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HEADACHE (R. HALKER SINGH, SECTION EDITOR)

A Review of Spontaneous Intracranial Hypotension

Parth Upadhyaya[1] · Jessica Ailani[2]

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Abstract

Purpose of Review Spontaneous intracranial hypotension (SIH) is an underdiagnosed phenomenon predominantly presenting with low cerebrospinal fluid (CSF) pressure and postural headache in setting of CSF leak. The goal of this paper is to provide updates on the pathology, diagnosis, and management of SIH. The utility of multiple imaging modalities and the use of epidural blood patches and fibrin glue polymers are explored.

Recent Findings In regard to diagnosis, new non-invasive modalities in detection of SIH including transorbital ultrasound and serum biomarkers are found. In addition, increased efficacy of large volume and repeated placement of multiple epidural blood patches (EBP) are seen. In addition, the management of refractory SIH using fibrin glue polymers has proved efficacious in recent case series.

Summary While the diagnosis may be challenging for clinicians, future research in SIH is leading to more rapid detection methods. Future studies may target optimal use of EBP in comparison to fibrin glue polymers, in addition to new developments in increased understanding of SIH physiology and phenotype.

Keywords SIH, spontaneous intracranial hypotension · CSF leak · Epidural blood patch · Postural headache · Fibrin glue

Introduction

History of Disease

Low-pressure CSF headache was first described by the anesthesiologist Bier in 1898 after administering spinal anesthetic via lumbar puncture [1]. Later, the German neurologist George Schaltenbrand first described spontaneous intracranial hypotension in 1938 as aliquorrhea, meaning no cerebrospinal fluid [2]. In time, spontaneous intracranial hypotension (SIH) has become a disorder of low CSF volume characterized by postural headache, brain sagging, and chronic subdural hematomas. While a framework via the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria exists, a mixed picture of magnetic resonance imaging (MRI), CSF pressure, and phenotypic findings makes clinical diagnosis difficult. Given both misconceptions of older treatments and diagnostic methodologies, this review article attempts to explore new developments in SIH diagnosis and treatment.

Epidemiology

SIH has a female predominance, peaking at age 40, with an estimated annual incidence of 5 in 100,000, although often overlooked as a diagnosis [3]. Risk factors for SIH can be hereditary or acquired. In a study of 50 patients with known CSF leak, 9 had connective tissue disease, 7 of which had SIH as the presenting symptom [4]. Dramatic weight loss may pose a risk as seen in a study of patients after bariatric surgery where 11 of the 338 patients suffered SIH after a mean of 5 years and 55 kg lost [5].

Symptomology

SIH typically presents with a postural headache with associated nausea, vomiting, tinnitus, vertigo, hypoacusis, neck stiffness, and photophobia [6•]. Cranial nerve involvement, including diplopia, facial weakness, paresthesias, and

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✉ Parth Upadhyaya
Parth.Upadhyaya@gunet.georgetown.edu

[1] Department of Neurology, Medstar Georgetown University Hospital, 3800 Reservoir Road NW, 7PHC, Washington, DC 20007, USA

[2] Department of Neurology, Medstar Georgetown Headache Center, Medstar Georgetown University Hospital, 3800 Reservoir Road NW 7PHC, Washington, DC 20007, USA

alterations in taste, has also been reported [7–9]. SIH has also been associated with compression of brain and spinal cord structures, leading to ataxia, paresis, infarction, movement disorders, and decreased level of consciousness [10–12].

The onset of headache can either be acute or insidious, and antagonized within 15 min of either sitting, standing, coughing, or straining, and is described as generalized or focal throbbing [13]. Relief is found by recumbent posture and seldom with analgesics. Time-dependent worsening of headache can occur as the day progresses—likely as more time is spent in upright posture. The lack of orthostatic headache should not exclude SIH. In time, the postural nature of the headache may wane with presentation of new chronic headache, and even reverse, resulting in worsening pain in the recumbent position [14]. One small prospective study of 6 patients prior to epidural blood patch found that all could not stand upright for > 30 min at a time [15•]. A recent study of 179 patients with SIH found that 161 patients had orthostatic headache, with the most commonly associated symptom being neck stiffness ($n = 113$), dizziness ($n = 92$), nausea ($n = 65$), tinnitus ($n = 31$), and diplopia ($n = 8$) [6•].

A notable case report portrayed cerebral venous thrombosis as a consequence of SIH. A 33-year-old female who initially presented with orthostatic headache and hemiplegia had subsequent imaging findings of frontotemporal hygromas and pituitary swelling, and a magnetic resonance venogram displaying venous thrombosis. Subsequent spinal MRI revealed a cervical fluid collection; her opening pressure was 20. The sinus thrombosis likely caused the increased CSF pressure. Venous engorgement, a known complication of CSF, may have slowed venous flow in addition to mechanical stretch of veins leading to thrombus formation [16•].

Pathophysiology and Etiology

Defects along the dura (including tears, fistulas) leading to CSF leak can be congenital and traumatic in etiology. SIH, previously thought of as a barometric drop of CSF pressure, is now thought of as a volumetric pathology arising from CSF leakage through the arachnoid membrane along the spine [17]. Structural abnormalities from congenital connective tissue disorders [18], lack of dura around nerve root sheaths [19], osteophyte protrusions, and spinal disc herniation [20] contribute to leaks. Arachnoid diverticula commonly at the thoracic and lumbar spine are a known source of focal weakness among the dura prone to leaks [21, 22].

Sequelae of SIH are due to drops in the CSF volume leading to decrease in buoyancy provided to the brain. This leads to sagging within the cranial vault likely causing traction on sensory nerves of the meninges. By the Monro-Kellie doctrine, low CSF leads to tandem venous dilation and increase blood volume adding to painful stretch of nerve fibers [23]. Due to these compensatory mechanisms and tractions, subdural hematomas are not uncommon in patients with SIH.

Diagnosis

SIH is classically associated with positional headaches that worsen with upright posture and typically can be pinpointed to a prior acute event. Phenotypic characterizations of SIH are shared with cervicogenic and primary cough headache; thus, a diagnosis of SIH will often need objective data including a constellation of imaging and diagnostic findings for confirmation.

Diagnosis Criteria

The ICHD-3 criteria use objective data of low CSF pressure (< 6 cmH_2O) and imaging of leak for headaches attributed to low CSF pressure. The criteria for spontaneous intracranial hypotension must fulfill the above in addition to lack of a procedure known to cause CSF leak and temporal relation to discovery of low CSF pressure or leak [24].

Differential

Due to the ubiquity of a postural headache, clinicians must consider a variety of other pathologies in addition to SIH. The differential may include a primary headache disorder like new daily persistent headache or secondary causes of SIH including subarachnoid hemorrhage, carotid or vertebral artery dissection, cerebral venous thrombosis, benign intracranial hypertension, posttraumatic headache, and meningitis [25]. Postural tachycardia syndrome (POTS) can also present similarly with chronic headache, dizziness, weakness, and blurry vision exacerbated by standing—not dissimilar to SIH [26]. Cervicogenic postural changes in neck posture that may exacerbate pain can be confused with postural influence. Fortunately, nerve blockade can aid in this diagnosis. Evaluation with MRI, angiography, and lumbar puncture can aid with navigating potential therapies.

Workup

Imaging

Evaluation of SIH should include brain and spinal MRI along with CSF pressure measurement if needed. A history of postural headache in the proximity of trauma or surgery is useful.

Brain MRI should be obtained with and without contrast, as diffuse uniform pachymeningeal enhancement is typically diagnostic [27]. In addition to a decreased size in ventricles and cisterns, subdural hematoma and hygromas, venous engorgement [28] and pituitary hyperemia, and increased

anterior-posterior diameter of the brainstem are common findings [29, 30]. Although cerebellar tonsillar herniation is often seen, it should be viewed in context of possible Chiari I malformation. As symptoms of SIH increase in duration, there is a noted decrement in MRI findings—dural enhancement and headache symptoms were seen on average for 15 weeks [31].

In a recent retrospective study of 165 with SIH, 103 had pachymeningeal enhancement on MRI and 31 with subdural hematoma [6•]. In patients with SIH, CSF leaks by imaging modality identified 152 of 165 patients with brain MRI, identified 43 of 48 with CT myelography, and MR myelography identified 111 of 117 [6•]. The same study found that 149 of 165 had multi-level leaks with predominance at the cervicothoracic junction at 63.9% [6•].

In patients with normal cranial MRI, MR spinal imaging, in particular fat-saturated axial slices of cervical and thoracic levels, may find tears and epidural collections that may lead to targeted therapy [32]. If suspicion remains high of SIH with non-diagnostic MRI, digital subtraction myelography and dynamic CT myelography can provide aid in localization of high-flow CSF leaks [33, 34]. However, even these modalities can miss SIH [35, 36].

No quantifiable diagnostic criteria exist for MRI findings in diagnosis of SIH. One study used distinct planes of reference to quantify the degree central incisural herniation as an objective measure of SIH [37•].

Lumbar Puncture and Other Modalities

Using the ICHD-3 criteria, a CSF opening pressure less than 6 cm is partly diagnostic, making lumbar puncture part of the evaluation. However, patients with normal or even elevated opening pressures with known CSF leaks have been described [38]. If MRI findings of SIH are present, a CSF opening pressure may not be necessary and may in fact worsen symptoms. He et al.'s evaluation of 165 patients with SIH found that an opening pressure of < 6 cmH_2O was most commonly seen ($n = 139$) versus patients with a pressure > 6 ($n = 26$) [6•].

Optic nerve sheath diameter measured with transorbital sonography in patients with orthostatic headache in supine and upright positions found significant decrease in diameter providing a novel non-invasive technique in evaluation of SIH [39].

In the evaluation for potential biomarkers, CSF of patients diagnosed with SIH using MRI was compared to that of non-SIH patients [40•]. Two proteins, lipocalin-type prostaglandin D synthase and brain-type transferrin, found a high sensitivity in the assessment of SIH and non-SIH patients. Prior studies have noted higher protein concentration in CSF compared to serum including albumin [40•].

Management

Case 1

A 45-year-old man with past history of hypertension presents to the emergency department (ED) with 2 days of progressive worsening of headache. It is associated with ear ringing and nausea. The headache pain is only relieved while lying flat. A non-contrast head CT is normal, and lumbar puncture is obtained showing normal CSF studies and an opening pressure of 7 cmH_2O. MRI with and without contrast was obtained, finding venous engorgement and pachymeningeal enhancement throughout. He was diagnosed with SIH and treated conservatively in the ED with intravenous fluids and caffeine. The patient's headache did not improve and anesthesia was called for an epidural blood patch. A single blood patch was placed and the patient was discharged home. He followed up with his outpatient neurologist with the headache only slightly improved. He was again sent to the ED for a second blood patch, with resolution of headache within a week.

Discussion—Case 1

This is a typical case of spontaneous intracranial hypotension. A patient with sudden onset and progressive worsening of headache is worrisome in most EDs, particularly with associated symptoms of nausea and photophobia, warranting an early lumbar puncture. As expected, a normal cell count, protein and glucose, is found with no xanthochromia, ruling out meningitis or subarachnoid hemorrhage. A non-contrast head CT rules out acute hemorrhage. MRI findings are diagnostic for SIH, including meningeal enhancement and venous engorgement. In this case, the CSF pressure is low normal. It should be noted that often, more than one blood patch is needed in the treatment of SIH, and the effects may not be felt immediately.

Case 2

A 75-year-old male with history of diabetes mellitus, hypertension, and hyperlipidemia presents to the ED with double vision, headache, neck pain, and light sensitivity. The double vision started 2 weeks prior, with photophobia starting the day prior. His headache is constant with no improvement with over-the-counter medications. He denies a history of trauma or migraine. The ED gives ketorolac and reglan with no improvement. A non-contrast head CT shows chronic subdural hygromas bilaterally. Given that neck pain and light sensitivity in an elder patient are without a history of migraine, an LP was completed, showing an opening pressure of 15 with no white cells and normal protein. MRI of the brain was normal. Given his neck pain, an MRI of his C-spine with contrast was completed. No signs of nerve stenosis or abnormal cord

enhancement were found. On further questioning, it is learned that the headache began 8 months ago and had a postural component, but it is now constant. Given that the LP was negative for infection, an epidural blood patch was completed and the patient was admitted. There was mild improvement in the headache and a second blood patch was placed. The headache continued to persist and a fibrin glue polymer was used. Patient's headache and double vision gradually began to resolve and he was discharged to follow up with a neurologist. Later, MR myelography found a CSF leak leading to surgical repair of the dura at T10-T11.

Discussion—Case 2

In this case, the patient's initial presentation is suggestive of meningitis versus another headache disorder. A combination of medications used to treat migraine was found to be minimally helpful in treating the patient's symptoms. Lumbar puncture was unrevealing yet again, but proved useful in the assessment of infection. The CT scan finding of subdural hygromas should lend suspicion of recurring falls versus intracranial hypotension. The typical MRI head findings of SIH are transient and thus can be missed. In addition, a patient's presentation of SIH can have cranial nerve deficits, like diplopia, given stretch of the brain stem at low pressures. Similar to the prior case, repeat epidural blood patches may be needed in addition to fibrin glue before symptomatic improvement. Even then, repeat imaging successfully identified a CSF leak leading to surgical repair.

Treatment

The majority of SIH cases resolve within 2 weeks spontaneously. Conservative management is usually bed rest, hydration, and caffeine.

Blood Patch

Autologous epidural blood patch (EBP) is an effective treatment for SIH with response rates varying from 30 to 90% [41]. Many patients require several EBP for resolution with one reported case in the literature that required 7 EBPs before lasting relief was achieved [42]. A recent study of 62 patients found the response rate to EBP to be 59.7% [43•]. This same study found no difference between the leakage site and the location of EBP injection in regard to response [43•]. The typical amount of blood for EBP ranges from 5 to 30 cc, with a response rate of 85%; however, this was in fluoroscopy-guided procedures in patients with prior lumbar puncture and SIH [44]. One small case series of 19 patients received high-volume EBP, 44.8± 21.6 cc [44]. Of the 9 patients who received high-volume EBP, 5 had concomitant chronic subdural hematomas that resolved after surgical drainage without returning, and 3 resolved without drainage [45•]. Of the10 patients who had postural headache, 7 resolved completely and 3 had some improvement [45•].

A recent retrospective study of 116 patients tracked those who underwent either a blind EBP at the cervicothoracic and thoracolumbar junctions versus a targeted patch after CT myelography [46•]. Both groups experienced nearly the same rate of initial complete relief, finding no significant difference in outcomes. In this study, blood patches were shown to have a cumulative effect with partial improvement typically with each procedure [46•]. Increased success was also associated with increased volume of blood injected [46•]. In a separate retrospective study, 179 patients were diagnosed with SIH using ICHD-3 criteria of which 165 were refractory to conservative therapy including hydration and bed rest [6•]. Those 165 were evaluated using MRI of the spine with contrast, MR myelography, and CT myelography to identify CSF leaks [6•]. A targeted EBP one-to-two vertebral levels below that identified leak with varying blood volumes < 10 cc to < 20 cc based on level was followed by strict bed rest after laying prone for 30 min [6•]. EBPs were then completed weekly if symptoms or multi-level leaks were present. One hundred forty-five of the 165 patients who originally did not respond to conservative therapy had good response after 1 EBP, 12 patients needing 2 EBPs, 7 needing 3 EBPs, and 1 needing 4 EBPs [6•].

Fibrin Glue

In one case report of a 58-year-old female, under CT guidance, *N*-butyl-cyanoacrylate was injected into the epidural space as packing after 2 failed autologous EBPs [47]. This successfully resolved her headache and altered mental status. In a second report with a 77-year-old male with recurring subdural hematomas, worsening mental status, and failed blood patch, it improved significantly with N-BCA within hours [47]. The authors recommend that the technique be reserved for those with large dural defects > 5 mm, who are refractory to EBP and a leak can be identified [47]. This would be utilized prior to surgical repair [47].

Surgical Repair

In some cases, refractory to multiple blood patches and fibrin glue surgical repair is pursued. The type of repair is dependent on the etiology of the tear from clips and sutures to resection and muscle flaps [48]. In a study from the Mayo Clinic of 10 patients undergoing surgical correction, all improved postoperatively, with most of the patients receiving epidural packing with gel foam at identified leak sites [48].

After correction of defects, a rebound intracranial hypertension should be monitored for. A brief course of

acetazolamide for headache due to correction of CSF pressure can be used [49].

Conclusion

SIH can occur without an identifiable preceding event and can have a variety of presentations, including a normal CSF pressure, a normal MRI brain, and a resolution of postural headache but with the presence of a daily headache. These factors can contribute to a delay in diagnosis. Its pathophysiology appears related to the interplay of low CSF volume and pressure leading to traction throughout the cranial vault. Contrast studies of the brain and spine, predominantly MRI and CT myelography, are key in detecting its cause and sequelae. Management, while typically conservative, can include repeated EBPs. More studies are needed to ascertain the value of fibrin glue polymers for SIH and when they should be introduced. Surgical repair should be restricted to cases with a clear leak and those who are not responding to the EBP or fibrin glue. If surgical repair is pursued, monitoring for post-surgical intracranial hypertension is warranted. Clinicians should be aware of SIH and its typical presentation, evaluation, and treatment.

Compliance with Ethical Standards

Conflict of Interest Jessica Ailani reports personal fees from Allergan, Alder, Amgen, Avanir, Eli Lilly, Biohaven, Teva, Impel, Promius, Electrocore, AlphaSites Consulting, Miller Medical Communications, Aptus Health, and *Current Pain and Headache Reports*, outside the submitted work. Parth Upadhyaya declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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