-15ml/100mg/min in Zone 2, and 22-25 ml/100mg/min in Zone 3, suggesting that neurons in zone 1 would be irreversibly ischemic in 14 minutes after the ICH occurs, zone 2 in 70 minutes, and that zone 3 is borderline ischemic. *Conclusions:* Our data suggests that there are zones of functionally impaired but potentially viable tissue surrounding an ICH. This may have implications regarding intervention and requires comparison with forthcoming clinical data. Broader implications of an accurate virtual model of the brain include predicting pressures in various scenarios (like surgical retraction, slower-growing lesions, trauma), to modelling neuronal electrical behaviour and performing virtual studies.

P-020

Does fenestration of the lamina terminalis prevent chronic hydrocephalus after subarachnoid hemorrhage? A proposal for a multi-center randomized controlled trial

C O'Kelly (Toronto), MC Wallace (Toronto)*

Chronic hydrocephalus complicates 10-23% of aneurysmal sub-arachnoid hemorrhage cases. This contributes directly to morbidity and mortality in these patients, while adding the burden of ventriculoperitoneal shunt insertion and complications related to

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shunt infection and failure. It has been suggested that fenestration of the lamina terminalis, a maneuver performed at the time of aneurysm surgery, can significantly reduce the incidence of hydrocephalus following sub-arachnoid hemorrhage. However, appropriate prospective evidence for this maneuver is lacking. To that end, we propose a multi-center, randomized controlled trial to determine whether lamina terminalis fenestration decreases the incidence of shunt-dependent hydrocephalus. Patients with a documented subarachnoid hemorrhage secondary to an anterior circulation aneurysm undergoing microsurgical clipping of their aneurysm will be eligible for randomization. Patients will be randomly assigned to fenestration of the lamina terminalis or a matched control group. The primary end point will be insertion of a shunt device by 6 months post subarachnoid hemorrhage. Secondary outcomes shall include Glasgow Outcome Scores and quality of life indices. Nonrandomized patients and ineligible patients, such as those with aneurysms treated by endovascular coiling and posterior circulation aneurysms, will be followed for comparison purposes. We hope to demonstrate that fenestration of the lamina terminalis prevents hydrocephalus and obviates the need for cerebrospinal fluid diversion in certain patients. We will seek to further demonstrate a positive impact on overall outcome and quality of life.

P-021

Intra-arterial tPA for central retinal artery occlusion: the Calgary experience

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Introduction: Central retinal artery occlusion (CRAO) represents a medical emergency with poor prognosis. Spontaneous improvement is estimated to occur in less than 15% of cases and conventional treatments including ocular massage, anterior chamber paracentesis, pentoxifylline, acetazolamide, and carboxygen inhalation are of limited benefit. Intra-arterial thrombolysis has been emerging as a potentially efficacious and safe treatment. *Methods:* We performed a retrospective chart review of all CRAO cases treated with intra-arterial tPA over the six year period from January 1998 to December 2003. *Results:* Six cases (4 males, 2 females) aged 59-77years were treated for left (3 cases) or right (3 cases) CRAO, 8-18 hours post-onset with intra-arterial tPA (10-15 mg over 15-60 mins). Visual acuity (VA) was unchanged in 3 cases. In the other 3 cases, VA improved from identification of hand movement only to counting fingers and identification of colours. There were no complications. *Conclusions:* Intra-arterial tPA for CRAO was associated with mild improvement in VAin 3 out of 6 cases and no adverse effects. Despite the prolonged time to treatment (i.e., > 8hrs), these findings represent a modest benefit for intra-arterial tPA as compared to conventional methods and the rate of spontaneous improvement.

P-022

Vertical clipping technique facilitates obliteration of wide-necked aneurysms while preserving anatomic circulation

G Pickett (London), S Lownie (London)*

Background: Wide-necked aneurysms, particularly of the middle cerebral artery (MCA) bifurcation, may be difficult to secure adequately with a single clip across the neck. Overly aggressive clipping can compromise M2 segments originating within the aneurysmal neck. However, a less aggressive approach can leave a remnant with hemorrhagic potential. We describe a vertical clipping approach which facilitates maximal aneurysmal obliteration while sparing distal branches. *Methods:* Sixteen patients with wide-necked, irregular aneurysms who underwent surgical treatment were considered intraoperatively for vertical clipping. Aneurysms were located primarily at the MCAbifurcation, ranging from 0.5 - 8 cm in diameter. Clips across the neck produced an unsatisfactory result in these cases, and vertical clipping was then attempted. Clips were placed parallel to the Sylvian fissure to avoid torque on the vessel. *Results:* Vertical clipping and reconstruction of the parent vessel was achieved in fifteen cases. It failed in one case due to an excessively redundant sac. Follow-up angiography confirmed complete clipping in eight cases, while the remaining seven had a tiny proximal neck dilation. Distal branches were preserved in all cases. *Conclusions:* The placement of multiple vertically-oriented clips is a useful technique for maximizing obliteration of aneurysms with wide necks or unusual geometry, while preserving parent and distal vessels.

P-023

Fatal cerebral air embolism complicating esophagogastroduodenal endoscopy

G Pickett (London), B Wehrli (London), D Lee (London)*

Objective: We report a case of intracranial arterial and venous air embolism following endoscopy of the upper gastrointestinal tract. *Case report*: A 71-year-old woman with a history of Crohns disease and intermittent small bowel obstruction underwent esophagogastroduodenal endoscopy for investigation of anemia. Deep prepyloric and duodenal ulcers were biopsied. Immediately post-procedure she was agitated, complaining of inability to breathe, and became hypoxic and unresponsive. She exhibited weak withdrawal to pain and eye deviation to the left. CT imaging demonstrated linear hypodensities over the frontal lobes consistent with intra-arterial air. Air was also noted in the cavernous sinuses and superior sagittal sinus. Repeat imaging two days later revealed bilateral infarcts in the anterior and middle cerebral artery territories. The patient's neurological status deteriorated further and life support was withdrawn. At autopsy, no arterial-venous shunt was detected. The prepyloric ulcer had eroded through to the liver. *Conclusions:* Air embolism producing cerebral infarction is a rare complication of endoscopy. To our knowledge, this is the first reported case demonstrating both arterial and venous intracranial air. Biopsy may increase the risk by exposing damaged vessels to high-pressure insufflated air. Arterial air emboli may occur in the absence of a demonstrable arterial-venous shunt.

P-024

Long term outcome of angiographic abnormalities in children with cranio-cervical arterial dissection

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Background: Duration of therapy and recurrence risk in children with cranio-cervical arterial dissection (CCAD) may be influenced by angiographic changes over time. *Methods:* Children, under 18-

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years, with CCAD, over 10-years, in two Canadian hospitals. Study neuroradiologist reviewed initial and follow-up conventional (CONA) and magnetic resonance angiography (MRA). *Results:* Sixteen patients, 8-males, mean age 10-years, had 17 CCAD. Dissection was confirmed by CONA. Initial MRA showed 3 stenosis, 5 occlusions and 1 intimal flap. Initial CONAdemonstrated 10 occlusions, 3 stenosis, 2 aneurysms and 2 intimal flaps. Fourteen patients received heparin followed by coumadin in 6 and aspirin subsequently. Follow-up angiography, for 11 CCAD, consisted of 7 MRA, 1 CONA and 3 both. Mean follow-up angiography interval was 62-weeks. Follow-up findings for 6 occluded sites: re-canalization 1, partial re-canalization 1, and persistent occlusion 4; for 2 stenotic sites: improvement 1; for 2 aneurysms: resolution 1; and for 3 intimal flaps: disappearance 2 and pouch development 1. Only one child had recurrent stroke. *Conclusions:* Long-term angiography in CCAD shows variable outcomes dependent on initial findings. Total occlusion appears to have the worst outcome for re-canalization whereas stenosis and intimal flap had better neuroradiologic recovery. Relationship of angiographic outcomes with recurrent strokes requires further study.

P-025

Unilateral lingual edema in acute ischemic stroke

A Rajput (Saskatoon*)

Background: Lingual edema has been reported in cases of acute ischemic stroke treated with tPA. While tongue weakness may be seen in lower brainstem stroke, there are no reports on unilateral lingual edema as a presenting feature of stroke. *Methods:* An 82-year-old male presented to the ER with complaints of dysarthria, facial droop and right hand weakness. Examination revealed significant dysarthria and dysphagia. He had right facial droop (sparing the forehead), and marked edema of the right half of the tongue only. Gag reflex was present bilaterally, but palate was not well-visualized. He had findings of ataxic-hemiparesis affecting the right upper limb, and gait was a bit slow and wide-based. *Results:* Head CT revealed no acute infarct. He was on warfarin for atrial fibrillation, and INR was only 1.4. Follow-up examination 12 days later revealed improved right lower facial droop. Tongue, palate and gag were normal, though he remained slightly dysarthric. Right Horners syndrome was noted. The right upper limb weakness had resolved, and coordination and gait had improved. Carotid dopplers were negative. Brain MRI revealed diffuse atrophy and findings consistent with microvascular ischemic change. There was no dissection on MRA. *Conclusions:* Unilateral tongue swelling may be seen in acute stroke not treated with tPA.

P-026

A review of all basilar tip aneurysms treated with detactable Guglielmi coils in Halifax.

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Background: To determine the safety and effectiveness of treatment of unruptured and ruptured basilar tip aneurysms with endovascularly placed Guglielmi detactable coils. *Methods:* All patients who presented with unruptured and ruptured basilar tip aneurysms were reviewed. The neuroendovascular program began in Halifax in 1996 and initially was designed for only coiling basilar tip aneurysms, however this has expanded to include any aneurysm with favorable anatomy and location. *Results:* The treatment of both unruptured and ruptured basilar tip aneurysms is analyzed with special attention to patient outcome and any associated complications. *Conclusions:* Endovascular treatment of basilar tip aneurysms with detactable Guglielmi coils appears to be a safe and effective choice.

P-027

The management of left hemispheric hypoperfusion syndrome

Naser Rizve (Edmonton*), *Tom Jeeratikell (Edmonton*), *Maher Saqqur (Edmonton*)

Acute hemispheric hypoperfusion syndrome has rarely been manifested by aphasia without hemiplegia. Acute perfusion (PI) MRI in acute stroke setting might shows regions of hypoperfused cortex associated with lexical deficits or hemispatial neglect, even when diffusion MRI (DWI) shows no infarct or only small subcortical infarct. So, MRPI-DWI mismatch indicates regions of functionally salvageable tissue. We report our case of a 75-year-old female with a left hemispheric hypoperfusion syndrome presented with aphasia without hemiplegia, Her acute MRI showed a diffusion perfusion mismatch 24 hours from her stroke onset. Patient was managed acutely for stroke by keeping her mean arterial pressure between 100-110 mmHg, which reversed her MRI perfusion and clinical deficit completely.

P-028

***In vivo* detection of abnormal taurine and glutamate by 1H magnetic resonance in neonatal hypoxic-ischaemic encephalopathy and seizures.**

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Background: Glutamate and glutamine (Glx) play a key role in the pathogenesis of neonatal hypoxic-ischaemic encephalopathy (HIE). Taurine (Tau) may inhibit toxic effects of excessive glutamate. Detecting these may help to assess the severity of neuronal injury. *Objective:* To detect Tau and Glx by proton magnetic resonance spectroscopy (MRS) in neonates with HIE and/or seizures (SZ). *Design/Methods:* Medical records of term newborns with HIE and SZ, who had MRS imaging, (July 2001-Nov 2003) were reviewed. Proton MRS was done using a single voxel PRESS sequence (TE = 144), centered in the basal ganglia, using a GE Sigma 1.5T scanner. Quantitative analyses were done using LCModel (Provencher 1993). Single factor ANOVA was used for analysis. *Results:* Forty-eight newborns were studied. 26 had both HIE and SZ, 6 had HIE, and 16 had SZ. 4 died and 44 survived to discharge. Creatine (Cr) and N-acetyl-aspartate (NAA) were significantly reduced in HIE+SZ. Glx was significantly elevated in the four infants who died, compared to those who survived (p=0.005). Taurine was not significantly elevated in different groups. *Conclusions:* Taurine and glutamate/glutamine can be detected *in vivo* by MRS in neonates with HIE and or seizures. Glutamate/glutamine was significantly elevated in neonates who died.

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P-029

Transient third nerve palsy following lumbar CSF drainage during aneurysm and skull base surgery

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Third nerve palsy, indicated by a dilated pupil, is often a cause for concern in the immediate postoperative period, and suggests ipsilateral mass lesions such as a hematoma of brain swelling. We present seven cases of third nerve palsy in the immediate postoperative period, which pursued a transient, benign cause and in whom CTscanning did not reveal any plausible cause. Manipulation near the oculomotor nerve did not occur in any of these cases. All cases had CSF drainage via a lumbar drain to facilitate brain tension, and relatively large volumes of CSF was removed. We believe that the combination of the CSF drainage and brain retraction was responsible for this alarming, but ultimately benign finding.

P-030

A patient with Sneddon's syndrome and eight times intra-uterine fetal death (IUFD)

NS Zadeh (Ahwaz, Iran)*

Background:: The combination of generalized broken livedoreticularis and cerebrovascular accident is known as Sneddon's syndrome. This syndrome is quite rare 4/mil/year. *Case history:* A 40-year-old woman presented to neurologic ward with left sided weakness and livedoreticularis on her skin. In the past medical history eight times intra-uterine fetal death, lower limbs edema, migraine type headache, pain and pallor of fingers in exposure to cold water were noted. Brain MRI, lower limbs venography, echocardiography, serologic tests, skin biopsy, kidneys sonography were done. The necessary treatment was done. *Conclusions:* Stroke and livedoreticularis is known as Sneddon's syndrome. In this rare syndrome because of the risk of other organ damage (heart, kidney) and intra-uterine fetal death the physicians should begin anticoagulant and / or antiplatelet therapy as soon as possible.

P-031

Magnetic resonance imaging (MRI) of the atherosclerotic plaque in post-radiation induced symptomatic high grade carotid stenosis: a case report

A Szymczak (Edmonton), V Mehta (Edmonton)*

Background: Although many cases of radiation-induced carotid stenosis have been reported, little is known about the incidence, natural history and distribution of the disease. Radiation initially induces an injury to the vasa-vasorum with the resultant pathology of radiation-induced carotid occlusive disease being either accelerated atherosclerosis or a panarteritis. *Method:* We present the case of a 46-year-old male who had a previous history (five years prior) of laryngeal cancer treated with radiation and chemotherapy. His only other risk factor for atherosclerotic disease was a history of smoking prior to his cancer. He presented with multiple progressive attacks of amaurosis fugax despite treatment with antiplatelet agents. A cerebral angiogram revealed critical high grade stenosis of the internal carotid artery. In order to better understand the nature of the occlusive lesion, a MRI of the focal area of stenosis was done. *Results:* The T1-weighted MRI-image confirmed a hyperintense expanded media of the vessel consistent with atherosclerosis. The patient elected to proceed with carotid endarterectomy as opposed to angioplasty and stenting. At the time of surgery the dissection was challenging due to fibrosis but the arteriotomy and atherosclerotic plaque removal were uneventful. *Conclusions:* MRI imaging of the area of stenosis in patients with radiation-induced stenosis can be helpful in discerning if the lesion is atherosclerotic in nature.

P-032

Audit of carotid endarterectomy

K Vaneet (Manchester, UK), M Asish (Manchester, UK), S Shumaiyla (Manchester, UK)*

The main aim of this audit is to consider the management and outcome of patients who undergo a carotid endarterectomy at North Manchester Hospital. The audit considered complications post surgery, if any, patient results post surgery, antiplatelet Rx, any symptoms of stroke / TIA within a year after surgery. A patient list was retrieved from Ingress identifying patients admitted to NMGH between 1/4/2002 to 31/5/2003 with carotid artery disease. Retrospective patient case notes were reviewed. A total of 77 completed pro-formas were returned to the Clinical Audit Department for analysis. 4% of patients suffered a stroke or death within 30 days after the operation, compared to 6.7 % NASCET study. Antiplatelet treatment was not given to 3% of patients (one of whom experienced complications and stroke within 30 days). The main recommendations from this audit are: patients need to be followed-up more vigorously at their 6 month and 1 year follow-up appointments. All patients should receive antiplatelet Rx. All patients should have postoperative medical Rx monitored by stroke physician/physician.

Inflammatory and Degenerative Disorders

P-033

Neurotrophic factors in experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis

J Ah-Sue (Calgary), VW Yong (Calgary)*

Background: Neurotrophic factors can confer neuroprotection, regeneration and immunomodulation in diseases of the CNS, including multiple sclerosis and its animal model, experimental autoimmune encephalomyelitis (EAE). We determined the expression profile of various neurotrophic factors over the course of EAE in order to elucidate their possible functions. *Methods:* Relapsing-remitting EAE was induced in female, 129/-SvEv mice. Mice were sacrificed at specific time points during EAE (6 days post-immunization, first sign of disease, peak disease, and remission) and lumbar/sacral spinal cords were extracted. The expression of multiple growth factors was assessed in the spinal cord using real time-PCR. *Results:* Multiple neurotrophic factors were elevated in EAE, including BDNF, GDNF, beta-NGF, CNTF, and IGF-1. There was differential expression amongst the growth factors, which varied at specific time points during the EAE time course. A prominent juncture for the upregulation of several

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neurotrophic factors was at disease resolution (remission). Current experiments seek to evaluate the cellular sources and the function of neurotrophic factors in EAE. *Conclusions:* Particular neurotrophic factors show different expression profiles throughout the EAE time course and may have a role in ameliorating EAE and in regeneration.

P-034

Disease modifying therapy use by pediatric patients in the Calgary MS clinic

JA Bakker (Calgary), CA Stoian (Calgary), J Mah (Calgary), LM Metz (Calgary)*

Background: Multiple sclerosis (MS) typically occurs in adults and, while current approved disease modifying therapies (DMT) have not been studied in children, approximately 5% of MS patients have disease onset before age 16. This study describes use of approved DMT in pediatric patients. *Methods:* The Calgary MS Clinic provides population-based MS care to over 4000 people in southern Alberta with MS or suspected MS. All are registered and followed by an administrative clinic database. Using this database, we identified patients diagnosed before 18 years of age and younger than age 21 as of December 2003. Demographic, disease and treatment characteristics were described using the database and clinic charts. *Results:* Nine patients were identified. Six were women (66.7%). Mean age at MS onset was 13.1 (range 9 to 17 years). All nine had relapsing remitting MS (RRMS) and all started DMT: 7 with glatiramer acetate, 1 with interferon beta-1a and 1 with interferon beta-1b. Two patients switched therapies due to side effects and 1 stopped because of needle intolerance. All cases will be presented along with reference data as needed describing our adult population. *Conclusions:* All patients had active RRMS and initiated DMT. DMT was tolerated as well as in adults.

P-035

Anti-inflammatory differentiation of human monocytes and microglia induced by glatiramer acetate (GA) therapy in MS: a new look at bystander suppression.

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Goal: To determine whether GA treatment modulates immune responses of human monocytes and microglia and to define the consequences of such effects on subsequent T cell responses. *Background:* GA is known to induce a Th2-shift in GA-reactive T cells of MS patients. Such cells are postulated to directly suppress proinflammatory auto-reactive T cells in the periphery and in the CNS. An alternate hypothesis is that GA may indirectly mediate anti-inflammation by modulating responses of antigen presenting cells (APC), such as circulating monocytes and/or resident CNS microglia. *Methods:* Adult human circulating monocytes and CNS-derived microglia were purified and cultured with T cell supernatants (sups) from GA-reactive T Cell lines, generated from either untreated or GA-treated patients with MS. Subsequent production of cytokines and chemokines by the monocytes and microglia, and their surface phenotypes, were analyzed by ELISA and FACS respectively. Similarly treated monocytes and microglia were then used as APC to purified naive CD4+ T cells, to evaluate possible immune-regulatory effects mediated by the differentially exposed APC. *Results:* Compared to the effects of T cell sups from untreated patients, T cell sups from GA-treated patients induced monocytes to secrete more IL-10 (460 vs. 290 pg/ml; p=0.016) but less IL-12 (43 vs. 168 pg/ml; p=0.028 and less of the inflammatory chemokine IP-10 (24 vs. 1260, p=0.0001). While neither of the T cell sups induced measurable IL-12 production from microglia, exposure to sups from GAtreated patients increased microglia IL-10 production (185 vs. 80 pg/ml; p=0.04) while decreasing TNFa (240 vs. 756; p=0.026) and IP-10 (1400 vs. 10, 000; p=0.002) production. Finally, when used as APC to naive T cells, pre-exposure of either monocytes or microglia to untreated sups resulted in Th1 T cell responses (IFNg =240 and IL-5=10 pg/ml, in response to monocytes; IFNg=180 and IL-5=60 pg/ml, in response to microglia). In contrast, pre-exposure of either APC to GA-treated sups resulted in a marked Th2 T cell deviation (IFNg =0 and IL-5=130 pg/ml, in response to monocytes; IFNg=0 and IL-5=240 pg/ml, in response to microglia). *Conclusions:* GA-reactive T cell products from GA-treated MS patients enhance anti-inflammatory (IL-10), and inhibit pro-inflammatory (IL-12 or TNFa, and IP-10), factor production from both human monocytes and microglia. These modulated APC very effectively mediate Th2 deviation of naive T cells. We propose a model in which GA therapy induces changes in T cell responses that generate Type-2 APC which, in turn, contribute to anti-inflammatory responses in MS, both peripherally (monocytes), and centrally (invading monocytes and resident microglia).

P-036

Multiple sclerosis prevalence in Canada: a population-based regional comparison

CA Beck (Calgary), LM Metz (Calgary), SB Patten (Calgary)*

Background: Multiple sclerosis (MS) prevalence has ranged from 85/100, 000 to 217/100, 000 in Canadian reports. Regional comparisons have been complicated by variability of ascertainment and study populations. The 2000/2001 Canadian Community Health Survey (CCHS) allowed regional comparisons. *Methods:* The CCHS was a large population health survey. Subjects aged 18+ were included in this analysis (N=116,109). Presence of MS was determined by self-report. MS prevalence was computed in five regions (Atlantic, Quebec, Ontario, Prairies, and British Columbia) using bootstrapping and sampling weights. Logistic regression was employed to compare regions and examine confounding/interaction by age and sex. *Results:* The overall weighted MS prevalence was 240/100,000 (95%CI:210-280). Prevalence ranged from 180 (95%CI:90-260) in Quebec to 350 (95%CI:230-470) in Atlantic Canada. Logistic regression revealed no statistical difference between the odds of MS in Quebec, Ontario, and British Columbia adjusted for age and sex. The adjusted odds of MS in the Prairies and Atlantic regions were significantly higher than the other regions combined, with odds ratios of 1.7 (95%CI:1.1-2.4, p<.01) and 1.6 (95%CI:1.1-24, p<.05) respectively. Sensitivity analysis demonstrated similar prevalence in the nonaboriginal/non-immigrant group (N=96, 219). *Conclusions:* Results suggest that Canadian MS prevalence may be higher than generally recognized, and may differ by region. Limitations include MS self-report, and relatively low precision.

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P-037

A retrospective evaluation of the efficacy of vagal nerve stimulation in intractable childhood epilepsy

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Background: Vagal nerve stimulation has recently become a modality of treatment for children with intractable seizures who are not candidates for surgery. Studies have shown some efficacy of this treatment. *Methodology:* We performed a retrospective chart review of 23 patients who underwent VNS implantation at the Montreal Children Hospital over a period of two years (July 2000 to July 2002). *Results:* At three months follow-up, 12/23 (52%) patients showed significant seizure reduction (60% reduction or more). At 6, 12, 24 and 36 months, seizure reduction was seen in 12/23 (52%), 16/23 (69%), and 12/16 (75%) and 4/4 (100%) patients, respectively. Additional results suggested that some groups of patients, based on their type of seizure, etiology of seizure or epilepsy syndrome, may be more likely to have a good response. This method of treatment was well-tolerated. All side effects were mild and 86% of patients presenting side effects got better with time. Finally, 77% of patients showed some improvement in their quality of life, mostly increased alertness and better interpersonal interaction. *Conclusions:* VNS is an effective treatment for children with intractable seizures. Improvement may be gradual. It can also have beneficial effects on other aspects of the patient life. It has few side effects. Careful patient selection may help determine which patients are more likely to have a beneficial response.

P-038

The MRI appearance of multiple sclerosis in children

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Background: The utility of MRI in supporting the diagnosis of multiple sclerosis (MS) is well-established in adults. However, only one previous case series has examined the MRI appearance of pediatric MS. Since inherent differences exist between adults and children in both the extent and the structure of myelin, it is likely that susceptibility to inflammation and neurodegeneration will differ between pediatric and adult MS patients, potentially producing a disparate pattern of brain lesions on MRI. *Methods:* In the current study, we will systematically evaluate the MRI appearance of the brains of 44 children with clinically definite MS, and 50 age-matched children with other white matter related neurological diseases (migraine, mitochondrial disease, chemotherapy, lupus). All subjects had MR imaging, including T2 and FLAIR scans, taken at the time of their clinical presentation. Each scan will be systematically assessed and scored by a trained investigator in a blinded manner according to criteria developed in conjunction with our neuroradiologists. Once all scans have been evaluated, results will be compared between groups using a multivariate analysis. *Results and Conclusions:* We hope to provide a detailed description of pediatric MS-associated changes that can be used to develop validated MRI-based criteria for diagnosing MS in children.

P-039

Butyrylcholinesterase activity in the human thalamus in alzheimer's disease

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Background: Butyrylcholinesterase (BuChE) is a co-regulator of the duration of action of acetylcholine in cholinergic neurotransmission. This has important implications for the function of BuChE in the nervous system, as well as for the course and treatment of diseases such as Alzheimer's disease (AD). The thalamus, an area involved in cognition, attention, and emotion, has BuChE and AChE containing neurons. Given that many thalamic nuclei show AD neuropathology, we hypothesized that BuChE-expressing neurons may be affected during the disease process. *Materials and Methods:* The distribution of BuChE in the thalamus was compared in four normal and four AD cases. The total number of neurons, as well as the number of BuChE neurons, was determined using densitometry and stereological methods. *Results:* There was intense staining for BuChE throughout the thalamus. BuChE staining was most intense and widespread in neurons in the anteroventral, mediodorsal, ventral, lateral and the pulvinar thalamic nuclei. There was no significant difference in the percentage of BuChE-expressing neurons between normal and AD brains. *Conclusions:* BuChE-expressing neurons appear to be preserved in AD and hence this enzyme is an ideal target for treatment of some of the symptoms in this disease

P-040

Serial neuropsychological assessments and treatment response in a case of proven cerebral Whipples disease

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Background: Whipples disease is a rare multisystemic disorder associated with *Tropheryma whippelii* infection. Arthralgias and digestive symptoms are the most common manifestations, but 7 to 31 percent of cases have cognitive impairment. Nevertheless, very few studies have documented these cognitive abnormalities. *Methods:* A 55-year-old woman with cerebral Whipples disease proven by brain biopsy was followed during a 2 year period with four serial neuropsychological assessments. *Results:* Initial testing revealed a significant anterograde and retrograde amnesia, confabulations, and a dysexecutive syndrome. Behavior was infantile, inappropriate and apathetic in the face of impaired insight. Accordingly, cerebral magnetic resonance imaging (MRI) showed lesions in the mesiotemporal and frontobasal regions. Attention, language, visuo-perceptual functions, constructional and ideomotor praxis remained normal throughout the follow-up. With antibiotic therapy, the MRI lesions regressed almost completely but amnesia persisted while behavior and executive functions improved mildly. *Conclusions:* We described the evolution of cognitive functions and behavior in a patient treated for Whipples disease. The partial recovery could either result from irreversible cerebral damage that occurred prior to treatment or from persistent infection. We are planning to obtain a polymerase chain reaction on cerebro-spinal fluid to help distinguishing between the two possibilities.

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P-041

Short-term decline in cognitively-impaired-not-demented (CIND) subjects affects language and delayed memory

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Background: It is known that CIND is associated with an increased risk of progression to dementia. However the pattern of cognitive decline that precedes this progression and may be predictive of it is not well-documented. This study investigated six-month declines in CIND subjects. *Method:* CIND was diagnosed if at least one but not all of the DSM-IV-TR criteria for dementia were met and delayed verbal recall was < 1 SD below age-specific norms. Fifteen CIND subjects and 17 controls were given the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at 0, 3 and 6 months. Reliable change index (RCI) scores at the 90% confidence interval were calculated for five domains to identify significant 0- to 6-month change. *Results:* Two CIND subjects (13%) converted to dementia. Among the remaining 13, 8 (61%) showed reliable decline in at least one domain. Decline occurred almost exclusively in language (6 subjects, 46%) and delayed memory (5 subjects, 38%). Only 3 controls (17%) declined in any domain. *Conclusions:* In CIND decline may manifest in the short term with a milder and more stereotypic pattern of impairment than at conversion. Future investigations will establish whether this pattern is predictive of dementia.

P-042

Matrix metalloproteinase-9 facilitates remyelination by processing the inhibitory NG2 proteoglycan

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Introduction: Matrix metalloproteinases (MMPs) are elevated in multiple sclerosis and may contribute to the pathology of the disease. However, our studies have previously shown that MMP-9 regulates process extension by cultured oligodendrocytes and thus MMPs could be important for remyelination after a demyelinating insult. Here, we test the hypothesis that MMP-9 is required for the remodeling of the extracellular matrix that occurs during remyelination. *Methods:* To test this hypothesis, we used a model of lysolecithin-induced demyelination to monitor remyelination in wildtype versus MMP-9 null mice. *Results:* MMP-9 mutant mice were deficient in their remyelinating capacity compared to wildtype animals. We observed fewer mature oligodendrocytes present in MMP-9 mutant mice one week after injury. Furthermore, a dense matrix of NG2 proteoglycan, described to be an inhibitory molecule for neurite extension in culture, was persistent in the lesion of MMP-9 null animals but not in wildtype controls. Finally, *in vitro* results demonstrate that NG2 is a substrate for MMP-9 cleavage. *Conclusions:* We propose that the lack of MMP-9 retards the degradation of the NG2 proteoglycan after injury; NG2 then accumulates and hinders the maturation of oligodendrocytes and the remyelination process. We conclude that MMP-9 plays an important role in remyelination.

P-043

Trigeminal neuralgia in multiple sclerosis patients treated by percutaneus radiofrequency rhizotomy – success, failure and complication rate compared to control group.

T Mandat (Vancouver), CR Honey (Vancouver)*

Object: The aim of this study was to evaluate the efficacy of percutaneus radiofrequency rhizotomy (PRR) to treat trigeminal neuralgia (TN) in patients with multiple sclerosis (MS). *Material:* In a four-year period (1999-2003), 131 patients had PRR for TN. In the cohort with MS (n=16) the follow-up ranged 1-36 months. In the cohort without MS (n=115) follow-up ranged 1-48 months. *Method:* Groups were compared by chi-squared test to determine if there was a significant difference in the proportion of patients that: i) were pain free off medication (cured), ii) were pain free with or without medication, and iii) required repeat surgery. *Results:* In the MS cohort, 69% of patients were cured and 24% were pain free on low doses of medications. 50% of patients required repeat PRR. In the cohort without MS, 81% were cured and 10% were pain free on low dose of medications. 16% required repeat PRR. There was no significant difference in success rate for the two patient cohorts. There was a significantly higher rate of repeat operations for the MS group. *Conclusions:* PRR for TN in MS is effective. The increased rate of reoperation in patients with MS may reflect the progressive nature of that disease.

P-044

The odds of having diabetes is reduced in people with multiple sclerosis

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Background: An increased association between type I diabetes and multiple sclerosis (MS) has been reported. However, populations with relative increased prevalence of type II diabetes have lower risk for MS. We evaluated the association between diabetes mellitus (DM) and MS. *Methods:* Using 2001 physician billing data from the Alberta Health Care (AHC) Insurance Plan, MS and DM patients were identified. The association between DM and MS was estimated after stratification by age and sex. Additionally, data from an MS epidemiological study conducted in Calgary and Montreal were evaluated separately then standardized morbidity ratios (SMR) referenced to provincial data were computed. *Results:* Of the 2, 968, 536 people analyzed, DM affected 3.38% and MS affected 0.30% (300/100, 000). The age-adjusted OR of having DM, if one had MS, was 0.76 (95%CI: 0.68-0.85, p<0.0001). There was no interaction with age and no confounding or interaction with sex. The SMR for diabetes in Calgary's MS population was 0.43 (95%CI: 0.21-0.76). Montreal data analysis is ongoing. *Conclusions:* There was a negative association between DM and MS in Alberta and a lower than expected number of DM patients in Calgary's MS population. These preliminary findings might elucidate mechanisms conferring increased or decreased MS risk.

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P-045

Comparison of the bioavailability of intravenous methylprednisolone and oral prednisone in people with multiple sclerosis

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Background: 3-5 days of high-dose intravenous methylprednisolone (IVMP) is the mainstay of relapse therapy in multiple sclerosis (MS). Oral therapy, however, is safe, inexpensive, and patient-preferred. *Methods:* The bioavailability, or area under the concentration-time curve (AUC), was compared in MS patients requiring corticosteroid treatment. Patients were randomized to 1250 mg oral prednisone (OP) or 1g IVMP. Serum prednisolone and methylprednisolone levels were determined between 0 and 48 hours. Means were compared using the two-sample t-test. *Results:* Sixteen patients participated. At 24 hours, mean AUC for IVMP was 37, 770.16 (SD 16, 244.27, 95%CI: 24, 189.61, 51, 350.71) and for OP was 26, 778.14 (SD 9, 664.61, 95%CI: 18 698.32, 34, 857.95). The difference was not statistically significant (p= 0.122). At 48 hours there was no significant difference (p = 0.185) but there was at 8 hours (p = 0.004), consistent with earlier peak methylprednisolone levels. Both groups had considerable inter-group variability. *Conclusions:* This study suggests there is no substantial difference in the bioavailability of IVMP and OP at 24 hours. Furthermore, OP results in more sustained serum levels, more closely approximating the optic neuritis treatment trial (250mg IV methylprednisolone every 6 hours). Thus, high dose oral prednisone should be considered a treatment option for MS relapses.

P-046

Characterization of Devics disease: the Toronto experience

N Parekh (Toronto), L Lee (Toronto)*

Background: Devics disease is characterized clinically by myelopathy and optic neuropathy. Whether it is a variant of multiple sclerosis (MS) remains controversial. We describe the Toronto experience with this entity over the past decade. *Methods:* Our case definition for this retrospective case series included patients with isolated clinical involvement of the optic nerves and spinal cord. A detailed review of the charts and investigations was performed. *Results:* 9/14 patients diagnosed with Devics disease matched the case definition. The median age of onset was 31 years. There was a predominance of women (67%) and Asian ancestry (67%). All patients followed a relapsing course. Oligoclonal banding was absent in all cerebrospinal fluid (CSF) samples (n=8). 8/9 patients had normal or nonspecific changes on brain MRI and none met MS criteria. All patients had spinal cord MRI abnormalities. *Conclusions:* The findings of this study are similar to previous reports. Devics disease affects women more frequently. Onset is commonly in the fourth decade, with normal brain imaging and extensive spinal cord changes. However, our series demonstrated a predominance of Asian patients as well as complete absence of oligoclonal banding. We propose that absent oligoclonal banding be included in the major supportive criteria for diagnosis.

P-047

See Epilepsy section (page 56)

P-048

Histology study of nerve endings in flava ligament in patients with discopathy

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Introduction: Flava ligament normally has neural ends so it has sensory role and help to protect vertebral column against different injuries. The aim in this study is to detect the neural ends in flava ligaments in patients with discopathy. *Method:* The samples were taken from flava ligaments of the patients with discopathy during surgery. One hundred samples were considered. Five hundred sections were obtained and stained with H & E method and were studied with light microscope. *Results:* Nerve corpuscles were found in none of the sections of the patients. *Discussion:* It seems that flava ligaments in patients have a loss in the nerve ends that leads to a decrease in proprioceptive information to control nervous system and may injure tissues like cartilage, bone and fascia.

P-049

Comparison of provincial governments multiple sclerosis therapies programs

CA Stoian (Calgary), LM Metz (Calgary), GR Currie (Calgary)*

Background: Four disease modulating therapies (DMT) for multiple sclerosis (MS) are approved for use in Canada, but each province determines reimbursement and eligibility criteria. The purpose of this study was to compare provincial MS drug programs. *Methods:* Information used to describe programs as of December 2001 was obtained through direct communication with program administrators and MS Clinic nurses as well as through search of available literature. *Results:* All provinces funded all four therapies, but patient eligibility, the funding process, and the amount of funding available varied by province. Patient eligibility varied by MS course, disability level, previous relapse requirements, and the need to screen for and manage co-existent depression. Process features that varied included requirement that an MS nurse be involved, limitations on which physicians can prescribe, and need for panel review. Funding provided also varied, sometimes by a formula used to calculate patients' ability to pay. *Conclusions:* Provincial funding for DMT is variable, thus contributing to disparity in health care provided and direct patient costs. Differences in eligibility and reimbursement may lead to patients being denied access in some provinces but not in others. Differences in process may only affect appropriateness of patient access and potentially enhance adherence.

P-050

Influence of mathematical valence signs on line bisection performance of normal subjects

T Stryker (Saskatoon), A Kirk (Saskatoon)*

Background: We set out to determine whether plus and minus mathematical signs (+ and -) would induce a representational bias thus affecting normal subjects line bisection performance. *Methods:* Thirty normal right-handed subjects were asked to bisect lines oriented horizontally, vertically, and radially. Plus and minus signs

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were placed at either end of each line. The end that each sign was placed at, as well as the length of the line, was varied. *Results:* Subjects demonstrated significantly greater line bisection error when the plus signs were located at the right, top, and distal ends of horizontal, vertical and radial down lines respectively than when the minus signs were located at these same ends. *Conclusions:* Our results suggest that the errors subjects made in line bisection are due to either a visual illusion of length or a higher order cognitive process whereby subject's biases are modified when a visual stimuli is presented that either conflicts or corresponds with their mental schema.

P-051

The effects of mercury and MMP-9 on T cell activation: a possible link with multiple sclerosis (MS)

TR Todoruk (Calgary), L Metz (Calgary), VW Yong (Calgary)*

Background: Aberrant T cell activity and dysfunction of matrix metalloproteinase (MMP) -9 are implicated in MS pathogenesis, as are environmental factors such as heavy metals. This study examines a possible link between heavy metals, particularly mercury, in MMP-9 activation and T cell function. *Methods:* Fluorogenic assays were used to evaluate the effects of mercury acetate on MMP-9 activity. Human and murine (wild type and MMP-9 -/-) T cells were cultured, activated and assessed for interferon (IFN) -gamma production and proliferation as markers of activation. *Results:* Many heavy metals affected MMP-9. Mercury acetate induced a bimodal response, with low and high concentrations activating and inhibiting MMP-9 activity, respectively. Mercury addition also induced the same bimodal response in IFN-gamma production by T cells. This was MMP-9 dependent as IFN-gamma upregulation did not occur in MMP-9 -/- mice which could be rescued by the addition of MMP-9 to MMP-9 -/- T cell cultures. The activation of T cells occurred at environmentally safe levels of mercury and at biologically relevant concentrations of MMP-9. *Conclusions:* The combination of MMP-9 and mercury, with the resultant activation of MMP-9, has a role in the activation of T cells and may be significant in the progression of MS.

P-052

Mitoxantrone chemotherapy in worsening relapsing remitting and progressive MS: a Canadian perspective

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Background: Mitoxantrone has been approved for the treatment of worsening relapsing remitting, progressive relapsing and secondary progressive multiple sclerosis, but is expensive and can cause significant adverse events. In order to determine clinical characteristics that would predict response to treatment, we conducted a retrospective and prospective analysis of patients referred for chemotherapy in the Multiple Sclerosis Clinic at St. Michaels Hospital in Toronto. *Methods:* 78 patients have been referred for treatment. Of these, sufficient follow-up is available in 67 patients. Response to treatment has been defined as: 1) improvement (a decrease in the annual relapse rate, or a decrease in the EDSS score of 0.5 points or more, or a decrease in the Ambulation Index (AI) score of 2 points or more at completion or discontinuation of treatment), or 2) stabilization (a change in the EDSS score of 0 points, or a change in the AI of 1 or 0). Non-response was defined as clinical deterioration (no change or an increase in the annual relapse rate, or an increase in the EDSS score of 0.5 points or greater, or in the AI of 2 points or greater). The results of this cohort will be presented. *Results:* On preliminary analysis, the following clinical characteristics were predictive of response: 1) younger age at referral (mean 37 years versus 51 years in nonresponders), 2) shorter disease duration (mean 7.6 years versus 21.4 years), 3) lower EDSS score at referral (mean 5.6 versus 6.9), 4) shorter duration in the progressive phase of the illness (mean 2.7 years versus 13.3 years) and 5) shorter time from last relapse to initiation of chemotherapy (mean 1 year versus 8.3 years). *Conclusions:* This preliminary analysis suggests that the efficacy and cost-effectiveness of Mitoxantrone chemotherapy can be improved by applying specific clinical criteria to patient referrals.

P-053

Common risk factors for multiple sclerosis and insulin dependent diabetes mellitus

S Warren (Edmonton), KG Warren (Edmonton)*

Background: There is growing evidence of a relationship between multiple sclerosis (MS) and insulin dependent diabetes mellitus (IDDM). This study examined possibly shared environmental causes. *Methods:* 125 patients who attended the University of Alberta's MS Clinic and 84 patients who attended the Metabolic Day Care Centre were matched to normal controls on gender and age. All participants answered a questionnaire including exposure to infectious diseases, living conditions, diet and exposure to trace elements prior to onset age. Odds ratios (ORs) and 95% confidence intervals (CIs) were initially used for analysis. *Results:* 75% of MS patients were female, but 70% of IDDM patients were male. Peak current age of MS patients was 40-49, and of IDDM patients was 20-29. More MS patients than controls (OR=2.7, CI=±.6) and more IDDM patients than controls (OR=10.8, CI=±1.5) had lived on a farm prior to onset age. More MS patients than controls (OR=2.1, CI=±.6) and more IDDM patients than controls (OR=3.2, CI=±1.1) regularly drank unpasteurized cow's milk prior to onset age. More MS patients than controls (OR=2.2, CI=±.6) and more IDDM patients than controls (OR=2.6, CI=±1.4) also drank well water. *Conclusions:* Researchers have suggested that one link between MS and IDDM could be milk consumption, but controversy remains over the role of cow's milk. If unpasteurized cow's milk in particular is related to the occurrence of MS and IDDM, more attention might be paid to microorganisms transmitted by unpasteurized cow's milk as a risk factor or supplements to pasteurized cow's milk as a protective factor in these diseases.

P-054

Creutzfeldt-Jakob disease presenting with complex partial status epilepticus

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Creutzfeldt-Jacob disease (CJD) is characterized by dementia and diffuse neurological symptoms. While EEG abnormalities and myoclonus are common, only three cases presenting with complex

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partial status have been reported. *Method:* Case report and literature review. Retrospective review of all probable/definite CJD cases (7) presenting to our hospital over 5 years, emphasizing initial presentation. *Results:* A 51-year-old Chinese man presented with intermittent episodes of altered level of consciousness, characterized by staring, oroalimentary automatisms, and dystonic posturing of the left hand. Initial EEG demonstrated continuous focal epileptiform discharges originating from the right hemisphere, controlled with IV ativan and dilantin. In retrospect, the family recognized similar episodes over the previous two weeks as well as a 6-month history of diplopia, progressive weakness, and memory loss. Startle myoclonus was present. On day 7-14 of admission, EEGs showed progressive increase in frequency and duration of periodic biphasic and triphasic sharp waves (right greater than left hemisphere) against a slow background, nonresponsive to treatment. CSF 14-3-3 protein was positive. Postmortem examination was refused by the family. *Conclusions:* The initial presentation and course of sporadic CJD is variable. CJD should be considered in the differential diagnosis of complex partial status.

P-055

Prediction of MS lesion development by MRI texture analysis

Y Zhang (Calgary), H Zhu (Calgary), LM Metz (Calgary), JR Mitchell (Calgary)*

Background: Accurate quantification of natural pathological changes in multiple sclerosis (MS) is critical for evaluating patients responses to treatment. We believe that as white matter becomes abnormal in MS, its texture in MRI will change. In this study, we utilized the new local Fourier analysis, the polar S Transform (PST) to characterize texture changes in T2-weighted (T2w) MRI prior to and during MS lesion development. *Methods:* Twenty untreated relapsing remitting MS patients were scanned bi-monthly for twelve months on a 1.5T MR system. Twelve regions of interest (ROIs) were chosen from corresponding slices to evaluate the evolution from NAWM, to active then inactive lesions. The local PSTspectrum was computed for every ROI. *Results:* The low frequencies were increased in MS lesions compared to NAWM. Active lesions had larger changes than inactive lesions. The sum of low frequency energy (f <= 2.88 cm-1) was significantly different between NAWM and active lesion (p=0.00035), NAWM and inactive lesion (p=0.0012), and between active and inactive lesion (p=0.0069). *Conclusions:* The local spectral distribution at low frequencies changed significantly during MS lesion evolution. This study suggests that the PST may allow prediction of MS lesion development, and help evaluate treatment effects in MS clinical trials.

EPILEPSY

P-056

The role of routine photic stimulation in the EEGs of adult patients

SN Ahmed (Edmonton), J Unterman (Edmonton), T Roberts (Edmonton), D Gross (Edmonton), B Sinclair (Edmonton)*

Background: Intermittent photic stimulation (IPS) is used as a routine activating procedure while conducting electroencephalograms (EEG). Although, IPS can provide useful diagnostic information in photosensitive epilepsies, the usefulness of its routine use in adults has not been established. We sought to address the supplementary diagnostic information obtained through routine use of IPS in the adult population. *Methods:* Hundred consecutive abnormal EEGs in patients who had undergone photic stimulation were reviewed. There were 52 females and 48 males. Ages ranged from 18 to 94. Indications included epilepsy, altered level of consciousness, psychosis, delirium, stroke and encephalopathy. Abnormalities identified on the EEG reports encompassed generalized and focal slowing, sharp waves, epileptiform discharges and combinations of these categories. Photic stimulation was conducted in a conventional manner at frequencies ranging from 1-30 hertz. *Results:* Nine patients had abnormalities noted on IPS. These consisted of sharp waves in 4 patients and focal slowing in five patients. One patient had abnormalities on IPS that led to a more definite classification of the suspected seizure type. *Conclusions:* The yield of picking additional abnormalities on routine IPS in adults is very low. Like sleep deprivation, this procedure should be conducted at the discretion of the ordering physician.

P-057

Ohtahara syndrome: atypical course and EEG features

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Introduction: Ohtahara syndrome (OS) is a well-defined progressive epileptic syndrome with an onset in the neonatal period. It is characterised by early onset seizures, tonic spasms, as the main seizure type, and suppression burst (BS) in both wakefulness and sleep. Usually this syndrome evolves into hypsarrythmia around 3 months of age. It is highly unusual for the BS pattern to persist beyond this period. *Methods:* Retrospective chart review and digital EEG analysis of an infant with OS. *Results:* We report a 22-month-old girl with OS that had atypical EEG features. She had early onset seizures consisting of mainly tonic spasms, and some focal seizures of limb jerking and chin twitching. Despite a classic clinical picture of OS, the EEG of this patient had two unusual features that are not seen with OS. First, the persistence of BS pattern with no evolution into other EEG patterns. Second, electrographic seizures were embedded in the suppression period when the sensitivity of the EEG is increased. *Conclusions:* These findings signify the importance of increasing the sensitivity to search for embedded seizures in the suppression interval, using digital EEG analysis in OS. Otherwise, electrographic seizures might be missed. The persistence of BS is also interesting.

P-058

Success and failure of topiramate monotherapy in the treatment of childhood epilepsy

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Background: Topiramate (TPM) is an anti-epileptic drug (AED) with multiple mechanisms of action. We examined the feasibility and effectiveness of TPM in children with epilepsy. *Methods:* Retrospective chart review of out-patient pediatric patients on TPM. *Results:* Twenty-nine patients, ranging in age from 10 months to 18 years, fulfilled our criteria. TPM monotherapy was achieved in 10

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and was successful with no seizures in 4, and 2 additional ones had more than 50% improvement. All but one of these patients had been on other AEDs previously. TPM was withdrawn in 9 patients because of adverse effects or lack of effectiveness. *Conclusions:* TPM is effective in children with epilepsy and can often be used alone with complete seizure control.

P-059

Hemispheric surgery for intractable epilepsy: outcome and complications

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Objectives: To describe outcomes and complications in children following hemispheric surgery for epilepsy. *Methods:* Retrospective review of medical records. *Results:* The study population comprised 24 children, with age at seizure onset 1 day to 7 years (mean 13.5 months). Seizure etiology was cortical dysplasia (7), infarction (7), Sturge-Weber syndrome (6) and Rasmussens encephalitis (4). Age at surgery was 3 to 174 months (mean 69 months). Peri-insular hemispherotomy was performed in 18, hemidecortication in 5 and anatomic hemispherectomy in one. Complications included hydrocephalus requiring shunt (3), shunt blockage (1), decubitus ulcer (1), aseptic meningitis (4) and transient 6th nerve palsy (1). 14 patients (58%), including all patients who had hemidecortication and anatomic hemispherectomy, required blood transfusion. At follow-up, range 3-228 months, (mean 72 months), 20 patients (83%) are seizure free, three have rare seizures (Engel II) and one has worthwhile improvement (Engel III). Patients with ongoing seizures have cortical dysplasia (3) and Rasmussen's encephalitis (1). 58% (14) patients are off antiepileptic medications. *Conclusions:* Hemispheric surgery is successful in controlling seizures in children. The most common complications include bleeding and hydrocephalus, and these may be less with peri-insular hemispherotomy.

P-060

Seizures and epilepsy in patients with multiple sclerosis

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Background: An increased prevalence of epilepsy in patients with multiple sclerosis (MS) has been reported, although recent work has refuted this association. Growing evidence of grey matter pathology in MS supports a potential etiology for seizures in these patients. *Methods:* Clinical characteristics of patients seen at the University of British Columbia Multiple Sclerosis Clinic between 1993 and 2003 were collected prospectively as part of an ongoing natural history study and database (COSTAR). Patients with clinically definite multiple sclerosis (CDMS) by Poser criteria were identified and screened retrospectively for the presence of seizures or epilepsy. Seizure type was defined where possible based on the International League Against Epilepsy classification. Traditional risk factors for epilepsy, age of onset of CDMS and of seizures and degree of disability as measured by the EDSS were reviewed for each patient. *Results:* 4161 patients with CDMS were identified. Of these, 224 (163 female, 61 male; mean age 50.7 years) had seizures or epilepsy for a prevalence of 5.4%, approximately five times higher than expected in the general population. *Conclusions:* MS is associated with an increased risk of seizures and epilepsy compared with the general population. CNS damage secondary to demyelination may predispose MS patients to seizures.

P-061

Frequency of behavior problems in epileptic children

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Background: Behavioral problems in epileptic children can be potentially difficult for the physician and family to deal with and often require significant community support. This study reports the results of a parent and physician survey of behavior issues in this group of patients. *Method:* Over a 3 month period all parents and participating neurologists were asked to complete a standardized questionnaire about the child's seizure disorder and behavior. In addition the parents were asked to complete the Behavior Childhood Checklist. To have been included in the study, patients had to be less than 18 years of age; diagnosed has having epilepsy; and had been treated for at least 6 months by one of the participating neurologist. *Results:* 173 patients were asked to participate in the study and 158 parents completed both the needs and the behavior survey (82 males, 76 females). The median age was 11 years old (range 4-17). The seizure types were partial seizures (56%), generalized seizures (23%) and multiple seizure types (21%). The mean number of programs used by parents was 1.18 ± 1.5. Physicians identified 30% of patients with behavioral problems while parents who completed the Childhood Behavior Checklist identified 20% had internalizing problems and 18% had externalizing problems. 56% of patients had some level of cognitive disability. Abnormal behavior correlated with children's intellectual and cognitive ability but not with the type of epilepsy or EEG pattern, physical disability or number of programs parents were using. *Conclusions:* Behavioral disorders are common in children with epilepsy and they correlate with children's cognitive abilities but not with children's epilepsy or EEG pattern.

P-062

Serotonin modulates experimental atypical absence seizures via 5-HT2 receptor activation

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Background: Serotonin modulates chronic atypical absence seizures (Can J Neurol Scien 2001; 28: S11). Serotonin acting on the 5-HT2Areceptors attenuates thalamocortical oscillations *in vivo.*We sought to determine the role of serotonin on slow-spike wave discharges (SSWD) in the AY-9944 (AY) treated rat. *Methods:* AY treated male Long Evans hooded rats (n = 26) with chronic monopolar epidural electrodes over the frontal and parietal cortices were tested for electrocorticographic (ECoG) recordings. Rats were either administered the serotonin precursor 5-HTP (12.5, 25, 50, or 100 mg/kg, n = 12), fluoxetine (10 mg/kg, n = 4), 5-HT2A agonist DOI (0.5, 1 or 2 mg/kg, n = 6), or 5-HT2Aantagonist ketanserin (2.5

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mg/kg, n = 4) in a counterbalanced randomized experimental design. *Results:* The total number and frequency of SSWD were significantly reduced in AY rats receiving 5-HTP at 50 and 100 mg/kg, whereas fluoxetine produced a nonsignificant increase in SSWD. DOI dose-dependently attenuated SSWD, whereas ketanserin significantly increased the frequency of SSWD. *Conclusions:* The serotonin precursor 5-HTP reduces SSWD in the AY treated rat probably by acting on the 5-HT2Areceptor. However, more work needs to be done to ascertain the differential effect of 5-HTP and fluoxetine on SSWD.

P-063

Triphasic waves associated with metabolic encephalopathy versus generalised nonconvulsive status epilepticus: electroencephalographic differentiation.

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Background:: Triphasic waves (TW) and generalised nonconvulsive status epilepticus (GNCSE) may share morphological features that create diagnostic ambiguity. Both conditions are seen in the intensive care unit in patients with altered consciousness. *Objective:* To describe electroencephalographic differences between TW and GNCSE. *Methods:* We compared retrospectively the EEGs of two groups of patients: TW associated with metabolic encephalopathy and GNCSE. We studied the following: demographics, clinical presentation and EEG morphological features. *Results:* We analysed 63 EEGs (54 patients) with TW and 22 EEGs (10 patients) with GNCSE. Decreased consciousness was present in all patients. When compared to TW, epileptiform discharges had a higher frequency (mean=2.6Hz vs 1.9Hz) (p=0.0001), showed more often extra-spikes components (60% vs 0%) (p=0.000003) and had less generalised background slowing (92.6% vs 20%) (p=0.000004). Lag of phase two was absent in all cases of GNCSE but present in 42.6% of patients with TW. Stimulation frequently increased the TW (47.4%) while it had no effect on the epileptiform pattern (p=0.008). Sleep decreased TW significantly but did not influence the epileptiform activity in 80% of cases. *Conclusions:* Stimulation, sleep and some EEG morphological criteria may help to distinguish between TW and GNCSE.

P-064

Favorable outcome in children with infantile spasms secondary to Aicardi syndrome treated with vigabatrin

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Background: The outcome of Aicardi syndrome is typically poor in regard to cognitive functions and mobility. The majority of patients are severely retarded. Only a few have been reported to walk and communicate with words. *Methods:* We report two children who developed infantile spasms at 4 and 5 months of age respectively. Their EEG showed a modified hypsarrhythmia. Both were treated with Vigabatrin. Investigation led to the diagnosis of Aicardi syndrome with agenesis of the corpus callosum and chorioretinal lacunae. No other chromosomal nor metabolic abnormalities were identified. *Results:* Neither child ever showed developmental regression and both went on to have a favorable outcome after the spasms stopped. Repeat EEGs were normal but both developed partial complex seizures well-controlled with conventional antiepileptic drugs. At their last follow-up both at age 3 years, they could walk, manipulate objects and make sentences. *Conclusions:* This suggests that early treatment with Vigabatrin could improve the outcome of children with Aicardi syndrome and infantile spasms, as described in children with tuberous sclerosis. We believe that Vigabatrin should be the drug of choice for these children. Disappearance of the hypsarrhythmia on EEG could also play a key role toward a favorable outcome.

P-065

Psychiatric manifestations of right temporal lobe seizures

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Background: The pathogenesis of commonly occurring psychiatric symptoms during epileptic seizures is not well-understood. We studied the underlying mechanism of ictal psychosis and panic attacks in two patients with temporal lobe epilepsy (TLE). *Methods:* Two adult patients with intractable epilepsy of right temporal origin manifesting with psychiatric symptoms are presented. *Results:* A 42-year-old man had a six year history of recurrent simple and/or complex partial seizures consisting of déjà vu, epigastric sensations, automatisms, abnormal smell and hypersexuality associated with overwhelming senses of doom, palpitations, pallor, tremulousness and diaphoresis secondary to a dysembryoplastic neuroepithelial tumor in the right anterior mesial temporal lobe. Symptoms abated after resection of the tumor. A 31-year-old woman with intractable TLE and rare generalized tonic-clonic seizures experienced frequent episodes of complex visual hallucinations occasionally associated with automatism and postictal confusion for 8 years. Electroencephalographic telemetry showed right posterior temporal origin of seizures despite normal imaging. *Conclusions:* These two cases illustrate two diverse psychiatric manifestations of seizures of right temporal origin: ictal panic attacks with anterior mesial temporal seizures; and ictal complex visual hallucinations originating posteriorly. Individual psychiatric manifestations of seizures appear to localize within specific regions within the right temporal lobe.

P-066

Zonisamide in pediatric epilepsy: how can we facilitate entrance of special access medications to the Canadian market?

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Background: Zonisamide is currently available in Canada through the Special Access Program. Such medications are supported by the Pharmacy in our center. We present our experience as an illustration to discuss the availability of medications which are effective but not readily available on the Canadian market. *Methodology:* Retrospective chart review of all children treated with Zonisamide identified through the Outpatient Pharmacy. Documented outcome measures included efficacy and tolerability. *Results:* Twenty-eight children (4 month - 17 years, mean 9 years) were treated for 1 week to 14 months (mean 6.2 months) to a

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maximum dose of 16 mg/kg/day (mean 9.3). Seizure syndromes included idiopathic generalized (9), symptomatic focal (9) and epileptic encephalopathy (10; 2 infantile spasms). Five were on monotherapy and 23 on polytherapy. Most were refractory (mean of 6 failed treatments). Fourteen (54%) children had a favorable outcome (>50% reduction) with 3 seizure free. Medication was discontinued in 8 children (4, inefficacy; 4, adverse effects). *Conclusions:* Zonisamide was well-tolerated with a favorable outcome was seen in 54%. Strategies which allow the Canadian marketing of medication such as Zonisamide which benefit only a small group of patients are needed.

P-067

***In vitro* hippocampal electrophysiology and pharmacology following *in vivo* treatment with AY-9944 during rat development.**

MA Cortez (Toronto), C Wu (Toronto), L Zhang (Toronto), OC Snead III (Toronto)*

Background: Atypical absence seizures arise from cortex, thalamus and hippocampus. We sought to further characterize the population synaptic activities (PSA) of the AY-9944 (AY) rat hippocampus. *Methods:* Thick hippocampal slices (1mm) from AY rats after separating dentate gyrus from CA3/CA1 area along hippocampal fissure, which preserve a relatively large hippocampal network than conventional slices (±0.5 mm in thickness), were maintained in a fast-perfusion chamber at 32^{o} C and monitored via extracellular recordings. *Results:* Spontaneous rhythmic PSA were observed from thick AY-hippocampal slices (N= 6 AY rats; 3-6 slices per rat). They exhibited stable synaptic field potentials following electrical stimulation of CA3 or CA1 afferents. Their waveforms and amplitudes were similar to control conventional slices of naïve rat hippocampus. Spontaneous rhythmic field potentials with frequencies of 1-3 Hz and variable amplitudes and durations were found in a majority of thick AY-slices examined. These rhythmic field potentials appeared to be of CA3 origin and then propagated to the CA1 area. They were reversibly abolished by perfusion of slices with the AMPA glutamate receptor antagonist CNQX (5 μM) or the GABA-B receptor agonist baclofen (0.5-1 μM). *Conclusions:* Data suggest that generation of these spontaneous rhythmic field potentials is dependent upon AMPA glutamatergic drive and possibly under the inhibitory control by GABA-B receptors. It remains to be determined whether or how these *in vitro* spontaneous field rhythms are related to *in vivo* EEG activities seen in AY rat hippocampus.

P-068

Development of a valid questionnaire for family history of febrile seizures

KE Gordon (Halifax), JM Dooley (Halifax), EP Wood (Halifax)*

Objective: To develop a brief, self-administered questionnaire to derive accurate quantitative information about 1st degree and 2nd degree family history for febrile seizures. *Methods:* Our question was based on Veritys Has your child ever suffered from seizures, convulsions, or any episode during which he/she became unconscious or abnormal movements occurred in any part of the body? Positive answers were probed for the presence of fever. This was iterated to provide the number of individuals with febrile seizures and the total number of relatives for 1st degree and 2nd degree relatives. The questionnaire was validated against an interview with a pediatric neurologist including pedigree development (N=84), and 4-6 week test-retest reliability (N=73). *Results:* Validity data demonstrated weighted Kappas of 0.71 (SE: 0.11) and 0.49 (SE 0.11) for counts of 1st and 2nd degree relatives with febrile seizures, and 0.83 (SE 0.07) and 0.85 (SE 0.06) for counts of the number of 1st and 2nd degree relatives respectively. Reliability data produced Kappas of 0.81 (SE: 0.10) and 0.66 (SE 0.09) for counts of 1st and 2nd degree relatives with febrile seizures, and 0.96 (SE 0.08) and 0.74 (SE 0.07) for counts of the number of 1st and 2nd degree relatives respectively. *Conclusions:* Our questionnaire is fast, accurate and reliable in providing qualitative family history data.

P-069

Oxcarbazepine: a clinical audit in three Canadian adult epilepsy clinics

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Background: Oxcarbazepine (OXC, Trileptal®), was released in Canada for the treatment of epilepsy in June, 2002. We have analysed all cases started on OXC from epilepsy clinics in Ottawa (N=45), Calgary (N=25) and Toronto (N=18) prior to November, 2003. *Methods:* Retention, duration of treatment, reasons for discontinuation, titration schedules and maintenance doses, concurrent therapy and response were analyzed. *Results:* Thirty-five males and 53 females, mean age 36.1 years, 87/88 with partial epilepsy, were treated: 40 monotherapy and 48 polytherapy. Continuing patients were followed for a mean of 8.5 mo (43/54 greater than or equal to 6 mo) and received a mean maintenance OXC dose of 1185 mg/day (monotherapy) and 1140 mg/day (polytherapy). All but 5 patients were titrated at less than 150mg increase every 5 days. OXC was discontinued in 34/88 (38.7%), largely due to dose-related side effects and rash in 3 patients. Discontinuations occurred in 11/40 monotherapy vs 23/48 polytherapy cases; 7/16 monotherapy cases where OXC was substituted for carbamazepine (CBZ) vs 1/12 where OXC was started *de novo*; 10/14 polytherapy cases where OXC was added to a regimen with CBZ vs 7/12 without CBZ. Efficacy was judged as good or better in 32/66 cases. *Conclusions:* Oxcarbazepine is well-tolerated in clinical use, especially in monotherapy and without concurrent carbamazepine. Discontinuations were largely due to dose-related side effects.

P-070

Utility of high field intraoperative MR imaging in the surgical treatment of children with refractory epilepsy

W Hader (Calgary), ST Myles (Calgary)*

Background: Complete resection, of a variety of pathologies responsible for intractable epilepsy, is a major factor in predicting seizure outcome after epilepsy surgery. We evaluate our experience with the surgical treatment of epilepsy in the setting of a mobile high field intraoperative MR imaging. *Methods and Results:* A total of 14 patients were identified. Patients had refractory seizures for 4 months to 15 years and the age at operation ranged from 6 months

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to 18 years. Eleven patients underwent lesionectomies, 4 in the frontal lobe, 5 in the temporal lobe, 3 parietal and 2 occipital. Two patients underwent a selective amygdalo-hippocampectomy and one a complete corpus callosotomy. Complete resections were completed in thirteen and a complete disconnection in one. Pathology included 5 patients with malformations of cortical development, 3 with gangliogliomas, one pleomorphic xanthoastrocytoma, one DNET and 2 low grade oligodendrogliomas. Eleven patients (Engel Class I, 78%) were seizure free at latest follow-up, two had occasional seizures (Engel Class II, 14%) and in one the seizure frequency was unchanged (Engel Class IV, 7%). Complications included an increase in hemiparesis in two. *Conclusions:* High field intraoperative MR imaging is a useful adjunct for the surgical treatment of refractory epilepsy in children to facilitate resections of lesions, selective mesial temporal lobe structures and confirm successful disconnection. Intraoperative MR imaging allows the best chance of complete resection and ensures the highest likelihood of favourable seizure outcome

P-071

The significance of positive temporal (PTS) and central sharp waves (PCS) in neonatal EEG – preliminary results

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Background: The significance of positive temporal (PTS) and central sharp waves (PCS) in neonatal EEG has remained unclear. PTS and PCS have been associated with a nonspecific injury to deep white matter. PTS has been associated with intracerebral hemorrhage in one study but not in another study. *Aim:* To identify the significance of PTS and PCS. *Method:* We reviewed retrospective 228 EEGs of 164 neonates, done between April 2002 to September 2003. PCS and PTS were reported in 184 EEGs of 144 neonates. Seven neonates were excluded as they did not have imaging done. We correlated the presence of PCS and PTS in the EEGs of a random sample of 53 neonates with neuroimaging data (US, CT or/and MRI). *Results:* The number of sharp waves varied from many (16%), some (40%) to few (40%). Normal imaging was found in 31% of neonates; ischaemic pathology was found in 31% and hemorrhagic pathology was found in 35% of neonates. The number and location of sharp waves did not correlated to a specific pathology. *Conclusions:* Positive central and temporal sharp waves are reported frequently in neonatal EEGs and signify nonspecific brain damage.

P-072

Epilepsy and Crohn's disease: searching for a genetic link

MS Hussain (Edmonton), SN Ahmed (Edmonton)*

Background: Seizures are described in Crohn's disease. The etiology of these seizures is unclear but is thought to be related to inflammatory or hypercoagulable mechanisms. We have found a group of such patients without significant abnormalities on imaging, raising the possibility of a genetic link. A genetic etiology has been described in Crohn's disease, specifically in relation to IBD 1 (NOD2) gene. Many genetic defects have also been found to increase susceptibility to seizures. We explored these cases to find support for a possible genetic link between seizures and Crohn's disease. *Methods:* Case series/literature review. *Case description:* The case presentations of 4 patients are described. Each patient has a history of seizures and Crohn's disease. The patients family histories are explored. All of our patients have positive family histories of either seizures or Crohn's disease. Two of the patients have family histories both of seizures and Crohn's disease. *Conclusions:* Genetic associations have been described for both seizures and Crohn's disease. Coexistence of two genetically transmitted diseases, such as Crohn's disease and epilepsy, can help in chromosomal and genetic localization. Our case series raises the possibility of this association and can serve as a nidus for future research.

P-073

Asymptomatic ictal bradycardia

M Ijaz (Edmonton), SN Ahmed (Edmonton)*

Background: Cardiac arrhythmias have been explored as a possible etiology for sudden unexpected death in epilepsy patients (SUDEP). Although ictal bradycardia in symptomatic patients has previously been described, asymptomatic ictal bradycardia has not been well-studied. We sought to identify asymptomatic patients with significant bradycardia in our telemetry patient population. *Methods:* We retrospectively reviewed 65 seizures in 25 consecutive patients admitted for EEG telemetry monitoring. There were 9 males and 16 females. Ages ranged from 19 to 62. There was no previous history of cardiovascular disorders. There were 11 seizures with frontal onset, 48 with temporal onset, 3 with parietal occipital onset and 3 that were non localized. *Results:* Fourteen patients had no ECG changes during seizures, with heart rate between 50 and 100, 44 patients had ictal tachycardia (102 to 168 beats per minute) and one patient demonstrated asymptomatic ictal bradycardia during three out of six seizures requiring a cardiac pacemaker (heart rate 15 to 30 beats per minute). *Conclusions:* Asymptomatic cardiac bradycardia is a rare entity but could be a possible explanation for SUDEP. It may be crucial to identify such patients and offer prophylactic management, such as a cardiac pacemaker.

P-074

Gating effects of mutations in the Cav3.2 T-type calcium channel associated with childhood absence epilepsy

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Childhood Absence Epilepsy (CAE) is a type of generalized epilepsy observed in 2-10% of epileptic children. No structural neuropathological findings are associated with CAE and 16-45% of patients have genetically identified positive family histories. In a recent study by Chen et al, (Ann Neurol 2003;54:239-243) 12 missense mutations were identified in highly conserved regions of the CACNA1H (Cav3.2) gene in 14 of 118 patients with CAE, but not in 230 control individuals. In the present study we have functionally characterized five of these mutations using the rat Cav3.2 T-type channel homologue and whole-cell patch clamp recordings in transfected HEK293 cells. Two of the mutations mediated a ~10mV hyperpolarizing shift in the half-activation potential of the channel. A third mutation caused a ~50% slowing of inactivation relative to control and shifted half-inactivation potential

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~10 mV towards more depolarized potentials. Mean time to peak current (at IV peak) was significantly altered for this mutation, but was unchanged for all others. No resolvable changes in the parameters of the IV relation or current kinetics were observed with the remaining mutations. Furthermore, no statistically significant alteration of the time-constant of recovery from inactivation was detected for any mutation relative to wild-type. Our study is first to report the functional consequences of mutations in a T-type calcium channel associated with CAE. The findings suggest that several of the Cav3.2 mutants allow for greater calcium influx during physiological activation.

P-075

A multiresolution transform for the analysis of time-frequency changes in normal and epileptic EEG

H Khosravani (Calgary), R Pinnegar (Calgary), B Goodyear (Calgary), J Mitchell (Calgary), P Federico (Calgary)*

Background: Visualization of time-frequency changes in EEG has traditionally been visualized using Fourier-based techniques (i.e. short time Fourier transform, STFT). This approach is limited given its fixed-length analysis window and the nonstationary nature of EEG signals. The S transform is a Fourier-based multi-resolution transform that has a variable length analysis window, thus circumventing the shortcomings of the STFT. In the present study, we introduce a novel application of the S transform for visualization of normal and epileptiform EEG phenomena. *Methods:* Selected recordings from five normal subjects and five patients with either focal or generalized epileptiform discharges were used. We identified a single channel that had a clear example of an electrographic feature of interest (e.g. alpha, mu, sleep spindles, eye blink, spike and wave, sharp wave) and applied the S transform to it. *Results:* The S transform provided clear visualization of the frequency components, in time, of the electrographic events. Some of the spectral attributes of these events were not immediately apparent on conventional review of the EEG. *Conclusions:* The application of the S transform to EEG is novel and can potentially be a useful tool for visualizing clinically relevant features in EEG.

P-076

Characterization of high frequency oscillations in an *in vitro* recurrent spontaneous model of seizures

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Background: The presence and role of high frequency oscillations (80-500Hz) in neuronal processing has been the focus of increasing attention. High frequency oscillations (HFOs) have been previously described in hippocampal, parahippocampal, entorhinal, and the neocortex of normal rats during anesthesia, behavioural immobility, and sleep/waking states. They have also been observed, *in vivo*, in several models of epilepsy. HFOs have been recorded in hippocampus and entorhinal cortex of epileptic patients preceding the onset of seizures. In the present study, we used time-frequency analysis of field potentials to characterize HFOs during the transition to seizure-like activity in an *in vitro* recurrent spontaneous model of seizures. *Methods:* Field recordings were obtained from the CA1 layer of horizontal rat brain slices (n=6, 5-8 seizures from each slice). For recording, slices were superfused in artificial cerebrospinal fluid with low [Mg^{2+}], resulting in recurrent spontaneous seizure-like events separated by epochs of interictal activity. Recordings were filtered at 625Hz and digitally acquired at 2KHz. The S transform (a multiresolution Fourier-based technique) was used to quantify the time-frequency evolution from interictal to seizure-like states. *Results:* Oscillations in ripple frequencies (100-200Hz) were observed 5-10s immediately before the start of each seizure-like event. The initial 20s of each seizure event was typified by a marked increase in HFOs (150-300Hz) without change in lower frequencies (0-100Hz). For each successive spontaneous episode, differences in duration and spectral power were observed, with a tendency of increased power for HFOs. *Conclusions:* High frequency oscillations were observed during the transition from interictal activity to seizure-like events in a low [Mg^{2+}] recurrent seizure model. High frequencies were most prominent in the few seconds just preceding the seizure with spectral power changing dynamically from one seizure to the next.

P-077

"Familial rectal pain" mimicking epilepsy

H Kolski (Edmonton), E Harris (Edmonton)*

Background: Familial rectal pain is a rare disorder presenting in the first year of life and is often misdiagnosed as epilepsy. *Methods:* Case report. *Results:* We describe a 11-month-old neurodevelopmentally normal female presenting with episodic tonic contractions of the body since 2 months of age. These were precipitated by bowel movements and diaper changes. In conjunction, the child would stare and variable erythema would develop in either the right or left lower extremities, extending into the perineal area. These were nonstereotypic and she seemed variably responsive. There were no consistent postictal features. They generally lasted approximately 10 seconds, up to a maximum of one minute, and would recur 1-3 times/month. These events did not respond to the administration of phenobarbital though dissipated with aggressive treatment of constipation. Between episodes, the patient behaved appropriately. There was no family history of similar events or seizures. Neurological examination was normal. Several interictal EEGs and prolonged telemetry were unremarkable. *Conclusions:* We aim to increase awareness of (familial) rectal pain, which may be an elusive diagnosis. Asymmetrical flushing of the lower extremities appears to be a hallmark sign. This condition may be more common than the literature suggests.

P-078

Diffuse hemispheric disease: EEG findings pre- and post-hemispheric surgery

B Landesman (Vancouver), S Smith (Vancouver), M Connolly (Vancouver)*

Objective: To describe the EEG findings pre -and post-hemispheric surgery in a cohort of children with epilepsy. *Methods:* Retrospective review of the electroclinical data. *Results:* The study population comprised 24 children: cortical dysplasia (7), infarction (7), Sturge-Weber syndrome (6) and Rasmussen's encephalitis (4). Peri-insular hemispherotomy was performed in 18, hemidecortication in 5 and anatomic hemispherectomy in 1. 83% are seizure free

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at mean follow-up of 6 years. Before surgery in 7 children with infantile spasms the EEG showed hemihypsarrhythmia, the remainder had focal seizures with/without secondary generalization. Multifocal delta and spikes in the affected hemisphere occurred in all with cortical dysplasia, infarction and Rasmussen's encephalitis. Independent epileptiform discharges were seen in the contralateral hemisphere in 7 patients. In all with Sturge-Weber syndrome, there was generalized suppression of EEG activity in the affected hemisphere with spikes in one. Following anatomic hemispherectomy and hemidecortication, there was suppression of EEG activity on the operated hemisphere. Following peri-insular hemispherotomy, the EEG demonstrated electrical seizures in 7. *Conclusions:* Hemihypsarrhythmia is common in EEGs with cortical dysplasia and infarction and suppression of EEG activity is characteristic of Sturge-Weber syndrome. In those with good recovery electrical seizures are common in EEGs following peri-insular hemispherotomy as epileptogenic cortex remains.

P-079

Landau-Kleffner syndrome (LKS): the EEG evolution

B Landesman (Vancouver), L Langill (Vancouver), M Connolly (Vancouver)*

Objective: To describe the video-EEG data in 2 children with LKS who went into remission. *Methods:* Retrospective review of medical and video-EEG records. *Results:* Patient #1, a 6-year-old boy presented with a 6 week history of acquired auditory agnosia and no clinical seizures. The EEG in sleep demonstrated bilateral temporal frontal central sharp and slow wave activity L>R. Prednisone resulted in recovery of the agnosia. The EEG was normal 9 months following diagnosis. He had 23 EEGs in total, and bilateral temporal central spike dipoles were the most frequent finding. At follow-up, 7.5 years following onset, he remains in remission and the EEG is normal. Patient #2, a developmentally normal 7.5-year-old girl presented with a 19 month history of language regression, auditory agnosia and no clinical seizures. The sleep EEG showed bilateral central-temporal spikes. She was treated with prednisone and the EEG, 2 months following diagnosis showed right temporal delta and bifrontal central spikes in sleep. There was minimal change in the agnosia. Sulthiame was added and resulted in a dramatic improvement. The EEG, one year following diagnosis shows no epileptiform activity. *Conclusions:* The EEG evolution in LKS is variable but bilateral temporal central spike dipoles are common.

P-080

Neuropsychological outcome after temporal resection.

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Background: There have been a number of reports describing the neuropsychological outcome after temporal resection for epilepsy. There is significant variability in the cognitive outcome following right and left sided temporal resections. In this retrospective cohort we have compared the neuropsychological outcome for patients who underwent right or left temporal resections. *Methods:* We have retrospectively reviewed a cohort of 38 patients following temporal lobe resections for epilepsy at the University of Alberta in Edmonton from 1990 to 2001. We compare patients after right or left sided resections. Neuropsychological assessments were completed preoperatively and at one year postoperatively. *Results:* Of the 38 patients who underwent surgery, 23 had right temporal resections (RTR) and 15 had left temporal resections (LTR). Overall, most patients showed improved cognitive function after both right and left sided resections. Of the 23 patients who had RTRs, 16 (69.5%) had improved PIQ (mean improvement 8.75) postoperatively, while four (17.3%) declined (mean decline 13.25). Of the 15 patients who had LTRs, nine (60%) had improved VIQ (mean improvement 8.0) and five (33.3 %) declined (mean decline 7.4). Although the results have been variable some patients following RTRs had VIQ declines postoperatively while patients with LTRs had PIQ declines postoperatively. *Conclusions:* Following temporal resections for epilepsy, most patients demonstrate improved cognitive function postoperatively. The cognitive morbidity is higher for left sided resections than for right sided resections.

P-081

Elevated GABAlevels measured by MRS in children with temporal lobe epilepsy

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Background: Epilepsy is due to an imbalance between excitation/inhibition. Loss of GABAergic inhibition or increased excitatory transmission are considered to contribute to epileptogenesis. The goal of this study is to measure GABA levels in children with newly diagnosed versus refractory temporal lobe epilepsy (TLE). *Methods:* Proton magnetic resonance spectroscopy (MRS) was performed on seven children. All newly diagnosed children (n=3) were on carbamazepine, while others (n=4) had failed multiple drugs. MRS voxels located over the hippocampi were studied to compare normal versus epileptic hippocampus. *Results:* Diagnosis was made at the mean age of six years (range: 8 months - 10 years). Ipsilaterally to the epileptic focus, all patients showed higher GABA levels with a mean of +65.1 % (range: 5.2 to 158.3 %). NAAlevels were lower in the four patients with refractory TLE (mean: -16.5 %; range: 1.7 to 33.3 %) but not in newly diagnosed children. *Conclusions:* Spectroscopic hippocampal GABA levels in TLE are elevated ipsilateral to the seizure focus early on and remain elevated. This could represent a compensatory response to seizures but could also contribute to the increased synchronization of principal cells. Further studies are required to better characterize the role of GABAin epileptogenesis.

P-082

Evaluation of an epilepsy education program for grade 5 students in Ontario: preliminary results

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Background: Increasing awareness and decreasing stigma about epilepsy are priorities of the WHO and the Canadian Epilepsy Alliance. There are no published studies on healthy children's

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knowledge or attitudes towards epilepsy or evaluating epilepsy education in Canada; worldwide there has been one evaluation of an epilepsy education program for children. Objective of this study was to evaluate an epilepsy education program designed for grade five students to improve their knowledge and attitudes about epilepsy. *Methods:* A stratified cluster randomized controlled trial was conducted with 20 schools from 2 SW Ontario school boards randomized to either the intervention (education) arm or delayed intervention control arm. Analyses were conducted using linear regression adjusted for clustering. *Results:* Pilot study results indicated that the evaluation questionnaire has acceptable test-retest reliability (ICCs in acceptable range at > 0.70); internal consistency reliability (Cronbachs alpha in recommended range; 0.69 for knowledge, 0.76 for attitudes, after removal of one item from questionnaire); as well as convergent and divergent validity. Results of the full trial of 20 schools (1200 students), will be presented with a comparison of epilepsy knowledge and attitudes before and after the intervention. *Conclusions:* Implications of this intervention trials findings for educational programming will be discussed.

P-083

Sensitivity and specificity of outpatient investigations for surgical decisions in patients with temporal lobe epilepsy

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Background: Ictal video-EEG telemetry (VET) remains the gold-standard in determining seizure localization and resectability, however, in well-selected patients, VETmay prove the obvious. Few studies have investigated how well outpatient investigations (MRI, EEG, neuropsychological tests) predict VET findings in temporal lobe epilepsy (TLE) patients. Using these outpatient investigations, we explored whether clinicians can predict VET findings and surgical decision in TLE patients. *Methods:* We reviewed 63 records of surgically treated patients with TLE and mesial temporal sclerosis (MTS). Three blinded epileptologists determined epileptogenic side and whether each patient should undergo a temporal lobectomy. A blinded neuroradiologist reviewed patient MRIs to determine MTS side and confidence of assessment. Sensitivity and specificity of the epileptologists decision was calculated, using VET as the gold-standard. *Results:* The neuroradiologist correctly predicted MTS side in 45 patients, with a definite or probable recommendation for surgery from an epileptologist. The epileptologists sensitivity and specificity for predicting side of TLE was 97% and 33%, respectively. *Conclusions:* Clinicians can predict side of TLE and surgical decision accurately (no errors) based on outpatient investigations. Epileptologists rarely made an incorrect recommendation for surgery, but erred on the side of caution by not identifying patients who might have been treated surgically.

P-084

Prolonged sensory "auras" in focal epilepsy

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Background: Continuous symptoms lasting hours or days prior to a seizure are well-recognized. This report describes persistence of such symptoms for years. *Methods:* Records were reviewed from selected patients who had surgery for intractable focal epilepsy. *Results:* Five patients age 21 to 61 years had continuous symptoms of two to nine years duration which were the same as but less intense than the aura experienced before a complex partial seizure – foul taste, nose pain, tingling in toe, epigastric sensation (two cases). Scalp and subdural recorded EEG telemetry showed no correlation of the ongoing symptoms with ictal activity. The symptoms were abolished by temporal lobectomy in three patients, started after temporal lobectomy in one patient and began after frontal lobectomy in another only to resolve three years later following a second operation. Pathology was mesial temporal sclerosis (n=3), cortical dysplasia (n=1) and low grade glioma (n=1). *Conclusions:* Continuous symptoms of prolonged duration in epilepsy suggest a permanent alteration in neuronal function and blur the line between ictal and interictal activity. Whether this represents a type of simple partial status epilepticus, a sensory form of epilepsia partialis continua or some other distinct pathophysiology remains to be determined.

P-085

Value of magnetoencephalography in the presurgical evaluation of intractable epilepsy in children with tuberous sclerosis

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Background: Seizures are very common among individuals with tuberous sclerosis complex (TSC) and are often medically intractable. Epileptogenic lesions of tuberous sclerosis are the result of a complex developmental disorder of neuronal migration and include cortical and subcortical tubers and areas of cortical dysplasia. As most patients with TSC have multiple potentially epileptogenic tubers, epilepsy surgery is often discouraged. *Methods:* Seven children with TSC (ages 4-6 years) underwent phase one evaluation, including scalp video-EEG monitoring, MRI and magnetoencephalography (MEG). *Results:* Ictal EEG was able to localize a principal epileptogenic tuber/region (ET/R) in five patients. MRI in all children revealed multiple tubers. The ET/R corresponded to a large discrete tuber on MRI in three patients. MEG detected multiple scattered spikes in all patients but a spike cluster was identified in two patients and corresponded to the ET/R in one patient. *Conclusions:* Ictal scalp EEG was able to localize a potential ET/R in five children with tuberous sclerosis. MEG detected multiple spikes in all patients mostly without showing a predominant ET/R that can be correlated to ictal scalp EEG focus. This can be explained by the ability of MEG to detect multiple spike sources in multiple areas of aberrant cortical development.

P-086

Magnetic resonance imaging evidence of the progressive nature of mesial temporal sclerosis in children with temporal lobe epilepsy

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Background: Whether mesial temporal sclerosis (MTS) is a cause or a consequence of seizures has long been debated. Experimental models show that prolonged seizures lead to MTS and this has also been reported in humans. *Objective:* To illustrate that

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MTS can appear over time in children with recurrent complex partial seizures (CPS) but no history of status epilepticus or complex febrile seizures. *Methods:* We reviewed charts and MRI results of children with symptomatic partial epilepsy referred to our comprehensive epilepsy clinic between 1994 and 2003. *Results:* Five patients with an initially normal MRI went on to demonstrate MTS. Mean delay for MTS to appear was 4 years, 4 months (range 2 years, 4 months to 8 years). Mean age of onset of CPS was 1 year, 10 months (range 2 months to 9 years). Mean seizure frequency was 180 annually (range 1 to 365). Three patients underwent temporal lobectomy for refractory seizures, which confirmed the diagnosis. *Conclusions:* These children illustrate that MTS can follow recurrent CPS, at least in a subgroup of patients. This reinforces the need for an early referral of children with refractory temporal lobe epilepsy to a specialized epilepsy centre.

P-087

Virtual intracranial epileptiform discharges of MEG using synthetic aperture magnetometry

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Purpose: Synthetic Aperture Magnetometry (SAM) is a spatial filtering technique for MEG data, using a minimum-variance beamformer. SAM can estimate the time-course of source activity from any specified location (SAM virtual sensors; SAM-VS) as if intracranial electrode was recording cortical activity. We compared the epileptiform discharges on SAM-VS with those on intracranial EEG. *Methods:* We studied 11 children who underwent long-term intracranial EEG and surgical excision for neocortical epilepsy. Their preoperative MEG was analyzed retrospectively, using SAM software (CTF Systems Inc.). Virtual sensors were computed for locations corresponding to the subdural grid electrodes. We reviewed the topographic distribution and morphological features of epileptiform discharges on SAM-VS and intracranial EEG. *Results:* The distributions of predominant epileptiform discharges on the SAM-VS correlated with those on intracranial EEG in all patients. The main features of epileptiform discharges on both SAM-VS and intracranial EEG were comparable, consisting of single discharges in 5 patients, polyspikes in 1 patient, trains of rhythmic discharges in 2 patients, or multiple independent discharges in 3 patients. SAM-VS showed prominent epileptiform discharges in deep fissures or sulci in 3 patients. *Conclusions:* The spatial distribution and morphology of epileptiform discharges on SAM-VS are comparable to those on intracranial EEG.

P-088

Withdrawn

P-089

Withdrawn

P-090

Refractory saccadic epileptic nystagmus: electroclinical, neuroimaging and neuropathological correlation

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Background: Epileptic nystagmus (EN) is an uncommon sign usually due to symptomatic focal epilepsy characterized by repetitive and rapid saccades in association with epileptic discharges. We describe the clinical, video-EEG telemetry, neuroimaging, pathological and neurosurgical outcome in a patient with occipital refractory saccadic epileptic nystagmus. *Methods and Results:* This 21-year-old right-hand dominant female had eye symptoms since age 5 years described as gradual build up increasing horizontal oscillopsia and blurred vision lasting up to 1 minute, averaging 8-10/day, with no aura, no LOC and no motor manifestations. The past history was unremarkable and family history negative for seizures. Goldman visual fields and tangent screen perimetry confirmed left homonymous inferior quadrantic scotoma. Seizures were refractory to all anticonvulsants. On EEG telemetry 5 simple partial seizures were recorded with horizontal left beating nystagmus. The EEG onset was 15-12 Hz recruiting rhythm maximum at O2-T6, lasting 45-50 secs. MRI showed (R) occipital focal cortical dysplasia (FCD) and on PET there was hypoperfusion. Lesionectomy was completed in the intraoperative MRI. Histo-pathology showed FCD without balloon cells. After surgery the visual field deficit extended into the superior quadrant of the left hemifield. At 18 months post surgery the patient was seizure free on no AEDs. *Conclusions:* Refractory saccadic EN is uncommon and rarely reported in the literature. The congruence of clinical, electrophysiological, neuroimaging and pathological confirmation is rarely documented. EN as an expression of focal seizures is more likely to be symptomatic and therefore a search for identifiable etiology should be vigorously pursued.

P-091

Neither patient population nor severity of intervention substantially influence threshold for worthwhile change in epilepsy patients

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Background: Clinicians must determine if therapy effects a meaningful impact on patients HRQOL. The MIC (minimum clinically important change) provides an anchor to determine if a change in score on an HRQOLinstrument is meaningful. This study examined if patient population and treatment type influences the MIC. *Methods:* Three cohorts were studied: (1) Outpatients who failed no more than 2 antiepileptic drugs (AEDs), contemplating change in drug therapy, (2) Outpatients who failed 3 or more AEDs, contemplating change in drug therapy, (3) Inpatients contemplating epilepsy surgery. A questionnaire that structured responses using a Likert scale ranging from 1 (=almost the same) to 7 (=very great deal of improvement) assessed MIC in three domains. Overall MIC is the mean of responses for all domains. *Results:* Cohort 1 (n=36, mean age 35.4 years, 61.1% female), Cohort 2 (n=37, mean age 32.1 years, 51.4% female) and Cohort 3 (n=56, mean age 35.8 years, 46.2% female) specified similar overall MICs. Overall MIC for all patients was 3.54 (95%CI:3.27, 3.81). Seizures impairing awareness was an inverse predictor of MIC {R-square=0.208, beta (95%CI):-0.768 (-1.40, -0.132) }. *Conclusions:* All cohorts specified similar MICs (~3.3-3.8 on 7-pt scale=Somewhat Better-Moderately Better). This MIC estimate, therefore, is invariant across a heterogeneous patient population and treatment type, a characteristic necessary for it to be useful clinically. This study overcomes limitations present in previous studies that used MIC for measuring worthwhile change.

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P-092

Post ictal psychosis or limbic seizures?A case report

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Background: Post-ictal psychosis (PIP) includes pleomorphic psychotic phenomena following bouts of complex partial seizures. This entity has been very rarely described in pediatric literature. *Methods and Results:* We report a case of PIP in a 12-year-old boy with fetal alcohol syndrome presenting with status epilepticus. His seizures were complex partial in nature associated with sensory aura in the tongue followed by right facial twitching with secondary generalization. His seizures responded to conventional status epilepticus treatment but this was followed by a significant deterioration in behavior and frank psychosis. He experienced visual hallucinations, grandiose and religious delusions. There were intermittent periods of agitation and violent behavior with interspersed lucid intervals. Initial lumbar puncture was suggestive of an underlying viral encephalitic process. Frequent EEGs showed right hemisphere slowing as well as intermittent temporo occipital sharp waves. Video EEG monitoring helped to delineate psychotic behavior from epileptic events. Treatment with anti-epileptic medications and atypical antipsychotics helped in significant improvement of symptoms. *Conclusions:* Although a rare clinical entity, prompt recognition of PIPby pediatric neurologists may have major diagnostic and therapeutic implications. Literature review of post-ictal psychosis will be presented.

P-093

Prednisone treatment in Landau-Kleffner syndrome (LKS): Short-term neuropsychological outcome

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Background: Corticosteroids have gained some acceptance as the treatment of choice for LKS based on case studies. These studies indicate normalization of epileptiform activity and variable resolution of language and behavioral disturbance. This variability of neuropsychological outcome reflects variable diagnostic criteria for LKS and lack of systematic testing. Results of neuropsychological testing are therefore presented for a subset of children with "pure" LKS. *Methods:* Four children, 6 to 11 years, with LKS according to strict diagnostic criteria (normal intelligence, language regression, epileptiform activity) were among 11 children with language regression who received prednisone, 1 mg/kg/day for 6 months. Neuropsychological assessments were done before and after treatment and included tests of intelligence, language, attention, memory, and behavior *Results:* Treatment effects were evaluated by repeated measures analysis of variance (ANOVA) done on standard scores from the WISC, Child Behavior Checklist, and other tests. Resultsshowed significant gains for all children for attention (.0001) and behavior (.01) and selective language improvement for two. *Conclusions:* Corticosteroid treatment for LKS results in prominent improvement in attention and behavior in addition to normalization of EEG. Mechanism of this effect may differ from the mechanism of language improvement, which varied among children.

P-094

Assessment of education program for women with epilepsy

J Soderstrom (Edmonton), DW Gross (Edmonton), SN Ahmed (Edmonton)*

Background: There is a need to provide epileptic women education on the effects epilepsy and medications may have on menstruation, pregnancy, and bone density, as well as the effects of hormonal fluctuations on seizure control. *Methods:* An education program was developed on women's health issues and administered to women in either didactic lecture or one-to-one session. Effectiveness was determined by comparing pre-test levels of knowledge with the post-test levels. *Results:* Didactic lecture was provided to 73 people; 20 completed the pre- and post-test. Duration of the disease was 1-50 years; mean years-with-epilepsy was 27.6 Mean score pretest 5.78. Mean score post-test 7.84. One-on-one education was provided to 4 people, all completing the pre- and post-tests. Duration of disease was 9-37 years; mean years-with-epilepsy was 23.25 years. Mean score pretest 4.75. Mean score post test 6.5. *Discussion:* Basic knowledge of women's health issues was low considering the duration of the disease. This emphasizes the need for education programs. Program effectiveness was slightly higher in the didactic setting, but subjects comfort level and ability to ask questions unabated also needs to be considered when developing an educational program.

P-095

Focal surgical resection for intractable epilepsy in double cortex syndrome results in a good outcome

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Background: Surgical results in a series of patients with double cortex syndrome (subcortical band heterotopia) have been reported. (Bernasconi et al. Epilepsia 2001). In this series patients who had focal resective surgery had poor postoperative outcomes. *Methods:* We report a patient with subcortical band heterotopia who underwent right anterior temporal lobectomy with a good postoperative outcome. *Results:* This 33-year-old woman had weekly seizures despite trials of six anti-epileptic drugs. Long-term video EEG demonstrated seizures with right frontal temporal buildup of rhythmic activity at onset and right temporal interictal epileptic discharges. MRI was originally read as normal though in retrospect it demonstrates typical features of a bilateral band heterotopia. In follow-up immediately after a right anterior temporal lobectomy in 1998, she was dramatically improved with only occasional brief episodes of hand numbness and no other seizures. Five years after surgery, she was having nocturnal complex partial seizures confined to the week prior to menstruation. *Conclusions:* In contrast to the conclusion by Bernasconi et al that focal surgical resection yields inadequate results in double cortex syndrome, our patient demonstrates a worthwhile improvement in seizure control five years postoperatively. Subcortical band heterotopia should not preclude consideration of surgical removal of epileptogenic tissue.

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P-096

Microdysgenesis in two patients with nonlesional, intractable, extra-temporal partial complex seizures

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Background: Microdysgenesis is an abnormality consisting of aberrant cortical and subcortical cytoarchitecture. Its relevance in epileptogenesis has been controversial. *Methods:* Case reviews. *Results:* Case 1. This 20-month-old boy presented with right eye twitching. Past medical history and physical examination were unremarkable. Appropriate developmental milestones were reached. Radiological and functional imaging was nonrevealing. Electrographic studies showed an epileptic focus in the left central region. Despite maximal medical therapy, the patient had speech regression and experienced 30-50 seizures daily. A central corticectomy of the face area and subpial transection of the hand region were performed. Examination of the resected tissue revealed microdysgenesis. Postoperatively, the seizure frequency had reduced substantially and the patient regained his developmental milestones. Case 2. This 25-month-old boy presented with episodes of staring and left sided lip twitching. Past medical history and physical examination were unremarkable; appropriate developmental milestones were reached. Radiological and functional imaging was noncontributory. Electrographic studies showed an epileptic focus in the right fronto-central region. This patient developed language regression and experienced greater than 50 seizures daily despite maximal medical therapy. Corticectomy of the pre-post central gyri of the face area with subpial transection was performed. Examination of the resected tissue revealed microdysgenesis. Postoperatively, the patient remains seizure free and has regained his developmental milestones. *Conclusions:* Microdysgenesis may underlie the epileptogenic focus in nonlesional, extra-temporal epilepsy. Resection of affected tissue may offer a more definitive treatment of these seizure disorders.

P-097

Systematic review of incidence and risk factors in sudden unexpected death in epilepsy

J Tellez-Zentano (London), S Wiebe (London), D Diosy (London)*

Introduction: The mortality of individuals with epilepsy is 2-3 times that of the general population. This is attributable both to the underlying disease and to epilepsy itself. Sudden unexpected death (SUDEP), an important epilepsy-related cause of death, has recently aroused great interest. *Objective:* To systematically review the evidence for the incidence and risk factors of SUDEP. *Methods:* Data sources. An expert in library resources and electronic databases searched electronic sources such as Medline, Index Medicus, and Cochrane database. We also searched bibliographies or pertinent review and original articles, book chapters and expert consultation. *Study selection:* Two reviewers independently applied the following inclusion criteria: articles with >5 patients with SUDEPwithout age limit, case-controls or cohort and population based studies. We excluded duplicate publications. The methodological quality of individual studies was assessed following established principles for epidemiological research. *Data extraction:* Two investigators independently extracted data, with disagreements resolved through discussion. *Results:* The definition of SUDEPvaried among studies. Of 399 initial articles, 120 potentially eligible studies were reviewed in full text, and 41 met the inclusion criteria. Nineteen studies provided data to evaluate incidence of SUDEP, 11 studies assessed risk factors, and 11 studies were case series reports without controls. The controls in all studies were different: in some cases they were deaths not attributed to SUDEPbut in other studies they were living patients. There was substantial variability in study populations. The annual incidence of SUDEP ranged from 1:200 to 1:3000, with a median of 1:500. Incidence was higher in epilepsy populations studies (1:200 to 1:1000) than in those from the general population (1:300 to 1:3000). Risk factors associated with SUDEP were male gender, frequent seizures, tonic clonic seizures, idiopathic generalized epilepsy, use of 33 antiepileptic drugs (AEDs), frequent AED changes, subtherapeutic AED levels, childhood onset epilepsy, concurrent use of neuroleptics or anxiolytics, and low IQ. *Conclusions:* Not all epilepsy patients have the same risk of SUDEP. Although common themes emerge in incidence and risk factors for SUDEP, there is substantial variability. This can be explained by differences in methodology and study populations. For example, SUDEP was more frequent in epilepsy clinics or surgery programs than in coroners reports, which could be explained because patients with more intractable and more severe epilepsy may have a higher risk of SUDEP. Many studies failed to satisfy minimum methodological criteria. In order to have a better understanding of SUDEP, and to identify patients at risk, it is necessary to create a consensus for case definition, definition of controls, and research methodology.

P-098

Systematic review of the long term results in epilepsy surgery

S Wiebe (London), J Tellez-Zenteno (London), R Dhar (London)*

Introduction: Although excellent short-term results of resective epilepsy surgery have been established, less is known about long term outcomes. It is important to perform a systematic review and meta-analysis of the evidence on this topic. *Objective:* To provide evidence-based estimates of long-term results of epilepsy surgery. *Methods:* Data source. An expert in library resources and electronic databases searched electronic sources such as Medline, Index Medicus, and Cochrane database. We also searched bibliographies of pertinent reviews and original articles, book chapters and expert consultation. *Study selection:* Two reviewers independently applied the following inclusion criteria: studies published since 1991 with more than 20 patients undergoing resective or nonresective epilepsy surgery; outcomes reported after a mean/median follow-up of 5 years. We considered all outcomes in children and adults. We used seizure freedom as defined by authors. *Data extraction:* Two investigators independently extracted data, resolving disagreements through discussion. *Results:* Of 914 available articles, 103 potentially eligible were reviewed in full text. Forty-seven studies fulfilled eligibility criteria. Twenty-six (55%) studies were in adults, five studies in children (11%), and 16 studies in adults and children (34%). Forty-five studies were in resective surgery (96%) and two studies (4%) in nonresective surgery. Twenty-six (58%) studies of resective surgery involved the temporal lobe, 4 the frontal lobe (9%), one the occipital lobe (2%), two were on hemispherectomy (4%), and 12 studies involved mixed localizations (27%). Of nonresective

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surgery studies one looked at multiple subpial transection (MST) and one at callosotomy. Long-term seizure freedom occurred in 30% patients with callosotomy and 10% with MST. In resective surgery, the median proportions with long-term seizure freedom were 62 (range 26-83) in temporal lobe resections, 38 (range 33-54) with frontal lobe resections, and 46 with occipital lobe resections. Finally in the studies with mixed localizations the median was 58 (range 10-75). Sources of heterogeneity and nonseizure outcomes were analysed. *Conclusions:* There are few controlled studies, and few look specifically at prognostic variables. There is substantial variation in outcome definition and methodology among studies. However, after adjusting for sources of heterogeneity some studies yield similar results. The long-term seizure free rate was high and sustained for some types of resective surgery. It was better in studies of temporal lobe epilepsy as compared to those of frontal, occipital and combined resections. In temporal lobe resection, the long-term outcomes were similar to those reported in short-term outcome studies. As expected, long term outcomes were better with resective than with nonresective surgery. Well-designed, long-term controlled studies assessing prognostic variables are needed.

P-099

Postictal rage and aggression: a video-EEG study.

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Background: Postictal rage and aggression have been described but have rarely been documented by EEG-video recording. *Methods:* We studied a patient with dramatic postictal rage and violence. *Results:* A 34-year-old mentally retarded man had a lifelong history of seizures. He developed increasing episodic rage and aggression during the last two years. His caregivers were afraid of him although there was no record of directed violence. In one of these episodes he fractured his tibia and fibula. Seizures started with restlessness, involuntary movements of the lower extremities, elevation of the right arm and lip smacking, followed by secondary generalization. The onset could not be clearly identified. During attacks there was fast activity from the left fronto-central region. Interictally bilateral epileptogenic abnormalities were recorded from both temporal areas independently. Immediately after cessation of the ictal discharge he became greatly agitated with undirected aggression, screaming loudly, kicking and fighting the restraints. A videoclip will illustrate the behavior. Imaging studies showed bilateral periventricular nodular heterotopia in the lateral aspect of both temporal horns, the trigone on the left, and in a series of contiguous nodules over the right trigone. A search for filamin mutations is underway. *Conclusions:* This patient with severe retardation and intractable seizures showed increasingly frequent and severe bursts of rage and aggression proven to be postictal. Documented attacks occurred while he was restrained and this may have been a factor in their severity. Such attacks, however, have been described while he was not restrained and these increased in severity and frequency. Developmental abnormalities with periventricular nodular heterotopia in the region of the trigones but also in inferomesial temporal areas are considered to be causally related to his retardation and epilepsy. To clarify complex clinical pictures intensive monitoring and high quality imaging are mandatory.

P-100

Focal inhibitory seizures

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Background: Negative phenomena are occasional manifestations of seizure activity. Examples of negative seizure phenomena include speech arrest, aphasia, amaurosis, amnesia, numbness, deafness, neglect and atonic seizures. Less commonly described in the literature are focal inhibitory motor seizures. *Methods:* Two patients presenting with rapidly progressive, prolonged hemiparesis, sensory neglect and hemi-visual field obscuration are described. *Results:* Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain did not reveal progression of known structural lesions or new lesions. The superficial cortex of the hemisphere contralateral to the hemiparesis and sensory neglect enhanced diffusely with gadolinium on T1-weighted MRI images. Electroencephalography (EEG) demonstrated background slow-wave activity and single photon emission computed tomography (SPECT) revealed hyperperfusion in the hemisphere contralateral to the hemiparesis and sensory neglect. The changes seen on MRI and SPECT resolved with resolution of the symptoms. *Conclusions:* Taken together with the clinical history, the results from these investigations suggest prolonged focal inhibitory seizure as the underlying etiology. A review of the literature and investigations helpful in making this difficult diagnosis will be provided.

P-047

Waiting for Keppra: the impact of a new antiepileptic drug (levetiracetam) in a tertiary care adult epilepsy outpatient clinic.

S Rahey (Halifax), R M Sadler (Halifax)*

Purpose: To review local experience with levetiracetam (lev). *Methods:* Retrospective chart review. Patient inclusion criteria: (a) treatment with lev in 2003 with minimum 3 month follow-up; (b) treatment less than 3 months if lev was discontinued. Patient data obtained from clinic charts and telephone follow-up. *Results:* 50 patients started lev in 2003; 27 met inclusion criteria. Among these 27 patients, mean age equals 36 years (range 23-45), duration of epilepsy equals 28 years (range 17-45), concurrent AEDs equals 2.3 (range 1-3), previous number of AEDs equals 7 (range 4-16), and 12 patients had previous epilepsy surgery and/or a vagal nerve stimulator. Of 22 patients with partial onset epilepsy, only 2 patients had a greater than 50 percent seizure reduction; an additional 2 patients had complete control of secondarily generalized tonic-clonic (GTC) seizures. Among 5 patients with primary generalized epilepsy, 2 were seizure free and 1 was free of myoclonus but not GTCs. 5 patients discontinued lev (1 with increased seizures, 3 with behavioural problems, and 1 because of a sore throat). *Conclusions:* Although well-tolerated, lev provided little benefit in this therapy resistant epilepsy population with the notable exception of 3 patients with primary generalized epilepsy. Additional patients and follow-up will be presented.

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Movement Disorders

P-101

Benefit of vestibular rehabilitation therapy in Parkinson's disease

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Objective: To examine the effectiveness of vestibular rehabilitation therapy (VRT) program on quantitative and clinical measures of postural stability in Parkinson's disease (PD) patients. The relationship between these measures and the fall history was also examined. *Design:* Cohort repeated measures clinical trial *Subjects:* 13 subjects (mean age 64 ± 12 SD; 4 females and 9 males) with idiopathic PD (Modified Hoehn-Yahr stage 2-3 ON stage medication) were recruited for the study. Intervention: 12-week, 3 times/week physiotherapist supervised VRT program designed specifically for PD patients. The program consisted of exercises designed to induce vestibular habituation and challenge postural stability reflexes. *Outcome Measurements:* The equilibrium composite score from the Equitest® protocol of computerized dynamic posturography (NeuroCom International) was the primary outcome measurement. Functional Reach Test (FRT), Berg balance scale (BBS), Activities-specific balance confidence (ABC) scale, and subjective impressions questionnaire were secondary measurements. *Results:* There was a statistically significant improvement in the equilibrium composite score (p-value 0.04). FRT distance showed a significant clinical increase. Improvements were also found in the ABC scale and the subjective impressions questionnaire. There was no detectable change in the BBS. *Conclusions:* VRT appears to independently improve postural stability in PD patients with mild to moderate severity disease. The Equitest® protocol and the FRT measurements were found to be useful clinical tools in the serial evaluation of postural stability in this PD population.

P-102

Valproic acid induced hypertonicity

A Attar (London), B Young (London)*

Background: Valproic acid (VA) has a wide range of known adverse effects. Most patients with VA overdose recover completely, but some are left with significant morbidities. Fatalities have been reported. *Methods:* Case report of VA overdose in an adult patient. *Results:* We report a 53-year-old, female patient with VA and ramipril overdose. She presented with reduced level of awareness and hypotension. In addition to other expected/known features of VA overdose; she developed persistent, transient spasticity, in all four extremities, lasting 12 days. Other signs of upper motor neuron (UMN) dysfunction were also present. No significant MRI abnormalities of the brain and cervical spine were noted. EEG showed suppression in the posterior head and no epileptiform abnormalities. She was treated with continuous veno-venous hemodialysis (CVVHD). The toxic levels of VA normalized gradually. Complete resolution of most of her symptoms occurred in two weeks, including all the UMN signs. Past history was significant for bipolar disorder, hypertension and previous suicidal attempts. *Conclusions:* Our patient represents the first reported case of VA induced hypertonicity. The mechanism by which hypertonicity occurred is unknown, but an imbalance between the inhibitory and excitatory inputs might be the cause of the paradoxical excitation.

P-103

Lamotrigine induced hypertonicity: a case report

A Attar (London), B Young (London)*

Background: Lamotrigine (LTG) is one of the newer antiepileptic drugs (AEDs). Although, LTG has a wide range of known adverse effects, data about its overdose are limited. This is true for both adults and children. *Methods:* Case report of LTG overdose in an adult patient. *Results:* We report a previously healthy, 46-year- old, male patient with LTG overdose. The estimated LTG ingested was 6000 mg. The patient became unresponsive and developed prolonged, convulsive, generalized tonic-clonic (GTC) seizures. The status epilepticus (SE) was difficult to abort. In addition to other expected features of LTG overdose he developed persistent, transient spasticity and other signs of upper motor neuron dysfunction, in the absence of any neuroimaging abnormalities. Continuous EEG showed evidence of diffuse encephalopathy. He was treated conservatively and remained in the intensive care unit (ICU) for five days before he was discharged home. *Conclusions:* Our patient represents the first reported case of LTG overdose in adults that lead to SE and hypertonicity. The mechanism by which hypertonicity occurred is unknown, but an imbalance between the inhibitory and excitatory inputs might be the cause of the paradoxical excitation.

P-104

Post streptococcal encephalitis lethargica in a teenager: a potentially treatable condition.

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Background: The spectrum of post streptococcal neurological complications includes Sydenhams chorea and autoimmune neuropsychiatric disorders. Recent evidence suggests that this list should also include encephalitis lethargica. In the light of this evidence, we present a novel approach to the immunologic management of post streptococcal encephalitis lethargica. *Case report:* A 17-year-old girl presented with neuropsychiatric deterioration, a progressive movement disorder (chorea and dystonia), mutism, dysphagia, sleep disturbance (daytime somnolence and nocturnal insomnia), autonomic dysfunction (labile blood pressure, urinary retention), hyperpyrexia, and muscle rigidity with marked elevation in creatinine kinase. A diagnosis of encephalitis lethargica was made. *Investigation and management:* Brain magnetic resonance imaging was normal. Cerebrospinal fluid analysis was normal apart from a marked lymphocytic pleocytosis. Serum antistreptolysin O and antibasal ganglia antibody titers were elevated. Influenza serology was negative. Treatment with intravenous immunoglobulin (2g per kg over 5 days) and methylprednisolone (1g per dose for 3 days) resulted in a marked improvement. *Conclusions:* This case indicates the need to consider encephalitis lethargica as a potentially treatable immunologic complication of group A streptococcal infection.

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P-105

Deep brain stimulation in early idiopathic torsion dystonia

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Background: Primary idiopathic torsion dystonia (ITD) is a neurodegenerative disorder, with a genetic basis. The central features are posture-assuming features or directional quality and patterned predictable involvement of a specific set of muscles. Deep brain stimulation (DBS) is widely used to manage dystonia, however, there is little data regarding its efficacy in early onset dystonia. We report the early clinical course of our first ITD patient to receive microelectrode implantation for DBS. *Methods:* A 13-year-old girl presented with a progressive idiopathic torsion dystonia, which seemed to be progressing relatively quickly. She is severely disabled and is intellectually very bright. Her disability has a severe impact on her quality of life, and because she had less mobility, her pain increased and she now has problems eating, because of the position of her head and body. She underwent a bilateral implantation of internal globus pallidus (GPi) DBS electrodes. At the time of writing, she is a year postoperative. *Results:* She has had an excellent response to the DBS. She is able to engage in home, is able to stand unassisted for up to 30 minutes at a time. No back pain. She is now independent for most activities of daily living including feeding, dressing, transferring and school activities in a way that she has not been able to do for several years. *Conclusions:* DBS of the internal globus pallidus has been reported to be safer and effective and offers the advantage of reversing both modulating pulses and procedure. It is necessary to study a larger number of patients with long-term follow-up to draw conclusions.

P-106

Infantile hypertonia: a novel presentation of rippling muscle disease

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Background: Rippling muscle disease (RMD, OMIM #606072) is an autosomal dominant disorder that was initially described in 1975 by Torbergson. Patients typically report symptoms of muscle stiffness, cramping and/or rippling after passive stretch, beginning in the late teens or early adulthood. Recent publications describe a childhood onset characterized by toe-walking and mild delay of motor milestones. There are no published reports of affected infants. *Results:* We report two cousins whose fathers are affected with RMD. They presented with infantile hypertonia which was significant enough to prompt neurologic consultation in one child and orthopedic consultation in the other. No specific cause for the increased tone was found and in both children it had resolved by age one. Their subsequent neurologic and cognitive development has been normal. The elder, now nine years, has a muscular phenotype, but no other features of RMD. *Conclusions:* Since these children are otherwise normal, we postulate that the most likely reason for their transient neonatal hypertonia is that they are affected with RMD, which is not yet clinically apparent. This manifestation of RMD has not previously been described. Proof of our hypothesis awaits molecular confirmation of the diagnosis or their development of the clinical features of RMD.

P-107

Withdrawn.

P-108

Deep brain stimulation in Huntington's Disease

M Hebb (Halifax*), *R Garcia (Halifax*), *P Gaudet (Halifax*), *R Hill (Halifax*), *I Mendez (Halifax*)

Background: Huntington's disease (HD) is one of several neurodegenerative disorders of related pathogenesis and is marked by progressive motor and cognitive decline, as well as psychiatric afflictions. Many patients suffer from disabling chorea that is refractory to current medical therapy. Deep brain stimulation (DBS) is widely used to manage the motor symptoms of Parkinson's disease, dystonia and other related movement disorders, however, there is little data regarding its efficacy in HD. We report the early clinical course of our first HD patient to receive microelectrode implantation for DBS. *Methods:* A 41-year-old male patient with genetically confirmed HD and severely disabling chorea had been followed for several years prior to neurosurgical consultation. Preoperative neuropsychiatric evaluation and disease assessments were obtained using the Unified Huntingtons Disease Rating Scale (UHDRS). In July 2003, microelectrodes were implanted bilaterally into the internal segment of the globus pallidus for management of motor symptomatology. At the time of writing, he is 6 months postoperative and has been evaluated at regular intervals for disease progression and symptom control. *Results:* Bilateral pallidal stimulation produced a dramatic and sustained reduction in choreiform activity and improvement of UHDRS scores. The patient also reported a marked increase in energy level and quality of daily living and family interactions. *Conclusions:* This is a case report where DBS in the internal segment of the globus pallidus was effective in attenuating the chorea produced by HD. Although this is an early clinical experience, the beneficial results merit further studies on the mechanism of action and optimal sites of microelectrode stimulation for control of chorea in HD.

P-109

Increased N-myristoyltransferase activity in cardiac muscle of rotenone rat model of Parkinson's disease

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Background: Rotenone is a systemic mitochondrial complex I inhibitor. Continuous infusion leads to clinical features and pathological changes of parkinsonism (PS) in rats. We have observed cardiac toxicity in the form of myocarditis and myocardial necrosis in some rotenone treated rats. N-myristoyltransferase (NMT) is an ubiquitous enzyme and part of the process causing apoptosis. We have examined NMT activity in cardiac muscle of rotenone treated rats. *Methods:* Male Lewis rats were given a continuous subcutaneous infusion of rotenone (9 rats) or vehicle placebo (3 rats). All rats were euthanized at 56 days. The heart was immediately removed, cleaned, and homogenized. The NMT assay was performed on the cardiac muscle supernatant. *Results:* PS features of variable severity were observed in all rotenone rats and

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none of the controls. NMT activity (unit/mg protein) was not significantly different between controls (mean 0.779, sd 0.0846) and treated rats with minimal PS (mean 0.853, sd 0.192). Treated rats with severe PS had significantly higher NMTactivity (mean 1.27, sd 0.0945) ($p < 0.01$). *Conclusions:* Rats with the most severe PS features had significantly increased levels of NMT activity suggesting that NMT may play a role in rotenone treated rat model of Parkinson's disease.

P-110

Withdrawn.

P-111

Referral patterns for movement disorder DBS surgery: are all the right patients having surgery?

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Background: Deep brain stimulation (DBS) is an excellent therapy for selected patients with tremor, Parkinson's disease and dystonia when medical management fails. Yet only a small proportion of patients are referred and of this group, not all proceed to surgery. We sought to determine (i) why patients referred for surgery do not undergo the procedure and (ii) whether those referred are representative of the movement disorder population. *Methods:* We compared demographic information of patients referred to the Surgery Program at the Calgary Movement Disorders Clinic between January 2001 and December 2003, to the existing database of 1694 Parkinson's, tremor and dystonia patients. We then categorized why patients did not proceed to the operating theatre, whether it was for medical reasons (neurologic, psychiatric, cognitive) or personal choice. *Results:* Of the 82 patients referred for DBS surgery, significantly more were male (N=57, 70%) than expected when compared to the total movement disorder population (52%, Z=3.042, P=0.002). Two-thirds of the patients (N=48) have not had surgery due to medical reasons, including cognitive decline (24%), psychiatric concerns (5%) and neurological reasons (37%) such as misdiagnosis or inadequate trials of medication. Of the males referred, 52% were denied surgery for medical reasons, as compared to 67% of females. *Conclusions:* A smaller proportion of females with movement disorders are being referred for DBS surgery than expected and among those referred, most do not have surgery, primarily for medical reasons. This may be due to neurologists not discussing surgical options with females earlier in the course of their disease or females refusing to consider surgery until more severely affected. We propose that education of both physicians and patients (and perhaps different strategies to approach females regarding surgery) may allow more patients to benefit from this treatment.

P-112

Long term follow-up after pallidotomy

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Background: Pallidotomy has been performed in Parkinson's disease (PD) patients for many years. However, little information on long-term effects is available. *Objective:* To assess long term outcome in PD after pallidotomy *Methods:* Retrospective analysis on data collected on PD patients undergoing pallidotomy in the Movement Disorder Program in Calgary, since onset of program in 1997 until December 2003. Data was collected using the CAPIT protocol. *Results:* A total of 23 PD patients underwent a successful pallidotomy; mean age was 64.73 (± 8). Four died from unrelated causes or were lost to follow-up. Eight required further surgery, either contralateral pallidal DBS and/or STN DBS. In all patients, dyskinesia scores showed a significant reduction contralateral to surgery which persisted throughout follow-up. In 11 patients with no further surgery, 3 are now in nursing homes, 2 died, and 6 are living independently. Following data is presented on 7 patients with full data set. UPDRS III ON: Pre-op: 15 (±8), 1 year: 18 (±6), 2 years: 22 (±10), 3 years: 26 (±9), 4 years: 31 (±8). N.S. UPDRS III OFF: Pre-op: 36 (±14), 1 year: 28 (±7), 2 years: 35 (±12), 3 years: 38 (±13), 4 years: 39 (±9). N.S. Dyskinesias: Pre-op: 4 (±2), 4 years: 0.6 (±1). Pvalue is < 0.0005. *Conclusions:* 1. Pallidotomy results in permanent decrease of dyskinesias. 2. Initial improvement seen in motor symptoms is transient. 3. 42.11% of patients require further surgery within 2 years. 4. Most patients become increasingly disabled due to progression of Parkinson's symptoms, requiring surgery and/or increasing care requirements.

NEURO-ONCOLOGY

P-113

Mesencephalic arachnoid cysts mimicking low-grade neoplasia: case report and review of the literature

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This presentation will describe a patient with progressive symptoms referable to the brainstem. Imaging revealed a non-enhancing, multi-cystic lesion in the midbrain. The case represented a diagnostic dilemma and went on to open biopsy which revealed equivocal evidence of low-grade neoplasia. However, a review of the literature revealed identical cases sporadically reported. Our case represents only the second recorded case with pathologic confirmation of the nature of these cystic lesions. The pathophysiology has been described as enlarged arachnoid spaces within the midbrain without underlying neoplastic involvement. Although a rare phenomenon, its presentation can produce a diagnostic challenge, and unless recognized may lead to un-necessary surgical intervention and treatment. We will describe the case in detail and review the pertinent literature.

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P-114

"Permanent" global amnesia due to limbic encephalitis

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Background: Limbic encephalitis is one of the paraneoplastic neurological disorders whereby an autoimmune response is mounted against neuronal proteins. This remote effect of cancer is almost always associated with anti-neuronal antibodies and certain primary tumours. It is characterized by neurologic signs and symptoms including memory loss, personality changes, and depression. The following case represents another manifestation of the broad spectrum of clinical presentations of paraneoplastic disorders. *Methods:* Case report. *Results:* A 50-year-old First Nations male presented with acute onset of global amnesia. T2 and axial flair magnetic resonance images revealed bilateral hyperintensities in the amygdala and hippocampi which were typical for limbic encephalitis. Both serum and cerebrospinal fluid were tested for antibodies, and were positive for an unclassified neuronal autoantibody. The patient subsequently developed a cervical lymphadenopathy. The biopsy results were consistent with metastatic squamous cell carcinoma with an unknown primary. *Conclusions:* The case presented here is remarkable for the high degree of specificity of the paraneoplastic autoimmune attack on the patient's hippocampi, without more generalized multifocal evidence of paraneoplastic encephalomyelitis. The enduring nature of the memory deficit in the context of an unclassified neuronal autoantibody is also of interest.

P-115

Postoperative growth of residual nonfunctioning pituitary adenomas

D B Clarke (Halifax), L Clarke (Halifax), RO Holness (Halifax)*

Background: Little is known about the time to progression of postoperative residual nonfunctioning pituitary adenomas (NFPAs), information that is important in making treatment decisions. *Methods:* Our Brain Tumour database includes prospective data for all patients having undergone pituitary surgery. Patients with NFPAs whose first pituitary surgery was after January 2001 were identified. Patients with no evidence of postoperative progression, but with less than 12 months of follow-up, were excluded. Initial postoperative MRI imaging assessing residual adenoma was compared with subsequent serial imaging, using time to progression as the endpoint. *Results:* We identified 22 patients that met our study criteria: 17 males, 5 females; median age 58 yrs (range: 38-82 yrs). Pre-operative maximal cross-sectional tumor diameter was 26mm (range: 14-56mm). Ten patients (9 male, 1 female; median age 53 yrs) had adenomas that showed postoperative growth at 13 months (range: 5-31 months). The remaining 12 patients (8 male, 4 female; median age = 67 yrs) showed no evidence of tumor regrowth at 22 months. *Conclusions:* Management of patients surgically treated for NFPAs must include close follow-up with serial MRI imaging. Our study indicates that almost half of these patients will show tumor progression at 13 months.

P-116

The effect of slit/robo signaling on medulloblastoma invasion

R Del Maestro (Montreal), T Werbowetski (Montreal), R Bjerkvig (Bergen), Y Rao (St Louis)*

Background: Chemotropic cues such as the slit, netrin and semaphorin families guide the migration of neuronal and glial cell precursors during neural development. These repellent and attractant molecules have also been implicated in angiogenesis and leukocyte migration. It is not known if these molecules contribute to directing the invasion of brain tissue by medulloblastoma and glioma cells. *Methods:* Three-dimensional type I collagen co-culture assays, and modified assays to include sodium alginate bead microencapsulation and time-delayed culture were used to examine the effect of slit-1 on brain tumour cells. RT-PCR was used to examine robo receptor expression. *Results:* Medulloblastoma cells are inhibited, but not repelled, by a localized concentration of slit-1 after 1-6 days in collagen. Slit-1 had no effect on glioma cell invasion. Medulloblastoma cell lines also express the slit receptor robo, and both functional blocking antibody and dominant negative robo experiments demonstrate a 50% rescue of the invasive phenotype compared with slit treatment alone. Netrin-1 and SDF-1 had little or no effect on glioma and medulloblastoma invasion. *Conclusions:* Our findings indicate that the effect of slit-1 is not conserved for all types of brain tumours, and that manipulation of slit-robo signaling may serve as a potential treatment for medulloblastoma tumours.

P-117

Maelstrom in the brain: an interesting case of an intracranial dermoid in a young woman

C DeSilva (London), D Lee (London), LC Ang (London), S Stewart (London), D Macdonald (London), J Megyesi (London)*

Background: Intracranial dermoid tumors typically occur in the midline and rarely enhance with intravenous contrast. We present an interesting case of a large intracranial dermoid occurring in the sylvian fissure and exhibiting an unusual pattern of enhancement. *Clinical Presentation:* A 34-year-old female presented with a 14 month history of progressive seizure activity. Recently her seizures consisted of right hand numbness, speech arrest, jerking of the head to the right followed by secondary generalization. MR imaging revealed a 7.8 x 3.5 x 5.6 cm lesion involving the left frontal and temporal lobes at the level of sylvian fissure. The lesion was low intensity on T1 and high intensity on T2. With gadolinium it exhibited a linear enhancement in a whorl like pattern resembling that seen at the eye of a hurricane. *Intervention:* The lesion was resected. Pathological examination of the lesion revealed fragments of keratin and a few hair shafts. There were stretches of stratified squamous epithelium with underlying stroma containing hair follicles and sebaceous glands. Final diagnosis was a dermoid. *Conclusions:* An intracranial dermoid tumor should be considered in the differential diagnosis of atypically enhancing lesions in the sylvian fissure.

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P-118

Frozen section at the time of stereotactic brain biopsy: how accurate is it?

C DeSilva (London), A Kirkwood (London), R Hammond (London), J Megyesi (London)*

Background: The goal of this study was to determine the accuracy of frozen sections obtained at the time of stereotactic brain biopsy. *Methods:* The charts of 91 patients who underwent stereotactic brain biopsy at the London Health Sciences Centre between 1998 and 2002 were reviewed. The frozen section and final pathology reports were independently analyzed and compared by two of the authors (neither being neuropathologists). The final pathology report was deemed to represent the correct diagnosis. *Results:* Frozen section identified 84 patients as having tumorous lesions, of which 83 (99%) were confirmed. Frozen section identified 7 patients as having nontumorous lesions, all of which were confirmed (100%). Of the tumorous lesions, frozen section identified 70 cases of glioma, of which 65 (93%) were confirmed, and 14 cases of nonglioma, all of which were confirmed (100%). The accuracy of frozen section for specific diagnostic categories was: inflammatory lesions (100%), meningioma (100%), high-grade glioma (88%), lymphoproliferative disorder (86%), metastases (83%) and low-grade glioma (58%). *Conclusions:* Frozen section is excellent at differentiating a tumorous lesion from a nontumorous lesion. This information may help initiate a patients treatment planning. Frozen section is fairly good at differentiating glioma from nonglioma. However, a specific diagnosis, and definitive patient treatment, should await the final pathology report.

P-119

Stereotactic biopsy of intracranial lesions: correlation between neuroimaging and final pathology

C DeSilva (London), A Kirkwood (London), D Lee (London), R Hammond (London), J Megyesi (London)*

Background: The goal of this study was to determine how well the neuroimaging diagnosis correlates with the final pathological diagnosis on tissue obtained from stereotactic biopsies in patients with intracranial lesions. *Methods:* The charts of 81 patients who underwent stereotactic brain biopsy at the London Health Sciences Centre between 1998 and 2002 were reviewed. The neuroimaging reports (MRI and/or CT) and the final pathology reports were independently analyzed and compared by two of the authors (neither being a neuroradiologist or a neuropathologist). The final pathology report was deemed to represent the correct diagnosis. *Results:* Neuroimaging provided a single clear diagnosis for 28/81 patients (35%), an uncertain diagnosis (one diagnosis preferred, but others suggested) for 16/81 patients (19%), and was indeterminate (multiple diagnoses suggested) for 37/81 patients (46%). Overall, neuroimaging correctly identified the tissue diagnosis in 26/81 patients (32%). Final pathology confirmed 68% of single neuroimaging diagnoses (19/28) but only 44% of uncertain diagnoses (7/16). Moreover, the accuracy of neuroimaging depended on the specific diagnosis: a neuroimaging diagnosis of high-grade glioma was correct 86% of the time, a neuroimaging diagnosis of low-grade glioma was correct 80% of the time, and a neuroimaging diagnosis of metastases was correct 29% of the time. A specific neuroimaging diagnosis of glioblastoma multiforme was correct 100% of the time. *Conclusions:* In most situations a neuroimaging diagnosis should be confirmed by a tissue diagnosis.

P-120

Phase II trial of 131-iodine labeled murine antitenascin monoclonal antibody 81C6 (131I-m81C6) administered to deliver a targeted radiation boost dose of 44Gy to the resection cavity perimeter of patients with newly diagnosed malignant brain tumors: preliminary results

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Background: Our group has established the efficacy and tolerance of 131I-m81C6 when injected into the surgically created resection cavity (SCRC) of malignant brain tumors. Dosimetry analyses demonstrate that a 44 Gy boost dose by 131I-m81C6 achieved optimal tumor control while minimizing toxicity. The current phase II study will assess the efficacy of 131I-m81C6 administered to achieve a 44 Gy boost. *Methods:* Eligibility criteria: a histologically-proven, newly diagnosed, unifocal, supratentorial, malignant CNS tumor; immunoreactivity with 81C6; gross total resection; no communication between SCRC and CSF spaces; KPS greater than 60%; and adequate bone marrow, hepatic and renal function. A pre-treatment dosimetry study is performed to determine the dose needed to achieve a 44 Gy boost. *Results:* Seventeen patients have been treated (GBM, n=13; AA, n=4). Median age is 51 years (range, 24-70). The median 131I-m81C6 dose administered is 52 Gy (range, 25-92). Toxicity: grade 3 neutropenia (n=1), and grade 3 infection (n=2). With a median follow-up of 24.9 weeks, 14 patients remain alive. A 44 ±10% Gy boost has been successfully achieved in all patients. *Conclusions:* To date, this approach is feasible and associated with encouraging survival and limited toxicity. Accrual is ongoing, an updated analysis of outcome will be presented.

P-121

Inhibition of human glioma xenograft malignant phenotype by a small molecule transforming growth factor-beta-receptor antagonist, SB431542

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Background: In normal cells, transforming growth factor beta (TGF-beta) acts as a tumor suppressor through decreasing proliferation. In cancers, the growth inhibitory response to TGF-beta is commonly lost, and TGF-beta promotes increased invasion, angiogenesis, and immune escape. Malignant gliomas secrete TGF-beta ligands and express receptors suggesting the presence of autocrine or paracrine loops. Because of these important effects of TGF-beta, targeting the TGF-beta pathway may offer benefit in the treatment of malignant gliomas. SB431542 is a novel, small molecule ATP-mimetic inhibitor of the Type I TGF-beta-receptor in early preclinical development. *Methods:* We examined the effects of SB431542 on a panel of human malignant glioma cell lines with

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variable responses to exogenous TGF-beta. *Results:* SB431542 blocked the activation of intracellular mediators of TGF-beta and blocked TGF-beta-mediated transcription. The expression of downstream targets of TGF-beta that mediate TGF-beta effects, including plasminogen activator inhibitor-1, was markedly reduced both at basal levels and in response to exogenous TGF-beta. SB431542 moderately inhibited malignant glioma cellular proliferation at low concentrations and significantly inhibited proliferation (50-80%) at 10 m. Tumor cell motility was also reduced by SB431542 treatment. *Conclusions:* These results suggest that small molecule inhibition of TGF-beta receptors may offer a novel therapy for malignant gliomas.

P-122

Epidermoid tumor: rupture of cyst presenting as psychiatric symptoms

S Ebenezer (Saskatoon), K Meguro (Saskatoon), S Meguid (Saskatoon), M Kelly (Saskatoon)*

Background: We present a case of a ruptured epidermoid cyst, manifesting with psychosis and cysts formation. *Case:* A 64 yr female presented in May 2001, with hearing loss. An epidermoid tumor of the left CPA was partially resected. In July 2002, she presented with ataxia, and memory loss due to hydrocephalus. Symptoms were resolved by shunting. 5 months later, she presented with emotional instability and insomnia. In Jan 2003 she was certified for psychotic depression, and treated with psychotropics. She was also left hemiparetic. MRI showed diminished size of tumor, suggesting spilling of the contents. Cystic fluid accumulation was noted in the right frontal region. CSF showed pleocytosis and high protein count. Dexamethasone was then started. By April 2003 her weakness had resolved. LP showed a diminished cell count and protein level. By June 2003, she was off dexamethasone and psychotropics. *Discussion:* Rupture of epidermoid cysts presenting with psychiatric findings has not been reported. Aseptic meningitis and cyst formation resulted in psychosis and hemiparesis. We must beware of atypical presentations of ruptured epidermoid cysts. Dexamethasone alleviated the patients' symptoms although the efficacy of this regimen has not been established.

P-123

Non-neoplastic peripheral nerve tumours

J Golan (Montreal), L Jacques (Montreal)*

Background: The majority of peripheral nerve tumours are nerve sheath neoplasms. Some of these lesions are neuromas and are thus non-neoplastic. While most are traumatic neuromas, there are other rare lesions that can mimic a neoplastic mass. The spectrum of these lesions is divided into reactive, inflammatory, infectious, hyperplastic, and other lesions. *Methods:* All peripheral nerve lesions surgically treated at McGill from 1997-2003 were retrospectively reviewed to identify non-neoplastic peripheral nerve lesions. Their clinical features, radiology, surgical findings, pathology, and follow-up results were then examined. *Results:* Nine cases were found. The results identified one localized hypertrophic neuropathy of the infraorbital nerve, one leprosy neuropathy of the common peroneal nerve, two fibrolipomas of the brachial plexus and the posterior tibial nerve, two nerve cysts of the radial and common peroneal nerves, one neuritis ossificans of the brachial plexus, and two other lesions of the brachial plexus that were only identified as hypertrophic neuropathies. In all cases, the diagnosis of a neoplasm was suspected preoperatively. *Conclusions:* Non-neoplastic peripheral nerve tumours are very rare lesions. Their pathological diagnosis can be difficult. Surgery is reserved for symptomatic patients or in situations where the diagnosis is unclear. Awareness of a non-neoplastic possibility is important in limiting unnecessarily aggressive surgical dissection and possible nerve damage.

P-124

Cerebral aspergillosis secondary to septic emboli presenting with rapidly progressive nonspecific lesions on CT in a patient with mediastinal T cell lymphoma: case report

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Background: Cerebral aspergillosis is a devastating disease in immunocompromised patients. The clinical presentation is non-specific and it is difficult to diagnose by culture or serology. We present a case of rapidly progressive cerebral aspergillosis with an unusual cardioembolic presentation. *Methods:* A 16-year-old with mediastinal T cell lymphoma, responding poorly to chemotherapy, had persistent fever with neutropenia secondary to chemotherapy and was treated with antibiotics and antifungals for respiratory distress. He presented with progressive confusion, aphasia and right hemiparesis. *Results:* Over three days, multiple CTs of the head with contrast showed increasing number and size of nonspecific well-defined hypodense lesions without enhancement in the grey and white matter, basal ganglia, corpus callosum and cerebellum. A CT head 2 days prior was normal. He became comatose and died. The postmortem diagnosis was invasive aspergillosis. The presence of a fungal atrial thrombus along with the rapidly progressive cerebral lesions implied a cardioembolic source of the cerebral infarctions. Histopathology of the brain confirmed perivascular fungal infection corresponding to the CTlesions. *Conclusions:* Cerebral aspergillosis is a significant cause of mortality in immunocompromised patients. Due to the angioinvasive nature of aspergillosis, one must be aware of its myriad of manifestations including thromboembolic cerebral infarction.

P-125

Successful surgical intervention for a thoracic chordoma

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Background: Chordomas of thoracic spine are extremely rare. These are locally aggressive tumors centered on a vertebral body. Usually anterior tumors in the thoracic region are not amenable to posterior approach due to risk of spinal cord injury. We present a case where, an anterolateral chordoma was successfully removed via laminectomy. *Clinical Presentation:* A 74-year-old male who, over a year, developed complaints of numbness in the right lower extremity, difficulty with ambulation especially upon smooth floors and impaired balance. He had chronic low back pain, which remained unchanged in character. Examination was consistent with a Brown-Sequard syndrome with a right T8 sensory level. Romberg's sign was positive. Right planter was upgoing. Radiology revealed a destroyed T3 vertebral body, with a soft tissue tumor

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displacing the thecal sac to the right and extending into the left thoracic cavity. *Intervention:* Due to an acute neurological deterioration, the patient was urgently taken for surgery and a decompressive T3, T4 laminectomy performed. The tumor was easily removed, including the thoracic extension. *Conclusions:* Postoperatively, the patient's neurological exam remained unchanged. The final pathology was chordoma. In some cases of thoracic chordomas, resection of an anterior tumour by laminectomy, without worsening the patient's neurological status is feasible.

P-126

Significance of shift in language areas in patients with brain tumors

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Background: Tumors involving the language areas of the brain can alter language functions. Functional MRI (fMRI) reliably maps cortical activations during language tasks. We used fMRI to study the organization of the anatomic locations of language areas in patients with brain tumors and correlated them with formal language testing. *Methods:* Three right handed adult patients (average age= 53±22 years) with a primary brain tumor were studied. They all had language testing that included the Boston Naming Test and the Western Aphasia Battery. *Results:* Anterior language areas were only minimally shifted forward and superiorly in one patient with a slowly growing and longstanding tumor involving the left anterior temporal lobe. This patient was mildly impaired in her formal language testing. The anterior language areas were markedly shifted forward to homologous regions of both frontal lobes in the second patient with a large malignant astrocytoma who was most severely impaired in formal language testing. There was no shifting of the language areas in the third patient with malignant astrocytoma whose language impairment was intermediate. *Conclusions:* Reorganization of the language functions can occur in adult patients with brain tumor. Major anatomical shift in language areas seems to correlate with greater severity of aphasia on language testing.

P-127

Surgical outcome of medulloblastoma and the Collins Law violation

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Background: We encountered an adult patient with a recurrence of medulloblastoma that had been treated when he was a child. The purpose of this study was to determine incidence, survival rate, and prognostic factors as well as the frequency of Collins Law violators (CLVs) in an unselected population of medulloblastoma patients. *Methods:* Using the Alberta Cancer Registry and hospital sources, a population-based review identified 49 patients with medulloblastoma (1975-96). All patients had a surgical resection, followed by radiotherapy (n = 48) and chemotherapy (n = 16). *Results:* The 5-year survival rate was 41%. Tumor recurrences occurred on average within 4 years and mean survival time was 1.2 years. The extent of surgical resection was the only significant prognostic factor for survival (Long rank test, $p< 0.0294$). All developed recurrent tumors following prolonged periods of remission (mean was 15.3 years after diagnosis) and are designated as Collins Law Violators. These 3 patients represent 21.4% of children who were initially thought to be long-term survivors. *Conclusions:* The survival rate in an unselected population of patients with medulloblastoma is poor. Aggressive resection of the tumors significantly prolongs survival. The Collins Law violators were not uncommon and we suggest this concept be reconsidered.

P-128

Cervical vagal schwannoma: a case report and review of literature

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Background: Vagal schwannomas are rare, with 60 cases reported worldwide. These tumours usually present as asymptomatic, slowly growing neck masses. Other presentations include hoarseness, Horner's syndrome, recurrent respiratory tract infections and aspiration. Bradyarrthymia with cardiac asystole is a possible intraoperative complication. Postoperative complications include paresis of vocal cords with hoarseness, difficulty controlling voice pitch, swallowing difficulties and aspirations. We report a case of cervical vagal schwannoma. *Methods:* A 41-year-old, neurologically intact woman presented to the Hamilton Health Sciences Neurosurgical Service with a six-month history of progressive enlarging, asymptomatic right lateral cervical mass. MRI revealed a well-circumscribed 4.6 X 3.3 X 5.0 cm lesion in the right carotid space, without intracranial extension. CT-guided biopsy suggested schwannoma. Preoperative angiogram showed no vascularity but displacement of the internal carotid artery. Right neck dissection was performed with gross total resection of the tumour. No intraoperative complication was noted. *Results:* Postoperatively, the patient experienced hoarseness. Her swallowing difficulties resolved with training. Pathology revealed areas of Antoni types A and B cytoarchitecture and palisades of Verocay body formations, consistent with schwannoma. *Conclusions:* Although rare entities, vagal nerve sheath tumours should be suspected in patients with lateral cervical masses. The primary therapy for vagal schwannomas remains surgery, with gross total resection.

P-129

Metastatic breast carcinoma to intracranial meningioma

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Background: The incidence of meningioma in patients with breast cancer is higher than expected. *Methods:* A 75-year-old female who had previous removal of intracranial meningioma (1983 and 1987) and carcinoma of the breast in 1997, presented in 2003 with a short history of right hemiparesis and slurred speech. Enhanced dural based mass was removed from the left parietal region. Pathology confirmed transitional meningioma and a metastatic carcinoma. *Conclusions:* Additional cases from the literature are reviewed. Common features of both tumours are

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discussed.

P-130

Ruptured dermoid cyst of the fourth ventricle – case report and review of literature.

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Background: Intracranial dermoid cysts account for 0.04 to 1.5% of brain tumors. They occur most frequently along the midline and in the supratentorial region. The frequency of rupture at presentation remains unspecified. *Methods:* We report the case of a symptomatic ruptured dermoid cyst in the fourth ventricle and present a clarification of epidemiology, location, and clinical presentation of these tumors. *Results:* From published data, 161 cases of intradural dermoid cysts were gathered. The male:female ratio was 1:1.1. Patients were 30 years old or younger in 63.4%. However 26.1% were in their 4th or 5th decade. Although most frequent location was along the midline, a paramedian location was reported in 38.5%. Location of dermoid cyst was: posterior fossa (34.8%), intraparenchymal nonbasal (19.3%), sellar/parasellar (16.1%), frontotemporobasal (12.4%), intraventricular (9.9%), citernal (3.7%), nonspecified (3.7%). Dermoid cysts were ruptured at diagnosis in 42.5% of cases of which 60.5% reported abrupt symptomatology. Ruptured dermoid cyst were found especially in the sellar/parasellar region. *Conclusions:* A case of ruptured dermoid cyst of the fourth ventricle is reported. Literature review showed that dermoid cysts occur often after the third decade, their localisation is not infrequently lateralised and their presentation is often due to an abrupt rupture.

P-131

Radiation-induced meningiomas: Review of the University of British Columbia with cytogenetic analysis

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Meningiomas are well-known to be a common radiation-induced CNS neoplasia. Controversy exists regarding the cytogenetics and natural history of these lesions compared to spontaneously arising meningiomas. We review the experience at the University of British Columbia/Vancouver General Hospital including an analysis of the cytogenetic makeup of these lesions. A discussion is made regarding the natural history of radiation-induced meningiomas as well as theories on the genetic pathophysiology of these tumors. This has implications on both management decisions in terms of adjuvant therapy and follow-up imaging as well as the nature of tumorogenesis.

P-132

Cranial neuropathies following intracranial Photofrin-photodynamic therapy for malignant supratentorial gliomas – a report of 3 cases

P Muller (Toronto), A Varma (Toronto), B Wilson (Toronto)*

Background and objective: In a prospective trial of photo dynamic therapy in malignant gliomas, three patients developed cranial neuropathies following photo illumination. Cranial neuropathy following intracranial PDT for has not been reported previously. *Material and methods:* Eighty patients were recruited into the study at the Toronto site. These included 39, 25, 12 and 4 tumors in the frontal, temporal, parietal and occipital regions respectively. Eighteen of the 25 patients with temporal lobe tumors were randomized to received PDT. *Results:* Three of the 18 patients with temporal lobe tumors developed cranial neuropathies, following PDT. The floor of the middle fossa received photo illumination in all the 3 patients. This complication was not seen in any other patients with tumors in the frontal, parietal or occipital regions or patients with temporal lobe tumors who did not receive PDT. Two patients developed seventh nerve paresis, which resolved completely in one patient, and partially in the other. The third patient developed transient neuralgic pain in the trigeminal nerve distribution. *Conclusions:* Cranial neuropathies could be the result of photo illumination of fifth and seventh cranial nerves during PDT of the temporal fossa. We recommend shielding of the middle fossa floor during PDT.

P-133

Brain tumor resection completeness by fluorescence-guidance in a preclinical model using 5-aminolevulinic acid (ALA)

P Muller (Toronto), A Bogaards (Toronto), A Varma (Toronto), S Collens (Toronto), J Bilbao (Toronto), B Wilson (Toronto)*

Background: Fluorescence-guided brain tumor resection [FGR] may assist the neurosurgeon by visualizing tumor tissue which is difficult to identify with white light illumination. *Methods:* We compared the maximum degree of tumor resection, determined by histopathology, after white light resection using an operating microscope versus additional fluorescence-guided resection. An intracranial rabbit VX2 tumor and a co-axial fluorescence imaging and spectroscopy system, exciting and detecting PpIX fluorescence at 405 nm and 630nm respectively was used. *Results:* FGR in addition to white light resection [WLR] significantly increased tumor resection completeness with a factor 1.4 ± 0.8 from 68% ± 38% to 98% ± 3.5% (1-sample t-test, $p = 0.01$). Residual tumor in the whole brain significantly decreased with a factor 16 ± 34 from 32% ± 38% to 2.0% ± 3.5% (1-sample t-test, $p = 0.01$) of the total tumor volume. Interestingly, the large standard deviation in tumor resection completeness using WLR (68% ± 38%) was a factor 11 smaller after FGR (98% ± 3.5%), which suggests FGR not only improves tumor resection completeness, but also enables the neurosurgeon to achieve more consistent resections between cases. *Conclusions:* FGR is a promising adjunct to surgical care. Optimizing FGR by correlating histology with quantitative fluorescence imaging at different ALA doses and application times is planned.

P-134

Preclinical feasibility of metronomic photodynamic therapy using 5-aminolevulinic acid induced protoporphyrin IX in a rabbit brain tumor model

P Muller (Toronto), A Bogaards (Toronto), A Varma (Toronto), S Bisland (Toronto), L Lilge (Toronto), B Wilson (Toronto)*

Background: Both fluorescence-guided resection (FGR) and Photodynamic therapy (PDT) have been investigated as brain tumor

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treatments. Metronomic PDT (mPDT) consists of a continuous light illumination of photosensitized tissue and has been shown to induce apoptosis. We investigated the preclinical feasibility of FGR followed by mPDT in order to delay tumor re-growth and improve survival. *Methods:* 18 rabbits with VX2 tumors were divided in 3 groups, A: no FGR - no mPDT, B: FGR-no mPDT and C: FGR+mPDT. mPDT was delivered using intracranial LED implants and automatic timer switch and battery in a backpack. Animals were sacrificed upon first signs of neurological defect. HandE, Gram and TUNEL stains were performed on brain sections to investigate, tissue morphology, bacteriological infection and PDT-induced apoptosis, respectively. *Results:* A survival increase was found performing FGR vs. no surgery. As a result of mPDTtumor selective mPDT induced apoptosis was demonstrated, indicating the potential of this treatment strategy. No infectious complication accrued. *Conclusions:* These initial results indicate the technical and surgical feasibility of FGR followed by mPDT. Further investigation is required to find optimum mPDT parameters that may lead to sufficient tumor cell death and thus improved survival.

P-135

Adult brainstem tumors of the oligodendroglial lineage: report of two cases and review of the literature

C O'Kelly (Toronto), W Mason (Toronto), S Nag (Toronto), M Bernstein (Toronto)*

Adult brainstem gliomas are uncommon tumors comprising less than 2% of all gliomas. Few cases of anaplastic oligodendrogliomas confined to the brainstem have been reported. The authors present a 37-year-old female with an anaplastic brainstem oligoastrocytoma and a 46-year-old female with an anaplastic brainstem oligodendroglioma. The patients underwent sub-occipital craniotomy for debulking of the exophytic portion of the lesions. Adjunctive therapy included fractionated external beam radiation and chemotherapy. Only 14 cases of adult brainstem tumors of the oligodendroglial lineage were identified in the literature. The management of these unusual lesion must be extrapolated from the approach to supratentorial oligo lineage tumors and nonoligo brainstem gliomas.

P-136

Hyperglycemia induced hemichoreoathetosis and MRI T1 putamenal hyperintensity in a young woman with recent onset type 1 diabetes

P Picard (Ottawa), R Wee (Ottawa), A Guberman (Ottawa)*

Background: Hyperkinetic movement disorder in older patients with hyperglycemia, associated with high signal intensity in the contralateral putamen on T1-weighted magnetic resonance (MR) scans, is a recently-described rare syndrome. *Case report:* We present a 20-year-old woman, the youngest patient described to date with this disorder. Seven days after being diagnosed with type 1 diabetes, she developed sudden onset right sided hemi-choreoathetosis which followed a 3-week period of resolving mild right hemiparesis. In addition to T1 hyperintensity in the contralateral putamen, she showed a T2-weighted hypointensity, and a decreased choline/creatinine ratio on MR proton spectroscopy in the affected area. Furthermore, while the diffusion weighted sequences showed hypointensity in the putamen on the trace image, a computed tomography perfusion study was found to be normal. Four weeks after her glucose was controlled with insulin, the hemichorea persisted. Haloperidol substantially reduced the hyperkinetic movements within 1-2 week. *Conclusions:* It remains unclear why most patients improve following normalization of glucose levels while some do not. We hope that this report will draw the attention of neurologists to this syndrome, which can be a cause of acute-onset chorea in younger as well as older patients, and possibly shed further light in its pathophysiology.

P-137

Synchrotron-supported diffraction-enhanced imaging (DEI) in an animal model of glioblastoma multiforme: a feasibility study

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Background: Our experiments were designed to test the potential usefulness of synchrotron-based diffraction enhanced imaging (DEI) for precise volumetric determination of C6 glioma cell tumors in living animals. *Method:* Step 1: C6 glioma cells were cultured. Some of the cell cultures were exposed to colloidal gold in the growth medium for 16 hr, after which the medium was replaced with fresh, gold-free medium. Cells were harvested and counted at 24, 48 and 72 hr after medium replacement. Cell counts were compared with those of cultures not exposed to colloidal gold. Step 2: Gold-loaded cells were implanted in the frontal lobes of adult male Wistar rats. Animals were sacrificed 2 weeks after implantation. Imaging of the tumors was performed with 1.5 T MRI and synchrotron-supported diffraction enhanced imaging (DEI) techniques. *Results:* Colloidal gold was taken up by the C6 glioma cells. Exposure of C6 glioma cells to colloidal gold did not interfere with cell proliferation. Delineation of the tumor tissue appears to be better with MRI at the present developmental stage of DEI technique. However, slice thickness of 14 micrometer, compared to 1.5 mm with MRI, allows much more precise volumetric measurements with DEI. Supported by SSI.

P-138

Human central nervous system tissue culture: a historical review and examination of recent advances

K Walsh (London), J Megyesi (London), R Hammond (London)*

Tissue culture has played an invaluable role in medical research. From modest beginnings, the scientific community has contributed numerous protocols and materials leading to the current variety of culture systems. While nonhuman cultures have traditionally been more widely used, their relevance in the study of human-specific disease is limited. Consequently, interest in human CNS tissue culture accelerated in the middle of the last century and there is an ongoing effort to develop and optimize protocols. In this study, we survey the history of human CNS tissue culture summarizing the advances that have led to the current breadth of options available (with reference to influential advances in nonhuman culture work).

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Topics addressed include: culture initiation, maintenance and culture ware; media, supplements and substrates; sources and formats. The manner in which cells are introduced to culture and the culture ware implemented to maintain them have been influential in the development of culturing options and the optimization of culture survival and propagation. From the humble beginnings of frog lymph, culture media has been extensively studied and optimized for a wide variety of applications, including how it influences the composition of the resulting cell populations. Different types of human CNS tissue culturing methods (including organotypic, explant, dissociated, enriched and cell line or stem cell preparations) will be described, summarizing the development, advantages, and modern neurobiological applications of each. Recently, our lab has developed reliable protocols for fetal and adult human CNS tissue culture. These cultures are composed of neurons and astrocytes (mixed neuroglial culture) or astrocytes alone. The protocols have been implemented effectively in the study of certain human neurological disorders. These will be described.

P-139

Early recurrence of extra-axial pilocytic astrocytoma of the cerebellopontine angle after subtotal resection: a report of two cases

R Yong (Vancouver), R Akagami (Vancouver)*

Background: Gliomas are rare among extra-axial neoplasms of the cerebellopontine angle (CPA), which themselves account for only 10% of all intracranial tumours. Of the seven extra-axial gliomas of the CPA reported in the literature, only two were pilocytic astrocytomas. We describe two additional cases, both of which demonstrated recurrence shortly after subtotal resection. *Methods:* A 29-year-old woman with neurofibromatosis type 1 and a 39-year-old previously healthy woman were found to have large, enhancing, exophytic lesions of the CPA on MRI. Debulking was achieved using retrosigmoid craniotomy with electrophysiological monitoring. Gross total resection could not be obtained in either case due to cranial nerve dysfunction detected intraoperatively. *Results:* Microscopic examination of both excised tumours showed the typical appearance of pilocytic astrocytoma. Mitotic figures were observed in one of the cases. Both patients were found to have new enhancing tissue within their resection cavities, consistent with recurrence, at three-month follow-up imaging. The two patients were subsequently treated with radiation. *Conclusions:* These two cases lend support to the hypothesis that the cranial nerve root entry zone may be the site of origin of extra-axial CPA gliomas. The pilocytic astrocytomas we treated in this region behaved unusually aggressively.

P-140

The chemokine stromal cell derived factor1a (SDF-1alpha) upregulates MT2-MMP in human glioma cells

J Zhang (Calgary), VW Yong (Calgary)*

Background: Chemokines have been found to alter tumor growth and metastasis. We have previously described that a particular chemokine receptor, CXCR4, was predominantly expressed in various glioma cell lines and in resected glioblastoma specimen. Herein, we examined the roles of CXCR4 in gliomas. *Methods:* The only known ligand of CXCR4, stromal cell-derived factor-1 (SDF-1, CXCL12), was chosen to stimulate two CXCR4-bearing human glioma cell lines. Real time PCR, Western blot and Flow cytometry were used to detect mechanisms downstream of CXCR4 activation that may promote glioma tumorigenecity. *Results:* 100ng/ml SDF-1alpha increased the expression of transcript encoding membrane-tyme 2-matrix metalloproteinase (MT2-MMP) ($p<0.01$) in both cell lines. This was selective in that the expression level of MT1-, MT3- and MT5-MMP did not change in response to SDF-1alpha. Similarly, two growth factors of relevance to glioma cells, VEGF and HGF, did not vary when treated with SDF-1alpha. SDF-1alpha also upregulated the protein expression of MT2-MMP. SDF-1alpha stimulated cells migrated faster compared to controls. Current experiments using RNAi seek to define whether MT2-MMP is critical to glioma biology. *Conclusions:* MT2-MMP may be an important downstream factor of CXCR4 activation that contributes to glioma motility and invasion.

NEUROMUSCULAR

P-141

Generalized peripheral nerve conduction failure during spine surgery: a case report

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Background: Intraoperative nerve conduction block related to systemic changes has not been previously reported. *Methods:* Bilateral tibial and right median nerve somatosensory evoked potentials (SSEPs) were intraoperatively recorded during posterior thoracic spine fixation in a 41-year-old man. *Results:* Ninety minutes after the induction of anesthesia there was a rapid, progressive loss of tibial and median nerve responses as well as cortically generated SSEP waveforms. Despite adequate oxygenation and fluid volume throughout the case, mean airway pressures remained high (33/6 cmH_20) and blood pressure remained low (80/45mmHg). The decrease in peripheral nerve responses corresponded with a drop in EtO_2% from 32 to 25. The patient's prone position enhanced ventilation problems. One hundred minutes later, the nerve response and cortically generated SSEPs recovered in 2 of 3 limbs monitored (related to improved ventilation). Following emergence from anesthesia it was clear that the patient had bitten and kinked the endotracheal tube thereby severely increasing the airway resistance. Postoperatively he had no new sensorimotor deficits. *Conclusions:* This is the first reported case where generalized nerve conduction block was intraoperatively detected. This alerted the surgical team to a systemic impairment (undiagnosed thoracic tamponade) resulting from a compromised endotracheal tube.

P-142

Muscle acetylcholine receptor antibodies in chronic hepatitis C

M D'Amour (Montreal), A Rinfret (Montreal), B Willems (Montreal)*

Background: A few cases of myasthenia gravis (MG) have been reported in chronic hepatitis C (CHC). Acetylcholine receptor antibodies (AchR) are specifically present in MG. Chronic hepatitis

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C has been linked with other autoimmune diseases. To determine if hepatitis C virus infection could induce AchR antibodies, we conducted AchR antibody testing in CHC patients. *Methods:* After informed consent, we studied 100 consecutive cases of CHC. All were positive for hepatitis C virus (HCV RNA). None had symptoms of myasthenia. We looked for AchR antibodies with an AchR antibody radioimmunoassay. Since AchR antibody sero-negative MG patients are at times positive for muscle-specific tyrosine kinase antibody MuSK, we tested for it*. *Results:* Only 1 out of these 100 consecutive CHC cases was positive for AchR antibodies. This patient was still positive on repeat testing in another laboratory. All were negative for MuSK antibodies. *Conclusions:* The prevalence of MG is considerably lower in the general population 14/100, 000 than the prevalence, 1/100 of anti-AchR antibodies, found in these HCV-infected patients. An immunological link between MG and CHC may exist but has yet to be formally demonstrated in HCV patients. Clinicians should be aware of such a possible link.* Done by Professor Angela Vincent, Oxford, UK

P-143

Adult-onset nemaline myopathy and monoclonal gammopathy of possible significance

A Frank (Ottawa*), *PR Bourque (Ottawa*), *J Woulfe (Ottawa*), *P Chakraborthy (Ottawa*)

Nemaline myopathy is a rare congenital myopathy that can present from a severe neonatal form that is invariably fatal, to an adult-onset form whose course is more benign. We describe the case of a 58-year-old man who presented with progressive disabling proximal weakness over a period of 2 years. Family history was negative for neuromuscular disease. He showed marked atrophy and weakness in a limb-girdle distribution with particular involvement of the scapular and pectoral muscles. Needle EMG showed abnormal motor unit configuration and early recruitment in keeping with a myopathy. Muscle biopsy revealed abnormal fiber diameter variation and abundant Gomori-positive inclusions typical of nemaline rods, found in intermyofibrillar, subsarcoplasmic and intranuclear distributions. Serum electrophoresis revealed a monoclonal IgG kappa gammopathy. Intense immunoglobulin positivity was demonstrated on sarcoplasmic membranes by immunofluorescence. ACTA1 (alpha-actin) gene testing showed no mutation. Trials of therapy with plasmapheresis and intravenous corticosteroids were unsuccessful. A few cases of adult-onset nemaline myopathy associated with monoclonal gammopathy have been described, which may indicate an immunologic pathogenesis distinct from the genetically based neonatal and early-onset forms of the disease. Although this raises the possibility that immunotherapy may be helpful in adult-onset nemaline myopathy, our patient showed no benefit from such treatment.

P-144

Peripheral neurostimulation in occipital neuralgia

R Garcia (Halifax*), *I Mendez (Halifax*), *I Beauprie (Halifax*), *P Gaudet (Halifax*)

Background: The term occipital neuralgia (ON) is used to describe a characteristic pain in the region innervated by the greater occipital nerve. The neurostimulation methods for control of ON are a new surgical approach. However, there is little literature regarding its efficacy in occipital neuralgia. We report the early clinical course of our first patient with ON to receive peripheral neurostimulation. *Methods:* A 43-year-old homemaker, who sustained a motor vehicle accident in 1999, subsequently suffered from intractable occipital neuralgia. She had an implantation of a peripheral occipital nerve stimulator for right occipital nerve. Surgically, Doppler identified the right occipital artery (OA) and just medially, the occipital nerve. We brought it to resume two lead stimulator electrodes in occipital nerve trunk. *Results:* Peripheral nerve stimulation produced significant and sustained reduction of occipital neuralgia, evaluated by Visual Analogue Scale; the patient reported good pain control, a reduction of at least 75 % of the pain. The patient reports a marked increase in a quality of daily living and family interactions. *Conclusions:* There is a new neurosurgical procedure, which involves stimulation of the occipital nerve. It is a much less invasive procedure that has been report to be successful for ON. It will be the procedure of choice in the future, as we will avoid more ablative procedures such a ganglionectomy.

P-145

Low-resistance exercise modifies disease progression in Duchenne's muscular dystrophy (DMD): a case report

J Jolivet (Burnaby*), *A Rawicz (Burnaby*), *K Wambera (Vancouver*)

Background: The efficacy of exercise in DMD is controversial. High-resistance exercise can accelerate muscle degeneration, and low-resistance exercise has been prescribed only to prolong ambulation. *Case Report:* B.R. is a 31-year-old male who presented with DMD at age four, with calf hypertrophy and proximal muscle weakness. Muscle biopsy and genetic studies confirmed the diagnosis. He lost ambulation at age nine due to skeletal deformities. Corticosteroids were tried briefly but discontinued because of side effects. By fourteen, his scoliosis had progressed to a Cobb angle of 45 degrees, and his respiratory capacity was greatly diminished. His weekly hour of physiotherapy was replaced with 8-10 hours of customized hydrotherapy, which was reduced to 2-4 hours after two years. His axial strength improved, and the scoliosis diminished to 10 degrees, and remained stable without surgical stabilization. He started nocturnal BiPAP at the age of 25 years. *Conclusions:* B.R. has not shown the typical rapid functional decline, which occurs following loss of ambulation and has shown a milder disease progression. We propose that his exercise regimen was a positive modifying factor. We further believe that this case demonstrates the benefit of a low-resistance exercise program in nonambulating DMD patients.

P-146

An unusual neurological cause of chest pain

Suhas K (Toronto*), *Toth C (Calgary*)

Neurological causes of chest pain are rare and unusual in nature. Frequently, the patient with a neurological cause for chest pain undergoes numerous unnecessary negative investigations for cardiac, pulmonary, and musculoskeletal etiologies of chest pain. We present the case of a female patient with a unique cause of neuropathy and neuropathic chest pain and its management.

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P-147

Is a multidisciplinary model of care for adolescent neuromuscular patients associated with increased patient satisfaction?

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Background: Children with neuromuscular diseases are typically cared for by numerous healthcare providers. Even though a multidisciplinary clinic is often advocated for such patients, it is unclear whether clients are satisfied with this model of care. *Methods:* Adolescents and caregivers who attended a multidisciplinary neuromuscular clinic completed the Client Satisfaction Questionnaire (CSQ) and either the Pediatric Quality of Life Inventory (PedsQL) or the Short-Form Health Survey (SF-36). Their responses were compared with families who attended other neurology clinics. *Results:* 123 families participated in the survey. Adolescent neuromuscular patients (n=34) had poorer physical health on PedsQL ($p<0.0001$), but their psychosocial health was similar to other adolescent neurology patients (n=89). Caregivers of neuromuscular patients had lower SF-36 mental health scores ($p=0.0298$). Patient satisfaction was uniformly high in neuromuscular and other neurology clinics (median CSQ = 28, range 18-32), except for adolescent headache patients (n=18), who scored lower on the CSQ ($p=0.0318$). *Conclusions:* Even though a multidisciplinary model of care was not associated with higher patient satisfaction, this may reflect greater physical needs of adolescent neuromuscular patients, and/or increased stress amongst their caregivers. Further studies may identify factors that influence quality of care and satisfaction, in order to improve compliance and health-related outcomes.

P-148

Ineffectiveness of distal repair in the presence of proximal nerve injury

S Mittal (Montreal), L Jacques (Montreal)*

Background: We present the case of a 32-year-old previously healthy man who sustained a traumatic amputation of the left upper extremity at the level of the elbow. The patient underwent extensive (16 hours) orthopedic, plastic, and vascular reconstructive surgery shortly after the motor vehicle accident. Six months later, he did not recover left arm function and underwent interposition nerve grafts to the median and ulnar nerves. *Methods:* Electromyography demonstrated denervation in the upper, middle, and lower trunks revealing evidence of proximal nerve injury. On examination, a Horner's syndrome was present indicative of C8 and T1 root avulsions. *Results:* The presence of a left pupil miosis, if noted at the time of initial assessment, would have led the treating physicians to establish the presence of root avulsions. Nerve grafting to the median and ulnar nerves in this context was therefore futile. *Conclusions:* Distal nerve repair will not carry function in the setting of proximal injury. A careful neurological examination is crucial for proper assessment of peripheral nerve injuries.

P-149

Sensory neuropathy among HIV/AIDS patients highly exposed to antiretroviral therapy: the potential roles of hepatitis B virus infection and protease inhibitors

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Background: HIV-sensory neuropathy (HIV-SN) is associated with advanced immunosuppression and specific antiretroviral therapies (ART). Our objective was to define clinical determinants of HIV-SN in ART-exposed patients. *Methods:* From a cohort of HIVseropositive patients from 1998 to 2003, those with and without HIV-SN were identified, including antiretroviral toxic neuropathy (ATN) and distal sensory polyneuropathy (DSP), based on established diagnostic criteria. Demographic and clinical data were reviewed together with extent of exposure to ddI, ddC, d4T, 3TC, AZT and protease inhibitors (PI). *Results:* Among 185 patients, 91 (49%) showed no evidence of SN (SN-free) but 57 (31%) and 37 (20%) exhibited DSPor ATN, respectively. Of the demographic and clinical variables assessed, age was greater in the ATN group ($p<0.05$). Hepatitis B seropositivity was associated with DSP ($p<0.05$) and ATN ($p<0.01$). Patients exposed to D4T were more likely to exhibit DSP ($p<0.05$) or ATN ($p<0.0001$). Similarly, exposure to PIs was associated with DSP ($p<0.05$) and ATN ($p<0.0001$). *Conclusions:* Hepatitis B seropositivity together with D4T and PI therapy were significantly associated with HIV-SN, particularly ATN. Hepatitis B seropositivity and PI exposure have not been previously shown to represent potential risk factors for HIV-SN. These findings underscore the complex effects of ART exposure and co-morbidity on the development of HIV-SN.

P-150

Unilateral atrophy of fungiform papillae associated with lingual nerve injury

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Background: Lingual nerve injury is a complication of common dental procedures. Sensory fibers from the lower gums, mucosa of the anterior two-thirds of the tongue, and sublingual mucosa travel in the lingual nerve. Taste fibers from the anterior two-thirds of tongue pass through the lingual nerve prior to entering the chorda tympany nerve. Injury to the lingual nerve results in loss of sensation and taste on the ipsilateral side. *Methods:* A case of lingual nerve injury with unilateral atrophy of fungiform papillae is described. We performed a literature search to ascertain the significance of this finding. *Results:* A 20-year-old male presented with a two year history of numbness and loss of taste on the right side of his tongue after wisdom tooth extraction. On examination, he exhibited decreased sensation to pinprick on the right half of the tongue and the lower gingival mucosa. The fungiform papillae on the right half were also visibly atrophied compared to those on the left side of the tongue. *Conclusions:* Atrophy of the fungiform papillae secondary to lingual nerve injury has rarely been described. The role of the chorda tympany/lingual nerve in maintaining the anatomical integrity of the fungiform papillae will be discussed.

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P-151

Porphyria with distal neuropathy and significant dysautonomia

M Shapiro (Saskatoon), A Rajput (Saskatoon)*

Background: The porphyrias are a group of disorders characterized by interruption of the heme biosynthetic pathway. In hepatic porphyrias, neuropsychological manifestations are prominent. While hereditary coproporphyria and variegate porphyria involve cutaneous signs, acute intermittent porphyria does not. Approximately fifty percent of attacks in acute intermittent porphyria are accompanied by peripheral neuropathy, which often begins in the proximal upper extremities. Autonomic polyneuropathy can be another feature, and typically manifests as tachycardia and hypertension. *Methods:* A 21-year-old previously healthy woman presented with significant weight loss, leg pain and weakness, wasting of the intrinsic hand muscles, orthostatic hypotension, and depression. She had no rashes. Family history was noncontributory. *Results:* Nerve conduction studies revealed diffuse axonal motor neuropathy. Porphyria screen was positive. Urine delta-aminolevulinic acid and porphobilinogen levels were elevated, and urine turned rose-colored when exposed to sunlight. Autonomic testing indicated both sympathetic and parasympathetic dysautonomia. Tilt table testing confirmed the diagnosis of postural orthostatic tachycardia syndrome (POTS). Neuro-imaging and cerebrospinal fluid were unremarkable. Abdominal ultrasound was normal. Campylobacter was negative, and arsenic, mercury, and lead levels were normal. Dietary intervention and treatment with hematin were initiated. *Conclusions:* Distal neuropathy and dysautonomia involving POTS and parasympathetic dysfunction can be prominent features of porphyria.

P-152

The "3C" myopathy in renal transplant patients

Z Siddiqi (Edmonton)*

Background: Renal transplant patients commonly take multiple medications to maintain immunosuppression and treat other concurrent medical conditions. Most drug regimens in such patients include cyclosporine and colchicine. *Methods:* Case series report of 3 patients. *Results:* Three post-renal transplant patients developed severe weakness after a cholesterol lowering agent was added to their regimen, which had included cyclosporine and colchicine for several years. Examination showed a myopathic pattern of severe proximal more than distal weakness, intact reflexes and normal sensory examination. Electromyography showed a necrotizing myopathy with widespread spontaneous activity (fibrillations and positive sharp waves) in all patients and myotonic discharges were noted in 2 patients. Muscle biopsy showed vacuolar changes typical for colchicine-induced myopathy. One patient died, 1 completely recovered and 1 patient is currently recuperating. *Conclusions:* Although renal transplant patients take two potentially myotoxic medications (cyclosporine and colchicine) for years without any noticeable problems, addition of a third myotoxic medication (a cholesterol lowering agent) may result in an acute and severe colchicine-induced myopathy in some patients. Whether this results from a drug-drug interaction or is an additive myotoxic effect remains to be determined. Physicians treating renal transplant patients should be aware of this serious and late complication of colchicine when the 3C agents are concurrently being used.

P-153

Unexpected electromyographic and motor nerve conduction abnormalities in patients with clinically isolated sensory neuropathy

C Toth (Calgary), D Zochodne (Calgary)*

Background: Nerve conduction studies (NCS) and electromyography (EMG) have remained as the most important diagnostic test for patients with peripheral neuropathy. The utility and findings or motor NCS and EMG in patients with clinically defined sensory neuropathy is uncertain. Abnormalities during NCS and EMG testing in this population may predict later development of motor symptoms and signs, or may be secondary to normal changes as reported in normal subjects. *Objective:* To describe changes in motor NCS and EMG in patients with selective isolated sensory neuropathy. *Methods:* We prospectively assessed 20 patients during routine diagnostic workup with clinically defined isolated sensory neuropathy with standard NCS and EMG of lower limb muscles using concentric disposable needle electrodes. *Results:* NCS identified abnormalities in 85% of patients, while EMG identified presence of abnormality in 75% of patients. Motor NCS of the lower extremities identified abnormalities of peroneal NCS in 45% of patients and of tibial NCS in 25% of patients. EMG identified unexpected abnormal spontaneous activity in only 15% of patients and identified abnormalities in motor unit potential (MUP) morphology such as large amplitude, long duration, and polyphasia in approximately 60% of all muscles tested. Abnormalities including reduction in recruitment of MUPs and an increased firing rate were also identified in approximately 50-60% of all muscles examined. The most sensitive muscle for EMG assessment in this population may be the extensor digitorum brevis. *Conclusions:* Patients with clinically diagnosed selective sensory neuropathies will frequently have abnormalities of motor NCS and EMG despite the absence of a clinical motor deficit. Such changes may predict later motor deficit in this population.

SPINE

P-154

Preliminary experience with Actipore ACF interbody cervical implant

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Background: Anterior cervical microdiscectomy and fusion is effective in well-selected patients, but the ideal fusion substrate remains controversial. Autologous bone graft (ABG) with or without plating is still the standard and most widely used technique. One important disadvantage of ABG is graft site complications/pain. New technologies have been developed to avoid autologous graft harvesting. *Methods:* Characteristics and preliminary results of a cohort of twenty-eight patients treated with a new cervical interbody fusion device, Actipore ACF, are presented. *Results:* Most patients presented with radiculopathy (66%) secondary to one-level cervical disc disease. The most common levels operated were C5-6 (36%) and C6-7 (41%). Two (7%) patients with partial graft migration required a second procedure. All the remaining patients improved clinically and showed adequate follow-up radiographs. *Conclusions:*

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Actipore ACF appears to be a relatively safe and reliable graft substitute for anterior cervical fusion after microdiscectomy. Longer follow-up is necessary in order to assess fusion rates. A larger, randomized controlled trial is required and will in fact be launched soon.

P-155

Closed reduction of cervical spine fracture dislocations with MRI guidance

T Darsaut (Edmonton), R Broad (Edmonton), M Lavoie (Edmonton), F Kortbeek (Edmonton), J Mahood (Edmonton), R Fox (Edmonton)*

Background: Closed reduction of the cervical spine for acute fracture dislocations has been a traditional technique used for reestablishing alignment and providing decompression of neural elements. The safety of this technique has been questioned, with concerns of disc migration and overdistraction cited as reasons to choose operative reduction and decompression as a safer option in some circumstances. *Methods:* A technique for monitoring the process of closed reduction using MRI scanning was developed. A case series of fifteen patients with cervical spine fracture dislocations for whom closed reduction was recommended and carried out with MRI guidance is reported. A novel device for cervical traction during MRI scanning is described. *Results:* Closed reduction provided immediate improvement in canal dimensions, even prior to complete reduction being achieved. *Conclusions:* MRI monitoring in closed cervical reduction is a useful research tool for this technique. Closed reduction appears to be safe as used in this preliminary study, and is effective in achieving immediate spinal cord decompression.

P-156

Outcome of laminectomy with discectomy compared to hemilaminectomy with discectomy

T Darsaut (Edmonton), D Yen (Kingston)*

Background: We endeavoured to measure radiographic stability in a group of patients who received laminectomy and discectomy and compare their clinical outcomes with patients who received partial hemilaminectomy and discectomy. *Methods:* Over a 37-month period, 10 patients underwent laminectomy and discectomy, while 48 underwent hemilaminectomy and discectomy. Before operation, and at 1 year follow-up, patients responded to the Roland-Morris Questionnaire (RMQ). Changes in RMQ score over one year of follow-up was compared between groups. Also, the laminectomy and discectomy group had flexion-extension radiographs taken at least 6 weeks postoperatively to measure spondylolisthesis and vertebral body rotation. *Results:* 80% of patients had improved clinical outcomes following laminectomy for discectomy, compared to 77% of the hemilaminectomy and discectomy group, seen by decreased RMQ scores. Postoperative spondylolisthesis and vertebral body rotation were within normal limits at 6 weeks following laminectomy for discectomy. *Conclusions:* Performing laminectomy for discectomy instead of hemilaminectomy did not result in a significant difference in clinical outcome, nor did laminectomy result in more radiographic instability.

P-157

Acute nontraumatic quadriplegia secondary to cervical disc herniation: case report and review of the literature

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Background: There are 6 previous case reports of acute progressive myelopathy secondary to nontraumatic cervical disc herniation. In most cases, acute symptoms were due to enlargement of the disc herniation coupled with pre-existing spinal canal stenosis. The authors describe an exceedingly rare case of acute nontraumatic cervical disc herniation resulting in quadriplegia. They also review the literature on nontraumatic cervical disc herniation. *Methods:* A previously healthy 42-year-old man developed weakness and numbness in his arms and legs immediately following a sneeze. On physical examination he had signs of myelopathy that progressed over a few hours to a complete C5 quadriplegia. An emergent magnetic resonance imaging study revealed a massive C4/5 disc herniation. He underwent emergency anterior cervical micro-discectomy and fusion. *Results:* Postoperatively, the patient remained a C5 quadriplegic. Eighteen days later, while receiving rehabilitation therapy, he developed a pulmonary embolus and died. *Conclusions:* Acute nontraumatic cervical disc herniation resulting in quadriplegia is exceedingly rare. This case demonstrates that this phenomenon may occur in patients without previous myelopathic symptoms or canal stenosis. Prompt diagnosis and emergent decompressive surgery is the key to prevention of severe myelopathy.

P-158

Occipitocervical fusion using the SUMMIT occipital plate and polyaxial screw-rod system: early experiences and results

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Background: No current consensus exists with respect to instrumentation for occipitocervical fusion. Rigid screw-rod systems provide good immobilization and fusion results but anatomical complexity may be challenging when placing screws in this region. We present our initial experience with a new system designed to maximize occipital screw purchase while minimizing risks of neural injury. *Methods:* Patients undergoing fusion using the SUMMIT system at our institution were reviewed. Fusion constructs utilized an occipital Y-shaped plate and lateral mass screws encompassing at least C3 and C4, supplemented by iliac crest bone graft. Somatosensory evoked potentials were monitored during all cases. *Results:* Five patients (mean age = 55±7 years) underwent occipito-cervical fusion over a three-year period for instability secondary to degenerative (2), neoplastic (2), or traumatic (1) conditions. No postoperative failures or infections were noted. Excellent anatomical fixation was achieved in all cases. Neurological outcomes were excellent in all but one patient who had long-standing deficits and showed mild improvement only. *Conclusions:* We find occipitocervical fusion with the SUMMIT system to be technically simpler and more robust than previous designs as it readily integrates into lateral mass and/or C1-C2 transarticular screw constructs and was well-tolerated by patients with good results in this series.

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Large spontaneous vertebral artery fistula with spinal cord compression: case report

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Background: Vertebral artery fistula (VAF) is uncommon. Etiologies include neck trauma, collagen-vascular disorders, and neurofibromatosis. Spontaneous lesions are extremely rare. The natural history of the disorder is unknown, with only a few reports of VAF in association with radiculopathy, spinal cord compression, and intracranial hemorrhage previously published. We present the case of a patient with a spontaneous VAF resulting in spinal cord compression treated with endovascular balloon occlusion. *Methods:* A 41-year-old woman presented with left occipital pain associated with a loud bruit and a vascular thrill. Neurological examination was normal. Magnetic resonance (MR) imaging, MR angiography, and digital subtraction angiography demonstrated a large VAF draining into the spinal canal through the left C5/6 neural foramen. Venous drainage culminated into a large distended internal jugular vein. *Results:* Complete thrombosis of the VAF was obtained with endovascular balloon occlusion. The patient remained neurologically intact after the procedure. *Conclusions:* Owing to the rarity of the lesion, the natural history of spontaneous VAF is unknown. Endovascular treatment options include balloon occlusion or stenting. Direct surgical obliteration of the fistula may be considered if endovascular methods are unsuccessful.

P-160

Spinal epidural abscess: prognostic factors

K Kumar (Regina), G Hunter (Regina)*

Background: The incidence of spinal epidural abscesses (SEA) is on the rise. While increased awareness has led to decreased mortality, morbidity remains unacceptably high with rapid deterioration of neurological status when there is a delay in recognizing the pathology. Thus the need for better understanding of prognostic factors and management strategies. *Methods:* We analyzed 20 cases of spinal epidural abscess over the last 5 years. A retrospective analysis of clinical, radiological, laboratory, and surgical findings was performed. A scoring system ranging from 1 (complete neurological recovery) to 5 (dead) was used to assess outcomes. We also analyzed the prognostic value of several factors, including demographics, clinical presentation, comorbidities, inflammatory markers, imaging findings, and timing of intervention. *Results:* Thirteen of 14 patients who had surgery within 24 hours had a good outcome (ambulatory without sphincter disturbance), in comparison to 2 of 6 who had surgery after 24 hours. Erythrocyte Sedimentation Rate, muscle strength at time of admission, and timing of intervention were found to have statistically significant prognostic value. C-Reactive protein had a soft relationship to outcome. Number of comorbidities, age, sex, and degree of thecal sac compression were found to have no prognostic value. *Conclusions:* The most important prognostic factor in SEA remains a high clinical suspicion, prompt investigation, and immediate intervention.

P-161

Anterior sacral meningocele associated with Marfan's syndrome

F Maroun (St John's), B Hoppe (St John's), J Jacob (St John's), P Bartlett (St John's), G Murray (St John's), A Furey (St John's)*

Background: Anterior sacral meningocele associated with Marfan's syndrome is extremely rare. An additional case report is presented. *Methods:* A 37-year-old female with a history of Marfan's syndrome and aortic dissection treated medically three years ago, presented with a history of episodes of severe back pain with intermittent weakness of both legs and frequent falls dating back for two years. No gross neurological finding. Neuroradiological investigations revealed a large sacral anteromeningocele. *Conclusions:* Anterior meningocele is rarely seen in connective tissue disorders such as Marfan's syndrome. A review of the literature is presented.

P-162

Retrospective chart review of anterior cervical spine surgery patients and their risk factors for airway and swallowing complications

AP Mitha (Calgary), C Gallagher (Calgary), CA Prusinkiewicz (Calgary), RA McTaggart Cowan (Calgary), RJ Hurlbert (Calgary)*

Background: A number of potential airway and swallowing complications can result from surgery on the anterior cervical spine. Predisposing factors, however, are inadequately studied. The purpose of this study is to characterize variables associated with airway and swallowing complications following anterior cervical spine surgery. *Methods:* A preliminary retrospective chart review of nonpolytrauma, anterior cervical spine procedures was carried out. Cases were examined for number of levels operated, neck drain placement, postoperative airway complications, swallowing difficulties, and length of stay (LOS). *Results:* Of 63 cases reviewed, there were no airway complications. Seven patients (11%) had swallowing difficulties. Eight patients received neck drains, one of which developed swallowing difficulties. Mean LOS in patients with drains was 4.4 days versus 7.5 days in others. Mean LOS based on number of levels operated were as follows: One level - 5.7 days (N=47), Two levels - 9 days (N=10), Three levels - 8.8 days (N=5), Four levels - 40 days (N=1). *Conclusions:* Our preliminary data shows placement of a neck drain is not associated with less airway and swallowing complications. Length of stay correlated positively with number of levels operated and negatively with drain placement. An extensive follow-up study is ongoing, and will further delineate factors affecting airway and swallowing complications after anterior cervical spine procedures.

P-163

Transplantation of adult rat spinal cord stem/progenitor cells into the injured rat spinal cord

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Background: There are no good treatments for acute spinal cord injury (SCI). Because neural stem cells can self-renew and are multipotential for both neuronal and glial progeny, it has been

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suggested they could be utilized for spinal cord repair. Improved locomotor recovery after SCI in adult rodents treated with fetal spinal cord cell transplants has been demonstrated. The purpose of this study was to determine the survival and fate of transplanted adult rat spinal cord stem/progenitor cells in the injured rat spinal cord. *Methods:* Adult male rat spinal cord stem/progenitor cells were cultured and transplanted into adult female Sprague Dawley rats injured at T8 by severe SCI produced by clip compression (35g clip). At either day 0 or day 9 after SCI, 500, 000 cells were injected into the injured area. Rats were sacrificed at 1, 7, 14, and 28 days. Transplanted cells were identified by pre-labeling cells with CFDA. Cell fates were examined using the following antibodies: nestin (intermediate filament protein), NeuN (neurons), GFAP(astrocytes), ED1 (macrophages), O4 (immature oligodendrocytes), and doublecortin (migrating neurons). *Results:* Transplanted cells were identified at 14 days from transplantation. *Conclusions:* Cell survival was determined to be at least 14 days using CFDAdye. Cell fates will be discussed.

P-164

Biomechanics of instrumented fixation for unilateral cervical facet dislocation

GE Pickett (London), N Duggal (London), RH Chamberlain (Phoenix), VKH Sonntag (Phoenix), CA Dickman (Phoenix), NR Crawford (Phoenix)*

Objective: The surgical management of cervical spine facet dislocation remains controversial. This *in vitro* study compared the construct stability provided by anterior cervical plating with that of posterior lateral mass plates in a model of unilateral cervical facet dislocation. *Methods:* A reproducible unilateral facet dislocation was created, and then reduced, in nine human cadaveric cervical spine segments. Nondestructive torques were applied to specimens that were intact, injured, reduced, fixated using posterior nonlocking lateral mass plates, and fixated using anterior bone graft and anterior nonlocking plate. Flexion, extension, lateral bending and axial rotation were measured stereophotogrammetrically. *Results:* Lateral mass plates performed significantly better than anterior plates in all modes of loading and in all motion parameters ($p<0.05$). In flexion and extension, both anterior and posterior plate constructs significantly reduced motion compared with the intact specimen. Anterior plating was less effective in limiting axial rotation. The difference was greatest in lateral bending where anterior plating allowed the greatest motion. *Conclusions:* Both anterior and posterior plating were effective in stabilizing a reduced unilateral facet dislocation. Lateral mass fixation was a more effective construct in limiting ROM.

P-165

The biomechanics of hangman's fractures

GE Pickett (London), N Duggal (London), RH Chamberlain (Phoenix), VKH Sonntag (Phoenix), NR Crawford (Phoenix)*

Objective: Optimal surgical treatment of hangman's fractures is still controversial. This biomechanical study compared various instrumentation constructs to document stability and resistance to subluxation forces. *Methods:* Human cadaveric spines were subjected to loading forces in flexion, extension, right and left lateral bending, and right and left axial rotation. Range of motion was measured initially, following a simulated hangman's fracture, and following three different types of instrumentation: C2 pedicle screws alone, C2 pedicle screws attached to C3 lateral mass screws, and anterior C2-3 discectomy with graft/plate. *Results:* Disc disruption and pars interarticularis fractures significantly destabilized the spine in all loading modes. Restabilization with direct pedicle fixation showed that disc disruption contributed to instability during flexion/extension, while bilateral pars disruption destabilized the spine during lateral bending and rotation. C2 pedicle screws alone were unable to adequately stabilize the spine in flexion/extension. The addition of lateral mass screws at C3 provided significantly better biomechanical stability. Anterior plating provided greater resistance to translation, but was less stable during lateral bending and axial rotation than the C2-3 posterior fixation. *Conclusions:* C2 pedicle screw fixation alone is insufficient to stabilize a hangman's fracture with associated disruption of the C2-3 disc. Anterior plating and posterior C2-3 fusion both appear to provide adequate spinal immobilization.

P-166

The Siemans C-arm mounted X-ray image intensifier for evaluation of atlantoaxial disorders

D Rabin (London), D McErlain (London), D Holdsworth (London), R Sahjpaul (London), N Duggal (London)*

Background: Three-dimensional C-arm fluoroscopy (3-D fluoroscopy) can function as a computed tomography (CT) scanner. In this pilot study, we compare imaging with 3-D fluoroscopy with helical CT for the evaluation of patients with disorders of the atlantoaxial complex. *Methods:* Pre- and postoperative imaging using the Siemens Multistar system and conventional helical CT imaging was performed to evaluate patients requiring either transarticular C1-2 or odontoid screw fixation. The images obtained with the Siemens Multistar system were subjectively compared with conventional helical CT. *Results:* Two odontoid and six transarticular screws were placed in six patients. Pre-operative 3-D fluoroscopic images were used to evaluate Type 2 odontoid fractures and the suitability of the atlantoaxial complex for transarticular screw fixation. Postoperative imaging demonstrated the accuracy of screw placement and extent of fracture reduction. The image resolution of the Siemens Multistar system was comparable to helical CT. 3-D fluoroscopy exposed patients to a mean dose of 0.049 mSv (SD 0.026 mSv) for preoperative imaging and 0.098 mSv (SD 0.026 mSv) for postoperative imaging. *Conclusions:* 3-D fluoroscopy techniques provided image quality comparable to helical CTin the peri-operative assessment of atlantoaxial disorders. Potential advantages of 3-D fluoroscopy include intra-operative real-time 3-D image guidance.

P-167

The role of interleukin-1 beta in spinal cord injury

T Rice (Calgary), J Wells (Calgary), VW Yong (Calgary)*

Background: After spinal cord injury (SCI), a number of inflammatory molecules and trophic factors become rapidly elevated. The role of neuroinflammation in SCI is unclear and the objective of the current study is to examine the role of Interleukin-1

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beta (IL-1 beta) in SCI. *Methods:* Spinal cord clip compression is used as a model for SCI in the mouse. Wild-type mice and mice genetically deficient for IL-1 beta are compared for differences in behavioural tests, histological parameters and expression levels of inflammatory molecules and trophic factors following SCI. *Results:* IL-1 beta is one of the early inflammatory molecules upregulated after SCI. IL-1 beta is implicated in the regulation of trophic factors after injury since several trophic factors increase within 48 hours of SCI in wild-type mice and this increase is less prominent in IL-1 beta null mice. Functionally, during the initial stages after SCI, IL-1 beta null mice perform better than wild-type mice. *Conclusions:* IL-1 beta null mice recover earlier than wild-type mice after SCI despite lower levels of trophic factors. Future experiments include correlating the spinal cord tissue histology with behavioural outcomes and examining possible reasons for the difference in recovery between IL-1 beta null and wild-type mice.

P-168

Delayed ischemic myelopathy after endovascular thoracic aortic aneurysm repair: response to corticosteroids

J Rivest (Sherbrooke), A Lamontagne (Sherbrooke), A Benko (Sherbrooke), T-B Bui (Sherbrooke), J Prévost (Sherbrooke)*

Case report: Paraplegia or paraparesis secondary to spinal cord ischemia is a known complication of endovascular aortic aneurysms repair. We report a case of delayed paraplegia after endovascular thoracic aortic aneurysm repair, 16 days after the procedure. Ten days after discharge, the patient presented sudden paraplegia, with loss of all sensory modalities below T8 without sacral sparing. On admission he was hypotensive (100/45) and was given i.v. fluids and put on Solumedrol 1g i.v. daily for 3 days; followed by oral Prednisone for 1 month. Both sensory and motor deficits recovered substantially during the first 3 days of treatment. The patient was able to walk independently. On discharge, sensory deficit over the sacral area and sphincter disturbances were the only residual remaining neurological deficit. *Conclusions:* This case illustrate the potential reversibility of deficits in this form of ischemic myelopathy, presumably by improving local perfusion.

P-169

The case of the missing screw

R Sahjpaul (North Vancouver)*

Background: Although rare with current-generation anterior plating systems, hardware complications can be life-threatening. *Methods:* A 58-year-old male underwent C6 vertebrectomy and C5-7 interbody fusion with a cage and ventral cervical plate at another institution. Following surgery he developed fever and recurrence of his symptoms and deficits. Investigations revealed a deep neck-space infection, and a missing inferior plate screw. Revision surgery was undertaken at which time an esophageal perforation was identified and closed primarily. Abdominal XRs and CT scan localized the screw in the large bowel, and serial XRs confirmed its passage out of the body. Despite a prolonged postoperative course complicated by pulmonary emboli, the patient recovered completely and continues to do well. *Conclusions:* Early detection and aggressive management are essential in the management of this fortunately uncommon but potentially fatal complication of spinal stabilization.

P-170

The Impact of spina bifida on the medical services of Newfoundland and Labrador (1977-2002)

S Sloka (St John's), F Maroun (St John's), R Kennedy (St John's), J Jacob (St John's), D Price (St John's), G Murray (St John's), G Pal (St John's), H Laishram (St John's)*

Background: This study reviewed all live spina bifida cases in Newfoundland and Labrador from 1977-2002 and compared the results with our previous study (1967-1990). *Methods:* 201 patient charts of spina bifida births from 1977 to 2002 were reviewed. These patients were assessed regularly at the Janeway Child Health Centre (the only provincial institution where neonatal surgery is performed). *Results:* The incidence rate significantly declined in 1998 ($p<0.0001$). Demographics were similar to the general population in terms of marital status ($p=0.79$), maternal age ($p=0.26$), gender ($p=0.24$), and the incidence was fairly uniform across the province ($p=0.15$) with no difference between the incidence rates in urban vs rural populations. MRI and CTdata were available for determining the location of dysraphism and associated anomalies. Rates similar to the previous study were noted for orthopedic (except for foot procedures, $p=0.0004$) and surgical procedures ($p>0.10$). There was a significant difference in the educational status of patients with spina bifida - more patients attend regular ($p<0.0001$) and special needs ($p=0.0024$) school than in the previous study. *Conclusions:* This study demonstrates that the impact on medical services continues to be significant, but there is an improvement in the quality of certain aspects of patients lives.

PEDIATRICS – GENERAL

P-171

The spectrum and prognosis of neurological complications of nonaccidental injury (NAI) in children in Saskatchewan

M Belletrutti (Saskatoon), M Moodley (Saskatoon)*

Purpose: To determine important clinical features, laboratory parameters and prognosis of neurological complications of NAI in children in Saskatchewan. *Background:* Physical abuse is the leading cause of serious head injury in infants but yet it is frequently overlooked or underdiagnosed because of its variable presentation. The neurologic complications are often serious leading to death or severe sequelae. A literature review of NAI in Canada revealed a paucity of studies describing the etiopathogenesis, clinical spectrum, and outcome of neurological injury due to NAI. *Methods:* A retrospective medical record review of neurological complications due to child abuse during the period January 1992 to December 2003 was conducted at the Royal University Hospital in Saskatoon *Results:* All but 1 patient was under 2 years of age, the majority sustaining severe neurological injury. All patients had CT brain scans, the commonest finding being subdural hematoma. Contributing factors included a severe dysfunctional family unit and substance abuse. Long-term follow-up was documented in all but 2 patients with more serious residual neurological sequelae in those with subdural hematomas and brain swelling. *Conclusions:* Neurological injury as a result of NAI in young children in Saskatchewan is usually severe with resultant serious neurological

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sequelae. Family history suggests that more comprehensive social support for families would be beneficial for reducing the incidence of NAI in children.

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Posterior reversible encephalopathy syndrome (PRES) – an unusual complication of cisplatin therapy

A Datta (Saskatoon), M Moodley (Saskatoon)*

Background: PRES is an increasingly recognized brain disorder associated most commonly with malignant hypertension, toxemia of pregnancy and the use of immunosuppressive agents. Although cisplatin and vincristine are commonly used chemotherapeutic agents, there are very few reports documenting an association of their use with PRES. *Patient:* An 11-year-old female with an unresectable hepatoblastoma was given a course of cisplatin on day 1; vincristine on days 3, 10 and 17 and 5 FU on day 3. Two days later she complained of dizziness and blurring of vision, followed a day later by 6 tonic clonic seizures controlled with intravenous lorazepam, and a loading dose of phenobarbitone. A day later she experienced a left homonymous hemianopia, which recovered completely 4 weeks later. *Results:* CT brain scan performed on the day she experienced seizures revealed bilateral white matter lesions in both the right and left parieto-occipital regions consistent with (PRES). Subsequent CT brain scans performed on weeks 1, 2 and 4, showed minimal resolution despite clinical improvement. CT brain scan at 3 months showed an almost complete resolution of the white matter changes with a normal neurological examination. *Conclusions:* Clinicians should be aware of the association of PRES with cisplatin and vincristine therapy as early recognition is essential for appropriate investigation and management.

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6-Pyruvoyl-tetrahydropterin synthase (PTPS) deficiency causing mild hyperphenylalaninemia, developmental delay, seizures and dystonia

M Demos (Vancouver), PJ Waters (Vancouver), H Vallance (Vancouver), M Connolly (Vancouver)*

Background: PTPS deficiency is the most common cause of tetrahydrobiopterin (BH4) deficiency. The severe form presents in infancy with developmental delay, seizures and abnormal movements and is usually detectable by neonatal screening for hyperphenylalaninemia. Urine neopterin/biopterin ratio is elevated, and diagnosis is confirmed with enzyme studies. Neurological symptoms improve with L-dopa/carbidopa, BH4, and 5-hydroxytryptophan. *Methods:* Review of findings in a child with mild hyperphenylalaninemia due to PTPS deficiency. *Results:* This patient was referred at 8 years with global delay, seizures and dystonia after a normal pregnancy of nonconsanguineous parents. Her developmental age equivalent was 3 years. Generalized seizures began at 2 months. Examination revealed normal head circumference, truncal hypotonia, axial dystonia and ataxia. Plasma phenylalanine was 166 μmol/L (normal 38-76). There was an elevated urinary neopterin/biopterin ratio and decreased BH4. CSF showed reduced homovanillic acid, 5-hydroxy-indoleacetic acid and BH4. PTPS deficiency was confirmed by PTPS enzyme assay. Dystonia and seizures improved with L-dopa/carbidopa, BH4 and 5-hydroxytryptophan. *Conclusions:* Patients with severe PTPS deficiency may have mild hyperphenylalaninemia, below the cutoff values routinely used in newborn screening. It is a treatable cause of dystonia and developmental delay.

P-174

Bilateral oculomotor nuclei lesions caused by late migration of ventriculoperitoneal shunt

C DeSilva (London), A Ranger (London)*

Background: Recognized complications of ventriculoperitoneal shunts include obstruction, infection and overshunting. Neurological deficits caused by ventricular catheters are uncommon and late deficits are rare. We present a case of bilateral oculomotor nuclei lesions caused by catheter migration with Edinger-Westphal nuclei spared. *Method:* A 12-yr-old boy with Dandy-Walker malfunction presented with lethargy, vomiting and headache for 18 hr. He had had three VP shunts in infancy; supratentorial, posterior fossa and third ventricular. CT showed ventriculomegaly. Shuntogram showed distal obstruction of the supratentorial shunt that cleared spontaneously. The child presented 48 hr later with bilateral ptosis, down and out eyes, spared pupillary reactions but no increased intracranial pressure. *Results:* CTdemonstrated migration of a metal connector associated with the third ventricular shunt into the mid-brain. MRI and surgical intervention were thought hazardous. Shuntogram showed good function of all shunts. After several weeks the left eye symptoms resolved but the right eye failed to improve. *Conclusions:* Ventricular catheter migration is rarely thought to cause neurological deficits. We suggest securing extracranial components to prevent intracranial migration and injury. This appears to be the first reported late oculomotor lesioning from catheter migration. It is also notable as an oculomotor nucleus lesion sparing Edinger-Westphal nucleus.

P-175

Canadian adolescents and their frequent headaches: validation of estimates, increasing frequency, and associated factors

JM Dooley (Halifax), KE Gordon (Halifax), EP Wood (Halifax)*

Objectives: To validate previous estimates of frequent headache prevalence among adolescent Canadians (26.6%) and their associated factors (CJNS 2003:30:S16). To explore whether estimates of headache frequency and associated factors remain stable. *Methods:* We analyzed the self-administered questionnaire microdata files of the National Longitudinal Survey of Children and Youth (NLSCY: 1998-1999). Respondents reported their headache frequency within the previous 6 months. 1849 respondents representing 792, 100 youth age 12-13 years were used to validate initial cohort data. From our initial cohort, 1857 respondents representing 866, 400 youth age 14-15 years were used to examine whether frequent headache prevalence or associated factors had changed. *Results:* 26.3% of 12-13-year-olds and 31.2% of 14-15-year-olds reported frequent headaches of about once a week or more often (p=0.001). Frequent headaches appear to be associated with many risk factors (school-related, lifestyle-related, or mental health). Of 22 previously identified risk factors, 15 were replicated within this iteration of the NLSCY, and 13/15 were associated (p<.01). For the initial cohort, now 14-15-year-olds, all 15 risk factors remained

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associated (p<.01). *Conclusions:* Estimates of frequent headache prevalence are reliable and increase over adolescence. Identified risk factors for frequent headaches are valid and are maintained over early-mid adolescence.

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Prevelence of reported migraine headaches in Canadian adolescents

KE Gordon (Halifax), EP Wood (Halifax), JM Dooley (Halifax)*

Objective: To present self-reported prevalence data for migraine among adolescent Canadians and to explore how reported migraine treatment varies by age. *Methods:* We analyzed the microdata files of the Canadian National Population Health Survey (NPHS: 1996-1997). Respondents reported whether they had migraine headaches diagnosed by a health professional and whether they received any treatment or medication for migraine headaches. *Results:* 99.9% of 173, 216 eligible respondents reported whether they had migraine headaches. 2.35% of Canadian youth age 12-14 years (95% CI: 1.99, 2.74) and 4.97% of Canadian youth age 15-19 years (95% CI: 4.58, 5.38) reported having migraine, as compared to 7.23% of Canadian adults (20 years or older) (95% CI: 7.08, 7.38), (chi-square, p<0.0001). Active treatment for migraine was reported by 1.06% of Canadian youth age 12-14 years (95% CI: 0.82, 1.33) and 2.27% of Canadian youth age 15-19 years (95% CI: 2.00, 2.56), as compared to 3.70% of Canadian adults (20 years or older) (95% CI: 3.59, 3.81), (chi-square, p<0.0001). *Conclusions:* We present robust estimates of self-reported diagnosed migraine prevalence, derived from a sizeable, nationally representative population survey. Estimates of prevalence of active treatment for migraine provide a conception of the burden of migraine within the population.

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The effects of family system dynamics on migraine disability in children

N Ho (Calgary), KM Barlow (Calgary), E Wirrell (Calgary), J Mah (Calgary)*

Children with migraines come from diverse family backgrounds that have different mechanisms for coping with stress and illness in the family. *Hypothesis:* Family system dynamics are significantly different in families of children with migraine when compared with population norms. *Methods:* Prospective cohort study of children (aged 6 to 18 years) referred to a tertiary pediatric neurology centre with migraine. The Pediatric MIDAS (PedMIDAS) score was used as a measure of migraine disability. The Family Assessment Measure-III (FAM-III) was used for assessing family functioning. *Results:* 25 children (11 male) with a median age of 12.5 years (range: 8-17.5 years). The mean FAM-III T-scores in the subject was 50.9 (SD ± 8.96) and parent was 51.29 (SD ± 7.36). There was no correlation between the PedMIDAS and the FAM=III scores in the child or parent. *Conclusions:* Preliminary results indicate that in children with newly diagnosed migraine, the family system dynamics are not different from populations norms and that there is no correlation between this and disability due to migraines. This study continues and will investigate whether family functioning influences response to treatment.

P-178

Idiosyncratic isoniazid neurotoxicity in an adolescent with distinct findings on DW-MRI

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Introduction: An increasing incidence of tuberculosis has increased isoniazid (INH) use. Neurotoxicity from INH usually involves metabolic acidosis, coma, and seizures and neuroimaging is usually normal. *Methods:* Case report. *Results:* An intelligent 13-year-old boy from Sudan started INH for TB prophylaxis. After 3 weeks, he developed stereotyped paroxysmal episodes lasting 20-200 minutes with quick recovery. Symptoms included headache and difficulty moving both legs followed by severe dysarthria. He had vertigo, dysphagia, and possible diplopia as well as drowsiness but his cognition appeared intact. Emergency room diagnosis was hysteria. Initial neurological opinion raised concern of brainstem ischemia. A witnessed episode included emotional lability and unusual behaviour and subsequent decrease in level of consciousness to the point of intubation. MRI demonstrated focal, symmetrical lesions of the centrum semiovale, corona radiata, and internal capsule with marked restriction of diffusion. Isoniazid and pyridoxine levels were low. Detailed lab investigations were normal as was EEG. After no response to pyridoxine, dilantin was started and symptoms resolved completely. The patient was normal at 2 weeks with nearly complete resolution of his MR lesions. *Conclusions:* We report a previously undescribed idiosyncratic neurological reaction to isoniazid characterized by features of pseudobulbar palsy with widespread subcortical white matter changes seen almost exclusively on DW-MRI.

P-179

Subacute sclerosing panencephalitis: a report on the Canadian Pediatric Surveillance Program

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Background: Subacute sclerosing panencephalitis (SSPE) is rare in developed countries with measles immunization programs. The Canadian Pediatric Surveillance Program (CPSP) for SSPE was designed to determine the epidemiology of affected Canadian children. *Methods:* The CPSP for SSPE was a prospective incidence study. Monthly, between 1997 and 2000, 2350 Canadian pediatricians and sub-specialists completed surveillance forms. *Results:* During the study period only two incident cases were identified, but two additional cases were reported to CPSP. Therefore, the incidence of SSPE in Canadian children was 0.06/million children/year. Of the four cases, diagnosed between ages four and 17 years, three children had measles infection in infancy, two prior to living in Canada. A further Canadian born child had only measles immunization. All children showed a progressive course of dementia, loss of motor skills and epilepsy. Two children were treated with isoprinosine and intra-ventricular interferon, one child with intra-ventricular ribavirin and one child received no therapy. Three children remain alive, but markedly impaired, up to nine years following diagnosis. *Conclusions:* The CPSP has demonstrated that Canadian pediatric neurologists will encounter cases of SSPE. This report highlights the clinical course of several affected

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Canadian children and provides a review of the current understanding of the disease and its management.

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Precise insertion of Ommaya reservoirs in children by combining navigational imaging and a stereotactic approach

K MacDougall (London), A Ranger (London), J Megyesi (London)*

Background: Pilocytic astrocytomas can cause neurologic deficits from cyst enlargement rather than tumor growth. Insertion of an Ommaya reservoir for cyst aspiration in the pediatric population necessitates precise insertion when dealing with lesions in or near the brainstem. *Methods:* We used a combined navigational approach by fusing MR and stereotactic CT images. The Stealth navigational imaging system was first used to plan an optimal trajectory. Once the insertion point and depth to the lesion was determined, the Leksell stereotactic frame was used to place the catheter into the cyst. We report on the placement of reservoirs into two children with pilocytic astrocytomas, one with a cyst in the midbrain and the other with a cyst in the hypothalamus. Successful placement and cyst drainage was confirmed with postoperative CT scanning. *Results:* Satisfactory placement of both reservoirs was achieved without complication or communication with the ventricle. Both patients realized a reduction in the size of their tumor cyst and arrest of their progressive neurologic symptoms. *Conclusions:* Navigational imaging and stereotactic surgery can be combined to place Ommaya reservoirs in the pediatric population. The procedure can be performed safely and alleviate midbrain compression from tumor cysts.

P-181

The Fog test

D Mack (London), S Levin (London)*

The Danish couple Drs. Elin and Mogens Fog published the feet-hands test in 1963. Since then, various authors have published modifications resulting in the practice of a test differing from its original description. Also known as the Fog test, this manoeuvre involves walking with the feet in different positions resulting in involuntary, characteristic associated movements or synkinesis of the upper limbs. These movements are dependent on motor maturation or the presence of neurological pathology. Few who use the Fog test know its origins or the physicians behind its development. Dr. Elin Fog was an accomplished paediatrician in Copenhagen. Dr. Mogens Fog was a professor and neurologist whose accomplishments are remarkable. His contributions to neurology include critical experiments demonstrating cerebral blood flow autoregulation and the Fog Test. His commitment to Denmark includes leadership of the Danish resistance during the Second World War, parliamentary representation, rectorship of Copenhagen University and significant contributions to education and public health, especially in the field of neurology. As June 9, 2004 marks the centenary of the birth of Dr. Mogens Fog, it is timely and appropriate that the story of the Fogs is recognised.

P-182

An infant with central nervous system complications of disseminated tuberculosis

J Mah (Calgary), J Kellner (Calgary), D Kunimoto (Edmonton), D Kaura (Calgary), MW Mah (Calgary)*

Background: In developed countries, young children usually acquire tuberculosis (TB) from an overtly infected adult, and are at risk for disseminated disease. We describe an infant with multiple brain tuberculomas, seizures, and ischemic infarcts due to disseminated TB. *Methods:* Case report. *Results:* A 9-month old Canadian-born white girl presented with one month of cough, irritability, fever, and persistent right upper lobe pneumonia. There was no known infectious diseases contact. After admission, she developed meningismus, bulging fontanelle, and right focal seizures. CTbrain showed multiple enhancing lesions in her cerebral hemispheres, brainstem, and cerebellum, with leptomeningeal enhancement. Bronchoalveolar lavage specimen was positive for acid-fast bacilli and confirmed TB. She received phenobarbital, antibiotics, dexamethasone, and anti-TB drugs. Four days later, she developed left focal seizures. Repeat brain imaging showed hydrocephalus and bilateral cerebral infarction due to vasculitis. Despite extensive brain injury, she made a remarkable recovery and remained on anti-TB drugs and a 6-week course of corticosteroids. *Conclusions:* A child with severe disseminated TB recovered with prompt empiric anti-TB therapy given despite absence of known TB contact. Adjunctive corticosteroids may reduce morbidity and mortality.

P-183

Does a single item report of global well-being correlate with SF-36 results in a caregiver satisfaction survey?

J Mah (Calgary), T Fung (Calgary), K Douglas-England (Calgary), M Verhoef (Calgary), S Tough (Calgary)*

Background: Caregivers are often asked to report on quality of care and responses are used to alter service delivery to meet client needs. Understanding underlying issues influencing satisfaction is critical to interpreting survey findings. *Methods:* Caregivers attending the Alberta Children's Hospital pediatric neurology clinic completed the Short Form Health Survey (SF-36), the Client Satisfaction Questionnaire (CSQ), the Family Centered Care Survey (FCCS), and a single item report on their overall physical or mental well-being. *Results:* 104/116 (90%) caregivers completed the survey. The majority (61.5%) were very satisfied, with median CSQ of 27.7 (range 15-32) and FCCS of 4.5 (range 2.1-5.0). Logistic regression identified caregiver's mental health (OR 1.07, 95% CI 1.01-1.14) as a significant predictor of satisfaction. Family income, severity of child's illness, caregivers marital status, and caregivers physical health did not influence satisfaction response. The correlation between the single self-report item and its corresponding SF-36 physical or mental score was high (both Rxy = 0.69). *Conclusions:* Given the significantly positive association between caregivers' mental health and satisfaction with health services, it is important to consider mental status as a covariate in interpreting satisfaction surveys. Caregivers self-report of well-being appears to be a reliable indicator of their SF-36 scores.

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P-184

The value of intravenous immunoglobulin (IVIG) in the treatment of malignant migrating partial seizures of infancy (MMPSI).

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Background: In 1995 Coppola et al described 14 infants with a previously unrecognized infantile epilepsy syndrome, (MMPSI), a malignant disorder with developmental arrest, seizure onset in infancy, nearly continuous electroencephalographic seizures involving multiple independent areas originating in both cerebral hemispheres with no identifiable cause and normal neuroimaging. The seizures are intractable to all known anticonvulsants including corticosteroids. We describe the first patient with MMPSI treated successfully with IVIG after conventional anticonvulsants failed. *Patient:* An 11-month-old female of normal neurodevelopment presented with a focal left sided tonic seizure with subsequent generalization. The seizures occurred in clusters of 5-10, each lasting 1-2 minutes or longer over a 2-3 hour period. *Results:* All investigations were normal except the EEG which showed features compatible with migrating partial seizures with epileptic activity from 2 separate locations in the left and 1 separate location in the right cerebral hemisphere. Conventional anticonvulsant therapy including clonazepam, vigabatrin and stiripentol failed. Two weeks later IVIG (1g/kg) over 6 hours given daily for 3 days resulted in complete resolution of her seizures. At a 1-year follow-up she remains seizure free with a normal EEG on clonazepam, stiripentol and 6 weekly IVIG therapy. *Conclusions:* IVIG should be considered as an adjunctive therapy for children whose seizures do not respond to conventional antiepileptic drugs as in MMPSI.

P-185

Neurological complications following bone marrow transplantation in sickle cell disease: report of the first two Canadian cases

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Background: Bone marrow transplantation (BMT) for treatment of sickle cell disease (SCD) is associated with a higher risk of neurological complications compared to other conditions. *Method:* We report the findings in the first two Canadian patients to have undergone BMT for SCD. *Results:* Both patients were 11-year-old females. Treatment was according to standard protocol. Antecedents included stroke and acute chest syndrome in the first and recurrent severe vaso-occlusive crises in the second. Neurological complications included partial secondarily generalized seizures and subarachnoid hemorrhage ten days after transplantation in the first and transient cortical blindness the day after transplantation in the second. Cyclosporine associated lesions in the first and small vessel thrombosis in the other were seen on magnetic resonance imaging. Electroencephalographic findings consisted of bilateral epileptic discharges in the first and background slowing in both. Cyclosporine was stopped at the time of neurological complications in both patients. Symptoms three months out consisted of seizure recurrence in the first patient. *Conclusions:* This first Canadian experience of BMT in SCD compels us to evaluate the clinical variables necessary to reduce the risk of neurological complications. A better understanding of the underlying pathophysiology is needed.

P-186

Withdrawn

P-187

Immunoglobulin therapy in children with myasthenia gravis: systematic review of adult and pediatric trials

MF Rafay (Toronto), J Vajsar (Toronto)*

Introduction: Therapies for myasthenia gravis (MG) are also aimed at immunomodulation with plasma exchange (PLEX) or immunoglobulin (IVIG). IVIG, compared to PLEX, is easy to administer in children, however, literature is limited regarding its efficacy in juvenile MG. It is unclear whether adult data can be extrapolated to juvenile MG. *Objective:* To evaluate the role of IVIG in juvenile MG. *Methods:* Systematic review of all adult and pediatric trials which included cases with MG and involved use of IVIG. *Results:* In adult literature, 11 open and 3 randomized trials were identified. Adult open trials found IVIG efficacy between 65%-75% and considered IVIG safe and effective alternative to PLEX for patients with exacerbation or progression. Adult randomized trials found IVIG efficacy comparable to PLEX with fewer side effects, except one inconclusive prematurely terminated study. In pediatric literature, 2 case reports, 3 open trials and no randomized trials were found.12 published and 6 unpublished MG cases were treated with IVIG. All except one improved with remission in 7. Safety profile was similar to adults. *Conclusions:* Like adults, IVIG appears to be safe and effective alternative treatment in juvenile MG. Lack of strong evidence, cumulative long-term efficacy and morbidity profile warrants randomized trials in juvenile MG.

P-188

Predicting kernicterus in severe unconjugated hyperbilirubinemia

P Satodia (Toronto), C Tan-Dy (Toronto), S Blaser (Toronto), S Fallagh (Toronto), A Moore (Toronto)*

Objective: To identify prognostic predictors of kernicterus in the newborn with severe unconjugated hyperbilirubinemia. *Methods:* Retrospective cohort study with follow-up to a mean age of 17 months of newborns > 35 weeks gestation at birth, (Jan 1999-March 2003) to a regional tertiary care center. Abstracted data included clinical presentation, peak bilirubin levels, neuroimaging, management, and long term follow-up. Predictors of kernicterus were identified by univariate and multivariate analyses. *Results:* 29 newborns were analysed. Peak bilirubin level ranged from 286 µmol/L to 780 µmol/L. All infants required an exchange transfusion. One died and 7 (27%) had findings of kernicterus at follow-up. Birth weight, gestational age, peak MBR, and age at presentation were not predictive of kernicterus. Evaluation PPV NPV sensitivity specificity pvalue neuro exam 89% 100% 100% 95% p<0.0001 seizures 83% 87% 62.5% 95% p=0.0053 ABR (acute) 67% 100% 100% 80% p<0.0001 (n =29) ABR 100% 100% 100% 100% p<0.0001 (follow-up) MRI (n=11) 45% 0% 100% 0% NS DWI (n=11) 0% 54% 0% 100% NS. *Conclusions:* Auditory evoked responses at 5-8 months of age were highly predictive of

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kernicterus. The usefulness of neuroimaging in the acute phase remains unclear.

P-189

Towards the identification of a developmental pathway of cognitive recovery from paediatric acquired brain injury (ABI)

LA Scott (Hamilton), C DeMatteo (Hamilton), S Hanna (Hamilton)*

Background: Given the results of our earlier follow-up study of children with TBI we designed a longer term prospective inception cohort study to follow school aged children with acquired brain injury (ABI). *Method:* Medical and demographic variables were collected on all 422 children with ABI admitted to McMaster Children's Hospital during a 24 month period. Functional and clinical outcome data was then collected on 187 participants at 8, 12 and 20/24 months post-injury. Upon admission pre-morbid cognitive and functional status was collected via questionnaires and review of all school reports. *Results:* Using regression analysis results are presented as to which medical and pre-morbid variables best predict cognitive outcome at the times sampled. Growth curve analysis also indicates the possible pattern (s) of cognitive recovery overtime. *Conclusions:* The influence of pre-morbid behavioural and cognitive factors are discussed on the cognitive outcome and recovery pathways from ABI. Some evidence is offered as to the impact and interplay amongst pre-morbid status, recovery and severity of injury.

P-190

A pilot study of CO-OP with children with traumatic brain injury (TBI)

LA Scott (Hamilton), C Dematteo (Hamilton), C Missiuna (Hamilton)*

Background: Following TBI, children experience persistent cognitive, motor and psychosocial deficits that affect school performance. Intervention typically focuses on retraining component skills (attention and memory) but generalization to other life skills has not been demonstrated. A cognitive, problem-solving approach, the Cognitive Orientation to daily Occupational Performance (CO-OP) is an individualized treatment that emphasizes teaching of a global executive problem-solving strategy and strategies necessary for successful task performance. CO-OP uses child-identified goals to address issues of generalization. *Method:* In this pilot study, ten children 7 to 15 years of age with moderate to severe TBI and ongoing school and self-care difficulties were identified. Following assessment, 8 children entered a single-case design study comprised of 10 weekly sessions provided by trained therapists. *Results:* Pre- to post-test treatment scores will be presented including: parent and child ratings of goals, adaptive behaviour, participation ratings and school report cards. *Conclusions:* Findings suggest that children with TBI successfully learn specific strategies that can be generalized across tasks and settings but have difficulty learning the global executive strategy goal-plan-do-check. Implications will be discussed.

P-191

Incidence of autoimmune thyroid disorders in juvenile myasthenia gravis

N Shah (Winnipeg), J Vajsar (Toronto), L Macmillan (Toronto), J Boyd (Toronto)*

Background: Myasthenia gravis (MG) occurs with autoimmune thyroid diseases (AITD) and other autoimmune disorders. Previous reports demonstrated a 2% incidence of AITD in juvenile MG. *Objectives:* To review the incidence of AITD and other autoimmune conditions in juvenile MG patients and their first degree relatives. *Methods and results:* A retrospective analysis of 20 patients (age 1-18 yrs., M: F ratio 1:3) with juvenile MG diagnosed and followed-up in a pediatric neuromuscular clinic. Ten of these patients had ocular MG; four had ocular MG that generalized while six had generalized MG at the onset. Acetylcholine receptor antibodies were positive in 9 of 12 tested patients. Thyroid studies were performed in 12 patients and were abnormal in 3. Two patients were diagnosed with Graves disease and one with autoimmune hypothyroidism with positive anti-microsomal and anti-thyroid globulin antibodies. One child with new onset of Graves disease with MG was in remission that relapsed with the onset of hyperthyroidism but improved after treatment with a combination of methimazole, steroids and mestinone. Family history of autoimmune disorders was positive in 4 patients, including AITD, Hashimotos thyroiditis, diabetes mellitus, rheumatoid arthritis and autoimmune dermatitis. One patient had a monozygotic twin sister with autoimmune hepatitis. *Conclusions:* We report a higher incidence (25%) of AITD in patients with juvenile MG and conclude that juvenile MG patients should be investigated for AITD. Treatment of coexistent AITD may improve the response of MG patients to immunomodulatory and symptomatic therapy.

P-192

Unique neuroimaging abnormalities in a child with hyperprolinemia type 2

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Background: Hyperprolinemia type 2 is a rare, autosomal recessive disorder associated with mental retardation and epilepsy in childhood. Proline is considered to act as a modulator of excitatory (glutamate) synaptic transmission. *Methods:* We report the clinical findings and unique neuroimaging abnormalities in a child with hyperprolinemia type 2. *Results:* This 18-month-old girl presented with absence seizures, hypotonia and mild developmental delay. The EEG showed electrographic absence seizures with atypical spike and wave activity. She had marked elevation of plasma proline (3171 μmol/L), and an O-aminobenzaldehyde urine test was positive. She had normal basal AST activity and normal percent stimulation by Vitamin B6, which argues against a functional vitamin B6 deficiency. The T2-weighted magnetic resonance imaging (MRI) sequences at age two years demonstrated symmetrical abnormal hyperintensity of tracts in the posterior pons and midbrain and subtle hyperintensity in the posteromedial lentiform nuclei in the globus pallidus. The cerebral cortex and white matter appeared normal. *Conclusions:* To our knowledge, this is the first report of neuroimaging abnormalities in a child with

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hyperprolinemia type 2. The MRI abnormalities correspond to sites of high neuronal activity in young infants. Biochemical tests did not support treatment with vitamin B6 in our child.

P-193

Reliability and stability of the gross motor function classification system (GMFCS) for young adults with cerebral palsy (CP)

E Wood (Halifax), D McLean (Halifax), W Stewart (Bangor), R Hung (Toronto), K Gordon (Halifax), J Dooley (Halifax)*

Background: GMFCS measures gross motor function in children with CP. Function is from I (most function) to V (least). There are 4 age bands (<2, 2-4, 4-6 and 6-12 years). Inter-rater reliability and stability from age 2 to 12 years is high. The objective of this study was to determine the inter-rater reliability and stability of the GMFCS into adulthood. *Methods:* Records from the children's hospital were matched with records from the rehabilitation centre. One rater reviewed the child's chart and assigned the GMFCS for each age band. Two blinded raters reviewed the adult chart and assigned a GMFCS from the last contact. *Results:* Matched records were available for 19 adults with CP. GMFCS at first contact (median 19 months) were: I:1, II:9, III:3, IV:3, V:3. GMFCS at last contact (median 23 years) were: I:1, II:7, III:1, IV:4 and V:6. Inter-rater reliability was 0.809 for the adult level. Kappa was greatest (0.829) between age 6-12 and adulthood, and least (0.671) between ages 2-4 and the adult level. *Conclusions:* The GMFCS relies on basic functional information, and can reliably be assigned retrospectively from the adult record. Young adults with CP show stable gross motor function, as described by their GMFCS level.

NEUROLOGY/NEUROSURGERY – GENERAL

P-194

Localized electrical transcranial motor evoked potentials for monitoring cranial nerves during skull base surgery

R Akagami (Vancouver), C Dong (Vancouver), B Westerberg (Vancouver)*

Objective: To describe a novel monitoring technique that allows "functional" assessment of cranial nerve continuity during skull base surgery. *Methods:* Facial motor evoked potentials (MEP) in 42 consecutive patients were obtained by localized transcranial electrical stimulation in all patients requiring facial nerve monitoring over a one-year period from November 2002 to November 2003. With transcranial electrical stimulation localized to the contralateral cortex, facial nerve MEP are obtained through stimulation of more proximal intracranial structures. *Results:* Logistic regression revealed that the only statistically significant variable to predict satisfactory immediate postoperative facial function is the final to baseline facial MEP ratio ($0.01>p>0.005$). Contingency table analysis showed high correlation (Chi square $p=0.0001$) and acceptable test characteristics using 50% final to baseline MEP ratio cut-off to predict House-Brackmann (HB) grade 1 and 2 function. *Conclusions:* Facial nerve MEPs recorded intra-operatively during skull base surgery using this technique predicts immediate postoperative cranial nerve outcome. This technique can be used prior to dural opening to detect any facial nerve injury during petrous bone or extradural skull base dissection, and can also be used to monitor other motor cranial nerves in skull base surgery.

P-195

Central nervous system involvement in miliary tuberculosis: a case report and review of the literature

A Attar (London), A Krayem (London), W Habhab (London)*

Background: Up to 10% of immunocompetent patients with tuberculosis (TB) develop central nervous system (CNS) involvement. TB meningitis is the most common presentation of CNS TB. Rarely, miliary TB produces disseminated CNS disease. *Method:* Case report and review of the literature. *Results:* We report a 79-year-old lady with miliary TB and CNS involvement. Subsequent to her presentation with dry cough and fever, she developed clinical features consistent with meningoencephalitis. Neuroimaging showed marked hydrocephalus, diffuse meningeal enhancement and widespread, ring enhancing lesions in the pons and both cerebral and cerebellar hemispheres. Chest X-ray revealed bilateral fine nodular interstitial lung infiltrate. The diagnosis of miliary TB was confirmed by trans-bronchial lung biopsy. She died of hydrocephalus and multi-organ failure, one day after institution of anti-TB medications and glucocorticoids. *Conclusions:* Disseminated TB should be considered early in patients presenting with both pulmonary and extra-pulmonary clinical features. The reported neuroimaging picture is rare but well-recognized. A diagnostic work up for CNS TB is warranted in cases of miliary TB, as the delay in instituting anti-TB treatment carries high mortality.

P-196

Frequency of some migraine initiating and aggravating factors

P Bahrami (Vancouver), A Bayat (Tehran, Iran)*

In order to obtain the frequency of some migraine initiating and aggravating factors, a descriptive study was performed on 200 outpatients of Tammin Ejtemai Hospital in Korramabad Lorestan University (Iran) in Autumn 2001. After diagnosis of disease by migraine criteria, patients were asked about the effect of some aggravating factors on severity of headache. The data were collected and analyzed by SPSS program. Noise was the most frequent aggravating factor (86.5 percent), 44% of females and 24% of males said bathing more than one hour, result in aggravating headache. This statistical difference between males and females underwent χ^2 test and was statistically significant (PV=0.04). Some different data about effect of foods on severity of headache were obtained. 31% of patients said that some foods cause aggravating of headache. 10% of patients said some foods reduce their headache and 45% told that foods had no effect on severity of headache.

P-197

Canadian survey: management of chronic/subacute subdural hematoma

A Cenic (Hamilton), M Bhandari (Hamilton), K Reddy (Hamilton)*

Background: To ascertain neurosurgical practices in the treatment of chronic/subacute subdural hematoma in the Canadian

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adult population. *Methods:* One page questionnaire faxed to each neurosurgeon in Canada with questions relating to their practice in the management of this common neurosurgical problem. Data were analyzed using Chi-Square statistic. *Results:* The response rate in this survey was 61% with the respondents being predominantly neurosurgeons. The respondents preferred 1- and 2-burr-holes significantly more than craniotomy or twist-drill as the procedure of choice for initial treatment of this disorder. Craniotomy and 2-burr-holes were preferred for recurrent subdural hematoma. Greater than 75% irrigated the subdural cavity, used a drain, and did not use anti-convulsants or corticosteroids. There appears to be a large variation with respect to keeping patients supine following surgery. Greater than 2/3 used ONLY pre-op antibiotics. Majority of the surgeons perform their procedures in the operating room. Majority of the group felt they would NOT alter their management based on patient's age, and that they would alter their management based only on the patient's clinical condition. *Conclusions:* Our survey has identified variations in practice patterns amongst Canadian neurosurgeons with respect to treatment of subacute and chronic subdural hematoma at their first and recurrent presentations. This survey is expected to form a basis for the design of a randomized controlled trial in the evaluation of the best treatment for this condition.

P-198

Clinical pathological conference: 58-year-old woman with progressive vertigo, deafness and weakness

D Chong (London), M Strong (London), M Shkrum (London), P Kalapos (London), R Hammond (London)*

Background: When the etiologies of severe, progressive neurological diseases cannot be ascertained by laboratory, imaging and electrophysiological examinations, paraneoplastic disorders are often considered. The pathology of one such case was thoroughly studied to correlate clinical features and investigations. *Methods:* Consent was obtained from the family for an autopsy. Pertinent sections from the mediastinum, brain, spinal cord, peripheral and cranial nerves were processed for pathological examination. The case was then presented in grand rounds format and a neurology consultant was asked to formulate a differential diagnosis. *Results:* Histology revealed disseminated inflammation affecting neocortex, hippocampus, cerebral white matter, basal ganglia, thalamic and hypothalamic nuclei, brainstem, cerebellum, spinal cord as well as cranial and spinal nerve roots. Parenchymal changes included extensive microglial activation, perivascular lymphocytic infiltrates and neuronophagia. *Conclusions:* The pathological diagnosis was paraneoplastic encephalomyeloneuritis secondary to undifferentiated small cell carcinoma, providing a striking example of the anti-Hu syndrome. Devastating neuronal damage escaped diagnosis through *in vivo* investigations, emphasizing that normal imaging does not exclude pathological changes. A review of the current literature of paraneoplastic syndromes, identifies controversies such as whether anti-neuronal antibodies are simply markers of destruction, or whether they reach cytoplasmic and nuclear antigens to cause cell death.

P-199

Recurrent low cerebrospinal fluid pressure headache following epidural anaesthesia

MB Cossoy (Halifax), IA Grant (Halifax)*

Background: Post-dural puncture headache is a known complication of epidural anaesthesia. Headache onset is usually one to two days following the procedure. The most successful treatment is an epidural blood patch (EBP). In patients requiring EBP, 91% are headache-free after two hours, with 87% satisfied long-term, although only 61% have both immediate and permanent relief. *Clinical Case:* A 19-year-old woman had an epidural anaesthetic during labour. She developed a low CSF pressure headache two days later. She received EBP after failing conservative management. Although she had immediate improvement, the headache recurred after 24 hours. She had a second EBP three weeks later with symptom resolution. The headache returned again after two weeks and she had a third EBP seven weeks after the previous EBP. She had no relief and was admitted to hospital where she had a course of oral prednisone. MRI demonstrated meningeal enhancement and downward displacement of the brain. She was symptom-free for three months before developing another postural headache which resolved after four weeks of conservative management. No recurrences were preceded by any recognized precipitants. *Conclusions:* Low CSF pressure headaches following epidural anaesthesia are presumed to be secondary to inadvertent lumbar puncture. The patient presented here is unusual both in the frequent failure of EBP with late relapses and in her recurrence after three months symptom-free. We were unable to find any similar reports in the literature.

P-200

Neurological complications after liver transplantation: incidence and predictive factors in 101 consecutive recipients

R Dhar (London), B Young (London), M Levstik (London), C Ghent (London), P Marotta (London)*

Background: Neurological complications may impart significant morbidity after liver transplantation (LT). The factors predictive of these events have not been well-described. *Methods:* Retrospective review of consecutive LT recipients evaluated preoperative variables and their association with specific neurological complications in the postoperative period. *Results:* Of 101 recipients, 52% had a pre-LT history of hepatic encephalopathy (HE) and 26% had active encephalopathy prior to LT. Child-Pugh scores ranged from 5-14 (median 9); 44% were Class C. The most common complication was encephalopathy, occurring in 28% (severe in 11%), while seizures and drug neurotoxicity occurred in 4% and 12% respectively. Mortality was 3%, all occurring in those with neurological complications. Median length of stay was 12 days, but was increased to over 20 days in those with postoperative encephalopathy. There was no association between indication or status for LT and risk of neurological events, but those with encephalopathy tended to be older with a higher Child-Pugh score (10.25 vs 8.55). However, the best predictors were a prior history of HE (OR 3.2, 95%CI 1.3-8.2) and immediate pre-operative HE (OR 8.4, 3.1-22.9). *Conclusions:* Encephalopathy is common after LT, results in greater lengths of stay, excess mortality, and is best predicted by pre-operative HE.

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P-201

Infectious myelitis and cauda equina syndrome complicating streptococcus pneumonia meningitis

R Dhar (London), B Young (London)*

Background: Spinal cord and cauda equina dysfunction are uncommon complications of bacterial meningitis. *Methods:* We describe a case of paraplegia resulting from contiguous spread of a paraspinal abscess into the meningeal space. *Results:* A healthy 55-year-old man developed fever, headaches and confusion after a flu-like illness with right lower back pain and focal tenderness. He subsequently became unresponsive with meningismus and a fixed dilated right pupil. Examination revealed right third, fourth, fifth, and seventh cranial nerve palsies as well as flaccid paraplegia. Aspiration from the lower back during attempted lumbar puncture revealed frankly purulent fluid; cultures grew *Streptococcus pneumoniae*. MRI showed hydrocephalus and diffuse leptomeningeal enhancement around the cord with loculated enhancing intradural fluid collections extending from the cervical spine down to and compressing the cauda equina nerve roots. There was signal abnormality in the cord from C7 to T5. The right L3-4 facet joint harboured a soft tissue infection. The patient recovered consciousness with no loss of upper limb function after penicillin and corticosteroid therapy but he remained paraplegic with urinary retention and cranial nerve palsies. *Conclusions:* Cauda equina syndrome and myelitis can complicate the course of bacterial meningitis and have a poor prognosis for recovery.

P-202

Hashimotos encephalopathy is not always associated with cerebral hypoperfusion on SPECT imaging

J Diggle (Calgary), P Chen (Calgary), P Federico (Calgary)*

Background: Hashimotos encephalopathy (HE) is a reversible encephalopathy observed in patients with Hashimotos thyroiditis. The mechanisms underlying HE are incompletely understood. Proposed mechanisms include an autoimmune neuronal process, a demyelinating disorder, and cerebral hypoperfusion secondary to a small vessel vasculitic process. Evidence supporting the latter mechanism comes from numerous recent reports of patients with HE who have normal cerebral angiograms and yet have abnormal single photon emission computed tomography (SPECT) scans. We describe a case of HE with normal SPECT imaging which does not support this putative mechanism. *Methods:* Case report. *Results:* A clinically euthyroid 43-year-old woman was admitted with a two day history of progressive confusion and was found to have highly positive anti-thyroglobulin and anti-thyroid peroxidase antibodies. Serum free T4 was normal and TSH was minimally elevated. Serial EEGs showed mild background:slowing consistent with an encephalopathy. No evidence of demyelination was found on structural MRI or CSF analysis (including oligoclonal bands). MR angiography, diffusion-weighted MR imaging, and a hexamethyl-propyleneamine-oxime (HMPAO) SPECT scan was normal, showing no evidence of hypoperfusion. *Conclusions:* The observation of normal SPECT imaging in the setting of HE calls in to question the proposed mechanism of a small vessel vasculopathy, at least in a subset of patients with HE. In addition, no evidence of demyelination was found. Thus, the possibility of an autoimmune neuronal process mediating the clinical syndrome of HE should be considered.

P-203

Brainstem seizures a clinical report

J Diggle (Calgary), N Pillay (Calgary)*

Background: In the rodent brain, there seems to exist two seizure systems that mediate generalized tonic-clonic seizures. Brainstem seizures are those with their primary electrophysiologic origin in the brainstem. Mechanisms of brainstem seizures in the rat have been proposed. In the human literature, there are a number of reports of suspected brainstem seizures. However, more recent reports are lacking despite ongoing recognition of paroxysmal events in patients with brainstem lesions. We believe the recognition of brainstem seizures as a distinct entity is waning. Recognition of brainstem seizures may hasten appropriate anti-epileptic therapy. We report a case of suspected brainstem seizures observed at our institution. *Methods:* Case report. *Results:* A 51-year-old woman was admitted with a subacute onset of hemi-sensory deficit, ataxia, and up-beating nystagmus. MRI revealed a lesion at the cervicomedullary junction that was felt to represent a post-infectious demyelinating lesion. In hospital, we observed episodes of tonic-clonic arm movements and facial twitching without impairment of consciousness. EEG was relatively silent, showing intermittent generalized slowing. There was a dramatic reduction in the frequency of events with phenytoin. *Conclusions:* In both animal models and previous case reports, brainstem seizures are described as having distinct clinical-electroencephalographic features. Despite this, we feel the potential epileptogenesis of the brainstem is underappreciated. We propose that in patients with brainstem lesions and paroxysmal events, brainstem seizures should be entertained in the differential diagnosis and appropriate therapies be pursued.

P-204

A case of superficial siderosis associated with chronic anticoagulation

W Fitzpatrick (Saskatoon), C Voll (Saskatoon)*

Background: Superficial siderosis is a rare syndrome caused by recurrent subarachnoid hemorrhage, with accumulation of hemosiderin in the leptomeninges, subpial layers and subependyma of the brain and spinal cord. With approximately 100 cases reported to date, the clinical spectrum ranges from severe and debilitating to potentially asymptomatic. Equally striking is the pathogenetic heterogeneity. *Methods:* We submit a poster presentation. *Results:* We present a case of a progressive lower motor neuron syndrome with radicular pain and MRI evidence of superficial siderosis in association with chronic anticoagulation. A 54-year-old female on coumadin for protein C deficiency first presented 8 years ago with low back pain, intermittently radiating down her left leg. Neurological exam was unremarkable. Nerve conduction studies (NCS), electromyography (EMG), CTmyelography and MRI of the spine were normal. Her symptoms persisted, with waxing and waning severity. She developed urinary hesitancy and retention, followed by wasting of the left calf. NCS demonstrated a polyradiculopathy. MRI of the brain and cord revealed the diagnosis of superficial siderosis. Cerebral and spinal angiography was

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normal. *Discussion:* Anticoagulation therapy has not been considered among the causes of superficial siderosis; however it has been previously reported. This case demonstrates that siderosis should be considered among the potential complications of chronic anticoagulation.

P-205

Review of current concepts in selective limbic surgery for intractable psychiatric illness

J Hall (Montreal*)

Background: Prior to the era of modern psychopharmacology, ablative procedures were proposed for several psychiatric conditions. The techniques initially employed were as crude as the rationale behind their apparent effectiveness. Injudicious application and complications of these initial procedures combined with more effective medical alternatives lead justifiably to a dramatic decline in this type of functional neurosurgery. Our knowledge of the neurobiology of psychiatric illness is expanding at a time when modern neuroimaging and neurosurgical technique continues to be refined. Despite current behavioural and pharmacologic treatment some patients with psychiatric conditions remain intractable and incapacitated. This presentation will review what is known about the types of selective limbic surgery currently practiced. *Methods:* Web-based, library literature review and personal communication with centers currently performing limbic surgery for psychiatric indications have been used to generate the data for this presentation. *Results / Conclusions:* The four most common ablative procedures for specific psychiatric indications are: cingulotomy, anterior capsulotomy, subcaudate tractotomy and limbic leucotomy. The risks and benefits of these procedures will be discussed along with available information on appropriate patient selection and outcome data.

P-206

Arachnoid cysts: a retrospective review

D Klironomos (Montreal*), *JL Montes (Montreal*), *JP Farmer (Montreal*)

Background: The aim of this retrospective review is to determine the optimal surgical management of intracranial arachnoid cysts. Arachnoid cysts are fluid-filled cavities which likely arise congenitally. They can arise in any cistern but most commonly are found in the sylvian fissure. They can present with symptoms of raised intracranial pressure, or seizures. *Methods:* A retrospective chart review was conducted. All the cases of intracranial arachnoid cysts seen at the Montreal Children's Hospital over the past 10 years were reviewed. The cases were compared with respect to surgical versus nonsurgical management and if surgery was employed, whether craniotomy and fenestration of the cyst into the basal cisterns or cystoperitoneal shunting resulted in a better outcome. These results were compared with other published series. *Results:* It was found that in this series, craniotomy and marsupialization of the cyst into the basal cisterns was as effective as cystoperitoneal shunting in reducing the size of the arachnoid cysts. There were slightly more complications in the group treated with cysto-peritoneal shunting, related to shunt malfunction. *Conclusions:* Although the precise management of intracranial arachnoid cysts depends on cyst location, shunt independence should be the goal of treatment.

P-207

MR spectroscopy in a case of cerebrotendinous xanthomatosis

T Lad (Saskatoon*), *S Harder (Saskatoon*), *J Donat (Saskatoon*)

Background: Cerebrotendinous xanthomatosis (CTX) is a rare inherited disorder of cholesterol metabolism. A deficiency of sterol-27-hydrolase produces defective bile acid synthesis and accumulation of cholestanol. The disorder is clinically characterized by the presence of juvenile cataracts, tendon xanthomas and progressive neurological impairment. Early diagnosis is essential, as treatment may prevent progression of disease. Neuroradiologic findings aid in the diagnosis of CTX, and are usually characterized by T2 hyperintensity within the dentate nuclei and surrounding cerebellum. Recently, MR spectroscopy has been suggested as a useful measure of disease severity and outcome. *Methods:* Case report and literature review. *Results:* We report the case of a 23-year-old male with a one year history of progressive spastic paraparesis. Initial MRI demonstrated globular areas of increased T2 signal within the deep cerebellar gray matter and dentate nuclei. Serum cholestanol levels were elevated, thus confirming a diagnosis of CTX. MR spectroscopy was within normal limits. *Conclusions:* Although MR spectroscopy has previously been reported to be abnormal in patients with CTX, this case demonstrates the absence of abnormal findings despite metabolically proven disease. MR spectroscopy may not always be abnormal in CTX, and therefore cannot be used as a predictor of severity and outcome in this subset of patients.

P-208

Management of nontraumatic intracranial purulent collections

B Lo (Hamilton*), *R DeVilliers (Hamilton*)

Background: Nontraumatic intracranial purulent collections arise infrequently in developed countries. In the UK and USA, they account for less than 5 cases/million/year. Surgical options include aspiration and surgical excision. *Methods:* We retrospectively (January 1 to December 31, 2003) reviewed four cases of surgically-treated intracranial pus at the McMaster Neurosurgical Service, which serves a population of over 662, 400. *Results:* (1) 47-year-old man: flu-like symptoms, headaches, decreased LOC. CT scan: R frontotemporal abscess with mass effect. CT-guided stereotactic aspiration; culture: *Streptococcus*. Treated with Cefotaxime and Flagyl. Postoperatively, L-sided weakness. (2) 60-year-old man: right mastoiditis and seizures. CT scan: R posterior temporal convexity epidural abscess. Right corticomastoidectomy, right temporal stealth-guided burr hole aspiration; culture: no growth. Treated with Ceftriaxone. Postoperatively, no neurological deficits. (3) 68-year-old woman: seizures, right ear discharge, headaches, decreased LOC. CT scan: R subdural empyema with mass effect. Right decompressive craniectomy; culture: *Streptococcus pneumonia*. Treated with Cefotaxime and Clindamycin. Postoperatively, L-sided weakness. (4) 20-year-old man: headaches, flu-like symptoms, decreased LOC. CT scan: L convexity subdural empyema with mass effect. Left decompressive craniectomy; culture: *Gemella morbillorum*. Treated with Cefotaxime and Flagyl.

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Postoperatively, R-sided weakness, cognitive deficits. *Conclusions:* Early clinical diagnosis is the key to successful treatment of intracranial purulent collections. Yet, modern management modalities are still associated with significant morbidity.

P-209

Sarcoidosis presenting as intracranial mass lesion

F Maroun (St John's), H Clarke (St John's), J Barron (St John's), J Jacob (St John's), N Hache (St John's), G Murray (St John's), G O'Brien (St John's)*

Background: Sarcoidosis presenting as intracranial neoplasm is extremely rare. *Methods:* A 35-year-old man with a past history of severe head injury fifteen years ago was followed for thickened optic chiasm of undetermined etiology. On follow-up MRI a right frontal mass lesion was discovered and removed. Pathology confirmed the granulomatous nature of the lesion. *Conclusions:* Clinical and therapeutic implications are discussed.

P-210

Guidelines for reoperation in patients with dural allografts: the Newfoundland experience

F Maroun (St John's), C Manuel (St John's), A Patten (St John's), G Murray (St John's), J Barron (St John's), A Engelbrecht (St John's), J Jacob (St John's), J Hutchinson (St John's)*

Background: Dural allografts (Lyodura and Tutoplast) have been used extensively in neurosurgical centers. Lyodura was no longer licensed in Canada since 1998 and Tutoplast since April, 2002. Guidelines for reoperation on those patients were never formulated. *Methods:* Reoperation on five patients harvesting dural allografts have been studied. Innovative surgical techniques to minimize financial implications are described. *Conclusions:* Guidelines should be established by neurosurgeons and Health Canada to deal with the ethical and financial implications of this group of patients.

P-211

A case of central pontine myelinosis (CPM) following liver transplantation and tacrolimus therapy

M Mehdiratta (Vancouver)*

Background: CPM is a clinical condition known best to occur following a rapid correction of hyponatremia. It is also a recognized entity which may occur post liver transplantation with normal sodium levels. *Methods:* A 67-year-old woman underwent liver transplantation and was maintained on tacrolimus. Postoperatively, the patient had difficulty weaning from the ventilator. Examination revealed a patient with a fluctuating LOC and normal brainstem findings. She had distal weakness (2/5), hyperreflexia (3+) with bilateral clonus and extensor plantars. The patient improved neurologically as her tacrolimus levels declined, though they were never in the toxic range. She did not have any major alterations in her sodium levels. *Results:* MRI spine and CT head were normal. MRI head revealed hyperdensities on T2 FLAIR imaging in the pons consistent with CPM. *Conclusions:* This patients CPM was likely related to her liver transplantation, as CPM may complicate this procedure. However, there are case reports of tacrolimus causing brainstem leukoencephalopathy. While it is difficult to differentiate the cause, it is important to recognize that the presenting features of CPM post liver transplantation are not classic. Most patients present with an absence of brainstem signs and only with stupor or weakness.

P-212

The circulation of CSF: a phylogenetic and ontologic review

J Pugh (Edmonton), K Aronyk (Edmonton)*

Background: As the central nervous system evolved phylogenetically from primitive animals to primates and humans, there has been a parallel development in the production and circulation of cerebrospinal fluid (CSF). In studying the production, circulation, and absorption of CSF using animal models these results may not be applicable to humans. Additionally, ontologic development recapitulates phylogenetic development, thus the adult situation most likely differs from the fetal. *Methods:* To determine at what phylogenetic level CSF begins to function and circulate in a fashion similar to that in humans, a review of the animal and human literature of the past 80 years was conducted. *Results:* Many studies, particularly those using animals with highly developed nasal/olfactory structures, have suggested that extracranial lymphatics play a major role in CSF absorption. This challenges the textbook description of cerebrospinal fluid absorption at the arachnoid granulations into the dural venous sinuses. *Conclusions:* By reviewing the phylogenetic development of brain structure and CSF circulation we can determine which animal models are most applicable to conduct research on CSF absorption that would apply to human hydrocephalus treatment.

P-213

Practice patterns of recent neurosurgical graduates in Canada: how do the numbers add up?

S Woodrow (Toronto), C O'Kelly (Toronto), M Wallace (Toronto)*

Background: As of 1997 the ABNS revoked the certification of Canadian neurosurgical training programs leading to a growing concern that there will shortly be a surplus of qualified neurosurgeons in Canada. The purpose of this study is to develop a better understanding of the employment trends of recently graduated neurosurgeons. *Methods:* All neurosurgeons who passed their Canadian fellowship examinations between 1990 and 2002, their year of certification, undergraduate medical school and current city of practice were identified from a RCPSC database. *Results:* Preliminary results indicate that of the 189 candidates who passed their fellowship examination, 39% are currently practicing in the USA, while an additional 8% do so in other foreign countries. Moreover, of the 52 foreign-trained medical graduates (FMGs) who are fellows of the RCPSC, only 31% have returned to their country of undergraduate medical training. *Conclusions:* Almost half of our neurosurgical graduates seek employment outside of Canada and a large proportion of FMGs do not return to their native countries. In the absence of a dramatic rise in the number of faculty positions available in Canada, it would seem that we are training an excess of new surgeons who cannot be accommodated into the current system.

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P-214

Time course and effect of methylprednisolone on lipid peroxidation levels after acute spinal cord injury in rats

SD Christie (Halifax*), *I Mendez (Halifax*)

Background: Oxidative stress leading to lipid peroxidation is a significant cause of secondary injury following spinal cord trauma. The objectives of this project were to determine the duration of lipid peroxidation following acute spinal cord injury (SCI) and the effect of both short- and long-term administration of methylprednisolone (MP). *Methods:* 226 female Wistar rats received a clip compression SCI. Animals naïve to treatment were sacrificed at various time points between 0 and 10 days. Treated animals received clinical doses of either MP or saline for either 24 hours or 7 days and were sacrificed between 0 and 7 days. Spinal cord tissue was assayed colorimetrically for malondialdehyde (MDA) as a marker for lipid peroxidation. *Results:* MDA levels initially peaked 4 hours post injury. By 12 hours, MDAlevels returned to baseline. A second rise was observed from 24 hours to 5 days. Both peak values differed statistically from the trough values ($p<0.008$). MP reduced MDA levels ($p<0.04$) within 12 hours of injury. No effect was seen at 24 hours or beyond. *Conclusions:* Oxidative stress persists for five days following SCI in rats. MP reduces MDA levels within the first 12 hours but had no effect from 24 hours to 5 days.

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BRIEF PRESCRIBING INFORMATION

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PrTOPAMAX*
topiramate

25, 100 and 200 mg Tablets and 15 and 25 mg Sprinkle Capsules

Antiepileptic

INDICATIONS AND CLINICAL USE

TOPAMAX (topiramate) is indicated as adjunctive therapy for the management of patients (adults and children two years and older) with epilepsy who are not satisfactorily controlled with conventional therapy.

There is limited information on the use of TOPAMAX in monotherapy at this time.

Geriatrics (> 65 years of age):

There is limited information in patients over 65 years of age. (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.

WARNINGS AND PRECAUTIONS

General

Antiepileptic drugs, including TOPAMAX (topiramate), should be withdrawn gradually to minimize the potential of increased seizure frequency. In adult clinical trials, dosages were decreased by 100 mg/day at weekly intervals.

Endocrine and Metabolism

Oligohidrosis and Hyperthermia

Oligohidrosis (decreased sweating) and hyperthermia, infrequently resulting in hospitalization, have been reported in patients treated with topiramate. Oligohidrosis and hyperthermia may have potentially serious sequelae and may be preventable by prompt recognition of symptoms and appropriate treatment. Decreased sweating and elevation of body temperature above normal characterized the cases reported in patients treated with topiramate. Some of the cases were reported after exposure to elevated environmental temperatures.

These reports have primarily involved children. Patients treated with TOPAMAX, especially pediatric patients, should be monitored closely for evidence of decreased sweating and increased body temperature, particularly in hot weather. Proper hydration before and during activities such as exercise or exposure to warm temperatures is recommended.

Caution should be used when TOPAMAX is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity. (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**)

Nutritional Supplementation

A dietary supplement or increased food intake may be considered if the patient is losing weight while on this medication.

Hepatic/Biliary/Pancreatic

Decreased Hepatic Function

In hepatically impaired patients, TOPAMAX should be administered with caution as the clearance of topiramate was decreased compared with normal subjects.

Neurologic

Central Nervous System Effects

Adverse events most often associated with the use of TOPAMAX were central nervous system related. In adults, the most significant of these can be classified into two general categories: i) psychomotor slowing: difficulty with concentration and speech or language problems, in particular, word-finding difficulties and ii) somnolence or fatigue.

Additional nonspecific CNS effects occasionally observed with TOPAMAX as add-on therapy include dizziness or imbalance, confusion, memory problems, and exacerbation of mood disturbances (e.g. irritability and depression).

These events were generally mild to moderate, and generally occurred early in therapy. While the incidence of psychomotor slowing does not appear to be dose related, both language problems and difficulty with concentration or attention increased in frequency with increasing dosage in the six double-blind trials, suggesting that these events are dose related (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Paresthesia

Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX therapy. These events were usually intermittent and mild, and not necessarily related to the dosage of TOPAMAX.

Ophthalmologic

Acute Myopia and Secondary Angle Closure Glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving TOPAMAX. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within a few days to 1 month of initiating TOPAMAX therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with TOPAMAX has been reported in pediatric patients as well as adults.

The primary treatment to reverse symptoms is discontinuation of TOPAMAX as rapidly as possible, according to the judgment of the treating physician. Other measures, in conjunction with discontinuation of TOPAMAX, may be helpful (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

In all cases of acute visual blurring and/or painful/red eye(s), immediate consultation with an ophthalmologist/emergency room is recommended.

Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss.

Renal

Kidney Stones

A total of 32/1,715 (1.5%) of patients exposed to TOPAMAX during its development reported the occurrence of kidney stones, an incidence about 10 times that expected in a similar, untreated population (M/F ratio: 27/1,092 male; 5/623 female). In the general population, risk factors for kidney stone formation include gender (male), ages between 20-50 years, prior stone formation, family history of nephrolithiasis, and hypercalciuria. Based on logistic regression analysis of the clinical trial data, no correlation between mean TOPAMAX dosage, duration of TOPAMAX therapy, or age and the occurrence of kidney stones was established; of the risk factors evaluated, only gender (male) showed a correlation with the occurrence of kidney stones. In the pediatric patients studied, there were no kidney stones observed.

Carbonic anhydrase inhibitors, e.g. acetazolamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. Concomitant use of TOPAMAX, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Patients, especially those with a predisposition to nephrolithiasis, may have an increased risk of renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Therefore, adequate hydration is recommended to reduce this risk. None of the risk factors for nephrolithiasis can reliably predict stone formation during TOPAMAX treatment.

Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with impaired renal function (CL_{cr}< 70 mL/min/1.73m^2) or with end-stage renal disease receiving hemodialysis treatments may take 10 to 15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function. As with all patients, the titration schedule should be guided by clinical outcome (i.e. seizure control, avoidance of side effects) with the knowledge that patients with known renal impairment may require a longer time to reach steady-state at each dose (see **DOSAGE AND ADMINISTRATION, Dosing Considerations**).

Information for Patients

Adequate Hydration

Patients, especially those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation. Patients also should be instructed to increase and maintain fluid intake prior to and during activities such as exercise and exposure to warm temperatures to help prevent complications from decreased sweating.

Effects on Ability to Drive and Use Machines

Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on TOPAMAX to gauge whether it adversely affects their mental and/or motor performance.

Acute Myopia and Secondary Angle Closure Glaucoma

Patients taking TOPAMAX should be told to immediately contact their doctor and/or go to the Emergency Room if they/their child experience(s) sudden worsening of vision, blurred vision or painful/red eye(s).

Special Populations

Pregnant Women:

Like other antiepileptic drugs, topiramate was teratogenic in mice, rats, and rabbits. In rats, topiramate crosses the placental barrier.

There are no studies using TOPAMAX in pregnant women. However, TOPAMAX therapy should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

In post-marketing experience, cases of hypospadias have been reported in male infants exposed *in utero* to TOPAMAX, with or without other anticonvulsants; however, a causal relationship with TOPAMAX has not been established.

The effect of TOPAMAX on labour and delivery in humans is unknown.

Nursing Women:

Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive excretion of topiramate into breast milk. Since the potential for serious adverse reactions in nursing infants exposed to TOPAMAX exists, the prescriber should decide whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother and the risks to the infant.

Pediatrics (<2 years of age):

Safety and effectiveness in children under 2 years of age have not been established.

Weight Loss in Pediatrics (>2 years of age)

TOPAMAX administration is associated with weight loss in some children that generally occurs early in therapy. Of those pediatric subjects treated in clinical trials for at least a year who experienced weight loss, 96% showed a resumption of weight gain within the period tested. In 2-4 year-olds, the mean change in weight from baseline at 12 months (n=25) was +0.7 kg (range -1.1 to 3.2); at 24 months (n=14), the mean change was +2.2 (range -1.1 to 6.1). In 5-10 year-olds, the mean change in weight from baseline at 12 months (n=88) was +0.7 kg (range -6.7 to 11.8); at 24 months (n=67), the mean change was +3.3 (range -8.6 to 20.0). Weight decreases, usually associated with anorexia or appetite changes, were reported as adverse events for 9% of patients treated with TOPAMAX. The long-term effects of reduced weight gain in pediatric patients are not known.

Geriatrics (>65 years of age):

There is limited information in patients over 65 years of age. The possibility of age-associated renal function abnormalities should be considered when using TOPAMAX.

Monitoring and Laboratory Tests

It has been observed in clinical trials that topiramate treated subjects experienced an average decrease in serum bicarbonate level of 4 mmol/L and an average increase in serum chloride level of 4 mmol/L.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adults

The most commonly observed adverse events associated with the adjunctive use of TOPAMAX (topiramate) at dosages of 200 to 400 mg/day in controlled trials in adults that were seen at greater frequency in patients treated with TOPAMAX and did not appear to be dose related within this dosage range were: somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, nystagmus, and paresthesia (see Table 1).

The most common dose-related adverse events at dosages of 200 to 1,000 mg/day were: nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, and mood problems (see Table 2).

Pediatrics

Adverse events associated with the use of TOPAMAX at dosages of 5 to 9 mg/kg/day in worldwide pediatric clinical trials that were seen at greater frequency in patients treated with TOPAMAX were: fatigue, somnolence, anorexia, nervousness, difficulty with concentration/attention, difficulty with memory, aggressive reaction, and weight decrease (See Table 3).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1: Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials in ADULTS [a,b]

(Events that occurred in ≥ 2% of patients treated with TOPAMAX and occurred more frequently in patients treated with TOPAMAX than placebo-treated patients)

Body System/ Adverse Event	TOPAMAX Dosage (mg/day) Placebo (n=216)	200-400 (n=113)	600-1,000 (n=414)
Body as a Whole			
Asthenia	1.4	8.0	3.1
Back Pain	4.2	6.2	2.9
Chest Pain	2.8	4.4	2.4
Influenza-Like Symptoms	3.2	3.5	3.6
Leg Pain	2.3	3.5	3.6
Hot Flushes	1.9	2.7	0.7
Nervous System			
Dizziness	15.3	28.3	32.1
Ataxia	6.9	21.2	14.5
Speech Disorders/Related Speech Problems	2.3	16.8	11.4
Nystagmus	9.3	15.0	11.1
Paresthesia	4.6	15.0	19.1
Tremor	6.0	10.6	8.9
Language Problems	0.5	6.2	10.4
Coordination Abnormal	1.9	5.3	3.6
Hypoaesthesia	0.9	2.7	1.2
Abnormal Gait	1.4	1.8	2.2
Gastrointestinal System			
Nausea	7.4	11.5	12.1
Dyspepsia	6.5	8.0	6.3
Abdominal Pain	3.7	5.3	7.0
Constipation	2.3	5.3	3.4
Dry Mouth	0.9	2.7	3.9
Metabolic and Nutritional			
Weight Decrease	2.8	7.1	12.8
Neuropsychiatric			
Somnolence	9.7	30.1	27.8
Psychomotor Slowing	2.3	16.8	20.8
Nervousness	7.4	15.9	19.3
Difficulty with Memory	3.2	12.4	14.5
Confusion	4.2	9.7	13.8
Depression	5.6	8.0	13.0
Difficulty with Concentration/Attention	1.4	8.0	14.5
Anorexia	3.7	5.3	12.3
Agitation	1.4	4.4	3.4
Mood Problems	1.9	3.5	9.2
Aggressive Reaction	0.5	2.7	2.9
Apathy	0	1.8	3.1
Depersonalization	0.9	1.8	2.2
Emotional Lability	0.9	1.8	2.7
Reproductive, Female	(n=59)	(n=24)	(n=128)
Breast Pain, Female	1.7	8.3	0
Dysmenorrhea	6.8	8.3	3.1
Menstrual Disorder	0	4.2	0.8
Reproductive, Male	(n=157)	(n=89)	(n=286)
Prostatic Disorder	0.6	2.2	0
Respiratory System			
Pharyngitis	2.3	7.1	3.1
Rhinitis	6.9	7.1	6.3
Sinusitis	4.2	4.4	5.6
Dyspnea	0.9	1.8	2.4
Skin and Appendages			
Pruritus	1.4	1.8	3.1
Vision			
Diplopia	5.6	14.2	10.4
Vision Abnormal	2.8	14.2	10.1
White Cell and RES			
Leukopenia	0.5	2.7	1.2

[a] Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX or placebo.

[b] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

Table 2: Incidence (%) of Dose-Related Adverse Events From Placebo-Controlled, Add-On Trials in ADULTS

Adverse Event	TOPAMAX Dosage (mg/day) Placebo (n=216)	200 (n=45)	400 (n=68)	600 - 1,000 (n=414)
Fatigue	13.4	11.1	11.8	29.7
Nervousness	7.4	13.3	17.6	19.3
Difficulty with Concentration/Attention	1.4	6.7	8.8	14.5
Confusion	4.2	8.9	10.3	13.8
Depression	5.6	8.9	7.4	13.0
Anorexia	3.7	4.4	5.9	12.3
Language problems	0.5	2.2	8.8	10.1
Anxiety	6.0	2.2	2.9	10.4
Mood problems	1.9	0	5.9	9.2

In six double-blind clinical trials, 10.6% of subjects (n=113) assigned to a TOPAMAX dosage of 200 to 400 mg/day in addition to their standard AED therapy discontinued due to adverse events, compared to 5.8% of subjects (n=69) receiving placebo. The percentage of subjects discontinuing due to adverse events appeared to increase at dosages above 400 mg/day. Overall, approximately 17% of all subjects (n=527) who received TOPAMAX in the double-blind trials discontinued due to adverse events, compared to 4% of the subjects (n=216) receiving placebo.

Table 3 lists treatment-emergent adverse events that occurred in at least 2% of children treated with 5 to 9 mg/kg/day TOPAMAX in controlled trials that were numerically more common than in patients treated with placebo.

Table 3: Incidence (%) of Treatment-Emergent Adverse Events in Worldwide Pediatric Clinical Trials Experience (2-16 years of Age)[a,b]
(Events that Occurred in ≥ 2% of Patients Treated with TOPAMAX and Occurred More Frequently in Patients Treated with TOPAMAX Than Placebo-Treated Patients)

Body System/ Adverse Event	Placebo (n=101)	Topiramate (n=98)
Body as a Whole - General Disorders		
Fatigue	5	16.3
Injury	12.9	14.3
Allergic Reaction	1	2
Central and Peripheral Nervous System Disorders		
Gait Abnormal	5	8.2
Ataxia	2	6.1
Hyperkinesia	4	5.1
Dizziness	2	4.1
Speech Disorders/Related Speech Problems	2	4.1
Convulsions Aggravated	3	3.1
Hyporeflexia	0	2
Gastrointestinal System Disorders		
Nausea	5	6.1
Saliva Increased	4	6.1
Constipation	4	5.1
Gastroenteritis	2	3.1
Metabolic and Nutritional Disorders		
Weight Decrease	1	9.2
Thirst	1	2
Platelet, Bleeding and Clotting Disorders		
Purpura	4	8.2
Epistaxis	1	4.1
Nervous Disorders		
Somnolence	15.8	25.5
Anorexia	14.9	24.5
Nervousness	6.9	14.3
Personality Disorder (Behaviour Problems)	8.9	11.2
Difficulty with Concentration/Attention	2	10.2
Aggressive Reaction	4	9.2
Insomnia	6.9	8.2
Mood Problems	6.9	7.1
Difficulty with Memory NOS[c]	0	5.1
Emotional Lability	5	5.1
Confusion	3	4.1
Psychomotor Slowing	2	3.1
Reproductive Disorders, Female		
Leukorrhea	0	2.3
Resistance Mechanism Disorders		
Infection Viral	3.0	7.1
Infection	3.0	3.1
Respiratory System Disorders		
Upper Respiratory Tract Infection	36.6	36.7
Pneumonia	1.0	5.1
Skin and Appendages Disorders		
Skin Disorder	2.0	3.1
Alopecia	1.0	2.0
Dermatitis	0	2.0
Hypertrichosis	1.0	2.0
Rash Erythematous	0	2.0
Urinary System Disorders		
Urinary Incontinence	2.0	4.1
Vision Disorders		
Eye Abnormality	1.0	2.0
Vision Abnormal	1.0	2.0
White Cell and RES Disorders		
Leukopenia	0	2.0

[a] Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX or placebo.

[b] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

[c] Not otherwise specified

None of the pediatric patients who received TOPAMAX adjunctive therapy at 5 to 9 mg/kg/day in controlled clinical trials discontinued due to adverse events. In open extensions of the controlled clinical trials, approximately 9% of the 303 pediatric patients who received TOPAMAX at dosages up to 30 mg/kg/day discontinued due to adverse events. Adverse events associated with discontinuing therapy included aggravated convulsions (2.3%), language problems (1.3%), and difficulty with concentration/attention (1.3%).
When the safety experience of patients receiving TOPAMAX as adjunctive therapy in both double-blind and open-label trials (1,446 adults and 303 children) was analyzed, a similar pattern of adverse events emerged.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Adverse events that occurred less frequently but were considered potentially medically relevant included: taste perversion, cognitive problems (not otherwise specified) and psychosis/psychotic symptoms.
In adult and pediatric patients, nephrolithiasis was reported rarely. Isolated cases of thromboembolic events have also been reported; a causal association with the drug has not been established.
In clinical trials with topiramate, the occurrence rate for all potential cases of oligohidrosis (decreased sweating) was 0.25%.

Post-Market Adverse Drug Reactions

In addition to the adverse experiences reported during clinical trial testing of TOPAMAX, the following adverse experiences have been reported in patients receiving marketed TOPAMAX from worldwide use since approval. There are insufficient data to support an estimate of their incidence or to establish causation.
The most frequently reported adverse events in spontaneous post-marketing reports on TOPAMAX include:
Psychiatric: somnolence or sedation, hallucination(s), depression, anorexia, aggressive reaction, psychosis, thinking abnormal, insomnia, emotional lability, suicide attempt, delusion, amnesia, confusion, nervousness, agitation, concentration impaired, personality disorder, anxiety
Central and Peripheral Nervous System: convulsions aggravated, paresthesia, speech disorder, ataxia, dizziness, convulsions, headache, hyperkinesia, convulsions grand mal
Metabolic and Nutritional: weight decrease, metabolic acidosis, hypokalemia, hyperchloremia
Vision: vision abnormal (includes vision decreased, vision blurred, visual disturbance, visual impairment, amblyopia); rarely reported: diplopia, glaucoma, myopia, eye pain
Gastrointestinal: nausea, diarrhea, abdominal pain, constipation, vomiting
Body as a Whole - General Disorders: fatigue, fever, dehydration, flushing, hot flushes
Urinary System: renal calculus
Skin and Appendages: rash, alopecia
White Cell and RES Disorders: leucopenia, thrombocytopenia
Oligohidrosis (decreased sweating) has been rarely reported with the use of TOPAMAX. The majority of spontaneous post-marketing reports have been in children. Adverse events that may be related to potential cases of oligohidrosis include dehydration, hyperthermia, and heat intolerance. Adequate hydration prior to activities such as exercise or exposure to warm temperatures is recommended (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**).
To date, there have been rare spontaneous, post-marketing reports of metabolic acidosis. In some cases, acidosis resolved after dosage reduction or upon discontinuation of topiramate.
Rare reports of encephalopathy with or without hyperammonemia have been received for patients treated with TOPAMAX while also taking valproate or other antiepileptic medications (see **DRUG INTERACTIONS**).
Reports of increases in liver function tests in patients taking TOPAMAX with and without other medications have been received. Isolated reports have been received of hepatitis and hepatic failure occurring in patients taking multiple medications while being treated with TOPAMAX.
Very rare reports have also been received for bullous skin and mucosal reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and pemphigus). The majority of these reports have occurred in patients taking other medications that can be associated with bullous skin and mucosal reactions.

DRUG INTERACTIONS

Drug-Drug Interactions

Antiepileptic Drugs

Effects of TOPAMAX on Other Antiepileptic Drugs

Potential interactions between TOPAMAX and standard AEDs were measured in controlled clinical pharmacokinetic studies in patients with epilepsy. The addition of TOPAMAX to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of TOPAMAX to phenytoin may result in an increase of plasma concentrations of phenytoin.
The effect of TOPAMAX on steady-state pharmacokinetics of phenytoin may be related to the frequency of phenytoin dosing. A slight increase in steady-state phenytoin plasma concentrations was observed, primarily in patients receiving phenytoin in two divided doses. The slight increase may be due to the saturable nature of phenytoin pharmacokinetics and inhibition of phenytoin metabolism ($CYP2C_{mep}$).
The addition of TOPAMAX therapy to phenytoin should be guided by clinical outcome. In general, as evidenced in clinical trials, patients do not require dose adjustments. However, any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

Effects of Other Antiepileptic Drugs on TOPAMAX

Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX may require adjustment of the dose of TOPAMAX. This should be done by titrating to clinical effect. The addition or withdrawal of valproic acid does not produce clinically significant changes in plasma concentrations of topiramate, and therefore, does not warrant dosage adjustment of TOPAMAX.
Rare post-marketing reports of encephalopathy with or without hyperammonemia have been received for patients treated with TOPAMAX while also taking valproate or other antiepileptic medications. Thus, caution is advised when polytherapy with valproate is necessary (see **ADVERSE REACTIONS, Post-Market Adverse Reactions**).
The effects of these interactions on plasma concentrations are summarized in Table 4.

Table 4: Drug Interactions with TOPAMAX Therapy

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	↔ **	↓ 59%
Carbamazepine (CBZ)	↔	↓ 40%
CBZ epoxide*	↔	NS
Valproic acid	↓ 11%	↓ 14%
Phenobarbital	↔	NS
Primidone	↔	NS

* Is not administered but is an active metabolite of carbamazepine
↔ No effect on plasma concentration (< 15% change)
** Plasma concentrations increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin
↓ Plasma concentrations decrease in individual patients
NS Not studied
AED Antiepileptic drug

Other Drug Interactions

Digoxin: In a single-dose study, serum digoxin AUC decreased 12% due to concomitant TOPAMAX administration. Multiple-dose studies have not been performed. When TOPAMAX is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.
CNS Depressants: Concomitant administration of TOPAMAX and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. It is recommended that TOPAMAX not be used concomitantly with alcohol or other CNS depressant drugs.
Oral Contraceptives: In a pharmacokinetic interaction study, epileptic patients received TOPAMAX as adjunctive therapy with valproic acid and a combination oral contraceptive product containing norethindrone (1 mg) plus ethinyl estradiol (35μ). In this study, TOPAMAX did not significantly affect the oral clearance of norethindrone. The serum levels of the estrogenic component decreased by 18%, 21% and 30% at daily doses of 200, 400 and 800 mg of topiramate, respectively. Consequently, the efficacy of low-dose (e.g. 20 μ oral contraceptives may be reduced in this situation. Patients taking oral contraceptives should receive a preparation containing not less than 30 μ of estrogen. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.
Metformin: A drug-drug interaction study conducted in 18 healthy volunteers, ages 18-37, evaluated the steady-state pharmacokinetics of metformin and topiramate in plasma when metformin (500 mg b.i.d.) was given alone and when metformin and topiramate (50, 75 and 100 mg) were given simultaneously for 6 consecutive days. The results of this study indicated that metformin mean C_{max} and mean AUC_{0-12h} increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with TOPAMAX (up-titrated to 100 mg b.i.d.). TOPAMAX did not affect metformin t_{max}. The effects of higher doses of topiramate (>100 mg b.i.d.) on metformin are unknown. The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When TOPAMAX is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.
Others: Concomitant use of TOPAMAX, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g. acetazolamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided if possible.

Drug-Food Interactions

There was no clinically significant effect of food on the bioavailability of topiramate.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

There are no known interactions of TOPAMAX with commonly used laboratory tests.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Patients with renal impairment
- Patients undergoing hemodialysis
- Patients with hepatic disease

Recommended Dose and Dosage Adjustment

TOPAMAX (topiramate) Tablets or Sprinkle Capsules can be taken without regard to meals.

Adults (Age 17 years and older)

It is recommended that TOPAMAX as adjunctive therapy be initiated at 50 mg/day, followed by titration as needed and tolerated to an effective dose. At weekly intervals, the dose may be increased by 50 mg/day and taken in two divided doses. Some patients may benefit from lower initial doses, e.g. 25 mg and/or a slower titration schedule. Some patients may achieve efficacy with once-a-day dosing.
The recommended total daily maintenance dose is 200–400 mg/day in two divided doses. Doses above 400 mg/day have not been shown to improve responses and have been associated with a greater incidence of adverse events. The maximum recommended dose is 800 mg/day. Daily doses above 1,600 mg have not been studied.

Children (Ages 2-16 years)

It is recommended that TOPAMAX as adjunctive therapy be initiated at 25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week followed by titration as needed and tolerated to an effective dose. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses). Some patients may benefit from lower initial doses and/or a slower titration schedule.
The recommended total daily maintenance dose is approximately 5 to 9 mg/kg/day in two divided doses. Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

Geriatrics

See **WARNINGS AND PRECAUTIONS** section.

Patients with Renal Impairment

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m^2), one-half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

Patients Undergoing Hemodialysis

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an antiseizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of TOPAMAX may be required. The actual adjustment should take into account 1) the duration of dialysis, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

Patients with Hepatic Disease

In hepatically impaired patients, topiramate plasma concentrations are increased approximately 30%. This moderate increase is not considered to warrant adjustment of the TOPAMAX dosing regimen. Initiate topiramate therapy with the same dose and regimen as for patients with normal hepatic function. The dose titration in these patients should be guided by clinical outcome, i.e. seizure control, and avoidance of adverse effects. Such patients will require a longer time to reach steady-state at each dose.

Missed Dose

The missed dose should be taken as soon as possible. If it is almost time for the next dose, the missed dose should not be taken. Instead, the next scheduled dose should be taken. Doses should not be doubled.

Administration

Tablets should not be broken. TOPAMAX Sprinkle Capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use. The sprinkle formulation is provided for those patients who cannot swallow tablets, e.g. pediatric and the elderly.

OVERDOSAGE

Ingestion of between 6 and 40 g topiramate has been reported in a few patients. Signs and symptoms included: headache, agitation, drowsiness, lethargy, metabolic acidosis and hypokalemia. The clinical consequences were not severe. All patients recovered.
A patient who ingested a dose calculated to be between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days.
General supportive measures are indicated and an attempt should be made to remove undigested drug from the gastrointestinal tract using gastric lavage or activated charcoal. Hemodialysis has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.

DOSAGE FORMS AND PACKAGING

Availability of Dosage Forms

TOPAMAX (topiramate) is available as embossed, round, coated tablets in the following strengths and colours: 25 mg white, 100 mg yellow and 200 mg salmon. They are marked as follows:

25 mg:	"TOP" on one side; "25" on the other.
100 mg:	"TOP" on one side; "100" on the other.
200 mg:	"TOP" on one side; "200" on the other.
Supplied:	25 mg tablets in bottles of 100 with desiccant.
	100 and 200 mg tablets in bottles of 60 with desiccant.

TOPAMAX (topiramate) Sprinkle Capsules contain small white to off-white spheres. The gelatin capsules are white and clear. They are marked as follows:

15 mg:	"TOP" and "15 mg" on the side.
25 mg:	"TOP" and "25 mg" on the side.
Supplied:	Bottles of 60 capsules without desiccant.

TOPAMAX is a Schedule F drug.
Product Monograph available upon request.

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PRESCRIBING INFORMATION

PrReminyl*

Galantamine hydrobromide tablets

PrREMINYL*

galantamine hydrobromide tablets
4 mg, 8 mg, 12 mg galantamine base
Cholinesterase Inhibitor

CLINICAL PHARMACOLOGY

Although the etiology of cognitive impairment in Alzheimer's Disease (AD) is not fully understood, it has been reported that acetylcholine-producing neurons degenerate in the brains of patients with Alzheimer's Disease. The degree of this cholinergic loss has been correlated with degree of cognitive impairment and density of amyloid plaques (a neuropathological hallmark of Alzheimer's Disease).

REMINYL (galantamine hydrobromide), a tertiary alkaloid, is a competitive and reversible cholinesterase inhibitor. While the precise mechanism of galantamine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible cholinesterase inhibition. It has also been postulated, based on *in vitro* data, that galantamine enhances the action of acetylcholine through binding to an allosteric site on the nicotinic receptors (see PRECAUTIONS). The clinical relevance to humans of these *in vitro* findings is unknown.

If these mechanisms are correct, galantamine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that galantamine alters the course of the underlying dementing process.

Pharmacokinetics

Absorption

The summary of related pharmacokinetic parameters in healthy subjects is presented in Table 1. After oral intake of a single 8 mg galantamine solution in 12 healthy males, absorption is rapid, with a peak plasma concentration (C_{max}) of 43 ± 13 ng/mL, which is reached after 1.2 hours (T_{max}), and a mean AUC_∞ of 427 ± 102 ng.h/mL.

The absolute oral bioavailability of galantamine is 88.5%. Bioavailability of the tablet was the same as the bioavailability of an oral solution in 27 healthy males. Food did not affect the AUC of galantamine but C_{max} decreased by 25% and T_{max} was delayed by 1.5 hours after repeated oral dosing of 12 mg galantamine b.i.d. in 24 healthy elderly subjects.

The maximum inhibition of anticholinesterase activity of about 40% was achieved about one hour after a single oral dose of 8 mg galantamine in healthy male subjects.

Table 1. Pharmacokinetic parameters of galantamine after single or multiple dose administration

	C_{max} (ng/mL)	t_{max} (h)	$C_{ss,av}$ (ng/mL)	C_{min} (ng/mL)	AUC† (ng.h/mL)	$T_{1/2}$ (h)
Single dose, 12 healthy males						
8 mg, solution p.o.	42.6 ± 13.1	1.2 ± 0.6	-	-	427 ± 102	7.3 ± 1.7
8 mg, 1 hr i.v. infusion	-	-	-	-	482 ± 112	7.4 ± 1.7
Food effect, single dose, 24 healthy elderly						
Fasted, 8 mg p.o.	57.5 ± 15.8	1.1 ± 0.5	-	-	562 ± 180	9.7 ± 3.1
Non-fasted, 8 mg p.o.	42.5 ± 7.5	2.6 ± 1.4	-	-	543 ± 176	9.7 ± 3.3
Multiple oral dose, 27 healthy males						
12 mg b.i.d. tablet	89.4 ± 18.3	1.0 ± 0.6	51.9 ± 12.2	30.7 ± 10.3	623 ± 147	-
12 mg b.i.d. solution	87.6 ± 20.5	1.1 ± 0.5	50.5 ± 13.0	29.8 ± 10.2	606 ± 156	-
Dose-proportionality, multiple oral dose, 18 healthy subjects						
4 mg b.i.d. tablet	30.7 ± 6.2	1.9 ± 0.8	17.7 ± 4.6	10.6 ± 4.0	212 ± 56	-
8 mg b.i.d. tablet	63.8 ± 14.2	1.7 ± 0.8	36.6 ± 9.8	20.6 ± 6.8	439 ± 117	-
12 mg b.i.d. tablet	97.4 ± 31.4	1.9 ± 1.1	53.1 ± 12.7	29.1 ± 9.3	637 ± 152	-
16 mg b.i.d. tablet	137 ± 36	1.7 ± 0.9	76.5 ± 20.3	41.5 ± 14.2	918 ± 244	7.9 ± 0.8

† AUC = AUC_∞ after single dose and AUC = AUC_τ after multiple dose

Distribution

Galantamine is a low-clearance drug (plasma clearance of approximately 300 mL/min) with a moderate volume of distribution (average Vd_{ss} of 175 L) after a one-hour i.v. infusion of 8 mg galantamine in 12 healthy males.

The plasma protein binding of galantamine is 18% at therapeutically relevant concentrations. In whole blood, galantamine is mainly distributed to blood cells (52.7%) and plasma water (39.0%), whereas the fraction of galantamine bound to plasma proteins is only 8.4%. The blood-to-plasma concentration ratio of galantamine is 1.2.

Metabolism

Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated and excreted unchanged in the urine. *In vitro* studies indicate that cytochrome CYP2D6 and CYP3A4 are the major cytochrome P450 isoenzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly (see PRECAUTIONS, Drug-Drug Interactions). O-demethylation, mediated by CYP2D6 is greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity.

Elimination

The elimination of galantamine is bi-phasic, with a terminal half-life in the order of 7-8 hours in young healthy subjects (n=4 males). Two studies in healthy elderly subjects indicated that the terminal half-life of galantamine is 8.5 hours (n=13 males and 16 females) and 9.7 hours (n=10 males and 14 females) after administering a single oral dose of 10 mg galantamine. Up to 8 hours post-dose, unchanged galantamine accounted for 39-77% of the total radioactivity in the plasma, and galantamine glucuronide accounted for 14-24%. Seven days after a single oral dose of 4 mg ^{3}H-galantamine, 93-99% of the radioactivity had been recovered, with about 95% in urine and about 5% in feces. Total urinary recovery of unchanged galantamine accounted for, on average, 32% of the dose, and that of galantamine glucuronide for another 12% on average.

After i.v. and oral administration, about 20% of the dose was excreted as unchanged galantamine in the urine in 24 hours, with a renal clearance of about 65 mL/min, which represents 20-25% of the total plasma clearance of about 300 mL/min.

CYP2D6 Poor Metabolizers

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of the CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar C_{max} and about 35% AUC_∞ increase of unchanged galantamine compared to extensive metabolizers.

A total of 356 patients with Alzheimer's disease enrolled in two Phase III studies were genotyped with respect to CYP2D6 (n=210 hetero-extensive metabolizers, 126 homo-extensive metabolizers, and 20 poor metabolizers). Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability due to observed inter-patient variability.

Hepatic Impairment

Following a single 4 mg dose of galantamine, the pharmacokinetics of galantamine in subjects with mild hepatic impairment (n=8; Child-Pugh score of 5-6) were similar to those in healthy subjects. In patients with moderate hepatic impairment (n=8; Child-Pugh score of 7-9), AUC and half-life of galantamine were increased by about 30% compared to normal subjects (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Impairment

In patients with renal insufficiency, elimination of galantamine decreases with decreasing creatinine clearance. Following a single 8 mg dose of galantamine, AUC increased by 37% and 67% in moderately (n=8; creatinine clearance of 30 to 60 mL/min/1.73 m^2) and severely (n=9; creatinine clearance of 5 to 29 mL/min/1.73 m^2) renal-impaired patients compared to normal volunteers (n=8) (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Patients with Alzheimer's Disease

Data from clinical trials in patients indicate that there is a difference in total clearance after oral administration between patients with Alzheimer's Disease and healthy subjects (13.2 L/h versus 19.4 L/h) based on pooled population analysis. Therefore, the plasma concentrations of galantamine in elderly patients (median age 75) with Alzheimer's Disease are 30-40% higher than in healthy young subjects (median age 28).

Gender and Race

No specific pharmacokinetic study was performed to investigate the gender differences. A population pharmacokinetic analysis (n=539 males and 550 females) suggests that galantamine clearance is about 20% lower in females than in males, which is explained by lower body weight in females.

Pharmacokinetic differences due to race have not been identified in a population pharmacokinetic analysis (n=1029 White, 24 Black, 13 Asian and 23 other).

Clinical Trials

Efficacy data for REMINYL (galantamine hydrobromide) in the symptomatic treatment of patients with Alzheimer's Disease were derived from 4 randomized, double-blind, placebo-controlled clinical trials in patients with probable Alzheimer's Disease [diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination Scores that were ≥10 and ≤24]. Doses studied were 8-32 mg/day given as twice daily doses. In 3 of the 4 studies, patients were started on a low dose of 8 mg, then titrated weekly by 8 mg/day to 24 or 32 mg as assigned (GAL-USA-1, GAL-INT-1, GAL-INT-2). In the fourth study (U.S. 4-week Dose-Escalation Fixed-Dose Study, GAL-USA-10) dose escalation of 8 mg/day occurred over 4 week intervals. The mean age of patients participating in the 4 REMINYL trials was 75 years with a range of 41 to 100. Approximately 62% of patients were women and 38% were men. The racial distribution was White 94%, Black 3% and other races 3%. Two other studies examined a three times daily dosing regimen; these also showed or suggested benefit but did not suggest an advantage over twice daily dosing.

Results for 2 of these studies are presented in this section. The data shown below were obtained from the Intent-To-Treat population (ITT analysis, i.e. all patients who were randomized to treatment, regardless of whether or not they were able to complete the study. For patients unable to complete the study, their last observation while on treatment was carried forward and used at endpoint).

Study Outcome Measures: In each study, the primary efficacy of REMINYL was evaluated using a dual outcome assessment strategy as measured by the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Impression of Change (CIBIC-plus).

The ability of REMINYL to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's Disease patients. The ADAS-cog examines selected aspects of cognitive performance, including elements of memory, orientation, attention, reasoning, language and praxis.

The patients recruited as participants in each study had mean scores on the ADAS-cog of approximately 27 units, with a range from 5 to 69. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's Disease suggests that they gain 6 to 12 units a year on the ADAS-cog. Lesser degrees of change, however, are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in REMINYL trials was approximately 4.5 units per year.

The ability of REMINYL to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC-plus. The CIBIC-plus used in the trials was a semi-structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of 4 major areas of patient function: general, cognitive, behavioural and activities of daily living. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC-plus evaluations from other clinical trials.

Among the secondary measures of efficacy, the Alzheimer's Disease Cooperative Study, Activities of Daily Living Inventory (ADCS/ADL) was used. The ADCS/ADL is a caregiver-rated evaluation which yields a compound score derived from a categorical scale of 23 items concerning participation in activities of daily living.

U.S. Twenty-One-Week Fixed-Dose Study (GAL-USA-10)

In a study of twenty-one weeks' duration, 978 patients were randomized to doses of 8, 16, or 24 mg of REMINYL per day, or to placebo, each given in 2 divided doses. Treatment was initiated at 8 mg/day for all patients randomized to REMINYL, and increased by 8 mg/day every 4 weeks. Therefore, the maximum dose-escalation phase was 8 weeks and the minimum maintenance phase was 13 weeks (in patients randomized to 24 mg/day of REMINYL).

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all four dose groups over the 21 weeks of the study. At 21 weeks of treatment, the mean differences in the ADAS-cog change scores for the REMINYL-treated patients compared to the patients on placebo were 0.8, 2.9 and 2.9 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo and to the 8 mg/day treatment. There was no statistically significant difference between the 16 mg/day and 24 mg/day dose groups.

Figure 1: Time-course of the Changes from Baseline in ADAS-cog Score (ITT Population)

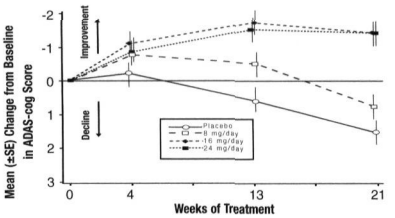
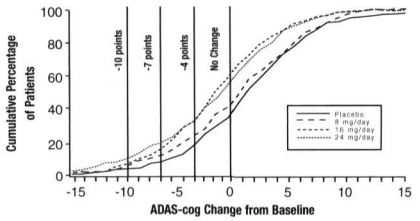


Figure 2 illustrates the cumulative percentages of patients from each of the four treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percentage of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to galantamine and placebo have a wide range of responses, but that the REMINYL groups are more likely to show the greater improvements.

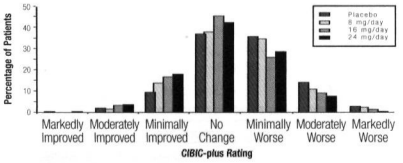
Figure 2: Cumulative Percentage of Patients with Specified Changes from Baseline in ADAS-cog Scores (ITT Population)



Treatment	Change in ADAS-cog -10	-7	-4	0
Placebo	3.7%	7.8%	19.0%	43.9%
8 mg/day	4.5%	11.4%	22.7%	47.7%
16 mg/day	6.4%	15.0%	33.1%	67.3%
24 mg/day	8.8%	19.8%	32.4%	62.6%

Effects on the CIBIC-plus: Figure 3 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the four treatment groups. The REMINYL-placebo differences for these groups of patients in the mean rating were 0.10, 0.32 and 0.38 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo. The differences vs. the 8 mg/day treatment for the 16 and 24 mg/day treatments were 0.22 and 0.28, respectively. There were no statistically significant differences between the 16 mg/day and 24 mg/day dose groups.

Figure 3: Distribution of CIBIC-plus Ratings at Week 21 (ITT Population)



Effects on ADCS/ADL Inventory: The Alzheimer's Disease Cooperative Study, Activities of Daily Living Inventory was used as a secondary efficacy measure. At baseline, mean ADCS/ADL scores (mean ± SE) were for the placebo group: 52.3 ± 0.89 units; for the 16 mg/day group: 51.6 ± 0.93 units; for the 24 mg/day group: 51.9 ± 0.98 units. At Week 21, the placebo group declined an average of 3.9 ± 0.55 units, and the 16 mg/day and 24 mg/day groups deteriorated minimally at 1.0 ± 0.51 units and 1.6 ± 0.56 units, respectively. The difference between the placebo group and the galantamine treatment groups (16 mg/day or 24 mg/day) was statistically significant.

U.S. Twenty-Six-Week Fixed-Dose Study (GAL-USA-1)

In a study of 26 weeks' duration, 636 patients were randomized to either a dose of 24 mg or 32 mg of REMINYL per day, or to placebo, each given in two divided doses. The 26-week study was divided into a 3-week dose-escalation phase and a 23-week maintenance phase.

Effects on the ADAS-cog: Figure 4 illustrates the time course for the change from baseline in ADAS-cog score for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean difference in the ADAS-cog change scores for the REMINYL-treated patients compared to the patients on placebo were 3.2 and 2.8 units for the 24 mg/day and 32 mg/day treatments, respectively. Both treatments were statistically significantly superior to placebo, but were not statistically significantly different from each other.

Figure 4: Time-course of the Changes from Baseline in ADAS-cog Score (ITT Population)

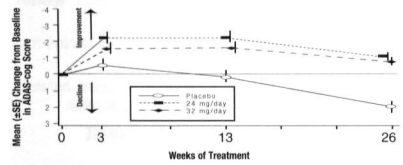
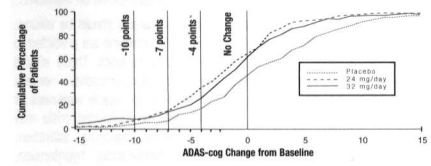


Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to galantamine and placebo have a wide range of responses, but that the REMINYL groups are more likely to show the greater improvements. Curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

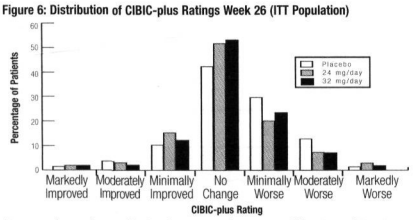
Figure 5: Cumulative Percentage of Patients with Specified Changes from Baseline in ADAS-cog Scores (ITT Population)



Treatment	Change in ADAS-cog -10	-7	-4	0
Placebo	2.3%	5.6%	16.4%	45.5%
24 mg/day	5.8%	14.0%	34.3%	63.8%
32 mg/day	7.7%	13.4%	25.8%	61.2%

Effects on the CIBIC-plus: Figure 6 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups. The mean REMINYL-placebo differences for these groups of patients in the mean rating were 0.22 and 0.17 units for 24 and 32 mg/day of REMINYL, respectively. The mean ratings for both groups were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 6: Distribution of CIBIC-plus Ratings Week 26 (ITT Population)



Age, gender and race: Patient's age, gender or race did not predict outcome of treatment.

INDICATIONS AND CLINICAL USE

REMINYL (galantamine hydrobromide) is indicated for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type. REMINYL has not been studied in controlled clinical trials for longer than 6 months.

REMINYL should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's Disease.

CONTRAINDICATIONS

REMINYL (galantamine hydrobromide) is contraindicated in patients with known hypersensitivity to galantamine hydrobromide, other tertiary alkaloid derivatives or to any excipients used in the formulation.

WARNINGS

Anesthesia

REMINYL (galantamine hydrobromide), as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Neurological Conditions

Seizures: In placebo-controlled trials with REMINYL, cases of seizure were reported; there was no increase in incidence compared with placebo. Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of Alzheimer's Disease. The risk/benefit of REMINYL treatment for patients with a history of seizure disorder must therefore be carefully evaluated.

REMINYL has not been studied in patients with moderately severe or severe Alzheimer's Disease, non-Alzheimer dementias or individuals with Parkinson's Disease features. The efficacy and safety of REMINYL in these patient populations is unknown.

Pulmonary Conditions

Like other cholinomimetic drugs, REMINYL should be prescribed with care for patients with a history of asthma or obstructive pulmonary disease.

Cardiovascular Conditions

Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and heart block. These actions may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction disorders, or to patients taking other drugs concomitantly which significantly slow heart rate. In clinical trials, patients with serious cardiovascular disease were excluded. Caution should be exercised in treating patients with active coronary artery disease or congestive heart failure. It is recommended that REMINYL not be used in patients with cardiac conduction abnormalities (except for right bundle branch block) including "sick sinus syndrome" and those with unexplained syncopal episodes.

In randomized controlled trials, bradycardia was reported at 2-3% for galantamine doses up to 24 mg/day compared with <1% for placebo, and it rarely led to treatment discontinuation. No increased incidence of heart block was observed at the recommended doses. Patients treated with galantamine up to 24 mg/day at the recommended dosing schedule showed a dose-related increase in risk of syncope (placebo, 0.7% [2/286]; 4 mg b.i.d., 0.4% [3/692]; 8 mg b.i.d., 1.3% [7/552]; 12 mg b.i.d., 2.2% [6/273]).

A 6-week cardiovascular safety clinical trial (GAL-USA-16; n=139) was performed to investigate the effect of galantamine at doses up to 32 mg/day. This dosing regimen was: 8 mg/day in Week 1, 16 mg/day in Week 2, 24 mg/day in Weeks 3 and 4, and 32 mg/day in Weeks 5 and 6. Heart block/pauses greater than two seconds were more common in galantamine-treated patients than in placebo-treated patients. It should be noted that a forced 1-week dose escalation was used in this study, which is not recommended. Whether these cardiac effects are attenuated by slower titration rates is not known. Particular caution is warranted during titration where the majority of pauses occurred in the above study.

Gastrointestinal Conditions

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, e.g. those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). In controlled clinical studies with REMINYL, patients with symptomatic peptic ulceration were excluded. Clinical studies of REMINYL have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding (see ADVERSE REACTIONS).

REMINYL, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting and diarrhea, anorexia and weight loss. These effects appeared more frequently at higher doses (see ADVERSE REACTIONS), with nausea and vomiting being more prevalent in women and patients with lower body weight and correspondingly higher plasma drug concentrations. Females are more sensitive to the cholinergic adverse effects associated with cholinesterase inhibitors and in general are more likely to experience nausea and vomiting than are males. In most cases, these effects were of mild to moderate intensity and transient and have resolved during continued REMINYL treatment or upon treatment discontinuation.

Weight Loss

Cholinesterase inhibitors as well as Alzheimer's Disease can be associated with significant weight loss. In controlled clinical trials, the use of REMINYL was associated with weight loss. Weight decrease occurred early during treatment and was related to dose. Weight loss of ≥7% occurred more frequently in patients treated with REMINYL and in female patients than in patients receiving placebo. Where weight loss may be of clinical concern, body weight should be monitored.

Genitourinary

Although not observed in clinical trials of REMINYL, cholinomimetics may cause bladder outflow obstruction.

PRECAUTIONS

Concomitant Use with Other Drugs

Use with Anticholinergics

Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with Cholinomimetics and Other Cholinesterase Inhibitors

A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

Use with other Psychoactive Drugs

Few patients in the REMINYL (galantamine hydrobromide) clinical trials received neuroleptics, antidepressants or anticonvulsants, there is thus limited information concerning the interaction of REMINYL with these drugs.

Use in Patients ≥85 Years Old

In controlled clinical studies, the number of patients aged 85 years or over who received REMINYL at therapeutic doses of 16 or 24 mg/day was 123. Of these patients, 70 received the maximum recommended dose of 24 mg/day. There is limited safety information for REMINYL in this patient population.

Since cholinomimetics as well as Alzheimer's Disease can be associated with significant weight loss, caution is advised regarding the use of REMINYL in elderly patients with low body weight, especially in those ≥85 years old.

Use in Elderly Patients with Serious Comorbid Disease

There is limited information on the safety of REMINYL treatment in patients with mild to moderate Alzheimer's Disease and serious/significant comorbidity. The use of REMINYL in Alzheimer's Disease patients with chronic illnesses common among the geriatric population, should be considered only after careful risk/benefit assessment and include close monitoring for adverse events. Dose escalation in this patient population should proceed with caution.

Renally and Hepatically Impaired Patients

There is limited information on the pharmacokinetics of REMINYL in renally and hepatically impaired patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics). It is therefore recommended that dose escalation with REMINYL in Alzheimer's Disease patients with renal impairment (creatinine clearance of 9 to 60 mL/min) or hepatic impairment be undertaken with caution and under conditions of close monitoring for adverse effects (see DOSAGE AND ADMINISTRATION, Special Populations). Since no data are available on the use of REMINYL in patients with a creatinine clearance of less than 9 mL/min and in patients with severe hepatic impairment (Child-Pugh score of 10-15), REMINYL is not recommended for these populations.

Drug-Drug Interactions

Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine so no single pathway appears predominant. Based on *in vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine. CYP2D6 was involved in the formation of O-desmethyl-galantamine, whereas CYP3A4 mediated the formation of galantamine-N-oxide.

Effect of Other Drugs on the Metabolism of REMINYL

Pharmacokinetic studies to assess the potential of REMINYL for interaction with cimetidine, ranitidine, ketoconazole, erythromycin, paroxetine, warfarin and digoxin were limited to short-term, mostly single-dose studies in young healthy volunteers. Similar studies in elderly patients were not done.

In vitro

CYP3A4 and CYP2D6 are the major enzymes involved in the metabolism of galantamine. CYP3A4 mediates the formation of galantamine-N-oxide, whereas CYP2D6 is involved in the formation of O-desmethyl-galantamine. Because galantamine is also glucuronidated and excreted unchanged in urine, no single pathway appears predominant.

In vivo

Cimetidine and Ranitidine: Galantamine was administered as a single dose of 4 mg on Day 2 of a 3-day treatment with either cimetidine (800 mg daily; n=6 males and 6 females) or ranitidine (300 mg daily; n=6 males and 6 females). Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the pharmacokinetics of galantamine.

Ketoconazole: Ketoconazole, a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, at a dose of 200 mg b.i.d. for 4 days, increased the AUC of galantamine by 30% when subjects were treated with galantamine 4 mg b.i.d. for 8 days (n=8 males and 8 females).

Erythromycin: Erythromycin, a moderate inhibitor of CYP3A4 at a dose of 500 mg q.i.d. for 4 days increased the AUC of galantamine by 10% when subjects received galantamine 4 mg b.i.d. for 6 days (n=8 males and 8 females).

Paroxetine: Paroxetine, a strong inhibitor of CYP2D6, increased the AUC of 4 mg b.i.d., 8 mg b.i.d. and 12 mg b.i.d. galantamine by 40%, 45% and 48%, respectively, in 16 healthy volunteers (8 males and 8 females) who received galantamine together with 20 mg/day paroxetine.

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Effect of Galantamine on the Metabolism of Other Drugs

In vitro

Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low.

In vivo

Warfarin: Galantamine at 12 mg b.i.d. had no effect on the pharmacokinetics of R- and S-warfarin (25 mg single dose) or on the prothrombin time (n=16 males). The protein binding of warfarin was unaffected by galantamine.

Digoxin: Galantamine at 12 mg b.i.d. had no effect on the steady-state pharmacokinetics of digoxin (0.375 mg once daily) when they were co-administered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia (n=8 males and 8 females).

Nicotinic Receptor Modulation

Single *in vitro* applications of galantamine dose-dependently modulate the effect on nicotinic receptors, having a positive allosteric (sensitizing) effect at concentrations below 0.28 µg/mL (1 µM) and an inhibitory effect at higher concentrations. Chronic *in vitro* or *in vivo* studies on nicotinic receptor modulation have not been conducted.

It is unknown whether galantamine has an effect on the pharmacodynamic action of other drugs that act on cholinergic nicotinic receptors (see CLINICAL PHARMACOLOGY).

Carcinogenesis, Mutagenesis and Impairment of Fertility

In a 24-month oral carcinogenicity study in rats, a slight increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m^2 basis or 6 times on an exposure [AUC] basis), and 30 mg/kg/day (12 times the MRHD on a mg/m^2 basis or 19 times on an AUC basis). No increase in neoplastic changes was observed in females at 2.5 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis or 2 times on an AUC basis) or in males up to the highest dose tested of 30 mg/kg/day (12 times the MRHD on a mg/m^2 and AUC basis).

Galantamine was not carcinogenic in a 6-month oral carcinogenicity study in transgenic (P 53-deficient) mice up to 20 mg/kg/day, or in a 24-month oral carcinogenicity study in male and female mice up to 10 mg/kg/day (2 times the MRHD on a mg/m^2 basis and equivalent on an AUC basis).

Galantamine produced no evidence of genotoxic potential when evaluated in the *in vitro* Ames *S. typhimurium* or *E. coli* reverse mutation assay, *in vitro* mouse lymphoma assay, *in vivo* micronucleus test in mice, or *in vitro* chromosome aberration assay in Chinese hamster ovary cells.

No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m^2 basis) for 14 days prior to mating in females and for 60 days prior to mating in males.

Pregnancy

In a teratology study in which rats were dosed from Day 14 (females) or Day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the MRHD on a mg/m^2 basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through Day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m^2 basis) during the period of organogenesis.

The safety of REMINYL in pregnant women has not been established. REMINYL should not be used in women of childbearing potential unless, in the opinion of the physician, the potential benefit to the patient justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether REMINYL is excreted in human breast milk and therefore REMINYL should not be used in nursing mothers.

Pediatric Use

The safety and effectiveness of REMINYL in any illness occurring in pediatric patients have not been established.

ADVERSE REACTIONS

A total of 2287 patients with mild to moderate Alzheimer's Disease were treated with REMINYL (galantamine hydrobromide) in Phase III controlled clinical studies using either a 1-week or 4-week dose-escalation period, and 761 patients received REMINYL 24 mg/day, the maximum recommended maintenance dose. The number of patients who completed the studies was 1686 (72%). The mean duration of treatment for all REMINYL groups was 130 days (range 1-214 days).

Adverse Events Leading to Discontinuation

Overall, 19% (441/2287) of patients treated with REMINYL discontinued from *Phase III controlled clinical trials due to adverse events compared to 8%* (98/1159) in the placebo group. For patients treated with REMINYL, the rate of discontinuation due to adverse events was 14% for males and 22% for females.

In the 4-week dose-escalation fixed-dose study (GAL-USA-10), 8% (55/692) of patients treated with REMINYL withdrew due to adverse events compared to 7% (20/286) in the placebo group. During the dose-escalation phase of this study the incidence of discontinuations due to adverse events was 4% for placebo, 5% for REMINYL 16 mg/day and 6% for REMINYL 24 mg/day. During the maintenance phase, 4% of patients who received placebo, 3% of patients who received REMINYL 16 mg/day and 4% of patients who received REMINYL 24 mg/day withdrew from this study due to adverse events.

Table 1 shows the most frequent adverse events leading to discontinuation for study GAL-USA-10, in which the recommended 4-week dose-escalation schedule was used.

Table 1: Most frequent adverse events leading to discontinuation in a placebo-controlled, double-blind trial with a 4-week dose-escalation schedule (GAL-USA-10)

Adverse Events	Recommended 4-week dose escalation		
	Placebo n=286	16 mg/day n=279	24 mg/day n=273
Nausea	<1%	2%	4%
Vomiting	0%	1%	3%
Anorexia	<1%	1%	<1%
Dizziness	<1%	2%	1%
Syncope	0%	0%	1%

Most Frequent Adverse Clinical Events Seen in Association with the Use of REMINYL

The most frequent adverse events, defined as those occurring at a frequency of at least 5% and at least twice the rate of placebo in study GAL-USA-10, in which *the recommended 4-week dose-escalation schedule was used are shown in* Table 2. These events were primarily gastrointestinal and tended to occur at a lower rate with 16 mg/day, the initial recommended maintenance dose.

Table 2: Most frequent adverse events in a randomized placebo-controlled clinical trial with a 4-week dose increment during dose-escalation and maintenance phases (GAL-USA-10)

Adverse Events	Week 1-12†			Week 13-21		
	Placebo n=286	16 mg/day n=279	24 mg/day n=273	Placebo n=259	16 mg/day n=243	24 mg/day n=241
Nausea	5%	11%	13%	<1%	4%	6%
Vomiting	<1%	5%	6%	<1%	2%	6%
Diarrhea	5%	9%	4%	2%	5%	2%
Anorexia	2%	5%	5%	1%	2%	5%

† *Dose escalation occurred with 4 weeks per dose increment.*

The majority of these adverse events occurred during the dose-escalation period. Nausea and vomiting, the most frequent adverse events, occurred more frequently at higher doses, lasted 5-7 days in most cases, and the majority of patients had one episode. The incidence of weight loss in this study was, during dose escalation (Weeks 1-12): placebo, 1%; 16 mg/day, 3%; 24 mg/day, 2%; and during the maintenance phase (Weeks 13-21): placebo, <1%; 16 mg/day, 3%; 24 mg/day, 3%.

Dose escalation should be cautious and maintenance dosing should remain flexible and be adjusted according to individual needs.

Adverse Events Reported in Controlled Trials

The reported adverse events in REMINYL trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behaviour and the types of patients treated may differ.

Table 3 lists the most common adverse events (adverse events occurring with an incidence of 2% with REMINYL treatment and in which the incidence was greater than with placebo treatment) for four placebo-controlled trials for patients treated with 16 or 24 mg/day of REMINYL. The combined values presented in Table 3 were derived from trials using a 1-week or the recommended 4-week dose-escalation period.

Table 3: Adverse events reported in at least 2% of patients with Alzheimer's Disease administered REMINYL and at a frequency greater than with placebo (combined 1- and 4-week dose-escalation data)

Body System / Adverse Events	Placebo (n=801)	REMINYL† (n=1040)
Body as a whole - general disorders		
Fatigue	3%	5%
Syncope	1%	2%
Central & peripheral nervous system disorders		
Dizziness	6%	9%
Headache	5%	8%
Tremor	2%	3%
Gastro-intestinal system disorders		
Nausea	9%	24%
Vomiting	4%	13%
Diarrhea	7%	9%
Abdominal pain	4%	5%
Dyspepsia	2%	5%
Heart rate and rhythm disorders		
Bradycardia	1%	2%
Metabolic and nutritional disorders		
Weight decrease	2%	7%
Psychiatric disorders		
Anorexia	3%	9%
Depression	5%	7%
Insomnia	4%	5%
Somnolence	3%	4%
Red blood cell disorders		
Anemia	2%	3%
Respiratory system disorders		
Rhinitis	3%	4%
Urinary system disorders		
Urinary tract infection	7%	8%
Hematuria	2%	3%

† *Adverse events in patients treated with 16 or 24 mg/day of* REMINYL *in three placebo-*controlled trials with a 1-week dose-escalation period and a 26-week fixed-dose REMINYL treatment, and one placebo-controlled trial with the recommended 4-week dose-escalation period and a 21-week fixed-dose REMINYL treatment are included.

No clinically relevant abnormalities in laboratory values were observed. In a cardiovascular safety clinical trial (GAL-USA-16), pauses greater than two seconds were more common in galantamine-treated patients than in placebo-treated patients during the dose-escalation period (see WARNINGS).

Other Adverse Events Observed During Clinical Trials

REMINYL has been administered to 3055 patients with Alzheimer's Disease during clinical trials worldwide.

A total of 2357 patients received galantamine in placebo-controlled trials and 761 patients with Alzheimer's Disease received galantamine 24 mg/day, the maximum recommended maintenance dose. About 1000 patients received galantamine for at least one year and approximately 200 patients received galantamine for two years. To establish the rate of adverse events, data from all patients for any dose of REMINYL in 8 placebo-controlled trials and 6 open-label extension trials were pooled. The methodology to gather and codify these adverse events was standardized across trials, using WHO terminology. All events occurring in approximately 0.1% of patients are included, except for those already listed elsewhere in labelling, WHO terms too general to be informative, or relatively minor events. Events are classified by body system and listed using the following definitions: *frequent adverse events* - those occurring in at least 1/100 patients; *infrequent adverse events* - those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to REMINYL treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole - General Disorders: *Frequent:* chest pain.

Cardiovascular System Disorders: *Frequent:* hypertension; *Infrequent:* postural hypotension, hypotension, dependent edema, cardiac failure.

Central & Peripheral Nervous System Disorders: *Infrequent:* vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia.

Gastrointestinal System Disorders: *Frequent:* flatulence; *Infrequent:* gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; *Rare:* esophageal perforation.

Heart Rate & Rhythm Disorders: *Infrequent:* AV block, palpitation, atrial fibrillation, QT prolonged, bundle branch block, supraventricular tachycardia, T-wave inversion, ventricular tachycardia.

Metabolic & Nutritional Disorders: *Infrequent:* hyperglycemia, alkaline phosphatase increased, NPN increased.

Platelet, Bleeding & Clotting Disorders: *Infrequent:* purpura, epistaxis, thrombocytopenia.

Psychiatric Disorders: *Infrequent:* apathy, paroniria, paranoid reaction, libido increased, delirium.

Urinary System Disorders: *Frequent:* incontinence; *Infrequent:* hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

In a postmarketing report, one patient who had been taking 4 mg of galantamine daily inadvertently ingested eight 4 mg tablets (32 mg total) on the tenth day of treatment. Subsequently, she developed bradycardia, QT prolongation, ventricular tachycardia and torsades de pointes accompanied by a brief loss of consciousness for which she required hospital treatment. ECG obtained just prior to initiation of galantamine treatment was normal.

Treatment

REMINYL (galantamine hydrobromide) has a plasma half-life of approximately 7-8 hours. It is recommended that, in case of asymptomatic overdose, no further dose of REMINYL should be administered and the patient should be monitored.

As in any case of overdose, general supportive measures should be utilized. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous system, and the neuromuscular junction. In addition to muscle weakness or *fasciculations, some or all of the following signs of cholinergic crisis may* develop: severe nausea, vomiting, gastrointestinal cramping, salivation, lacrimation, urination, defecation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

Tertiary anticholinergics such as atropine may be used as an antidote for REMINYL overdosage. Intravenous atropine sulphate titrated to effect is recommended at an initial dose of 0.5 to 1.0 mg i.v., with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics. It is not known whether REMINYL and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included hypoactivity, tremors, clonic convulsions, salivation, lacrimation, chromodacryorrhea, mucoid feces, and dyspnea.

DOSAGE AND ADMINISTRATION

REMINYL (galantamine hydrobromide) tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's Disease.

Adults

The dosage of REMINYL shown to be effective in controlled clinical trials is 16-32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16-24 mg/day given in a b.i.d. regimen. The dose of 24 mg/day did not provide a statistically significant greater clinical benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg of REMINYL might provide additional benefit for some patients.

The recommended starting dose of REMINYL is 4 mg twice a day (8 mg/day). After a minimum of 4 weeks of treatment, if this dose is well tolerated, the dose should be increased to 8 mg twice a day (16 mg/day). A further increase to 12 mg twice a day (24 mg/day) after a minimum of 4 weeks at the previous dose may be considered following appropriate assessment of clinical benefit and tolerability.

REMINYL should be administered twice a day, preferably with morning and evening meals.

Patients and caregivers should be warned that if therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

The abrupt withdrawal of REMINYL in those patients who had been receiving doses in the effective range was not associated with an increased frequency of adverse events in comparison with those continuing to receive the same doses of that drug. The beneficial effects of REMINYL are lost, however, when the drug is discontinued.

Concomitant Treatment

In patients treated with potent CYP2D6 or CYP3A4 inhibitors, dose reductions can be considered.

Special Populations

Dose escalation for elderly patients (>85 years old) with low body weight (especially females) or serious comorbid diseases should be undertaken with particular caution.

Hepatic Impairment

Galantamine plasma levels may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), dosing could begin with 4 mg once daily for at least 1 week. Then the dosage should be increased to 4 mg twice a day for at least 4 weeks. In these patients, daily doses should not exceed 8 mg twice a day (16 mg/day). Since no data are available on the use of REMINYL in patients with severe hepatic impairment (Child-Pugh score of 10-15), REMINYL is not recommended for this population (see PRECAUTIONS).

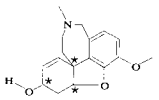
Renal Impairment

For patients with renal impairment (creatinine clearance of 9 to 60 mL/min), dose escalation should proceed cautiously and the maintenance dose should generally not exceed 16 mg/day. Since no data are available on the use of REMINYL in patients with a creatinine clearance less than 9 mL/min, REMINYL is not recommended for this population (see PRECAUTIONS).

In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision.

PHARMACEUTICAL INFORMATION

Drug Substance

Trade Name:	REMINYL
Common Name:	galantamine hydrobromide
Chemical Name:	(4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide
Structural Formula:	 [4aS-(4aa,6b,8aR*)] Hydrobromide (1:1)
Molecular Formula:	$C_{17}H_{21}NO_3 \cdot HBr$
Molecular Weight:	368.27
Ionization Constant:	pKa=8.2 (azepine moiety)
Partition Coefficient:	log P=1.09, between n-octanol and an aqueous buffer solution at pH=12.0
Melting Point:	257.3°C
Description:	Galantamine hydrobromide is a white to almost white powder. It is freely soluble in water (pH=5.2), 0.1 N hydrochloric acid (pH=1.0) and 0.1 N sodium hydroxide (pH=8.3).

Composition

REMINYL (galantamine hydrobromide) tablets are available in three strengths containing 4, 8, 12 mg of galantamine per tablet, as galantamine hydrobromide. The inactive ingredients are lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, propylene glycol, talc, and titanium dioxide. The 4 mg tablet also contains yellow ferric oxide. The 8 mg tablet also contains red ferric oxide. The 12 mg tablet also contains red ferric oxide and FD & C yellow #6 (also known as orange yellow S aluminum lake).

Stability and Storage Recommendations

REMINYL tablets should be stored between 15°C–30°C.

AVAILABILITY OF DOSAGE FORMS

REMINYL (galantamine hydrobromide), expressed as galantamine base, is available as film-coated tablets in the following strengths:

4 mg tablets which are off-white, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G4" on the other side;
8 mg tablets which are pink, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G8" on the other side;
12 mg tablets which are orange-brown, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G12" on the other side.
REMINYL is available in bottles of 60 tablets and in blisters of 56 tablets per carton.

Product Monograph available to healthcare professionals upon request.

JANSSEN-ORTHO

19 Green Belt Drive, Toronto, Ontario M3C 1L9

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Pr Axert*

almotriptan malate tablets

**PrAXERT*
almotriptan malate tablets
6.25 mg and 12.5 mg
almotriptan**

**5-HT$_1$ Receptor Agonist
Migraine Therapy**

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

AXERT (almotriptan malate) is a selective 5-hydroxytryptamine$_{(5\text{-}HT_{1B/1D})}$ ($5\text{-}HT_{(B,D)}$) receptor agonist. Almotriptan binds with high affinity to $5\text{-}HT_{1D}$, $5\text{-}HT_{1B}$ and $5\text{-}HT_{1F}$ receptors. Almotriptan has a weak affinity for $5\ HT_{1A}$ and $5\text{-}HT_7$ receptors, but has no significant affinity or pharmacological activity at $5\text{-}HT_2$, $5\text{-}HT_3$, $5\text{-}HT_4$, $5\text{-}HT_5$, alpha or beta adrenergic; adenosine (A_1, A_2); angiotensin (AT_1, AT_2); dopamine (D_1, D_2); endothelin (ET_A, ET_B); or tachykinin (NK$_1$, NK$_2$, NK$_3$) binding sites.

Current theories on the etiology of migraine headaches suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from the sensory nerve endings in an activated trigeminal system. The therapeutic activity of almotriptan in migraine can most likely be attributed to agonist effects at $5\text{-}HT_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack, and on the nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of the neuropeptide release, and reduced transmission in the trigeminal pain pathways.

Pharmacokinetics

Absorption

Almotriptan is well absorbed following oral administration. The mean oral absolute bioavailability is approximately 70%, and peak plasma concentrations of approximately 40 ng/mL are reached 1 to 3 hours after a single 12.5 mg dose. The rate and extent of absorption are not affected by food intake or by administration during a migraine attack. Almotriptan does not undergo substantial first-pass elimination.

Distribution

Almotriptan is extensively distributed. Almotriptan is minimally protein bound (approximately 35%), and the mean apparent volume of distribution is approximately 180 to 200 litres.

Metabolism

Almotriptan is metabolized by one minor and two major pathways. Monoamine oxidase (MAO)-mediated oxidative deamination (approximately 27% of the dose) and cytochrome P450-mediated oxidation (approximately 12% of the dose) are the major routes of metabolism, while flavin mono-oxygenase is the minor route. MAO-A is responsible for the formation of the indoleacetic acid metabolite, whereas cytochrome P450 (3A4 and 2D6) catalyzes the hydroxylation of the pyrrolidine ring to an intermediate that is further oxidized by aldehyde dehydrogenase to the gamma-aminobutyric acid derivative. Both metabolites are inactive.

Excretion

The mean half-life of almotriptan is between 3 and 4 hours. The primary route of elimination is via renal clearance, accounting for 75% of the administered dose. Approximately 40% of an administered dose is excreted unchanged in urine. Renal clearance exceeds the glomerular filtration rate by approximately 3-fold, indicating an active mechanism. Approximately 13% of the administered dose is excreted via feces, both unchanged and metabolized.

Special Populations

Geriatric

Renal and total clearance, and amount of drug excreted in the urine (10 L/h, 33 L/h and 30% respectively) were lower in elderly non-migraineur volunteers (aged 65 to 76 years) than in younger non migraineur volunteers (aged 19 to 34 years), resulting in longer terminal half-life (3.7 h vs. 3.2 h) and higher area under the plasma concentration time curve (405 ng.h/mL vs. 325 ng.h/mL) in the elderly subjects. However, the differences do not appear to be clinically significant.

Pediatric

The pharmacokinetics of almotriptan have not been evaluated in pediatric patients.

Gender

No significant gender differences have been observed in pharmacokinetic parameters.

Race

No significant differences have been observed in the pharmacokinetic parameters between Caucasian and African-American volunteers.

Hepatic Impairment

The pharmacokinetics of almotriptan have not been assessed in this population. Based on the known mechanisms of the clearance of almotriptan, the maximum decrease in expected almotriptan clearance due to hepatic impairment would be 60% (see DOSAGE AND ADMINISTRATION and Hepatic Impairment in PRECAUTIONS).

Renal Impairment

The clearance of almotriptan was approximately 65% lower in patients with severe renal impairment (CrCl = 19.8 L/h; creatinine clearance between 10 and 30 mL/min) and approximately 40% lower in patients with moderate renal impairment (CrCl = 34.2 L/h; creatinine clearance between 31 and 71 mL/min) compared to healthy volunteers. Maximum plasma concentrations of almotriptan increased by approximately 80% in these patients (see DOSAGE AND ADMINISTRATION and Renal Impairment in PRECAUTIONS).

CLINICAL STUDIES

The pharmacological activity of almotriptan in the treatment of migraine has been assessed in Phase II and Phase III clinical trials.

The efficacy of AXERT (almotriptan malate) tablets was established in 3 multicentre, randomized, double-blind, placebo-controlled trials. Patients enrolled in these studies were primarily female (86%) and Caucasian (more than 98%), with a mean age of 41 years (range of 18 to 72). Patients were instructed to treat a moderate to severe migraine headache. Two hours after taking one dose of study medication, patients evaluated their headache pain. If the pain had not decreased in severity to mild or to no pain, the patient was allowed to take an escape medication. If the pain had decreased to mild or to no pain at 2 hours but subsequently increased in severity between 2 and 24 hours, it was considered a relapse and the patient was instructed to take a second dose of study medication. Associated symptoms of nausea, vomiting, photophobia, and phonophobia were also evaluated.

In these studies, the percentage of patients achieving a response (mild or no pain) 2 hours after treatment was significantly greater in patients who received either AXERT 6.25 mg or 12.5 mg, compared with those who received placebo. In study 1, almotriptan 12.5 mg was superior to placebo as early as 30 minutes after drug administration (pairwise comparison, p = 0.0485). A higher percentage of patients reported pain relief after treatment with the 12.5 mg dose than with the 6.25 mg dose. Doses greater than 12.5 mg did not lead to significantly better response. These results are summarized in Table 1.

Table 1. Pain Relief Rates 2 Hours Following Treatment of Initial Headache

	Placebo	AXERT 6.25 mg	AXERT 12.5 mg
Study 1	32.5% (n=80)	56.3%* (n=167)	58.5%† (n=164)
Study 2	42.4% (n=98)	–	56.5%†† (n=184)
Study 3	33.9% (n=176)	57.3% (n=360)	64.6%† (n=373)

* p value 0.002 in comparison to placebo
† p value < 0.001 in comparison to placebo
†† p value 0.008 in comparison to placebo

These results cannot be validly compared with results of anti-migraine treatments in other studies. Because studies are conducted at different times, with different samples of patients, by different investigators, employing different criteria and/or different interpretations of the same criteria under different conditions (dose, dosing regimen, etc.), quantitative estimates of treatment responses and the timing of responses may be expected to vary considerably from study to study.

For patients with migraine-associated photophobia, phonophobia, nausea, and vomiting at baseline, there was a decreased incidence of these symptoms following administration of AXERT compared with placebo.

Two to 24 hours following the initial dose of study medication, patients were allowed to take an escape medication or a second dose of study medication for pain response. Escape medication was taken more frequently by patients in the placebo groups than by those in the active almotriptan treatment groups.

The efficacy of AXERT was unaffected by the presence of aura; by gender, weight, or age of the patient; or by concomitant use of common migraine prophylactic drugs (e.g. beta-blockers, calcium channel blockers, tricyclic antidepressants), or oral contraceptives. There were insufficient data to assess the effect of race on efficacy.

INDICATIONS AND CLINICAL USE

AXERT (almotriptan malate) tablets are indicated for the acute treatment of migraine with or without aura in adults.

AXERT is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, ophthalmoplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of AXERT have not been established for cluster headache, which presents in an older, predominantly male population.

CONTRAINDICATIONS

AXERT *(almotriptan malate) is contraindicated in patients with history*, symptoms, or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias). In addition, patients with other significant underlying cardiovascular diseases (e.g., atherosclerotic disease, congenital heart disease) should not receive AXERT. Ischemic cardiac syndromes include, but are not restricted to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction, *and silent myocardial ischemia. Cerebrovascular syndromes include,* but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see WARNINGS).

Because AXERT may increase blood pressure, it should not be given to patients with uncontrolled hypertension (see WARNINGS).

AXERT should not be administered within 24 hours of treatment with another 5-HT$_1$ agonist, or an ergotamine-containing or ergot-type *medication, such as dihydroergotamine or methylsergide.*

AXERT should not be given to patients with hemiplegic, ophthalmoplegic or basilar migraine.

AXERT is contraindicated in patients who are hypersensitive to almotriptan or any other ingredients in AXERT.

WARNINGS

AXERT (almotriptan malate) tablets should only be used where a clear *diagnosis of migraine has been established.*

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events

Because of the potential of this class of compounds (5-HT$_{1B/1D}$ agonists) to cause coronary vasospasm, AXERT should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that 5-HT$_1$ agonists (including AXERT) not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors such as: hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age, unless a cardiovascular examination provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular diseases or predisposition to coronary artery vasospasm is modest at best. If, during the cardiovascular evaluation, the patient's medical* history, electrocardiogram (ECG) or other evaluations reveal findings indicative of, or consistent with, coronary artery vasospasm, or myocardial ischemia, AXERT should not be administered (see CONTRAINDICATIONS).

These evaluations, however, may not identify every patient who has cardiac disease, and in very rare cases, serious cardiac events, such as myocardial infarction or coronary ischemia have occurred in patients without evidence of underlying cardiovascular disease.

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of AXERT take place in a clinical setting, such as the physician's office or a similarly staffed medical facility, unless the patient has previously received almotriptan. Because cardiac ischemia can occur in the absence of any clinical symptoms, consideration should be given to obtaining an ECG during the interval immediately following the first use of AXERT in a patient with risk factors. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations.

If symptoms consistent with angina occur after the use of AXERT, ECG evaluation should be carried out to look for ischemic changes.

It is recommended that patients who are intermittent long-term users of AXERT and who have or acquire risk factors predictive of CAD as described above undergo periodic interval cardiovascular evaluation as they continue to use AXERT.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease are inadvertently exposed to AXERT.

Cardiac Events and Fatalities Associated with 5-HT$_1$ Agonists

Serious adverse cardiac events, including acute myocardial infarction have been reported within a few hours following administration of almotriptan. Life-threatening disturbances of cardiac rhythm and death have been reported within a few hours following the administration of other 5-HT$_1$ agonists. Due to the common pharmacodynamic actions of 5-HT$_1$ agonists, the possibility of cardiovascular effects of the nature described below should be considered for all agents of this class. Considering the extent of use of 5-HT$_1$ agonists in patients with migraine, the incidence of these events is extremely low.

AXERT can cause coronary vasospasm; at least one of these events occurred in a patient with no cardiac history and with documented absence of coronary artery disease.

Patients with symptomatic Wolff-Parkinson White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders should not receive AXERT.

Premarketing experience with almotriptan

Among the 3865 subjects/patients who received AXERT in premarketing clinical trials, one patient was hospitalized for observation after a scheduled ECG was found to be abnormal (negative T-waves on the left leads) 48 hours after taking a single 6.25 mg dose of AXERT. The patient, a 48-year old female, had previously taken 3 other doses for earlier migraine attacks. Myocardial enzymes at the time of the abnormal ECG were normal. The patient was diagnosed as having had myocardial ischemia, and it was also found that she had a family history of coronary disease. An ECG performed 2 days later was normal, as was a follow up coronary angiography. The patient recovered without incident.

Postmarketing experience with almotriptan

Serious cardiovascular events have been reported in association with the use of AXERT. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to definitely determine the proportion of the reported cases that were actually caused by almotriptan or to reliably assess causation in individual cases.

Cerebrovascular Events and Fatalities with 5-HT$_1$ Agonists

Cerebral hemorrhage, subarachnoid hemorrhage, stroke and other cerebrovascular events have been reported in patients treated with other 5-HT$_1$ agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted, however, that patients who suffer from migraine may have an increased risk of certain cerebrovascular events such as stroke, hemorrhage or transient ischemic attack.

Other Vasospasm-Related Events

5-HT$_1$ agonists may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported with 5-HT$_1$ agonists.

Increases in Blood Pressure

Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension treated with other 5-HT$_1$ agonists. AXERT is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). In volunteers, small increases in mean systolic and diastolic blood pressure relative to placebo were seen over the first 4 hours after administration of 12.5 mg of almotriptan (0.21 and 1.35 mm Hg, respectively). The effect of AXERT on blood pressure was also assessed in patients with hypertension controlled by medication. In this population, mean increases in systolic and diastolic blood pressure relative to placebo over the first 4 hours after administration of 12.5 mg of almotriptan were 4.87 and 0.26 mm Hg, respectively. The slight increases in blood pressure in both volunteers and controlled hypertensive patients were not considered clinically significant (see ADVERSE REACTIONS and PRECAUTIONS).

Special Cardiovascular Pharmacology Studies With Another 5-HT$_1$ Agonist

In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT$_1$ agonist at a subcutaneous dose of 1.5 mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by four subjects. Clinically significant increases in blood pressure were experienced by three of the subjects (two of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and 1 had insignificant coronary artery disease.

In an additional study with this same drug, migraine patients (n= 35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving a subcutaneous 1.5 mg dose in the absence of a migraine attack. Reduced coronary vasodilatory reserve (~10%), increased coronary resistance (~20%), and decreased hyperaemic myocardial blood flow (~10%) were noted. The relevance of these findings to the use of the recommended oral dose of this 5-HT$_1$ agonist is not known.

Similar studies have not been done with AXERT. However, owing to the common pharmacodynamic actions of 5-HT$_1$ agonists, the possibility of cardiovascular effects of the nature described above should be considered for any agent of this pharmacological class.

Hypersensitivity

Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred in patients receiving other 5-HT$_1$ agonists. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. Owing to the possibility of cross-reactive hypersensitivity reactions, AXERT should not be used in patients having a history of hypersensitivity to chemically related 5-HT$_1$ receptor agonists. (see ADVERSE REACTIONS and PRECAUTIONS).

PRECAUTIONS

General

AXERT should be administered with caution to patients with diseases that may alter the absorption, metabolism or excretion of drugs, such as those with impaired hepatic or renal function (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION).

Cardiovascular

As with other 5-HT$_1$ agonists, sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck and jaw have been reported after treatment with AXERT (almotriptan malate). These events have not been associated with arrhythmias or ischemic ECG changes in clinical trials. Because drugs in this class,

including AXERT, may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of the medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following the use of any 5-HT_1 agonist, are candidates for further evaluation (see CONTRAINDICATIONS and WARNINGS).

Neurologic Conditions

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT_1 agonists for severe headache that were subsequently shown to have been secondary to an evolving neurological lesion. For newly diagnosed patients or patients presenting with atypical symptoms, the diagnosis of migraine should be reconsidered if no response is seen after the first dose of AXERT.

Corneal Opacities

Three male dogs (out of a total of 14 treated) in a 52-week toxicity study of oral almotriptan developed slight corneal opacities that were noted after 51, but not after 25, weeks of treatment. The doses at which this occurred were 2, 5, and 12.5 mg/kg/day. The opacity reversed in the affected dog at 12.5 mg/kg/day after a 4-week drug-free period. Systemic exposure (plasma AUC) to parent drug at 2 mg/kg/day was approximately 2.5 times the exposure in humans receiving the maximum recommended daily dose of 25 mg. A no-effect dose was not established.

Binding to Melanin-Containing Tissues

When pigmented rats were given a single oral dose of 5 mg/kg of radiolabelled almotriptan, the elimination half-life of radioactivity from the eye was 22 days, suggesting that almotriptan and/or its metabolites may bind to the melanin of the eye. Because almotriptan could accumulate in the melanin-rich tissues over time, there is the possibility that it could cause toxicity in these tissues over extended use. However, no adverse ocular effects related to treatment with almotriptan were noted in any of the toxicity studies. Although no systemic monitoring of ophthalmic function was undertaken in clinical trials, and no specific recommendations for ophthalmic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmic effects.

Carcinogenesis

The carcinogenic potential of almotriptan was evaluated by oral gavage for up to 103 weeks in mice at doses of up to 250 mg/kg/day, and in rats for up to 104 weeks at doses up to 75 mg/kg/day. These doses were associated with plasma exposures (AUC) to parent drug that were approximately 40 and 78 times, in mice and rats respectively, the plasma AUC observed in humans receiving the MRDD of 25 mg. Because of high mortality rates in both studies, which reached statistical significance in high-dose female mice, all female rats, all male mice and high-dose female mice were terminated between weeks 96 and 98. There was no increase in tumors related to almotriptan administration.

Mutagenesis

Almotriptan was not mutagenic, with or without metabolic activation, when tested in two gene mutation assays, the Ames test and the *in vitro* thymidine locus mouse lymphoma assay. Almotriptan was not determined to be clastogenic in two *in vitro* cytogenetics assays in human lymphocytes and an *in vivo* mouse micronucleus assay. Almotriptan produced an equivocal weakly positive response in *in vitro* cytogenetics assays in human lymphocytes.

Impairment of Fertility

When female rats received almotriptan by oral gavage prior to and during mating and up to implantation at doses of 25, 100, and 400 mg/kg/day, prolongation of the estrous cycle was observed at a dose of 100 mg/kg/day (exposure, based on mg/m^2, was approximately 40 times exposure in humans receiving the maximum recommended daily dose (MRDD) of 25 mg). No effects on fertility were noted in female rats at 25 mg/kg/day (exposure approximately 10 times human exposure at MRDD). No adverse effects were noted in male rats at 400 mg/kg/day (160 times the human exposure based on mg/m^2).

Pregnancy

When almotriptan was administered orally during organogenesis to pregnant rats at doses of 125, 250, 500 and 1000 mg/kg/day, an increase in embryolethality was seen at the 1000 mg/kg/day dose (maternal exposure [based on plasma AUC of parent drug] was approximately 958 times the human exposure at MRDD of 25 mg). Increased incidences of fetal skeletal variations (decreased ossification) were noted at doses greater than the no-observed-effect level in rats of 125 mg/kg/day (maternal exposure 80 times human exposure at MRDD). Similar studies in rabbits conducted with almotriptan at doses of 5, 20 and 60 mg/kg/day demonstrated increases in embryolethality at 60 mg/kg/day (maternal exposure, based on mg/m^2, 50 times human exposure at MRDD). When almotriptan was administered to rats throughout the periods of gestation and lactation at doses of 25, 100 and 400 mg/kg/day, gestation length was increased and litter size and offspring body weight were decreased at the high dose (maternal exposure, based on mg/m^2, 160 times human exposure at MRDD). The decrease in pup weight persisted throughout lactation. The no-observed-effect level in this study was 100 mg/kg/day (maternal exposure 40 times human exposure at MRDD).

There have been no adequate and well-controlled studies in pregnant women; therefore AXERT should only be used during pregnancy if the potential benefit justifies the risk to the fetus.

Hepatic Impairment

AXERT should be used with caution in patients with hepatic impairment. The maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg is recommended (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION).

Renal Impairment

AXERT should be used with caution in patients with severe renal impairment. The maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg should be used (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and DOSAGE AND ADMINISTRATION).

Psychomotor Effect

Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that AXERT does not affect them adversely.

Use in the Elderly

Clinical studies of AXERT did not include sufficient numbers of subjects over 65 years of age to determine whether they respond differently from younger subjects. Renal and total clearance, and amount of drug excreted in the urine were lower in elderly non-migraineur volunteers (age 65 to 76 years) than in younger non-migraineur volunteers (age 19 to 34 years), resulting in longer terminal half-life and higher area under the plasma concentration-time curve. Although clearance of almotriptan was lower in elderly volunteers, there were no differences in the safety and tolerability between the two populations (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations). In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal, cardiac, and hepatic function, and of concomitant disease or other drug therapy.

Use in Children

The safety and effectiveness of AXERT in pediatric patients has not been established; therefore, AXERT is not recommended for use in patients under 18 years of age.

Post-marketing experience with other triptans include a limited number of reports that describe pediatric (under 12 years of age) and adolescent (12 - 17 years of age) patients who have experienced clinically serious adverse events that are similar in nature to those reported as rare occurrences in adults.

Use during Lactation

It is not known whether almotriptan is excreted in human milk. Since many drugs are excreted in human milk, caution should be exercised when AXERT is administered to a nursing woman.

Dependence Liability

Although the abuse potential of AXERT has not been specifically assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behaviour was observed in patients who received AXERT in clinical trials or their extensions. The 5-$HT_{1B/1D}$ agonists, as a class, have not been associated with drug abuse.

Drug Interactions

All drug interaction studies were performed in healthy volunteers using a single 12.5 mg dose of almotriptan and multiple doses of the other drug.

Ergot-containing drugs

These drugs have been reported to cause prolonged vasospastic reactions. As there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (dihydroergotamine or methysergide) and AXERT within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

Monoamine oxidase inhibitors

Coadministration of almotriptan and moclobemide (150 mg b.i.d. for 8 days) resulted in a 27% decrease in almotriptan clearance and an increase in C_{max} of approximately 6%. No dose adjustment is necessary.

Propranolol

Coadministration of almotriptan and propranolol (80 mg b.i.d. for 7 days) resulted in no significant changes in the pharmacokinetics of almotriptan.

Selective serotonin reuptake inhibitors (SSRIs)

Coadministration of almotriptan and fluoxetine (60 mg daily for 8 days), a potent inhibitor of CYP2D6, had no effect on almotriptan clearance, but maximal concentrations of almotriptan were increased by 18%. This difference is not clinically significant. SSRIs (e.g. fluoxetine, fluvoxamine, paroxetine, sertraline) have been rarely reported to cause weakness, hyperreflexia and incoordination when coadministered with 5-HT_1 agonists. If concomitant treatment with AXERT and an SSRI is clinically warranted, appropriate observation of the patient, for both acute and long term adverse events, is advised.

Verapamil

Coadministration of almotriptan and verapamil (120 mg sustained-release tablets b.i.d. for 7 days), an inhibitor of CYP4503A4, resulted in a 20% increase in the area under the plasma concentration-time curve, and in a 24% increase in maximal plasma concentrations of almotriptan. Neither of these changes is clinically significant.

Other 5-$HT_{1B/1D}$ agonists

Concomitant use of other 5-$HT_{1B/1D}$ agonists within 24 hours of treatment with AXERT is contraindicated (see CONTRAINDICATIONS).

Ketoconazole and other potent CYP3A4 inhibitors

Coadministration of almotriptan and the potent CYP3A4 inhibitor ketoconazole (400 mg q.d. for 3 days) resulted in an approximately 60% increase in the area under the plasma concentration-time curve and maximal plasma concentrations of almotriptan. Although the interaction between almotriptan and other potent CYP3A4 inhibitors (e.g. itraconazole, ritonavir, and erythromycin) has not been studied, increased exposures to almotriptan may be expected when almotriptan is used concomitantly with these medications.

Laboratory Tests

Almotriptan is not known to interfere with any commonly employed clinical laboratory tests. No specific laboratory tests are recommended for monitoring patients.

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following use of other 5-HT_1 agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasms, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Serious cardiac events, including myocardial infarction, coronary artery vasospasm and intermediate coronary syndrome, have occurred following the use of AXERT tablets. These events are extremely rare and have been reported mostly in patients with cardiovascular risk factors (see WARNINGS and POST-MARKETING ADVERSE REACTIONS).

Experience in Controlled Clinical Trials with AXERT (almotriptan)

Typical 5-HT_1 Agonist Adverse Reactions

As with other 5-HT_1 agonists, AXERT has been associated with sensations of heaviness, pressure, tightness or pain which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limbs.

Increases in Blood Pressure

Significant elevations in systemic blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension treated with other 5-HT_1 agonists. AXERT is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). In volunteers, small increases in mean systolic and diastolic blood pressure relative to placebo were seen over the first 4 hours after administration of 12.5 mg of almotriptan (0.21 and 1.35 mm Hg, respectively). The effect of AXERT on blood pressure was also assessed in patients with hypertension controlled by medication. In this population, mean increases in systolic and diastolic blood pressure relative to placebo over the first 4 hours after administration of 12.5 mg of almotriptan were 4.87 and 0.26 mm Hg, respectively. The slight increases in blood pressure in both volunteers and controlled hypertensive patients were not considered clinically significant (see also CONTRAINDICATIONS and WARNINGS).

Acute Safety

Adverse events were assessed in controlled clinical trials that included 1840 patients who received one or two doses of AXERT (almotriptan malate) tablets and 386 patients who received placebo.

The most common adverse events during treatment with AXERT were nausea, somnolence, headache, paresthesia, and dry mouth. In long-term, open-label studies where patients were allowed to treat multiple attacks for up to one year, 5% (63 out of 1347 patients) withdrew due to adverse experiences.

Table 2 lists the adverse events that occurred in at least 1% of the patients treated with AXERT, and at an incidence greater than in patients treated with placebo, regardless of drug relationship. These events reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behaviour, and the kinds of patients treated may differ.

Table 2. Incidence of Adverse Events in Controlled Clinical Trials (Reported in at Least 1% of Patients Treated with AXERT, and at an Incidence Greater than Placebo)

Adverse Event	Percentage of Patients Reporting the Event		
	AXERT 6.25 mg (n=527)	AXERT 12.5 mg (n=1313)	Placebo (n=386)
Digestive			
Nausea	1	2	1
Dry Mouth	1	1	0.5
Nervous			
Paresthesia	1	1	0.5

AXERT is generally well tolerated. Most adverse events were mild in intensity and were transient, and did not lead to long-lasting effects. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, age, presence of aura, or use of prophylactic medications or oral contraceptives. There were insufficient data to assess the effect of race on the incidence of adverse events.

Other Events

The frequencies of less commonly reported adverse events are presented below. However, the role of AXERT in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used AXERT in controlled clinical trials and reported an event, divided by the total number of patients exposed to AXERT in these studies. All reported events are included, except the ones already listed in the previous table, and those unlikely to be drug related. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; and *rare* adverse events are those occurring in fewer than 1/1000 patients.

Total Body System: *Frequent* was headache. *Infrequent* were abdominal cramp or pain, asthenia, chills, back pain, chest pain, neck pain, fatigue, and rigid neck. *Rare* were fever and photosensitivity reaction.

Cardiovascular: *Infrequent* were vasodilation, palpitations, and tachycardia. *Rare* were intermediate coronary syndrome, abnormal cardiac rhythm, hypertension, and syncope.

Digestive: *Infrequent* were diarrhea, vomiting, and dyspepsia. *Rare* were decreased appetite, increased appetite, colitis, gastritis, gastroenteritis, esophageal reflux, increased thirst, and increased salivation.

Metabolic: *Infrequent* were hyperglycemia and increased serum creatine phosphokinase. *Rare* were increased gamma glutamyl transpeptidase and hypercholesteremia.

Musculoskeletal: *Infrequent* were myalgia and muscular weakness. *Rare* were arthralgia, arthritis, and myopathy.

Nervous: *Frequent* were dizziness and somnolence. *Infrequent* were tremor, vertigo, anxiety, hypesthesia, restlessness, CNS stimulation, insomnia, and shakiness. *Rare* were change in dreams, impaired concentration, abnormal coordination, depressive symptoms, euphoria, hyperreflexia, hypertonia, nervousness, neuropathy, nightmares, and nystagmus.

Respiratory: *Infrequent* were pharyngitis, rhinitis, dyspnea, laryngismus, sinusitis, bronchitis, and epistaxis. *Rare* were hyperventilation, laryngitis, and sneezing.

Skin: *Infrequent* were diaphoresis, dermatitis, erythema, pruritus, and rash.

Special Senses: *Infrequent* were ear pain, conjunctivitis, eye irritation, hyperacusis, and taste alteration. *Rare* were diplopia, dry eyes, eye pain, otitis media, parosmia, scotoma, and tinnitus.

Urogenital: Dysmenorrhea was *infrequent*.

Long-Term Safety

In a long term open label study, 762 patients treated 13,751 migraine attacks with AXERT over a period of up to 1 year. Migraine headaches could be treated with either a single dose of 12.5 mg AXERT or an initial 12.5 mg dose followed by a second 12.5 mg dose if needed. In this study, 3% (24 of 762) of patients withdrew due to an adverse experience. The most common adverse events (defined as occurring in more than 3% of patients) in descending order frequency were as follows: back pain (8%), bronchitis (6.4%), influenza-like symptoms (5.8%), pharyngitis (4.6%), vomiting (4.2%), rhinitis (4.1%), skeletal pain (3.4%) and sinusitis (3.4%). Due to the lack of placebo control in this study, the role of AXERT in causation cannot be reliably determined.

POST-MARKETING ADVERSE REACTIONS

In addition to the adverse experiences reported during clinical trials of AXERT, the following adverse events have been reported in patients receiving marketed AXERT from worldwide use since approval. Due to the uncontrolled nature of post-marketing surveillance, it is not possible to definitely determine the proportion of the reported cases that were actually caused by AXERT or to reliably assess causation.

Serious cardiovascular adverse events, including acute myocardial infarction, coronary vasospasm and angina pectoris have been reported within a few hours following administration of AXERT.

Although very rare, AXERT can cause coronary vasospasm; at least one of these events occurred in a patient with no cardiac history and with documented absence of coronary artery disease (see CONTRAINDICATIONS, WARNINGS, ADVERSE REACTIONS and PRECAUTIONS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Patients and volunteers receiving single oral doses of 100 to 150 mg of AXERT did not experience significant adverse events. During the clinical trials, one patient ingested 62.5 mg in a five-hour period, and another patient ingested 100 mg in a 38-hour period. Neither patient experienced adverse reactions.

Based on the pharmacology of 5-HT_1 agonists, hypertension or other more serious cardiovascular symptoms could occur after overdosage. Gastrointestinal decontamination (i.e. gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with AXERT. Clinical and electrocardiographic monitoring should be continued for at least 20 hours, even if clinical symptoms are not observed.

The effects of hemodialysis or peritoneal dialysis on plasma concentrations of almotriptan are unknown.

DOSAGE AND ADMINISTRATION

In controlled clinical trials, single doses of 6.25 mg and 12.5 mg of AXERT (almotriptan malate) were effective for the acute treatment of migraine in adults, with the 12.5 mg dose tending to be a more effective dose (see CLINICAL STUDIES). Individuals may vary in response to doses of AXERT. The choice of dose should therefore be made on an individual basis.

If the headache returns, the dose may be repeated after 2 hours, but no more than two doses should be given within a 24-hour period. Controlled trials have not adequately established the effectiveness of a second dose if the initial dose is ineffective. The safety of treating an average of more than four headaches in a 30-day period has not been established.

Hepatic Impairment

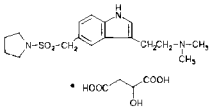
The pharmacokinetics of almotriptan have not been assessed in this population. The maximum decrease expected in the clearance of almotriptan due to hepatic impairment is 60%. Therefore, the maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg should be used (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS).

Renal Impairment

In patients with severe renal impairment, the clearance of almotriptan was decreased. Therefore, the maximum daily dose should not exceed 12.5 mg over a 24-hour period, and a starting dose of 6.25 mg should be used (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS).

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	almotriptan malate
Chemical Name:	1-[[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]-methyl]-sulfonyl] pyrrolidine-hydroxybutanedioate
Structural Formula:	
Molecular Formula:	$C_{17}H_{25}N_3O_2S \cdot C_4H_6O_5$
Molecular Weight:	469.56
Physical Form:	Almotriptan is a white to slightly yellow crystalline powder.
Solubility:	Freely soluble in water and in methanol, but practically insoluble in ethanol and methylene chloride.
pKa:	8.77 at 22 ± 2°C
Melting Point:	167 - 173°C
pH:	1% solution in purified water has pH 4.1
Partition Coefficient:	A partition coefficient of 0.008 between octanol and water was determined, when measured at the normal pH value (5.4-6.3) for purified water.

Composition

Active Ingredient: almotriptan malate equivalent to 6.25 or 12.5 mg of almotriptan.

Inactive Ingredients: mannitol, cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, titanium oxide, hydroxypropyl methylcellulose, polyethylene glycol, propylene glycol, iron oxide (6.25 mg only), FD&C Blue No. 2 (12.5 mg only), and carnauba wax.

Stability and Storage Recommendations

AXERT tablets should be stored between 15-30°C.

AVAILABILITY OF DOSAGE FORMS

AXERT (almotriptan malate) tablets are available through prescription only.

AXERT 6.25 mg tablet contains 6.25 mg of almotriptan and is a white, circular, biconvex tablet, printed in red with the code "2080". Available in unit dose (aluminum blister pack) of 6 tablets.

AXERT 12.5 mg tablet contains 12.5 mg of almotriptan and is a white, circular, biconvex tablet, printed in blue with a stylized "A". Available in unit dose (aluminum blister pack) of 6 tablets.

AXERT is a Schedule F drug.

Product Monograph available to healthcare professionals upon request.

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