Spontaneous Intracranial Hypotension Syndrome Treated with Fludrocortisone

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Spontaneous intracranial hypotension is a rare syndrome characterized by orthostatic headache not associated with trauma or dural puncture. In most cases, it is caused by a spontaneous spinal cerebrospinal fluid leakage as demonstrated by neuroradiological studies. The standard of care consists of conservative treatment including bed rest, hydration, and administration of caffeine or glucocorticoids. When such conservative therapy fails, an epidural blood patch is recommended. In this report, we describe the treatment of 2 patients with spontaneous intracranial hypotension who failed conservative treatment and went on to have complete and sustained resolution of their symptoms after the administration of oral fludrocortisone. (A&A Case Reports. 2015;4:8–11.)

Spontaneous intracranial hypotension (SIH) is a rare syndrome characterized by low cerebrospinal fluid (CSF) pressure and severe postural headaches.[1] This syndrome was first described in 1938 by Schaltenbrand,[2] who defined it as "spontaneous aliquorrhea". The incidence of low CSF pressure headaches has been estimated at 5 per 100,000 per year with a peak around 40 years of age, affecting more women than men with a female to male ratio of 2:1.[3]

Treatment of headaches secondary to SIH is still a matter of debate. Initial therapy for most patients consists of conservative measures commonly including bed rest, hydration, and caffeine or glucocorticoids. For patients failing conservative therapy, an epidural blood patch (EBP) is performed and repeated if necessary. Additional treatment options may include continuous epidural saline infusion, epidural infusion of dextran, epidural fibrin glue, or surgical repair of the defect.[4] In this report, we describe the use of the mineralocorticoid, fludrocortisone, in 2 patients with severe SIH; in the first patient, both conservative medical treatment and EBP failed, while complete resolution occurred after oral fludrocortisone administration. The second patient received fludrocortisone as a first-line therapy and had complete resolution of his symptoms.

Both patients gave permission for the authors to publish the report.

CASE DESCRIPTION

Case 1

A healthy 26-year-old woman presented to the emergency department with a 3-day history of abrupt severe pressure-like headache, localized to the occipital area. The headache intensified while erect, was partially relieved while supine, and was associated with nausea, vomiting, and tinnitus. Her general physical and neurological examinations were within normal limits. After admission, a lumbar puncture revealed a very low opening pressure whereby CSF fluid was only obtained after a Valsalva maneuver. Her brain magnetic resonance image (MRI) showed dural thickening and enhancement mainly along the skull base, whereas her spine MRI showed increased meningeal enhancement at the base of the skull and the ventral aspect of the cervical spine (Fig. 1). Computed tomography myelography showed epidural contrast leak at multiple root levels extending from T7 to L2 consistent with SIH (Fig. 2). An EBP was performed at the L2–L3 level with 20 mL of autologous blood resulting in transient clinical improvement for 2 days, but 1 week later, she was readmitted for recurrence of her symptoms. At that time, fludrocortisone 0.1 mg daily was started orally after which the patient reported gradual reduction in the severity of her headaches and complete resolution by the third day of therapy. She was discharged home to receive fludrocortisone 0.1 mg daily for 3 months and instructed to carefully reduce salt intake in order to avoid the development of hypertension, edema, or weight gain. Periodic checking of her serum electrolyte levels did not reveal any abnormalities during the 3-month period. Fludrocortisone was discontinued after 3 months, and at her last follow-up 12 months after treatment, the patient was still free of symptoms.

Case 2

A 47-year-old man presented with sudden onset of intractable headache. Both general physical and neurological examinations were normal. Computed tomography myelography showed a single-level epidural contrast leak at C5. The different treatment modalities along with risks and benefits were discussed with the patient. In view of our encouraging results with its prior use in SIH, and with patient consent, fludrocortisone treatment was initiated at 0.1 mg per day orally. Gradual improvement of symptoms was reported with complete resolution within 2 to 3 days after initiation of treatment. At 3-month follow-up, the patient was still symptom-free, at which point fludrocortisone was discontinued.

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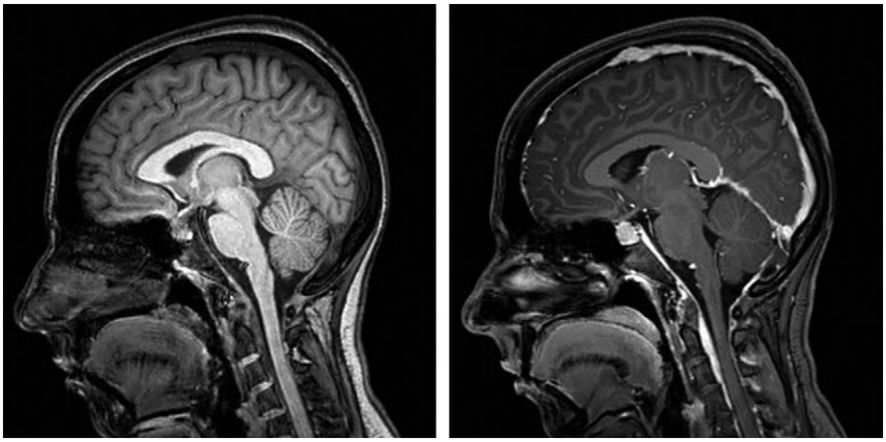

Figure 1. Pre- and postcontrast T1W magnetic resonance images of the brain showing strong meningeal enhancement mainly at the base of skull and upper cervical cord.

Figure 2. Computed tomography-myelography showing epidural leakage of contrast along the left T7 root.

DISCUSSION

The dura mater is made up of layers of dense tissue comprising elastic fibers and collagen. Classically, a longitudinal arrangement of the fibers in the rostrocaudal axis has been described; however, Fink and Walker[5] have instead shown a nonspecific orientation of the fibers. The CSF has a volume of approximately 150 mL, half of which is spinal and the other half inside the cranial cavity. The normal production is 0.35 mL/min, or approximately 500 mL/day and is reduced by dehydration, a febrile state, and certain drugs, such as acetazolamide and the proton pump inhibitor, omeprazole.[6,7] The CSF pressure at the lumbar level is in the range of 5 to 15 cm H_2O while supine and exceeds 40 cm H_2O in the upright position. A breach in the dura mater, whether traumatic (postdural puncture headache) or spontaneous (SIH), leads to a CSF leak into the epidural space, decreasing intrathecal pressure, which in turn can be detected as a sagging of the intracranial structures, as seen on MRI, and meningeal enhancement due to vasodilation. The International Headache Society has established diagnostic criteria for both, postdural puncture headache and headaches induced by CSF leaks and SIH.[8]

The cause of spontaneous leakage of CSF is unknown but is presumed to be secondary to structural weaknesses. Several hypotheses have been proposed, including a viral origin, but most involve pathology of the connective tissue.[9] Indeed, two-thirds of patients present with connective tissue symptoms, such as ligamental hyperlaxity, a history of spontaneous retinal detachment, Marfans or Ehlers-Danlos syndromes. A history of trauma, sometimes minor (coughing, heavy lifting, sports activities), is found in approximately one-third of the patients. In rare cases, skeletal pathology, including osteophytes or a protruding intervertebral disk, is the cause of the breach in the dura mater. The leak may occur at any level of the spine but is most often in the thoracic portion.

The treatment of headaches secondary to SIH is still controversial and principally targets restoring normal CSF pressure. Two different hypotheses for the pathogenesis of SIH have been proposed. First, the CSF leak leads to sagging of the brain and traction on sensitive intracranial and meningeal structures particularly leptomeninges, bridging veins and cranial nerves, which are thought to cause the headache and some of the associated symptoms.[3] In the upright position, this traction is exaggerated, hence the postural component of the headache. Secondary vasodilation of the cerebral vessels to compensate for low CSF pressure may contribute to the vascular component of the headache by increasing brain volume.[4] A second hypothesis proposes that SIH results primarily from decreasing venous pressure within the inferior vena cava, which is amplified by displacement of blood toward the heart due to activation of leg muscles during standing and walking. The lower vena cava pressure leads to epidural venous hypotension and outflow of CSF along the spinal canal, and in some cases precipitates actual CSF leaks from existing radicular arachnoid diverticula or cysts.[10] In this paradigm, symptoms are not attributed to dural tears but rather a consequence of the low epidural pressure.

Conservative management including bed rest, hydration, caffeine intake, and theophylline has been the mainstay for treating SIH, while oral steroids have also be reported to provide resolution of symptoms.[11–13]

Steroids may exert their beneficial effect by favoring reabsorption of CSF from the extradural space and thus increasing CSF volume.[14] Alternatively, they may relieve the headache by suppressing arachidonic acid production through lipocortin-induced phospholipase inhibition, which ultimately inhibits production of algogenic prostaglandins (PGE2 and PGI2) and leukotrienes (LT-B4), or by blocking production of proinflammatory cytokines such as interleukin-1, interleukin-2, and tumor necrosis factor-α.[15,16] Despite these effects, some reports fail to show any therapeutic effect of glucocorticoids on SIH headache.[17,18]

EBP is considered the treatment of choice in patients failing conservative measures. It has been reported in 1 series to have a favorable outcome in 50 % of patients after the first procedure and in an additional 40% after repeated EBP. A similar success rate of 90% was also reported with EBP performed with the patient in Trendelenburg position and premedicated with acetazolamide.[19–21] Inconsistency in the success rates of lumbar EBP is possibly due to the location of the leak rostral to the low thoracic/lumbar levels.

Fludrocortisone (9α-fluorocortisol or 9α-fluorohydrocortisone) is a synthetic corticosteroid with moderate glucocorticoid potency and much greater mineralocorticoid potency. Fludrocortisone has been commonly used in the treatment of cerebral salt wasting.[22] It is used primarily to replace the missing hormone aldosterone in various forms of adrenal insufficiency such as Addison's disease and the classical salt wasting (21-hydroxylase deficiency) form of congenital adrenal hyperplasia. Fludrocortisone is the treatment of choice for most patients with orthostatic hypotension.[23] The approximate plasma half-life of fludrocortisone is 3.5 hours or more and the biological half-life is 18 to 36 hours and is well tolerated by most patients. Fludrocortisone increases blood volume and enhances the sensitivity of blood vessels to circulating catecholamines and may increase intracranial pressure.[24] Other potential modes of action include enhancing norepinephrine release from sympathetic neurons and increasing vascular fluid content. Chobanian et al. suggested that sodium retention and plasma volume return to normal with long-term use of fludrocortisone, but the pressor effect persists due to increased peripheral vascular resistance.[25,26]

In our reported cases, oral treatment with fludrocortisone resulted in sustained relief of the headache within several days. We hypothesize that the beneficial effects occurred due to one or more of the various mechanisms of action associated with mineralocorticoids. First, being a synthetic corticosteroid, fludrocortisone may decrease edema and inflammation induced by the sagging effect of the brain and the cranial nerves and favor the reabsorption of CSF from the extradural space, thereby increasing CSF volume.[14] Second, benefit may result via its mineralocorticoid properties, promoting sodium retention and consequently increasing the effective circulating blood volume and central venous pressure. This latter mechanism is in line with the recommended conservative measure of IV normal saline hydration. Third, fludrocortisone increases intracranial pressure and thus may directly act to reverse the intracranial hypotension.[27] Finally, and in addition to enhancing norepinephrine release from sympathetic neurons, it has been shown that fludrocortisone increases the sensitivity of blood vessels to circulating catecholamines, which might counteract the observed vasodilation of cerebral vessels contributing to the vascular component of the SIH headache.[24]

In conclusion, our report identifies a new effective therapy for SIH. Fludrocortisone, with its acceptable safety profile, may potentially be used as a first-line therapy for SIH, or in patients failing traditional conservative therapy or EBP. Obviously, larger prospective randomized studies are needed to establish the safety and effectiveness of fludrocortisone in patients with SIH.

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