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Residents and Fellows

Headache Rounds: Sudden Onset Chronic Daily Headache

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Key words: headache, spontaneous intracranial hypotension, low cerebrospinal fluid pressure, pseudo-Chiari, Trendelenburg position

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The following article is a Thomas Jefferson Headache Center headache rounds presentation. A 37-year-old woman, who reports a history of chronic sinusitis, developed sudden onset headache 1 1/2 years prior to her initial presentation at the Jefferson Headache Center. At that time she noted acute severe pressure-like pain bilaterally in her neck, which radiated to her forehead above her eyebrows. She denied fever, rashes, or nasal discharge at the time. The pain was much more intense than her usual "sinus headaches" and associated with a positional component, occurring only upon standing, reaching a peak intensity of 10/10 that would only last seconds and remaining as a dull milder continuous frontal pain for up to 12 hours. She had nausea and vomiting but no photophobia, phonophobia, or osmophobia. There was no rhinorrhea, conjuctival injection, or eye tearing. The pain was alleviated upon lying down. After several emergency department visits, a head computed tomography was performed revealing chronic sinus disease that led her to sinus surgery with no improvement of symptoms. For several months, she was unsuccessfully treated with preventive therapy including topiramate, duloxetine, gabapentin, onabotulinumtoxin A, and abortive therapy including triptans, nonsteroidal anti-inflammatory drugs, barbiturates, and muscle relaxants. Acupuncture and occipital nerve blocks provided limited relief. The patient denied a prior medical and family history of migraines. Since the onset of symptoms, the patient continued to have intermittent explosive frontal headaches that would be triggered by standing and improved upon lying down. As time elapsed, she also noticed suboccipital pain and neck discomfort

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worsened by Valsalva maneuvers such as straining and coughing. She also reported bilateral upper extremity paresthesias along with subjective weakness.

Query by Discussant William B. Young, MD, FAHS, FAAN, Professor of Neurology, Thomas Jefferson University, Philadelphia, PA

How would you initially approach this case? What would be the possible differential diagnosis?

Response by Stephanie W. Goldberg, Headache Fellow, Thomas Jefferson University, Philadelphia, PA.—Several differential diagnoses should be considered for a headache that is daily from onset including primary and secondary headaches depending if an underlying disease process is present.

By definition, primary headache (such as migraine and tension-type headache) is a category of disorders unto itself, not a result of another underlying disease or process. Secondary headache, conversely, is a manifestation of a separate underlying condition and, therefore, when suspected, requires more extensive investigation. When managing patients with headaches, the clinician should be attentive to signs and symptoms suggestive of secondary headaches also referred to as "red flags" especially as some of these conditions can be life threatening. In our patient, the red flags included the abrupt onset of headaches that can be a clinical presentation of ruptured aneurysm and subarachnoid hemorrhage, change in baseline headaches (sinus headaches), presence of focal neurological complaints (upper extremity weakness and paresthesias), and headache triggered by Valsalva maneuver. Finally, an associated postural component warranted investigation of abnormal intracranial pressure.

New daily persistent headache (NDPH) is a primary headache syndrome marked by a unique temporal profile that is daily from onset. That being said, many primary and secondary headaches manifest as daily from onset, making NDPH a diagnosis of exclusion.[1]

Among the chronic primary headache disorders, migraine and tension-type headache rarely present as daily from onset and rather evolve from their episodic forms.[2] Given our patient's age, sex, and associated symptoms of nausea and vomiting, an initial diagnosis of migraine headache was considered. As her headaches progressed, this diagnosis became even less likely especially with the significant postural component, which is not typical for persons with migraine. Patients with migraine may report improvement of their headache upon lying down but this should be further clarified as being related to rest and control of exacerbating factors, not necessarily to the supine position. In our case, failure of common abortive and preventive therapy, the abrupt onset of pain without antecedent escalation of headache frequency, and absent personal or family history of migraines also spoke against this diagnosis.

Low pressure headache without apparent provocation is termed spontaneous intracranial hypotension (SIH) and usually presents as a postural headache – eased by lying down and worsened in the upright position. SIH may present as a daily headache from onset not responsive to traditional treatment similar to NDPH.[2] When a prior procedure like a dural puncture, trauma, or neurosurgical intervention is believed to be the cause of the leak, the terminology changes to either postdural puncture headache or cerebrospinal fluid (CSF) fistula headache.

A variety of conditions such as postural orthostatic tachycardia syndrome (POTS), the syndrome of the trephined and colloid cyst of the third ventricle may present with a positional headache that is not necessarily caused by a CSF leak.[3-5] Autonomic studies showing evidence of orthostatic intolerance with an increase in heart rate of $\geq$30 beats per minute helps establishing the diagnosis of POTS. Syndrome of the trephined or "sinking skin flap syndrome" is a rare complication following a large craniectomy, with a sunken skin above the bone defect associated with many neurological symptoms besides severe headache such as mental status changes, focal deficits, and seizures.[6]

*Further Comments on Differential Diagnosis as Time Elapsed and New Symptoms Developed – Dr. Young.—*As time elapsed, patient developed Valsalva induced headaches. Many headaches can be triggered or aggravated by this maneuver (such as coughing, sneezing, straining, heavy lifting, bending, pushing). In congenital Chiari malformation type I, as the cerebellar tonsils descend, by definition >5 mm, the subarachnoid space at the craniocervical junction can be

Table 1.—Differential Diagnosis of Sudden Onset Chronic Daily Headache

Primary Headaches	Secondary Headaches
New daily persistent headache	Spontaneous intracranial hypotension
	Provoked intracerebral hypotension
Chronic migraine	Colloid cyst of the third ventricle
Chronic tension-type headache	Postural orthostatic tachycardia syndrome
Primary cough headache and other Valsalva induced headaches	Chiari I or pseudo-Chiari (when associated with cerebrospinal fluid hypovolemia)
Primary thunderclap headache	Secondary thunderclap headache: subarachnoid hemorrhage, cerebral venous sinus thrombosis, carotid artery dissection, and pituitary apoplexy

compressed leading to obstruction of CSF outflow. Headache is usually occipital or suboccipital, of short duration (less than 5 minutes), and can be provoked by cough or other Valsalva-like maneuver.[7]

The term pseudo-Chiari or acquired Chiari is used when this displacement is caused by the depletion of CSF intracranial volume and subsequent loss of brain buoyancy.[8,9] The clinical and radiological findings cannot be distinguished but usually in pseudo-Chiari the orthostatic headaches precede the Valsalva headaches, like in our patient, and can be improved or even reversed once the CSF hypovolemia is treated.[10]

When no underlying condition is found to be the cause of the headaches, they are named after their specific causative maneuver, like "primary cough headache."[11]

In rare cases, SIH can present as a thunderclap headache, when it becomes imperative to exclude life threatening conditions such as subarachnoid hemorrhage from aneurysmal rupture, cerebral venous sinus thrombosis, carotid artery dissection, and pituitary apoplexy.[12] See Table 1 for differential diagnosis.

Query by Dr. Young.—What is the patient's most likely diagnosis?

Response by Dr. Goldberg.—First described by Schaltenbrand in 1938, SIH is thought to result from loss of cerebral spinal fluid through an occult breach in the dura mater and, consequently, low CSF pressure.[13] Most leaks occur typically at a spinal level and only rarely from the skull base.[14] It was only later, after 1950s, that new imaging technology such as radioisotope cisternography and CT myelography supported these findings.[15] With the advance of magnetic resonance imaging (MRI), a broader clinical and radiological spectrum of the disorder was recognized[8] although, unfortunately, the syndrome remains commonly misdiagnosed.[16] CSF hypovolemia is believed to be the main pathogenetic factor of this disorder while CSF opening pressure, MRI findings, and clinical features are highly variable and not necessarily abnormal.[17] Some authors even question the terminology SIH and prefer alternative terms such as CSF volume depletion, CSF hypovolemia, or spontaneous CSF leak.[18,19] The estimated prevalence of this condition is 1 in 50,000 adults,[20] although the true incidence is unknown.

Several authors have suggested that an underlying connective tissue disorder may lead to dural weakness, increasing the chances of a dural leak.[21,22] Meningeal diverticula and other dural abnormalities leading to SIH have been reported in patients with Marfan syndrome.[23-25] In 2007, Puget et al reported a case of a 12-year-old girl with Marfan syndrome who presented with headaches and secondary Chiari I from dural ectasia. The patient responded well to blood patch treatment. Overall, the majority of patients do not present with such an obvious comorbid condition.[26]

The headache in SIH is typically postural and in severe cases may lead the patient to become bed bound. Associated features may include neck stiffness, diplopia, tinnitus, dizziness, hypoacusia, and often photophobia, nausea, and vomiting.[27] Rarely, the headache may start as a thunderclap headache, as described by our patient.[12] In some cases, the orthostatic features may disappear along the course of the disease being substituted by a chronic daily headache or may not be present at all, which often makes the diagnosis even more difficult.[28] As already mentioned, SIH should be considered in any patient who

presents with a daily persistent headache from onset or in those with daily headaches unresponsive to treatment.[29] The orthostatic component of the headache should be questioned as early as possible when eliciting a history. In the presence of tonsillar herniation, referred to as pseudo-Chiari, headache may be triggered by Valsalva maneuver as reported by our patient.

Vigorous exercise and work-related trauma can induce small dural tears preceding the onset of SIH and, if not investigated, may result in perpetuation of trauma and treatment refractoriness.[30,31]

Given the variable clinical and radiological manifestations of SIH, in 2011 Schievink et al.[32] proposed a revision of the 2004 International Classification of Headache Disorders (ICHD II) as an attempt to improve diagnosis and treatment of patients suffering from this disorder. Compared with the ICHD-II,[33] authors believed that no time limit should be set between the change in orthostatic position and headache onset. Associated symptoms were not considered useful to the diagnosis and more importantly, a universal response to an epidural blood patch (EBP) was no longer necessary. The headache in SIH usually occurs immediately or within seconds of assuming an upright position and resolves quickly (within 1 minute) after assuming a supine position. However, this timing is not always accurate and head pain may develop within minutes or hours of being upright and may improve, often not completely resolving, within minutes or hours of being supine.

In the most recent ICHD 3-beta,[34] the diagnosis of SIH does not require radiographic confirmation of the CSF leak and can be made based on low CSF pressure (<60 mm CSF) and typical clinical scenario previously described. In some cases of severe hypoliquorrhea, CSF can only be obtained via Valsalva maneuver or by aspiration.[31]

Most cases of SIH headache resolves spontaneously within a period of weeks to several months,[30,35] although postural headache may persist for up to 2 years.[36]

Continuation of Case.—After the sinus surgery and medication trials, MRI of the cervical spine revealed 6–7 mm tonsilar downward displacement below the level of the foramen magnum, qualifying as a Chiari I malformation. The patient underwent occipital decompression and C1-C2 partial laminectomy, which resolved the neurological symptoms in her arms but her headaches remained unchanged. Shortly after, a cervical spinal cord stimulator was implanted without headache improvement. The patient was then referred to our headache center and instructed to assume "Trendelenburg position" during one of her headache attacks, which completely resolved her pain.

Complete Neurological Exam During Initial Visit at Thomas Jefferson Headache Center Did Not Reveal Any Abnormalities.—Normal neurological exam including normal fundoscopic findings with sharp discs and no vascular changes.

The initial presurgical MRI studies were not available for independent review. A postsurgical MRI brain without and with contrast revealed surgical resection at the base of the occiput, an enlarged pituitary gland, and subtle pachymeningeal enhancement. MRI cervical spine revealed postsurgical changes, including removal of part of the posterior arch of C1 and subtle subdural spinal fluid collection extending from C2 to C6 levels.

Query by Dr. Young.—How are the MRI findings related to patient's diagnosis?

Response by Dr. Goldberg.—While the findings were subtle, the MRI of the brain and cervical spine provided additional clues of SIH including a large pituitary (Fig. 1), pachymeningeal enhancement (Figs. 2 and 3), and spinal subdural hygroma (Fig. 4). The gravitational downward displacement of the brain through the foramen magnum mimicking a Chiari malformation resulted from the low CSF pressure and, as previously mentioned, is termed pseudo-Chiari or acquired-Chiari (Fig. 5). The abrupt onset of headache, adult onset, lack of pure cough/Valsalva headache pattern, and absent cervical cord syrinx also suggests against a congenital Chiari malformation.

The descent of the brain during upright position leads to traction of pain-sensitive structures explaining the orthostatic nature of the headache. Blood vessels that connect the cortical surface of the brain to a

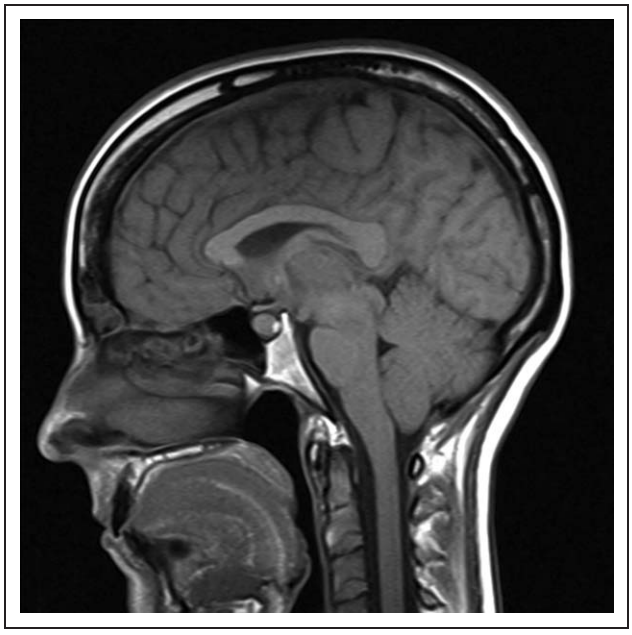

Fig. 1.—Sagittal view enlarged pituitary.

dural sinus (termed bridging veins) may be stretched and torned leading to subdural hematomas.[37,38] Hygromas such as the one detected in our patient at the level of the cervical spine can result from passive effusion of fluid accumulating in the dissected dura-

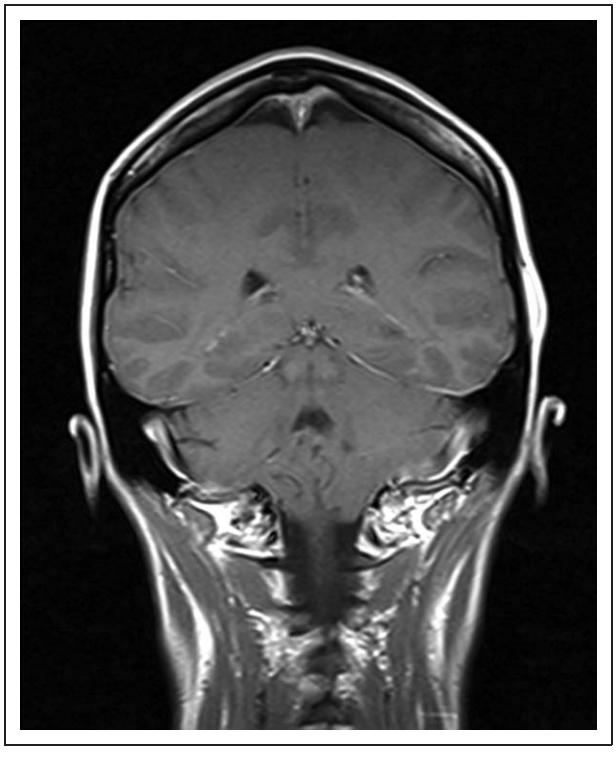

Fig. 2.—Coronal view pachymeningeal enhancement.

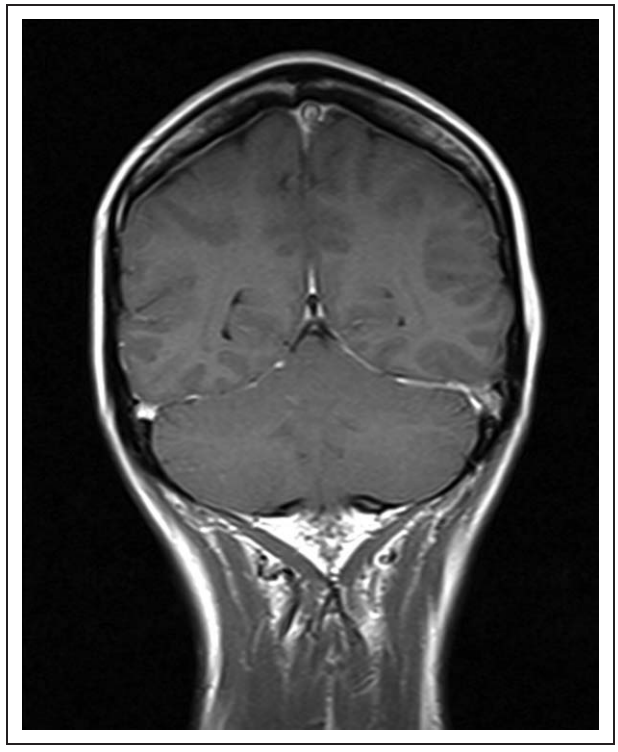

Fig. 3.—Coronal view pachymeningeal enhancement.

arachnoid interface.[39,40] Following the Monroe-Kellie Doctrine, a decrease in CSF volume causes a compensatory dilatation of the cerebral veins, venous sinuses, and meningeal vessels, which may also contribute to pain arousal.[36] Diffuse meningeal

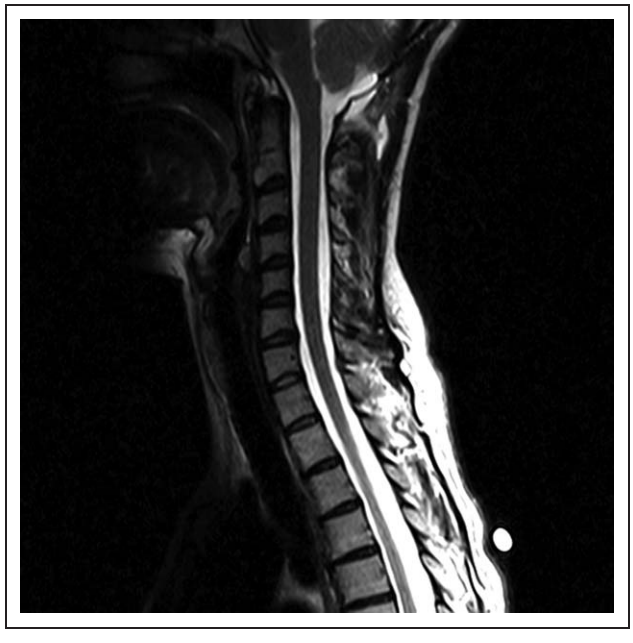

Fig. 4.—Sagittal subdural hygroma.

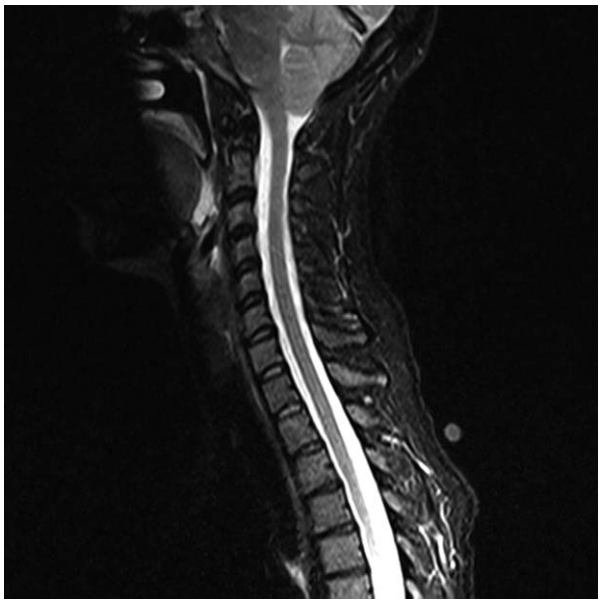

Fig. 5.—Sagittal view pseudo-Chiari or acquired-Chiari.

vessel engorgement will result in pachymeningeal but not leptomeningeal contrast enhancement since only the latter is protected by a blood–brain barrier.[14,41]

Interpretation of the Neurological Symptoms – Dr. Young.—Upper extremity paresthesias and weakness in this case are related to the pseudo-Chiari. Traction, distortion, or compression of posterior fossa and upper cervical structures such as cranial nerves, brainstem, and cerebellar tonsils are responsible for various associated symptoms in SIH. Cranial nerve palsies, cochleovestibular manifestations (tinnitus, hearing change, dizziness), radiculopathies, and even galactorrhea (attributed to traction of the pituitary stalk) have been described.[42-44]

Query by Dr. Young.—How can you diagnose SIH?

Response by Dr. Goldberg.—Diagnostic investigation includes a spinal puncture to evaluate CSF pressure and neuroradiological exams. CSF opening pressure is typically but not invariably low (it is not rare to find patients with symptomatic CSF leaks and normal CSF pressure). The fluid is typically clear and occasionally xanthochromic, protein concentration may be normal or elevated (up to 1000 mg/dL), and sugar content is always within normal limits. CSF leukocyte is normal or elevated: a primarily lymphocytic pleocytosis up to 50 cells/mm^3 is common. Cytology and microbiology are always normal.[13] Considering the above changes and the presence of pachymeningeal enhancement, caution should be taken so an erroneous diagnosis of aseptic meningitis is not made.[45]

Table 2.—Magnetic Resonance Imaging Abnormalities in Spontaneous Intracranial Hypotension

Diffuse pachymeningeal enhancement
Narrowed Sylvian fissure and infratentorial cisterns
Inferior displacement and flattening of the optic chiasm
Crowding of the posterior fossa
Pituitary engorgement mimicking pituitary hyperplasia or tumor
Subdural fluid collections (hygromas, hematomas)
Engorged cerebral venous sinuses

The Trendelenburg position (head-down tilt), believed to cause a rapid increase in intracranial CSF pressure, has been suggested as an accurate and inexpensive screening tool for low CSF pressure syndromes. This easy to perform maneuver can predict a correct diagnosis of SIH and promote further pain control even in patients who do not present with a positional headache component.[29] Our patient had complete resolution of her headache with this maneuver, which led us to proceed with further diagnostic testing.

Computed tomographic myelography with water-soluble contrast remains the gold standard diagnostic test for locating the site of CSF leak, which is most commonly at the cervico-thoracic level.[14] Radioisotope cisternography with Indium-111 is an alternative test but usually not chosen as first option. It may reveal paucity of activity over the cerebral convexities, with rapid disappearance of radioactive tracer from the subarachnoid space and accumulation in the bladder. More desirable but less frequently, the site of CSF leak can be identified as a zone of parathecal activity. MRI study provides the advantage of being a noninvasive procedure avoiding further dural sac puncture and a new potential leak, and may reveal a multitude of pathognomonic findings (Table 2). Diffuse pachymeningeal enhancement at both supratentorial and infratentorial levels is the most common abnormality, best seen on coronal sequences.[46] Other

Table 3.—Spontaneous Intracranial Hypotension Treatment Modalities[14]

Conservative measures (nonpharmacological)
Bed rest, hydration
Conservative measures (pharmacological)
Analgesics, nonsteroidal drugs, caffeine, tricyclic antidepressants, ergot preparation, and steroids
Abdominal binder
Binders, corsets
Epidural injections
Epidural blood patch, fibrin glue
Other measures
Epidural and intrathecal saline infusions (uncertain, unpredictable efficacy or durability; risk of infection), epidural infusion of dextran
Surgical repair of the leak
Surgical closure, reinforcement with muscle and/or fibrin sealant

peculiar radiographic abnormalities include pituitary engorgement mimicking pituitary hyperplasia or tumor[47,48] and features of brain sagging such as tonsillar herniation, narrowed Sylvian fissure/infratentorial cisterns ("ventricular collapse"),[49] inferior displacement/flattening of the optic chiasm, and crowding of the posterior fossa. Subdural fluid collections previously mentioned can also be detected. MRI study with subtraction analysis is an innovative and reliable option for evaluation of ectopic CSF collection.[50]

Similar findings may happen at the spinal level such as extra-arachnoid fluid collections, spinal dural enhancement and engorgement of epidural venous plexus and intradural spinal veins.[14] A dynamic CT myelogram (CTM) is faster than a myelography study and therefore useful in patients with fast-flow leak. Usually in these cases, by the time the myelography is performed the contrast has already extravasated and spread, making it difficult to determine the actual site of the leak. Both tests involve piercing of the dura for contrast injection in the subarachnoid space and, therefore, are considered invasive, but conversely they offer the opportunity to simultaneously check the CSF opening pressure. They are also helpful for patients who cannot undergo MRI studies.[51] Despite the above options, leakage is demonstrated in only 20% of cases.[52]

Case Approach – Dr. Goldberg and Dr. Young.—A tiered approach to therapy is typically used (Table 3). Conservative, noninvasive management such as bed rest, hydration, analgesics, nonsteroidal anti-inflammatory drugs, caffeine, tricyclic antidepressants, ergot preparation, and steroids are usually the first line of treatment. When patients fail this initial approach, the next step is to try an EBP, which unfortunately provides variable benefit.[13] Even those patients who respond to the first EBP may not have a sustained or complete relief of symptoms requiring a second or even third procedure.[53] In a retrospective study of 25 patients with documented CSF spinal leak, approximately 30% responded to the first EBP, 30% to the second EBP and 50% to the third EBP. At least one-fourth of patients are not cured by epidural blood patching and about half require more than one blood patch to improve from symptoms.[54,55] The majority of these studies are not controlled and mostly based on clinical observation, and are thought to be more efficacious in postlumbar puncture leaks.[56] Surgical intervention may be required, if the site of the leak has been definitely identified.[14] Epidural injection of fibrin glue has been reported to successfully treat persistent CSF leaks. It consists of a fibrin monomer gel obtained by mixing different components of the patient plasma.[57] Epidural and intrathecal saline infusion are reserved for refractory cases.[45,58] Binder et al. reported a case of a 43-year-old man with low CSF pressure headaches complicated with bilateral subdural hygromas and posterior fossa contingent herniation who failed repeated large-volume (30-mL) lumbar (L3–L4) EBPs. The patient's profound obtundation was successfully treated with intrathecal saline infusion.[59]

Case Follow-Up.—In May of 2015, the patient underwent a CTM, which did not identify a CSF leak. We advised the patient to have the spinal stimulator removed to improve accuracy of further imaging testing and to decrease risk of infection with future EBP.

SUMMARY OF CASE AND LEARNING POINTS – MATTHEW S. ROBBINS, MD, SECTION COEDITOR

Drs. Goldberg and Young present an instructive case of a young woman who, at the age of 37, developed the abrupt onset of severe, daily headache. Unfortunately, she was treated with three separate surgical therapies that did not lead to any

improvement. A careful revisiting of the differential diagnosis led to a rational diagnosis of SIH, though specific treatment has not yet been used.

SIH is clinically recognized more easily when there is a robust orthostatic headache pattern but, as Drs. Goldberg and Young note, in many patients that pattern is lacking. This patient presented with an NDPH syndrome, and many such patients may have undiagnosed SIH. As in this case, the diagnostic delay is often protracted over months to years, exposing patients to unnecessary and potentially harmful diagnostic tests and therapies.[5]

Diagnosing SIH can often be difficult, but a diagnostic algorithm has recently been devised.[60] This algorithm places MRI of the brain with and without contrast and MRI of the spine without contrast as the first line investigations before proceeding with more specific testing and therapies. The authors devised the algorithm after comparing spine MRI with CT myelography as the gold standard in 12 patients with a confirmed CSF leak. The sensitivity of spine MRI was 91.7%, mainly by demonstrating extradural fluid collections in the spine. Over half of these patients had dural enhancement in the spine as well.

SELF-ASSESSMENT QUESTIONS

1. What is the differential diagnosis of a patient presenting with NDPH, and what clinical clues may suggest a disorder of intracranial pressure or volume?
2. What are the clinical and radiographic features that distinguish a true Chiari malformation from a pseudo-Chiari malformation?
3. What are the clinical features that are specific for the diagnosis of SIH?
4. How should the diagnostic workup proceed for a patient suspected of having a CSF leak?
5. What noninvasive and invasive therapies are available to treat SIH?

This case presentation and discussion address the following areas of competency in postgraduate medical education: patient care, medical knowledge, practice-based learning and improvement, communication skills, and systems-based practice.

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