Idiopathic Intracranial Hypertension Associated With Either Primary or Secondary Aldosteronism

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Abstract: *Background:* Idiopathic intracranial hypertension (IIH) is a syndrome consisting of headache, visual field defects and papilledema of uncertain etiology. The prospect was raised previously as to an association between aldosteronism and increased intracranial pressure in 2 middle-aged women with IIH and primary aldosteronism (PAL). Since then, 2 additional adults were identified and 2 other cases were reported from the United Kingdom, whereas 6 cases of IIH and secondary aldosteronism (SAL) in children have been reported in the English literature worldwide. *Methods:* A retrospective analysis of cases from author institutions and published literature comparing clinical features, laboratory findings and therapeutic interventions in these 12 cases. *Results:* The female-to-male ratio was 10:2. The mean age of the PAL patients was 49 ± 3 years—all hypertensive, with adrenal pathology in most. The mean age of the SAL patients was 11 ± 2 years—mostly normotensive, with 3 having Bartter's and 2 Gitelman syndromes, and 1 renal congenital hypoplasia. Plasma aldosterone levels were elevated (31 ± 5 ng/dL) in PAL and SAL, whereas plasma renin activity was suppressed in PAL. Hypokalemia (3.2 ± 0.2 mmol/L), hypomagnesemia (1.6 ± 0.3 mg/dL) and a putative metabolic alkalosis (serum HCO_3 30 ± 1 mmol/L) were observed. IIH symptoms were controlled by spironolactone in 5, amiloride in 1, correction of hypokalemia and hypomagnesemia in 2, discontinuation of nonsteroidal anti-inflammatory drugs in 2, and reduction of body weight in 1. One patient required serial lumbar punctures, 2 a ventriculoperitoneal shunt, whereas all 3 patients with adrenal adenoma underwent surgical resection. *Conclusions:* An association between IIH and PAL occurs in hypertensive middle-aged women, whereas normotensive girls having an inherited renal tubular defect may have IIH with SAL. Patients with IIH should be evaluated for aldosteronism and considered for spironolactone therapy.

Key Indexing Terms: Idiopathic intracranial hypertension; Pseudotumor cerebri; Primary aldosteronism; Secondary aldosteronism. **[Am J Med Sci 2013;346(3):194–198.]**

Idiopathic intracranial hypertension (IIH), also commonly known as pseudotumor cerebri, is a disorder defined by characteristic symptoms and signs that arise secondary to increased intracranial pressure with no apparent cause evident on neuroimaging or other routine evaluation.[1] Once called benign intracranial hypertension, to distinguish it from secondary intracranial hypertension produced by a neoplastic malignancy, it is not a benign disorder as many patients suffer from intractable, disabling headaches, and there is a risk of severe permanent loss of vision.[1–3] Most common among presenting symptoms is headache, with or without visual disturbances and field defects. Papilledema, a hallmark finding in IIH, is often found by routine funduscopic examination at the time of presentation[2,4–11]; rarely is it discovered in an asymptomatic patient.[2,6] IIH has been documented in the absence of papilledema.[12]

The annual incidence of IIH is 1 to 2 per 100,000 population.[13] Among adults ranging in age from 20 to 50 years with symptomatic IIH, the female-to-male ratio ranges from 4 to 15:1, with a clear preponderance of overweight women who not infrequently have a history of mild-to-moderate hypertension.[2,4–11,14] With the increasing obesity epidemic in the United States and other parts of the world, the incidence and prevalence of IIH is rising.[15] Although IIH is, by definition, idiopathic, a number of systemic diseases (mostly endocrinopathies) and risk factors (pregnancy, corticosteroid therapy withdrawal and obesity) are associated with it.[16] It has been observed in members of the same family presenting in either an autosomal dominant or recessive manner.[11,17–22]

Although many theories for IIH have been proposed, its precise pathogenesis remains unknown. Its pathophysiological basis has been attributed to abnormalities in each of the 3 intracranial compartments: increased volume of cerebrospinal fluid (CSF), cerebral interstitial edema or increased intracerebral blood volume.[4,5,7,23–25] In 1955, Foley[5] suggested that "an underlying endocrine imbalance with presumably a disturbance of electrolytes is in some way connected with the alteration of intracranial pressure." The possibility of a "water-electrolyte imbalance brought about by hormonal disturbance" has been suggested.[26–32] In keeping with this proposition were 2 middle-aged women having symptomatic IIH found to be associated with primary aldosteronism (PAL) and reported in this journal by one of us (K.T.W.) in 2002.[33] This was the first report to appear in the English literature drawing attention to an association between increased intracranial pressure and aldosteronism and where the prospect of mineralocorticoid-induced fluid and electrolyte shifts by epithelial cells of the choroid plexus was raised. We since identified 2 additional patients.[34] Of interest, 2 other patients were recently reported from the United Kingdom.[35] Scanning the worldwide literature, we found 5 separate reports of children having IIH and secondary aldosteronism (SAL), including 1 most recently reported from Italy by one of us (V.S.).[36–41] In this study, we summarize these 12 patients having IIH with either PAL or SAL.

METHODS

Included in this report are 12 patients with IIH and aldosteronism, 6 of whom are adults with PAL and IIH of whom 4 were identified by Weber et al[33]: 2 patients seen at the University of Missouri Health Sciences Center and reported in this journal in 2002, and 2 others identified here at University of Tennessee Health Science Center and reported in 2011.[34] Two were recently reported from the United Kingdom in 2010.[35] The other 6 are children with SAL and IIH. One of these children has been followed by one of us (V.S.) in Messina, Italy, and recently reported in 2012.[41] The remaining 5 children were found by literature search using the MEDLINE database. Characteristics noted in each case included sex; age at the time of diagnosis of IIH,

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PAL or SAL; etiology of PAL or SAL; history or presence of systemic HTN; symptoms and signs of IIH (including headache, visual changes, papilledema); opening pressures on CSF examination; serum levels of electrolytes (K^+, Na^+, Mg^{2+}, HCO_3), aldosterone, renin activity and aldosterone/renin ratio (ARR); therapeutic interventions and outcomes. Group data are presented as mean ± standard error of the mean.

RESULTS

Demographics

There was a clear female preponderance, with an overall female-to-male ratio being 10:2, and all patients having SAL were of female sex. The 6 patients with PAL were 46 ± 3 and 49 ± 3 years old at the time of diagnosis of IIH and PAL, respectively. In contrast, all 6 girls with SAL were children or adolescents, with the mean age of 13 ± 2 and 11 ± 2 years at the time of diagnosis of IIH and PAL, respectively (Table 1).

Etiology of Aldosteronism

Adrenal imaging in PAL revealed the following: 1 bilateral hyperplasia, 1 unilateral hyperplasia, 1 unilateral adenoma, 1 bilateral adenoma, 1 unilateral adenoma with contralateral hyperplasia and 1 with no detectible abnormality. Of the 6 patients with SAL, 3 had Bartter's syndrome; 2 had Gitelman syndrome, both with *SLC12A3* gene mutation; and 1 had renal congenital hypoplasia and tubular dysfunction.

Clinical Features

All patients with PAL were hypertensive and resistant to multiple antihypertensive agents, whereas all but 1 patient with SAL were normotensive. Six of 7 patients for whom data were available were either overweight or obese. All patients had characteristic features of IIH including headache, visual field defects and papilledema, and no apparent cause of intracranial hypertension was evident on neuroimaging. CSF opening pressure was elevated at 34 ± 2 cm H_2O (normal, 5–18 cm H_2O) overall and was comparable in patients with PAL and SAL, that is, 35 ± 3 and 34 ± 2 cm H_2O, respectively (Table 1).

TABLE 1. Demographics and blood chemistries of patients with IIH having either PAL or SAL

Parameters	PAL	SAL	Overall (where comparable)
n	6	6	12
Female:male	4:2	6:0	10:2
Age (yr) at diagnosis of aldosteronism	49 ± 3	11 ± 2	
Age (yr) at diagnosis of IIH	46 ± 3	13 ± 2	
No. (%) patients having systemic hypertension	6 (100)	1 (17)	
CSF opening pressure (cm H_2O)	35 ± 3	34 ± 2	34 ± 2
Plasma aldosterone level (ng/dL)	35 ± 7	24 ± 4	31 ± 5
Plasma renin activity (ng/mL/hr)	0.31 ± 0.08	13.9 ± 3.3	
Aldosterone/renin ratio	271 ± 135	2.1 ± 0.8	
Serum K^+ (mmol/L)	3.4 ± 0.2	2.8 ± 0.3	3.2 ± 0.2
Serum Mg^{2+} (mmol/L)	1.9 (n = 1)	1.4 ± 0.5	1.6 ± 0.3
Serum HCO_3 (mmol/L)	30 ± 2	29 ± 2	30 ± 1
Serum Na^+ (mmol/L)	141 ± 1	144 (n = 1)	141 ± 1

CSF, cerebrospinal fluid; IIH, idiopathic intracranial hypertension; PAL, primary aldosteronism; SAL, secondary aldosteronism.

Laboratory Findings

Plasma aldosterone levels (31 ± 5 ng/dL) were elevated in both PAL (35 ± 7) and SAL (24 ± 4; normal, 1–16 ng/dL). Patients with PAL had a suppression of plasma renin activity at 0.31 ± 0.08 ng/mL/hr (normal, 0.15–2.33 ng/mL/hr) to account for markedly elevated ARR of 272 ± 135 (ARR >20 indicates PAL). In contrast, patients with SAL had an elevated plasma renin activity at 13.9 ± 3.3 ng/mL/hr to account for low ARR of 2.1 ± 0.8. Both serum potassium and magnesium levels were low at 3.2 ± 0.2 mmol/L (normal, 3.6–5.0 mmol/L) and 1.6 ± 0.3 mg/dL (normal, 1.8–2.5 mg/dL), respectively, while a putative metabolic alkalosis with serum HCO_3 of 30 ± 1 mmol/L (normal, 21–28 mmol/L) was present. Serum sodium levels were mostly normal at 141 ± 1 mmol/L (normal, 135–145 mmol/L; Table 1). Renal function, as gauged from serum creatinine concentration, was normal in our 4 patients with IIH and PAL and the child with IIH and SAL.

Therapies and Outcomes

In all 5 patients with either PAL or SAL who were treated with spironolactone, an aldosterone receptor antagonist, symptoms of IIH and systemic hypertension were effectively controlled. Other therapies used to control symptoms of IIH include amiloride, an Na^+/H^+ antiporter, in 1; correction of hypokalemia and hypomagnesemia in 2; discontinuation of nonsteroidal anti-inflammatory drugs in 2; and reduction of body weight in 1. Acetazolamide given to a single patient and was unable to control symptoms of IIH. One patient required repeated therapeutic lumbar punctures, 2 patients ultimately received a ventriculoperitoneal shunt, whereas all 3 patients having underlying adrenal adenoma underwent surgical resection.

DISCUSSION

In this study, we have reviewed the 12 patients in whom IIH was reported as coexistent with either autonomous or renin-dependent adrenal aldosterone production. Among both groups, there was a female preponderance, and among adults most were either obese or overweight. Patients with PAL were middle-aged and had longstanding history of arterial hypertension of mild-to-moderate severity resistant to various antihypertensive agents. Patients with SAL were female children or adolescents who were mostly normotensive. Both groups had chronic intermittent headaches associated with visual disturbance and hypokalemia, hypomagnesemia and metabolic alkalosis.

In patients with IIH published between 1937 and 1982,[2,4–11] more than 3/4 were women, ranging in age from 19 to 54 years, and many were obese and hypertensive, whereas serum electrolytes were often reported to be normal. A causal linkage between obesity, IIH and aldosteronism remains uncertain. Aldosteronism is integral to the cardiometabolic syndrome, which includes obesity, hypertension and diabetes.[42] Leptin is a protein secreted by adipose cells. Increased plasma leptin levels are found in obese women with IIH compared with obese controls without IIH[43] and where they are associated with increased expression of leptin receptors in adrenal gland tissue and tumors.[44] Leptin may provide a link between obesity, IIH and hypertension.[45] In addition to its occurrence in siblings (autosomal recessive transmission), IIH has been observed in