

Familial Benign Intracranial Hypertension and Depression

C. EDWARD COFFEY, DONALD R. ROSS, E. WAYNE MASSEY, C. WARREN OLANOW

SUMMARY: *Two sisters developed benign intracranial hypertension (BIH) two weeks following the resolution of a major depressive episode. The association of BIH and a major affective disorder in genetically related individuals has not been previously reported to our knowledge. Both conditions are associated with disturbances in the hypothalamic-pituitary-adrenal axis. Falling corticosteroid levels in a resolving depression may result in impaired cerebrospinal fluid absorption and subsequent BIH.*

RÉSUMÉ: *Deux soeurs ont développé une hypertension intracrânienne bénigne (BIH), deux semaines après la fin d'un épisode dépressif majeur. A notre connaissance, c'est la première fois que l'association d'un BIH et d'un trouble affectif majeur chez des individus génétiquement reliés, est rapportée. Les deux conditions seraient associées à des troubles de l'axe hypothalamo-pituitaire-surrénal. Des taux décroissants de corticostéroïdes lors d'une dépression s'améliorant pourraient causer un trouble dans l'absorption du liquide céphalo-rachidien et d'un BIH consécutif.*

INTRODUCTION

The syndrome of benign intracranial hypertension (BIH), or "pseudotumor cerebri", is manifested by features of increased intracranial pressure in the absence of lateralizing neurological signs (Weisberg, 1975). The pathophysiology is not known but BIH has been reported in association with obstruction of intracranial venous drainage, endocrine and metabolic disturbances, and a variety of systemic disorders, drugs and toxins (Buchhett et al, 1969; Greer, 1974; Weisberg, 1975). Familial BIH has been reported (Buchhett, 1969; Howe et al, 1973; Rothner & Brust, 1974; Traviesa et al, 1976) but to our knowledge no association of BIH with depression has been previously described. We now report two sisters who each developed BIH two weeks following the resolution of a major depressive episode.

CASE #1

A 19-year-old female was admitted to hospital with a two-week history of right frontal headache accompanied by photophobia, nausea and vomiting. Physical examination revealed a non-obese female with bilateral papilledema and normal visual acuity. Her only medication was an oral contraceptive (Demulen-28R) which she was taking for menstrual irregularity. Laboratory studies including hemograms, serum chemistries, thyroid function tests, serum TSH, and serum cortisol were normal; electrocardiogram, chest x-ray, and skull films were normal. CT scan of the brain was within normal limits and the ventricles were of normal size. Opening pressure on lumbar puncture was 580 mm of water. Cerebrospinal fluid (CSF) cell count, protein, glucose, VDRL and cultures were normal. Lumbar punctures performed during the next week resulted in a gradual return to normal of the CSF opening pressure associated with total relief of

headache and subsequent resolution of the papilledema. Following hospitalization, contraceptive medications were discontinued. The patient has remained asymptomatic without recurrence of papilledema.

Twelve months prior to hospitalization she experienced the insidious onset of a major depression (7) characterized by feelings of hopelessness and helplessness, dysphoria, anhedonia, and decreased energy. Shortly thereafter, she developed endogenous features of depression including sleep disturbance, anorexia resulting in a 35 pound weight loss, and decreased libido. Psychiatric referral was recommended on several occasions and involuntary psychiatric commitment was considered. One month prior to hospitalization and 11 months after the onset of her depressive symptoms, she had a spontaneous remission.

CASE #2

A 27-year-old non-obese woman (sister to case #1) was admitted with a two week history of global headache, stiff neck, confusion and anxiety. Physical examination demonstrated bilateral papilledema and meningismus. Hemogram, serum chemistries, chest x-ray, EKG, thyroid functions, serum TSH and serum cortisol were all normal. Brain CT scan was within normal limits with the ventricles being of normal size. The opening pressure on lumbar puncture was 420 mm of water. CSF cell count, protein, glucose, VDRL and cultures were within normal limits. Three additional lumbar punctures in hospital resulted in normalization of the CSF pressure with relief of symptoms and gradual disappearance of papilledema. The opening pressure has remained normal on follow-up lumbar punctures and the patient has remained asymptomatic without recurrence of papilledema.

From the Departments of Neurology and Psychiatry, Duke University Medical Center, Durham, N.C. 27710

Reprint Requests to: C. Edward Coffey, M.D., Box 31090, Duke University Medical Center, Durham, N.C. 27710, 919-684-8111.

Eight months prior to this hospitalization, she developed a major depressive disorder characterized by progressive despondence, anhedonia, easy fatigability, low self-esteem, feelings of hopelessness, anorexia manifested by a 40 pound weight loss, loss of libido and sleeplessness. She had suicidal thoughts. She was hospitalized on the psychiatric service and received intensive psychotherapy and imipramine 150 mg hs. She responded to treatment with resolution of her depression and normalization of her sleep pattern and appetite. She was discharged from the psychiatric service one month prior to her current admission on her antidepressant medication.

DISCUSSION

Two cases of BIH developing shortly after the resolution of a major depressive disorder are described in two sisters. The sisters had been living apart for five years and there was no common environmental factors contributing to the depression in either patient. The depressive events were separated by six months and neither sister was aware of the others illness. The association of a primary affective disorder and BIH in genetically related individuals has not been previously reported and there are only four reports of familial BIH in the literature (Buchhett et al, 1969; Howe et al, 1973; Rothner & Brust, 1974; Traviesa et al, 1976). Nine cases have been described of whom eight were female and obese. Two of the patients in one family were receiving oral contraceptives (Buchhett et al, 1969). No other condition thought to be associated with BIH was described in these families and no patient was reported to be depressed.

While familial BIH is relatively rare, unipolar depression has a well-defined familial occurrence with a morbidity rate of ten percent in first degree relatives (Mendlewicz & Shopsin, 1979).

Alterations in corticosteroid homeostasis are well described in major affective disorders. The production or secretion rate of cortisol is consistently elevated in patients suffering from depression (Carroll & Mendels, 1963).

Patients with unipolar depression exhibit elevated ACTH secretion (Carroll, 1978), loss of the normal circadian rhythm of cortisol secretion (Sachar et al, 1973), and early escape from dexamethasone suppression (Carroll & Mendels, 1963). These abnormalities may result in elevated serum cortisol levels in the range approaching that of Cushing's syndrome (Carroll, 1978). These disturbances are not felt to represent a simple stress response in that they are unrelated to periods of sleeping or dreaming, or to breakdown of ego defenses (Carroll & Mendels, 1963). All of these abnormalities including the elevated serum cortisol return to normal with resolution of the depression (Carroll, 1978).

Abnormalities of steroid metabolism have also been described in cases of BIH (Oldstone, 1966) where an increased resistance to CSF flow across the arachnoid villi has been demonstrated (Martins, 1973). The mechanism leading to increased intracranial pressure in BIH is unknown but evidence suggests that the primary lesion is related to reduced CSF absorption across the arachnoid villi (Johnston, 1975). CSF isotope studies in humans reveal delayed CSF flow, reduced absorption of CSF, and increased resistance to CSF transfer across the absorptive channels (Bercaw & Greer, 1970; Johnston & Paterson, 1974). Experimentally increased resistance to CSF outflow with secondary reduction in CSF absorption can be produced in animals by acute steroid withdrawal following prolonged steroid administration (Johnston et al, 1975). Furthermore, BIH has been reported in association with steroid withdrawal (Cohn, 1976; Neville & Wilson, 1970; Walter & Adamkiewicz, 1964). The role of steroids in CSF absorption is unclear although they may facilitate the formation of transient transport vacuoles (Howe et al, 1973).

On the basis of these neuroendocrine disturbances, a hypothesis can be formed to explain the development of BIH following a major depression. One can postulate that normalization of a steroidal abnormality accompanying depression creates a relative state of steroid withdrawal. This in turn may

lead to increased resistance across the arachnoid villi resulting in reduced CSF absorption and BIH.

Although both patients were on medications (Case 1 - oral contraceptive, Case 2 - imipramine) their relationship to BIH is uncertain. Four cases of BIH were described by Walsh, et al (1965) in his review of the neuroophthalmologic complications of oral contraceptives. Two had focal features raising doubt as to the diagnosis of BIH. The other two had discontinued their medications one and three months respectively prior to the onset of symptoms. The possibility that these symptoms may have been related to drug or steroid withdrawal has been considered (Dickman et al, 1980). These cases differ from our Case 1 where typical features of BIH developed while the patient continued to take oral contraceptive medication.

There is only one report of BIH in a patient receiving imipramine (Blumberg & Klein, 1961). This patient was also taking thioridazine preventing the incrimination of either drug. Furthermore this patient was recovering from depression which in light of our cases may have been the more important factor. Our Case 2 was continued on imipramine throughout the course of treatment without adverse effect.

Depressive illnesses are common and it is possible that this is just a chance association with BIH, but the striking similarity in presentation where BIH developed two to four weeks following resolution of a major depression, suggests that resolving depression was the precipitating factor. It may be that a reduction in CSF absorption occurs in other cases of resolving depression but compensatory mechanisms prevent a significant rise in intracranial pressure (ICP). The development of ICP in our patients may reflect a genetically based inability to compensate for a reduction in CSF absorption. The relationship between affective disorders, impaired CSF absorption and the development of increased intracranial pressure may be more important than has previously been appreciated and deserves further investigation.

REFERENCES

- BERCAW, B.K., GREER, M.: 131I RISA in benign intracranial hypertension. *Neurology* 1970; 20:787-790.
- BLUMBERG, A.G., KLEIN, D.F.: Severe papilledema associated with drug therapy. *Am J Psychiatry* 1961; 118:168-169.
- BUCHHETT, W.A., BURTON, C., HAAG, B., SHAW, D.: Papilledema and idiopathic intracranial hypertension. *New Engl J Med* 1969; 280:938-942.
- CARROLL, B.J.: Neuroendocrine function in psychiatric disorders. In: Lipton M.A., MiMascio, A., Killam, K.F., ed. *Psychopharmacology: A Generation of Progress*. New York, Raven Press, 1978, pp 487-495.
- CARROLL, B.J., MENDELS, J.: Neuroendocrine regulation in affective disorders. In: Sachar E.J., ed. *Hormones, Behavior, and Psychopathology*. New York, Raven adrenal st eroids. *J Neurosurg* 1963; 20:784-786.
- COHN, G.A.: Pseudotumor cerebri in children secondary to administration of Press, 1976, pp 193-224.
- Diagnostic and Statistical Manual of Mental Disorders*. Third Edition. Washington DC, American Psychiatric Association, 1980.
- DICKMAN, M.S., SOMASUNDARAM, M., BRZOZOWSKI, L.: Pseudotumor cerebri and hyperthyroidism. *N.Y. State J Med* 1980; 80:1118-1120.
- GREER, M.: Benign intracranial hypertension. In: Vinken, P.J. and Bruyn, G.W., ed. *Handbook of Clinical Neurology*. Volume 16. Amsterdam, North Holland Co., 1974, ch 4, pp 150-166.
- HOWE, J.G., SAUNDERS, M., CLARKE, P.R.R.: Familial benign intracranial hypertension. *Acta Neurochirurgica* 1973; 29:173-175.
- JOHNSTON, I.: The definition of a reduced CSF absorption syndrome: A reappraisal of benign intracranial hypertension and related conditions. *Med Hypotheses* 1975; 1:10-14.
- JOHNSTON, I., GILDAY, D.L., HENDRICK, E.B.: The effects of steroids and steroid withdrawal on CSF absorption: An experimental study in dogs. *J Neurosurg* 1975; 42:690-695.
- JOHNSTON, I., PATERSON, A.: Benign intracranial hypertension - CSF pressure and circulation. *Brain* 1974, 37:301-312.
- MARTINS, A.N.: Resistance to drainage of cerebrospinal fluid: Clinical management and significance. *J Neurol Neurosurg Psychiat* 1973; 36:313-318.
- MENDLEWICZ, J., SHOPSIN, B.: Genetic Aspects of Affective Illness. New York, SP *Medical and Scientific Books*, 1979, pp 10-12.
- NEVILLE, B.G.R., WILSON, J.: Benign intracranial hypertension following corticosteroid withdrawal in childhood. *Brit Med J* 1970; 3:554-556.
- OLDSTONE, M.B.: Disturbance of pituitary-adrenal relationships in benign intracranial hypertension (pseudotumor cerebri). *J Clin Endocr Metab* 1966; 26:1366-1369.
- ROTHNER, A.D., BRUST, J.C.M.: Pseudotumor cerebri: Report of a familial occurrence. *Arch Neurol* 1974; 30:110-111.
- SACHAR, E.J., HELLMAN, L. ROFF-WERG, H.P., HALPERN, F.S., FUKUSHIMA, D.K., GALLAGHER, T.F.: Disrupted 24-hour patterns of cortisol secretion in psychotic depression. *Arch Gen Psychiatry* 1973; 28:19-24.
- TRAVIESA, D.C., SCHWARTZMAN, R.J., GLASER, J.S., SAVINO, P.: Familial benign intracranial hypertension. *J Neurol Neurosurg Psychiat* 1976; 39:420-423.
- WALKER, A.E., ADAMKIEWITZ, J.J.: Pseudotumor cerebri associated with prolonged corticosteroid therapy. *J Amer Med Assc* 1964; 188:779-784.
- WALSH, F.B., CLARK, D.B., THOMPSON, R.S., NICHOLSON, D.H.: Oral contraceptives and neuro-ophthalmologic interest. *Arch Ophthal* 1965; 74:628-640.
- WEISBERG, L.A.: Benign intracranial hypertension. *Medicine* 1975; 54:197-207.