ORIGINAL ARTICLE

Recurrent Ataxia in Children and Adolescents

Michael S. Salman, Samantha F. Klassen, Janine L. Johnston

ABSTRACT: ***Background:*** Recurrent ataxia is encountered infrequently in clinical pediatric neurology practise and presents with diagnostic challenges. It is caused by several disorders. Our aims were to describe the epidemiology and clinical features in children with recurrent ataxia. ***Materials and Methods:*** A retrospective review was undertaken in 185 children with chronic ataxia, who presented during 1991 to 2008. Several databases were searched to ensure optimum ascertainment. Patients with brain tumors or isolated disorders of the peripheral nerves or vestibular system were excluded. ***Results:*** Recurrent ataxia was reported in 21 patients. Their age range was between 6 and 32.75 years (males = 12). The crude period prevalence rate for the 18-year study period was 7.44/100,000. Eight patients had episodic ataxia and seven had inflammatory and metabolic disorders. In the rest the etiology was unknown. Many patients presented with ataxia, dizziness, and vertigo. The frequency and duration of the ataxic episodes varied from several per day to one every few months. Other clinical features included developmental delay and seizures. Neuroimaging in episodic ataxia was normal and abnormal in inflammatory or metabolic disorders. Acetazolamide provided symptomatic relief in patients with episodic ataxia, while steroids were beneficial in patients with an inflammatory etiology. One child with a metabolic disorder died. ***Conclusions:*** Recurrent ataxia is an uncommon presentation in children and mortality is rare. Genetic, metabolic, and inflammatory disorders should be considered in these patients. Neuroimaging is essential. Acetazolamide in selected patients provides good symptomatic relief.

RÉSUMÉ: Ataxie récurrente chez les enfants et les adolescents. ***Contexte:*** L'ataxie récurrente est observée peu fréquemment dans la pratique clinique en neurologie pédiatrique et pose des problèmes en matière de diagnostic. Elle est aussi causée par plusieurs troubles. Notre objectif est donc de décrire chez des enfants l'épidémiologie et les traits cliniques de ce trouble de coordination. ***Matériel et méthodes:*** Nous avons mené une analyse rétrospective chez 185 enfants atteints d'ataxie chronique qui ont fait l'objet d'une consultation entre 1991 et 2008. Des recherches ont également été conduites en lien avec plusieurs bases de données. Les patients présentant une tumeur au cerveau ou des troubles isolés du système nerveux périphérique ou du système vestibulaire ont été exclus. ***Résultats:*** Des cas d'ataxie récurrente ont été signalés chez vingt-et-un patients. Leur tranche d'âge allait de 6 à 32,75 ans (hommes = 12). Durant cette période d'étude de 18 ans, le taux de prévalence brut a été de 7,44/100 000. Huit patients ont souffert d'ataxie épisodique et sept d'entre eux de troubles inflammatoires et métaboliques. Pour ce qui est des autres patients, leur étiologie est demeurée inconnue. Beaucoup d'entre eux se sont présentés avec des symptômes d'ataxie, d'étourdissement et de vertige. La fréquence et la durée des épisodes ataxiques ont varié de plusieurs fois par jour à une fois tous les quelques mois. D'autres traits cliniques ont notamment inclus des retards de développement et des troubles convulsifs. Dans le cas de l'ataxie épisodique, les résultats en neuro-imagerie se sont révélés normaux ; ils sont toutefois apparus anormaux en ce qui regarde les troubles inflammatoires et métaboliques. L'acétazolamide a procuré un soulagement symptomatique aux patients souffrant d'ataxie épisodique alors que des stéroïdes ont été bénéfiques pour les patients chez qui on avait observé une étiologie inflammatoire. Enfin, mentionnons qu'un enfant atteint d'un trouble métabolique est décédé. ***Conclusions:*** L'ataxie récurrente demeure inhabituelle chez les enfants ; qui plus est, c'est très rarement qu'on en meurt. Dans le cas de ces patients, on doit envisager la présence de troubles génétiques, métaboliques et inflammatoires. Les techniques de la neuro-imagerie, elles, demeurent essentielles. Quant à l'acétazolamide, il procure à des patients sélectionnés un soulagement symptomatique efficace.

Keywords: Recurrent ataxia, intermittent ataxia, episodic ataxia, pediatrics

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Introduction

Ataxia is caused by numerous disorders affecting the central and/or peripheral nervous system.[1,2] Children with chronic ataxia are encountered relatively frequently in pediatrics.[2] Recurrent ataxia however, defined as ataxia that recurs after complete or almost complete resolution of an acute or subacute episode of ataxia, appears to be uncommon in children. Recurrent ataxia may be caused by a channelopathy, conventionally called episodic ataxia.[3,4] Alternatively, recurrent ataxia may be caused by other diseases including inflammatory or toxic disorders, some types of migraine such as migraine with brainstem aura, and metabolic syndromes such as mitochondrial diseases and urea cycle defects.[5-8] When recurrent ataxia is caused by these disorders

From the Section of Pediatric Neurology, Winnipeg Children's Hospital and Department of Pediatrics and Child Health (MSS); Section of Neurology, Departments of Medicine and Ophthalmology (JLJ); Max Rady College of Medicine, Faculty of Health Sciences (MSS, SFK, JLJ); University of Manitoba, Winnipeg, Manitoba, Canada.

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Correspondence to: Michael S. Salman, Section of Pediatric Neurology, Children's Hospital, AE 308, 820 Sherbrook Street, Winnipeg, MB, R3A 1R9, Canada.
Email: msalman@hsc.mb.ca

(i.e. disorders not caused by a channelopathy or a presumed channelopathy) we have used the term 'intermittent ataxia' for the purposes of this paper.

We found no studies that have systematically and comprehensively described the epidemiology and clinical spectrum of recurrent ataxia in pediatric patients in Canada. We hypothesized that the incidence and prevalence rates of recurrent ataxia are low, and that episodic ataxia is rare in children. The aims of this study were to systematically describe the epidemiology, clinical findings, investigations, and management in a cohort of pediatric patients with recurrent ataxia.

Method

From several hospital resources and databases we identified patients who had ataxia when they were less than 17 years old between 1991 and 2008. We then selected patients with chronic ataxia only, which we defined as recurrent ataxia or ataxia lasting longer than two months. All patients were seen in Winnipeg Children's Hospital for a clinical evaluation of their ataxia. Patients from neighboring provinces who attended Winnipeg Children's Hospital were included. An additional female patient with episodic ataxia was identified later. She was originally seen by an otolaryngologist at the Health Sciences Center in Winnipeg and was subsequently evaluated by one of the authors (JLJ). Further information on the ascertainment of the patients is available in detail elsewhere.[2] We excluded patients whose ataxia was caused by primary brain tumours, isolated diseases of the peripheral nerves and vestibular system including migraine, and patients with developmental coordination disorder. Details on the methodology, epidemiology, ethnicity, and geographic distribution have been published on this cohort.[2,9]

Ethical approval for the study was given by the Research Ethics Board of the University of Manitoba. Demographic and clinical information, diagnostic data, and neuroimaging reports were retrieved from the patients' hospital medical charts as described previously.[2,10] Patients were investigated extensively. Almost all patients had neuroimaging (mostly MRI and rarely CT). Routine tests (including full blood count, ESR, glucose, electrolytes, calcium, magnesium, phosphorus, albumin, creatinine kinase, liver, and thyroid function tests), alpha fetoprotein, immunoglobulins, autoimmune (including ANA, ANCA), metabolic (including ammonia, lactate, amino acids, urine organic acids, uric acid, total and free carnitine, acylcarnitine, very long chain fatty acids, lysosomal enzymes, vitamins E and B12, CSF neurotransmitters), and genetic tests (including karyotype, FISH, calcium channel mutations, mutations in selected spinocerebellar ataxia genes) on blood, urine, and CSF were performed in a stepwise manner. Nerve conduction studies, electromyogram, EEG, and skin and muscle biopsies were also done in selected patients.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 22 (IBM, Armonk, NY, USA). Mean and standard deviation were used to describe normally distributed data, while median and range were used when the data were skewed.

Results

Of the 185 patients (93 females) with chronic ataxia who satisfied the inclusion criteria, 21 patients had recurrent ataxia (11.4%). Their age range was between 6 and 32.75 years at end of study period in 2008 (12 males). There were two pairs of siblings with episodic ataxia. Twenty of the 21 patients resided in Manitoba. One female with multiple sclerosis resided in a town in the neighbouring province of Ontario. Based on Statistics Canada censuses for Manitoba[11] for the years 1991, 1996, 2001, and 2006, the crude incidence rate for the 18-year study period was 6.32 in 100,000 based on the mean number of the population at risk living in the province during the four censuses performed during the study period (17 new cases in 268,770 children and adolescents during 1991-2008). The crude period prevalence rate for the 18-year study period was 7.44 in 100,000 (20 cases in 268,770 children and adolescents during 1991-2008). There was one death during the study period, a male patient with carbamoyl phosphate synthetase deficiency at age eight years and six months. He developed cerebral edema with fluctuating hyperammonemia for which he received maximal medical therapy including hemodialysis. Medical support was withdrawn when imaging showed lack of blood flow to the brain. The crude mortality rate for the 18-year study period was 0.37 in 100,000 (one death in 268,770 children and adolescents during 1991-2008).

Following extensive investigations, the etiology was elucidated in 15 of the 21 patients with recurrent ataxia. Eight of the 15 patients had episodic ataxia: Four of the eight had a calcium channelopathy. Two siblings had a mutation and one patient a deletion in the *CACNA1A* gene consistent with episodic ataxia type 2. One further patient had a mutation in *CACNB4* gene characteristic of episodic ataxia type 5.[12] We labeled the remaining four patients as having presumed episodic ataxia since there was a family history of episodic ataxia in first degree relatives. Three of these had no mutations in the episodic ataxia genes and one had no genetic testing per the family's wish. One of these four patients also had a mild phenotype of Noonan syndrome. The etiology of intermittent ataxia in the other seven of 15 patients was: Multiple sclerosis (n = 2), multiphasic acute disseminated encephalomyelitis (ADEM) (n = 1), polyarteritis nodosa (n = 1), carbamoyl phosphate synthetase deficiency (n = 1), GLUT1 deficiency syndrome caused by a missense mutation R93W in the glucose transporter gene[13] (n = 1), and a mitochondrial disorder caused by complex 1 deficiency (n = 1). The etiology of intermittent ataxia was unknown in the remaining six patients. Patients with malformations of the cerebellum did not present with recurrent ataxia. Table 1 shows the demographic details. Table 2 shows the presenting symptoms and triggers of the ataxic episodes. The most common presenting symptom was ataxia (n = 16). Other presenting symptoms were dizziness/vertigo (n = 9), visual complaints (n = 6), and weakness (n = 5).

Patients with episodic ataxia generally developed ataxia during the second decade of life and had their first clinical assessment during adolescence. In contrast, patients with intermittent ataxia of unknown etiology developed ataxia and had their first assessment more than a decade earlier (Table 1). The frequency of the episodes ranged widely, from several per day to one per month. The patient with GLUT1 deficiency syndrome had at times three ataxic episodes per week, lasting about 13 minutes. The patient with mitochondrial disease developed ataxia at age 13 months that almost resolved two months later. In the ensuing year he had several acute exacerbations of his ataxia over his mild baseline wide-based gait. In four patients with intermittent ataxia that was not yet diagnosed (NYD), the frequency varied from 20 episodes per day to one episode per month. In the rest the frequency was not documented.

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Table 1a: Demographic details of patients with episodic ataxia

	Episodic ataxia (calcium channelopathy) (n = 4)	Episodic ataxia (with positive family history of episodic ataxia) (n = 4)	All episodic ataxia* (n = 8)
Gender M/F	2/2	1/3	3/5
Median age [range] at end of study	28y 8mo [22y 4mo- 32y 9mo]	26y 1mo [14y 9mo- 31y 1mo]	26y 11mo [14y 9mo- 32y 9mo]
Median age [range] at ataxia onset	7y 9mo [3y 3mo-14y]	14y 11mo [12y- 16y 11mo]	12y 9mo [3y 3mo- 16y 11mo]
Median disease duration [range]	11y 4mo [5y 8mo- 15y 9mo]	3y 7mo [1y 8mo- 5y 2mo]	5y 5mo [1y 8mo- 15y 9mo]
Median age [range] at first clinical assessment	11y 6mo [2y 2mo- 15y 5mo]	15y 1mo [13y 8mo- 16y 11mo]	14y 6mo [2y 2mo- 16y 11mo]
Median age [range] at last clinical assessment	18y 1mo [16y 2mo- 22y 4mo]	18y [15y 4mo- 21y 6mo]	18y [15y 4mo- 22y 4mo]
Median duration [range] of clinical follow up	9y 5mo [9mo- 14y 5mo]	1y 10mo [1y 5mo- 5y]	3y 3mo [9mo- 14y 5mo]
Number of deaths during the study period	0	0	0

y = years; mo = months.
*This column is a summary of the first two columns.

The duration of the ataxic episodes in patients with episodic ataxia varied from 30 seconds to seven days, with many episodes lasting less than 24 hours, while the duration of ataxia in patients with intermittent ataxia NYD ranged from a few minutes to (rarely) several weeks, reflecting their heterogeneous etiology.

The patient with multiphasic ADEM had a total of two ataxic episodes four months apart, each lasting about 21 days. The two patients with multiple sclerosis each had a total of two ataxic episodes 15 and eight months apart. The duration of their ataxia varied between 15 days and four months. The patient with polyarteritis nodosa had ataxic episodes lasting between 16 and 24 hours.

Table 3 shows other clinical features in our cohort of patients with recurrent ataxia. A family history of seizures or migraine (n = 10) and developmental delay (n = 9) were common. Non-febrile seizures occurred in patients with metabolic etiologies (n = 3). Having first degree relatives with episodic ataxia was an exclusive feature in patients with episodic ataxia. Nystagmus, saccadic smooth pursuit, dysarthria, and signs of limbs incoordination occurred non-specifically among the different etiologies. Dyskinesia was reported in the patients with GLUT1 deficiency syndrome and mitochondrial disease, one patient with episodic ataxia, and two other patients in whom the etiology was unknown. At least 20 patients walked independently and most had wide-based ataxic gait.

Neuroimaging was normal in patients with episodic ataxia and GLUT1 deficiency syndrome (one had CT, seven had MRI, one had no neuroimaging). Patients with multiple sclerosis and multiphasic ADEM showed multifocal hyperintense T2 signal abnormalities in one or more of the following regions: Cerebral and cerebellar white matter, brainstem, corpus callosum, cervical and lumbar spinal cord, and left optic nerve, with new lesions with or without contrast enhancement (Figure 1). In addition, in the patient with multiphasic ADEM there were T2 signal abnormalities in the basal ganglia and thalami. All the abnormalities in that patient resolved on subsequent MRIs. The MRIs in the patient with polyarteritis nodosa showed hyperintense T2 signal abnormalities both with and without restricted diffusion or

Table 1b: Demographic details of patients with rarer or unknown causes of intermittent ataxia

	Multiple sclerosis (n = 2)	ADEM (n = 1)	Mitochondrial disease (n = 1)	CPS deficiency (n = 1)	PAN (n = 1)	GLUT1 deficiency (n = 1)	Intermittent ataxia NYD (n = 6)
Gender M/F	0/2	1/0	1/0	1/0	1/0	1/0	4/2
Age at end of study	17y 1mo, 19y 9mo	9y 7mo	6y	Died at 8y 6mo	12y 9mo	15y 7mo	10y 10mo [9y 5mo- 18y 9mo]
Age at ataxia onset	15y, 12y 7mo	7y 10mo	1y 1mo	6y 2mo	2y 6mo	1y 6mo	1y 8mo [1y 3mo- 8y 7mo]
Disease duration	3y 2mo, 5y 6mo	10mo	7y 9mo	8y 6mo	11y 8mo	16y 1mo	2y 10mo [9mo- 8y 8mo]
Age at first clinical assessment	15y 1mo, 12y 7mo	7y 10mo	1y 1mo	1 day	2y 9mo	3y	1y 8mo [1y 4mo- 8y 7mo]
Age at last clinical assessment	18y 1mo, 17y 11mo	8y 11mo	8y 7mo	8y 6mo	13y 7mo	17y 8mo	5y 3mo [2y 9mo- 16y 3mo]
Duration of clinical follow up	3y, 5y 4mo	1y 1mo	5y 10mo	8y 6mo	10y 10mo	13y	3y 6mo [1y 1mo- 12y 5mo]
Number of deaths during the study period	0	0	0	1	0	0	0

ADEM = multiphasic acute disseminated encephalomyelitis; CPS = carbamoyl phosphate synthetase; PAN = polyarteritis nodosa; NYD = not yet diagnosed; y = years; mo = months.

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Table 2a: Frequency of the presenting symptoms and triggers in patients with episodic and intermittent ataxia NYD*

	Episodic ataxia (calcium channelopathy) (n = 4)	Episodic ataxia (with positive family history of episodic ataxia) (n = 4)	All episodic ataxia† (n = 8)	Intermittent ataxia NYD (n = 6)
Presenting symptoms	Number of patients			
Ataxia	3	2	5	6
Dizziness/ vertigo	3	3	6	1
Head tilt	1	0	1	2
Weakness	0	2	2	0
Headache	2	1	3	0
Visual disturbance	2 (diplopia, blurred vision)	0	2	1 (eye rolling, photophobia)
Dysarthria	1	0	1	1
Tremor	0	0	0	1
Seizures	1 (Episodic ataxia type 5)	0	1	0
Gross motor delay	1	0	1	0
Triggers	Exertion, ambient temperature changes, exercise, or intercurrent illness in 4	Emotional or physical stress in 2		Exercise/ activities, playing video games, febrile illness, or excitement in 4

NYD = not yet diagnosed.
*Some patients presented with multiple symptoms.
†This column is a summary of the first two columns.

enhancement in different parts of the brainstem, more than the thalami, suggestive of infarcts followed by recovery or gliosis. On a subsequent scan right frontal lobe hemorrhage developed that left a gliotic cavity. The MRI in the patient with mitochondrial disease caused by complex 1 deficiency showed abnormal T2 signal intensity in the white matter of the frontal and parietal lobes and also the basal ganglia (Figure 2). These MRI findings are consistent with Leigh syndrome. The CT in the patient with carbamoyl phosphate synthetase deficiency, performed before he died, showed generalized cerebral edema, effacement of the basal cisterns, and small lateral ventricular size. Patients with intermittent ataxia NYD had a variety of findings that were either not diagnostic, including mega cisterna magna, small posterior fossa, and enlarged cerebellar size, or were suggestive of a metabolic etiology with progressive hyperintense T2 signal abnormality in the dentate nucleus, and hyperintense T2 signal abnormality in the periventricular white matter of the frontal lobes. One patient had normal MRI.

Acetazolamide was used in 14 patients, nine of whom benefited and six of whom had a full response. These six patients had episodic ataxia caused by a calcium channelopathy (n = 3) or a positive family history of episodic ataxia (n = 3). Three of nine patients showed a partial response, two had intermittent ataxia NYD, and one had GLUT1 deficiency syndrome. One patient with intermittent ataxia NYD. In the remaining four of 14 patients who either had episodic ataxia or intermittent ataxia NYD, the response to acetazolamide was not recorded. Immunosuppressive

Table 2b: Frequency of the presenting symptoms and triggers in patients with rarer causes of intermittent ataxia*

	Multiple sclerosis (n = 2)	ADEM (n = 1)	Mitochondrial disease (n = 1)	CPS deficiency (n = 1)	PAN (n = 1)	GLUT1 deficiency (n = 1)
Presenting symptoms	Number of patients					
Ataxia	2	1	1	0	0	1
Blurred vision/ diplopia	2	1	0	0	0	0
Altered level of consciousness	1	1	0	1	0	0
Weakness	2	1	0	0	0	0
Dizziness/ vertigo	1	0	0	0	1	0
Speech/ language delay	0	0	0	0	0	1
Seizures	0	0	0	1	0	0
Triggers	None	Febrile illness	Febrile or intercurrent illness	Intercurrent illness	None	Activity or heat

ADEM = multiphasic acute disseminated encephalomyelitis; CPS = carbamoyl phosphate synthetase; PAN = polyarteritis nodosa.
*Some patients presented with multiple symptoms.

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Table 3: Frequency of other clinical features in patients with recurrent ataxia

	Episodic ataxia (n = 8)	Multiple sclerosis (n = 2)	ADEM (n = 1)	Mitochondrial disease (n = 1)	CPS deficiency (n = 1)	PAN (n = 1)	GLUT1 deficiency (n = 1)	Intermittent ataxia NYD (n = 6)
Seizures	2 (febrile seizures)	1 (febrile seizures)	0	1	1	0	1	0
Developmental delay	2	1	0	1	1	0	1	3
Family history of ataxia in first degree relatives	8	0,?	0	0	0	0	0	0
FH of migraine or seizures	4	0	0	0	0	1	1	4
Consanguinity	0	0	0	0	0	?	0	0
Strabismus	1	1,?	0	?	0	0	1	1
Saccadic smooth pursuit	4	1,?	1	1	?	1	1	1
Nystagmus	6 (5 GEN, 2 DN)	1 GEN,?	1 GEN	1	0	1 GEN	0	1 GEN
Abnormal optic discs	1 (mild pallor OS)	2 (pallor)	0	0	0	0	0	0
Slurred/ scanning speech	2	?	0	Averbal	1	1	1	3
Dyskinesia	1	?	0	1	0	?	1	2
Tone	2 (decreased)	?	normal	Increased	normal	normal	increased	decreased in 1
Decreased strength	1	1	0	0	0	1 (mild)	0	0
Intention tremor	1	0	1	0	0	1	1	1
Dysmetria	2	2	1	0	0	1	1	0
Dysdiadochokinesia	1	2	1	0	1	1	1	0
Abnormal heel-to-shin test	1	0	1	0	0	1	1	1
Asymmetrical findings on exam	1	?	1	?	1	1	0	2
Abnormal reflexes	2 (decreased)	brisk,?	down	Brisk	0	Brisk	brisk	brisk in 1
Babinski sign	4	0	0	1	0	1	0	1
Decreased joint position sense	0	?	0	?	?	0	?	3
Walk independently	8	1,?	1	1 with a walker	1	1	1	6
Ataxic/ wide-based gait	6	2	0	1	1	1	1	6

NYD = not yet diagnosed; GEN = Gaze-evoked nystagmus; DN = downbeat nystagmus; ADEM = multiphasic acute disseminated encephalomyelitis; CPS = carbamoyl phosphate synthetase; PAN = polyarteritis nodosa; FH = family history; ? = unknown.

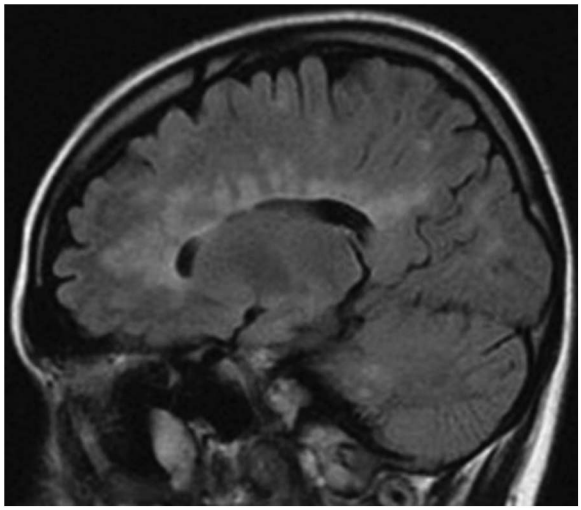

Figure 1: *Brain MRI of a girl with relapsing-remitting multiple sclerosis performed when she was 15 and a half years old. Her parasagittal FLAIR image (TR 8002, TE 155) shows multiple hyperintense signal abnormalities within the pericallosal white matter (Dawson fingers), subcortical cerebral white matter, and brachium pontis.*

therapy, mainly steroids, was used in patients with multiple sclerosis, multiphasic ADEM, and polyarteritis nodosa. All four patients benefited. Disease modifying drugs were used in the two patients with multiple sclerosis. The ketogenic diet was used in the patient with GLUT1 deficiency syndrome which improved his ataxic symptoms. The patient with carbamoyl phosphate synthetase deficiency was treated with protein restricted diet, sodium phenylbutyrate, and citrulline to reduce ammonia level in the blood.

The course of the ataxic symptoms and signs in six of the eight patients with episodic ataxia became progressive only during long-term follow up, with residual deficits between the ataxic episodes. Only two patients showed complete recovery between attacks on long-term follow up. Three patients with intermittent ataxia NYD recovered fully between attacks, two showed residual deficits between attacks, and one showed full recovery following several attacks with incomplete recovery among the initial attacks. The two patients with multiple sclerosis developed mild residual neurological deficits on follow up. The patient with the multiphasic ADEM recovered fully between and after the last attack. The patient with GLUT1 deficiency syndrome improved on the ketogenic diet but continued to have baseline deficits, with clumsiness between his attacks. The patients with polyarteritis nodosa and mitochondrial disease showed a fluctuating and progressive course followed by a static course that never normalized. The patient with carbamoyl phosphate synthetase deficiency had no residual ataxia between the ataxic episodes but showed a progressive disease course with death at eight years and six months.

Discussion

Recurrent ataxia occurs infrequently in pediatrics and mortality is rare. The etiology includes genetic, inflammatory, or more rarely, metabolic causes. Table 4 summarizes various causes of recurrent ataxia. A specific diagnosis was possible in 71% of our cohort, usually following extensive investigations.

Brain MRI is particularly helpful in the diagnosis since our patients with genetic diseases had a normal brain MRI. Having a normal brain MRI does not exclude underlying abnormalities, because there may be many microscopic neuropathological changes that are below the resolution of MRI. Such abnormalities may even require special stains to manifest adequately. Patients

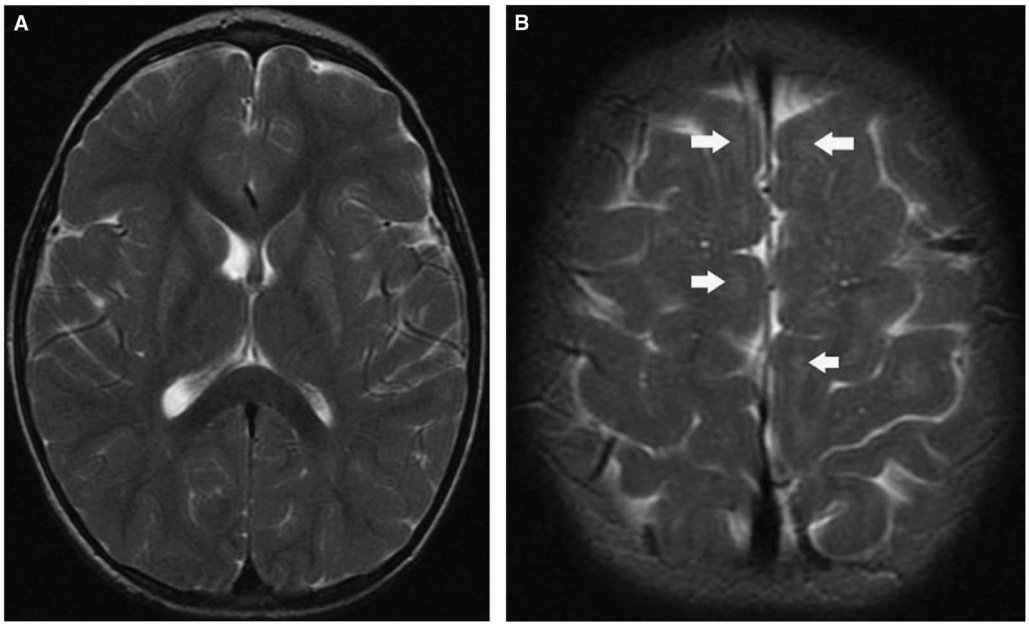

Figure 2: *Brain MRI of a boy with mitochondrial disorder caused by complex 1 deficiency performed when he was 4 years and 8 months old. Axial T2-weighted images (TR 2417, TE 123.3) showing hyperintense signal abnormalities in the basal ganglia, especially in the head of the caudate nuclei and putamina (A), and subcortical cerebral white matter bilaterally (arrows) (B).*

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Table 4: Causes of recurrent ataxia

A) Episodic ataxia	Types 1-7 (potassium channel gene mutations in EA1, calcium channel gene mutations in EA2 and EA5, and glutamate transporter gene mutation in EA6)
B) Intermittent ataxia:	
Migraine	Migraine with brainstem aura
	Vestibular migraine
	Benign paroxysmal vertigo
	Benign paroxysmal torticollis
Inflammatory	ADEM, MS, PAN, recurrence of acute cerebellar ataxia
Metabolic	Urea cycle defects e.g. Ornithine transcarbamylase deficiency
	Aminoacidopathies e.g. Maple syrup urine disease
	Organic acidopathies e.g. Isovaleric acidemia
	Pyruvate dehydrogenase deficiency
	Pyruvate decarboxylase deficiency
	Other mitochondrial disorders
	GLUT1 deficiency
	CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, sensorineural hearing loss)
Intoxication	Accidental or non-accidental
Paraneoplastic	Relapsing opsoclonus-myoclonus-ataxia syndrome

EA = episodic ataxia; ADEM = multiphasic acute disseminated encephalomyelitis; MS = multiple sclerosis; PAN = polyarteritis nodosa.

with inflammatory or metabolic diseases had abnormalities that were diagnostically helpful. However, the cause of the intermittent ataxia was unknown in six patients despite extensive investigations that included neuroimaging and detailed metabolic and genetic testing available at the time. None of these six patients had cerebellar cortical biopsy. We found no studies that support such an invasive procedure when the etiology is uncertain, except when neuroimaging reveals a lesion that may be indicative of a tumor. Tumors were an exclusion criterion in our cohort.

Migraine occurs commonly in children and adolescents. Some types of migraine are associated with self-limiting ataxia or imbalance, such as migraine with brainstem aura, vestibular migraine, benign paroxysmal vertigo, and benign paroxysmal torticollis.[8] These patients were excluded from our investigation. Our study focus was on rarer and less known disease etiologies in childhood that are associated with recurrent ataxia. We refer the interested reader to recent studies and reviews on migraine and its variants including vestibular migraine.[8,14,15]

The most common diagnosis in our investigation was episodic ataxia. This may reflect the genetic background of Manitoba's population and the study design.[9] Potential clinical clues may help identify the patients with episodic ataxia versus other diseases with intermittent ataxia. For example, interictal myokymia and neuromyotonia are features of episodic ataxia type1 while interictal nystagmus is a feature of episodic ataxia type 2.[3] In addition, triggers for episodic ataxia include sudden movements in episodic ataxia type 1 and emotional stress or physical exertion in episodic ataxia type 2.[3,4] One pair of siblings and one further patient had episodic ataxia type 2. The latter patient had a large deletion in *CACNA1A* gene. Her case was published in 2011 (individual #444).[16] Another patient had episodic ataxia type 5. A study describing his genetic abnormality has also been published (individual IV-16).[12] We found no prior definitive epidemiological studies on episodic ataxia.

Ataxia and dizziness, or vertigo, were common presenting symptoms. Other symptoms reported in our patients including weakness, blurred vision or diplopia, headaches, and seizures have been described not only in patients with episodic ataxia, but also in inflammatory and metabolic diseases that cause recurrent ataxia with or without encephalopathy.[4,5,7,17-19] Many of our patients had significant co-morbidities such as developmental delay and seizures, and less commonly, dyskinesia. These important features have been reported in patients with recurrent ataxia caused by genetic, inflammatory, and metabolic diseases.[1,4,5,7,12,13,19] Motor, ocular motor, and speech abnormalities consistent with cerebellar dysfunction were noted in our cohort as anticipated. Furthermore, seizures and upper motor neuron signs were seen in patients with diseases affecting the cerebral hemispheres such as multiple sclerosis and mitochondrial disease.

In some subtypes of episodic ataxia, for example episodic ataxia type 2, an abnormal function of the calcium channels in Purkinje cells is implicated in the pathogenesis of ataxia. In inflammatory disorders, dysfunction caused by demyelination within cerebellum and/ or other parts of the cerebellar network (e.g. inferior olivary or red nuclei in the brainstem, and thalami) connected through cerebellar afferent and efferent projections are implicated. Other postulated mechanisms that could potentially predispose to recurrent cerebellar deficits or cause ataxia are maturational delay in cerebellar system neurons and synapses, or aberrant synaptogenesis and synaptic plasticity, as reported in a genetic mouse model of ataxia.[20]

A trial of acetazolamide in selected patients may be helpful, especially in those with normal brain MRI since they most likely have episodic ataxia.[4] Episodic ataxia types 2, 3, 5, 6 and to a lesser extent type 1, respond to acetazolamide.[3,21] Anticonvulsants such as phenytoin can be effective in episodic ataxia type 1.[3] Steroids and other immunosuppressive agents were

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beneficial in our patients with inflammatory diseases. Multiple sclerosis, ADEM, and polyarteritis nodosa typically respond well to immunosuppressive therapies.[17,18] GLUT1 deficiency syndrome should be specifically considered, particularly in children with seizures, dyskinesia, or both, since treatment with the ketogenic diet is available.[19] Interestingly, the ataxia in the patient with GLUT1 deficiency syndrome responded to acetazolamide according to reports from his family.[13] This medication was given many years before his diagnosis was made because of his intermittent ataxia. The anecdotal benefit of acetazolamide in this disease requires further corroboration.

The course and prognosis of recurrent ataxia are related to the underlying etiology.[4,19,22,23] Initially, patients with episodic ataxia typically make full recovery between attacks. However, long-term follow up has revealed that progression with residual ataxia occurs relatively commonly,[4] as was seen in several of our patients. Like our two patients with multiple sclerosis, many pediatric patients with multiple sclerosis have a similar course, with relapses and remissions before developing residual deficits. Patients with multiphasic ADEM usually recover, as noted in our patient. The majority of patients with mitochondrial disease caused by Complex 1 deficiency develop symptoms in early childhood and do not typically recover to their normal baseline,[22] which is consistent with our patient's clinical course. The clinical course in patients with carbamoyl phosphate synthetase deficiency is variable and depends mostly on the residual enzyme activity. Survival beyond early childhood is rare but has been reported.[23]

Our retrospective, hospital-based study limitations include inaccurate, missing, and incomplete information in the hospital charts. The study period was long and it is possible that some more recently described diseases were missed among the patients with intermittent ataxia NYD. Next generation sequencing has improved the diagnostic yield in patients with ataxia.[24] New genetic causes of episodic ataxia have been described.[25] In addition, alternative genetic techniques have been used to investigate patients with episodic ataxia type 2-like features, in whom no mutations in the episodic ataxia genes had been identified previously. In some of these patients, large genomic deletions in *CACNA1A* were found, thus identifying a new disease mechanism.[16]

Conclusions

Recurrent ataxia occurs infrequently in children and mortality is rare. Genetic, inflammatory, and metabolic disorders should be considered in these patients once a migraine variant has been excluded. Neuroimaging with MRI is essential. A trial of acetazolamide in selected patients may be helpful, especially in those with normal brain MRI. Future studies should investigate patients with recurrent ataxia who remain without a diagnosis despite investigations, using whole exome sequencing if their microarray, specific gene testing, or ataxia gene panels are negative.

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