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Headaches Due to Low and High Intracranial Pressure

By Deborah I. Friedman, MD, MPH, FAAN

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Address correspondence to Dr Deborah I. Friedman, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, MC 9322, Dallas, TX 75390, *Deborah.Friedman@UTSouthwestern.edu*.

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Dr Friedman has received personal compensation for serving on the advisory boards of Alder BioPharmaceuticals, Inc; Amgen Inc; Avanir Pharmaceuticals, Inc; Biohaven Pharmaceutical; ElectroCore, LLC; Supernus Pharmaceuticals, Inc; Teva Pharmaceutical Industries Ltd; and Zosano Pharma Corporation.
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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Friedman discusses the unlabeled/investigational use of acetazolamide for the treatment of pseudotumor cerebri syndrome, the use of gadolinium for MRI myelography for the diagnosis of spontaneous intracranial hypotension, and the use of zonisamide for the treatment of associated headache.

ABSTRACT

PURPOSE OF REVIEW: Headache disorders attributed to low and high intracranial pressure are commonly encountered in specialty headache practices and may occur more frequently than realized. While the headaches resulting from intracranial pressure disorders have what are conventionally thought of as defining characteristics, a substantial minority of patients do not manifest the "typical" features. Moreover, patients with intracranial pressure disorders may also have a preexisting primary headache disorder. Heightening the complexity of the presentation, the headaches of intracranial pressure disorders can resemble the phenotype of a primary disorder. Lastly, patients with so-called intracranial "hypotension" often have normal CSF pressure and neuroimaging studies. Thus, a high index of suspicion is needed. The published literature has inherent bias as many types of specialists evaluate and treat these conditions. This article reviews the key points to emphasize the history, examination, and laboratory evaluation of patients with intracranial pressure disorders from a neurologist's perspective.

RECENT FINDINGS: Lumbar puncture opening pressure in patients with spontaneous intracranial hypotension was low enough to meet diagnostic criteria (≤60 mm CSF) in only 34% of patients in one study. Most patients had an opening pressure in the low normal to normal range, and 5% had an opening pressure of 200 mm CSF or more. Diskogenic microspurs are a common cause of this syndrome. The Idiopathic Intracranial Hypertension Treatment Trial found that most participants had a headache phenotype resembling migraine or tension-type headache. No "typical" or characteristic headache phenotype was found, and headache-related disability was severe at baseline. Headache disability did not correlate with the lumbar puncture opening pressure at baseline or at the 6-month primary outcome period. Although participants who were randomly assigned to acetazolamide had a lower mean CSF opening pressure at 6 months, headache disability in that group was similar to the group who received placebo.

SUMMARY: Significant overlap is seen in the symptoms of high and low CSF pressure disorders and in those of primary headache disorders. Neurologists are frequently challenged by patients with headaches who lack the typical clinical signs or imaging features of the pseudotumor

cerebri syndrome or spontaneous intracranial hypotension. Even when characteristic symptoms and signs are initially present, the typical features of both syndromes tend to lessen or resolve over time; consider these diagnoses in patients with long-standing "chronic migraine" who do not improve with conventional headache treatment. While the diagnostic criteria for pseudotumor cerebri syndrome accurately identify most patients with the disorder, at least 25% of patients with spontaneous intracranial hypotension have normal imaging and over half have a normal lumbar puncture opening pressure. Detailed history taking will often give clues that suggest a CSF pressure disorder. That said, misdiagnosis can lead to significant patient morbidity and inappropriate therapy.

INTRODUCTION

Although they represent opposite extremes on the intracranial pressure spectrum, many similarities occur between the clinical features of high- and low-pressure disorders. Additionally, both conditions share properties seen with primary headache disorders (TABLE 6-1 and TABLE 6-2). Both syndromes can produce new daily persistent headaches, although the headaches are not always daily in either disorder. No typical headache phenotype exists for either condition; nocturnal awakening and worsening with bending over or Valsalva maneuvers are helpful clues for both conditions but are not specific. The longer the duration of symptoms, the more difficult it is to confirm either diagnosis by brain imaging techniques, and even the lumbar puncture opening pressure can be misleading. Although neurologists usually evaluate patients with these conditions because of headaches and other neurologic symptoms, either disorder can be asymptomatic or acephalgic. Finally, there is a fine line between being hypervigilant when considering the two diagnoses in clinical practice and overdiagnosing these conditions, which can lead to inappropriate investigations and treatments, potentially causing harm.[2]

SPONTANEOUS INTRACRANIAL HYPOTENSION

The term *spontaneous intracranial hypotension* is a misnomer. The syndrome is not always spontaneous; a precipitating event is often identified. Additionally, the majority of patients with spinal CSF leaks do not have low CSF pressure, defined as a lumbar puncture opening pressure below 60 mm CSF.[3] It is more accurately conceptualized as low CSF volume, low CSF pressure, and possibly low compliance of the caudal spinal dura. "Intracranial" implies that the problem is within the skull. While most of the clinical manifestations are intracranial, the underlying defect is spinal.[4]

TABLE 6-3 lists the diagnostic criteria for spontaneous intracranial hypotension.[5] The estimated prevalence of spontaneous intracranial hypotension is 1 per 50,000, with an annual incidence of 5 per 100,000.[6] This is likely an underestimation, as patients without typical brain imaging findings are less likely to be diagnosed and are therefore excluded from population-based studies. Additionally, such studies rely on a specific diagnosis code, which does not currently exist for this disorder. Spontaneous intracranial hypotension is more common in women than men and typically presents in the fourth or fifth decades, although it may occur at any age, and patients may have symptoms for years or even decades before being

TABLE 6-1 **Overlap of Clinical Features of High and Low Cerebrospinal Fluid Pressure Disorders and Primary Headache Disorders**

Feature	Pseudotumor Cerebri Syndrome	Intracranial Hypotension	Primary Headache Disorder
Location of pain	Often frontal or retro-orbital but varies	Often posterior but varies	Varies
Timing	Worse in the morning or no fluctuation	Worse as the day progresses	Patterns vary by headache type; migraine is often present upon awakening
Nocturnal awakening	Yes	Yes	Yes; frequent in cluster headache, infrequent in migraine, defining of hypnic headache
Worse with Valsalva maneuver, exercise, bending over	Yes	Yes	Yes; migraine, primary exertional headaches, secondary causes (eg, reversible cerebral vasoconstriction syndrome, aneurysm, Chiari malformation)
Effect of caffeine	None or worsens	Improvement	Either; caffeine may provoke migraine or relieve it
Orthostatic/positional component	Sometimes worse lying flat	Usually better lying flat	Varies; patients with migraine often prefer to lie down, which may be related to avoiding movement
Effect of high altitude	Usually worsens	Usually improves	Either; migraine is a risk factor for headache at high altitude[1]
Effect of Trendelenburg position	None (may theoretically worsen)	Often improves	None
Pulsatile tinnitus	Common	Rare (but may have nonpulsatile tinnitus)	Not associated
Transient obscurations of vision	Common	No	No; transient visual loss in migraine lasts longer than 1 to 2 minutes and is not postural
Joint hypermobility	Not associated	Common	Not associated
Neck or back pain	Common	Common	Common
Radicular pain	Common	Rare	No
Papilledema	Usually present	No	No
Spontaneous venous pulsations	Absent	Usually present	Usually present
Associated with cerebral venous sinus thrombosis	Yes	Yes	No
Sex	Marked female preponderance after puberty	More common in females	Male or female; depends on primary headache diagnosis
Body habitus	Usually obese	Often slim or normal	No association

Comparison of Diagnostic Tests Between High and Low Cerebrospinal Fluid Pressure Disorders and Primary Headaches

TABLE 6-2

Feature	Pseudotumor Cerebri Syndrome	Intracranial Hypotension	Primary Headache Disorder
Sella/pituitary[a]	Usually empty sella	Usually enlarged and hyperemic pituitary	No pattern
Ventricular size	Normal	Normal	Normal
Tonsillar descent	Possible	Common, may resemble Chiari malformation	No relationship
Flattening of anterior pons	No	Common	No
Optic nerve sheath complex	Distended and/or tortuous	Narrowed, straight	No
Lumbar puncture opening pressure[b]	High	Low or normal, occasionally high	Usually normal
Post–lumbar puncture headache possible	Yes	Yes	Yes
Headache improves after lumbar puncture	Often	No, symptoms may worsen	Possibly

[a] Pituitary gland may enlarge during pregnancy.
[b] May be elevated with Valsalva maneuver, extreme pain.

Diagnostic Criteria for Spontaneous Cerebrospinal Fluid Leak and Intracranial Hypotension[a]

TABLE 6-3

A Demonstration of a spinal CSF leak (ie, presence of extrathecal CSF)
Or, if criterion A not met,

B Cranial MRI changes of intracranial hypotension (ie, presence of subdural fluid collections, enhancement of the pachymeninges, or sagging of the brain) and the presence of at least one of the following:

1 Low opening pressure (≤60 mm H_2O)

2 Spinal meningeal diverticulum

3 Improvement of symptoms after epidural blood patching
Or, if criteria A and B not met:

C The presence of all of the following or at least two of the following if typical orthostatic headaches are present:

1 Low opening pressure (≤60 mm H_2O)

2 Spinal meningeal symptoms

3 Improvement of symptoms after epidural blood patching

Note: Patients with onset of symptoms after dural puncture or other penetrating spinal trauma are excluded.

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.
[a] Reprinted with permission from Schievink WI, et al, AJNR Am J Neuroradiol.[5]

KEY POINTS

- Although they represent opposite ends of a spectrum, spontaneous intracranial hypotension and pseudotumor cerebri syndrome share many clinical similarities.
- Neurologists are often faced with the dilemma of evaluating patients who may have either spontaneous intracranial hypotension or pseudotumor cerebri syndrome, but are "atypical."
- When evaluating a patient with possible spontaneous intracranial hypotension or pseudotumor cerebri syndrome, there is a fine line between being hypervigilant when considering the two diagnoses in clinical practice and overdiagnosing the conditions, which can lead to inappropriate investigations and treatments, potentially causing harm.
- Spontaneous intracranial hypotension is not necessarily spontaneous, is not of intracranial origin, and may not arise solely from low CSF pressure. CSF volume and compliance of the caudal dura may also be contributing factors.
- Typical orthostatic and "end of the day" headaches may be less prominent in spontaneous intracranial hypotension over time.
- A marked variability occurs in the location and character of spontaneous intracranial hypotension–related headaches.

correctly diagnosed. Predisposing factors include hypermobility disorders, including Ehlers-Danlos and Marfan syndromes, and degenerative disk disease. It is postulated that individuals with connective tissue disorders and hypermobility have dural weakness leading to tears and diverticula that allow CSF to egress into the epidural space.[6] TABLE 6-4 lists other causes of the syndrome, such as trauma, intentional or accidental dural puncture, and various physical activities.[8] The physical trauma may be trivial or related to usual activities, such as exercise.

The most common symptom of spontaneous intracranial hypotension is headache. Spontaneous intracranial hypotension is a secondary cause of new daily persistent headache, and the headache may start abruptly. The classic headache is orthostatic, worsening in the upright posture and improving with recumbence. This feature suggests that downward traction on pain-sensitive upper cervical and cranial structures (nerve roots, meninges, ligaments, veins) is responsible for the headache. However, nocturnal awakening is not uncommon, and paradoxical headaches (worse in recumbence and improved in the upright posture) may rarely occur.[9] Patients will often relate that their headache is absent or least intense when they first awaken. It may worsen almost immediately after sitting or arising or progressively worsen throughout the day. Others will experience headache that begins later in the day, sometimes starting at a very specific time. The location and quality of the headache are extremely variable, with the latter ranging from annoying to completely incapacitating. Bilateral posterior head pain is commonly present, but the pain may be unilateral and in any cranial location. Associated neck pain commonly occurs, and trigeminal neuralgic pain has been reported.[10] The orthostatic component may dissipate over time.

Exacerbating factors, which may also occur with intracranial hypertension and other headache disorders, include coughing, sneezing, laughing, lifting, bending, straining (Valsalva maneuver), sexual activity, and exercise. (Worsening with Valsalva maneuvers seems paradoxical, but such maneuvers may exacerbate the CSF leakage through spinal dural defects.) The headache may improve at high altitude, with caffeine, with greater occipital nerve blockade, and possibly with onabotulinumtoxinA injections.[11,12]

Other manifestations of spontaneous intracranial hypotension include chest or back pain ("coat hanger" headache), photophobia, diplopia, blurred vision, facial pain, imbalance, hearing abnormalities, tinnitus, cognitive and mental status changes, hyperkinetic and hypokinetic movement disorders, galactorrhea, subdural fluid collections, and intracranial hemorrhage (TABLE 6-2).

Diagnosis

The key to diagnosis is a high level of clinical suspicion and a careful history. As the manifestations vary and neuroimaging may be normal, the diagnosis may be delayed for many years. The neurologic examination is usually normal or may reveal abnormalities referable to the nonheadache symptoms. Spontaneous venous pulsations on fundoscopy are supportive although not universally present. Patients may be slim with an elongated, slender neck. Improvement of symptoms in the Trendelenburg position (10- to 20-degree head-down tilt for 5 to 10 minutes) is highly suggestive of spontaneous intracranial hypotension.[13] Patients should be queried and examined for joint hypermobility; the Beighton scale is a helpful assessment tool.[13,14] These points are demonstrated in CASE 6-1.

Laboratory Studies

Lumbar puncture is only helpful for diagnosing spontaneous intracranial hypotension if the CSF pressure is low (≤60 mm CSF). In a study of 106 patients meeting the diagnostic criteria of headache due to spontaneous intracranial hypotension developed by Schievink and colleagues,[15] 34% of patients had a CSF pressure of 60 mm CSF or less, 45% had opening pressures between 60 mm CSF and 120 mm CSF, 16% had opening pressure between 120 mm CSF and 200 mm CSF, and 5% had pressures greater than 200 mm CSF.[3,15] Thus, most patients with spontaneous intracranial hypotension have normal CSF pressure. A 24-gauge needle is recommended to avoid a post–dural puncture leak that may

Causes and Predisposing Factors for Spontaneous Intracranial Hypotension Syndrome[a] TABLE 6-4

Connective Tissue Matrix Disorders

- Marfan syndrome
- Ehlers-Danlos syndrome type II
- Autosomal dominant polycystic kidney disease
- Joint hypermobility: hyperflexibility, "party tricks," naturally good at gymnastics, dance, or yoga (inquire about flexibility in childhood)
- Retinal detachment at a young age
- Personal or family history of arterial dissection, aneurysms, nonrheumatic valvular heart disease
- Secondary to unrecognized intracranial hypertension

Trauma

- Previous spine surgery
- History of lumbar puncture
- Nerve root sleeve tears or avulsions
- Previous spinal or epidural anesthesia
- Trivial trauma
  - Valsalva related: heavy lifting, coughing, straining
  - Repetitive truncal torsion: tennis, golf, yoga, kayaking, canoeing
- Impact: motor vehicle accident, whiplash, sports injury

Spine Disorders

- Calcified herniated disks
- Osteophytes and spondylotic spurs
- CSF venous fistula

Bariatric Surgery[7]

Unknown

CSF = cerebrospinal fluid.

[a] Modified with permission from Mokri B, Continuum (Minneap Minn).[8]

worsen the condition. Rarely, spontaneous intracranial hypotension mimics aseptic meningitis with a lymphocytic pleocytosis or elevated CSF protein.[16]

Contrast-enhanced MRI of the brain is generally the first imaging study obtained and is abnormal about 75% of the time. The typical findings are brain sag with cerebellar tonsillar descent, pituitary enlargement and hyperemia, flattening of the anterior pons, straightening of the optic chiasm, distention of the cerebral venous sinuses, ventricular collapse, venous sinus dilatation, and descent and distortion of the midbrain (FIGURE 6-2). Most findings are best viewed on the midline sagittal T1-weighted images. Coronal images reveal thickening and enhancement of the pachymeninges resulting from venous distention (FIGURE 6-3).[17] Subdural fluid collections, subdural hematoma, cerebral venous sinus thrombosis, evidence of reversible cerebral vasoconstriction syndrome, or subarachnoid hemorrhage may be seen. Spontaneous intracranial hypotension occurring in children and young adults may alter the skull morphology with calvarial thickening, expansion of the

CASE 6-1

A 31-year-old woman developed diplopia and intermittent headaches that had become constant within 2 weeks of onset. One month prior to the onset of symptoms, she had begun taking vigorous aerobic exercise classes, and she rode a roller coaster a few days prior to symptom onset. An optometrist had found a right abducens palsy, and a CT scan of the orbits was normal. Two weeks later, the diplopia persisted, and the headache became constant.

At her neurologic evaluation 2 months later, the headache had evolved into a right temple pain with intermittent burning of the right cheek and right ear and sharp retro-orbital pain. The initial dull pain spread to the right neck and occipital regions with intermittent sharp pain just to the right of the vertex. She had severe phonophobia, mild photophobia, nausea, confusion, tinnitus, and dry heaves. The headache was rated 4 out of 10 intensity upon awakening and worsened over hours to 8 out of 10 by the end of the day. It awakened her from sleep at times. Coughing, sneezing, and bearing down increased the pressure sensation in her neck. Lying completely flat improved the headache, and standing worsened it. Caffeine helped the headache. She reported being "double jointed" with a strong family history of joint hypermobility and heart murmurs.

MRI of the brain with contrast was normal (FIGURE 6-1). Neurologic examination showed 50% of normal right eye abduction and normal fundi with spontaneous venous pulsations. Joint hypermobility was present in the fingers, wrists, and hips. Cardiac auscultation was normal. Headache severity prior to the Trendelenburg test was rated 3 out of 10; the patient's headache resolved, and the right abducens palsy improved after being in the Trendelenburg position for 10 minutes.

She underwent two sequential high-volume lumbar epidural blood patches with brief rebound intracranial hypertension that was treated with acetazolamide. Genetic testing for Ehlers-Danlos syndrome was negative. Her symptoms ultimately resolved.

paranasal sinuses, aeration of bones at the skull base, and reduction in the size of the sella turcica.[18]

In one series, patients without dural enhancement had a longer duration of symptoms than those with enhancement; brain sag and venous distention did not correlate with symptom duration.[19] Misinterpretation of the findings may have devastating consequences for the patient. Brain sag may be erroneously diagnosed as a Chiari malformation type I, leading to unnecessary surgery that may make the patient worse. Draining resultant subdural hematomas without addressing the intracranial hypotension may cause rebleeding that can be fatal.

Spinal imaging modalities are incorporated to identify the site, nature, and cause of a leak in order to plan therapy. Collaboration with a neuroradiologist having expertise in the techniques used to diagnose spinal CSF leaks is critical for optimal patient management. Areas of dural thinning and dehiscence allow the herniation of the arachnoid layer through the dural defect, leading to meningeal diverticula that are prone to tear.[19] These diverticula tend to be located along the

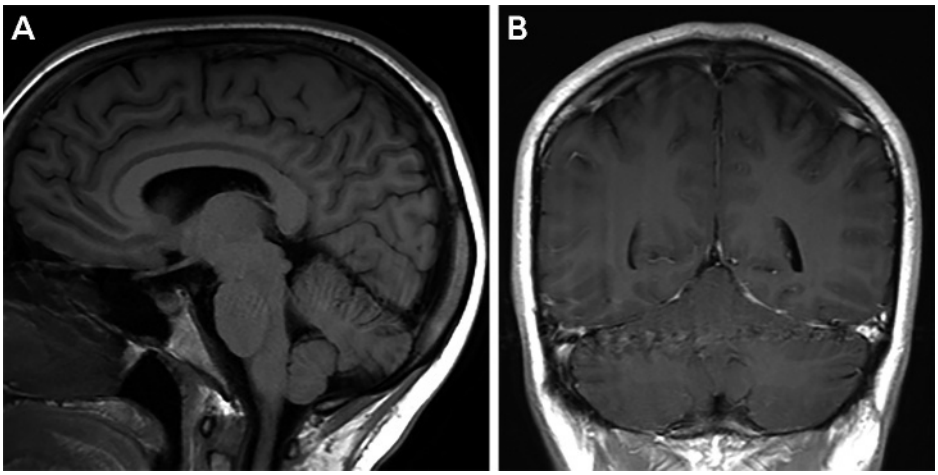

FIGURE 6-1

Imaging of the patient in CASE 6-1. *A*, Sagittal noncontrast T1-weighted MRI shows no evidence of brain sag, pituitary enlargement, or chiasmal flattening. *B*, Coronal postcontrast T1-weighted image reveals normal meningeal contrast enhancement.

COMMENT

Despite normal brain imaging, the patient's symptoms were highly suggestive of spontaneous intracranial hypotension. She had orthostatic head, face, and neck pain that worsened during the day and was associated with tinnitus. Predisposing factors included joint hypermobility, vigorous exercise, and riding a rollercoaster. The headache and sixth nerve palsy improved in the Trendelenburg position. Intracranial hypertension may occur after epidural blood patches, which can usually be managed medically.

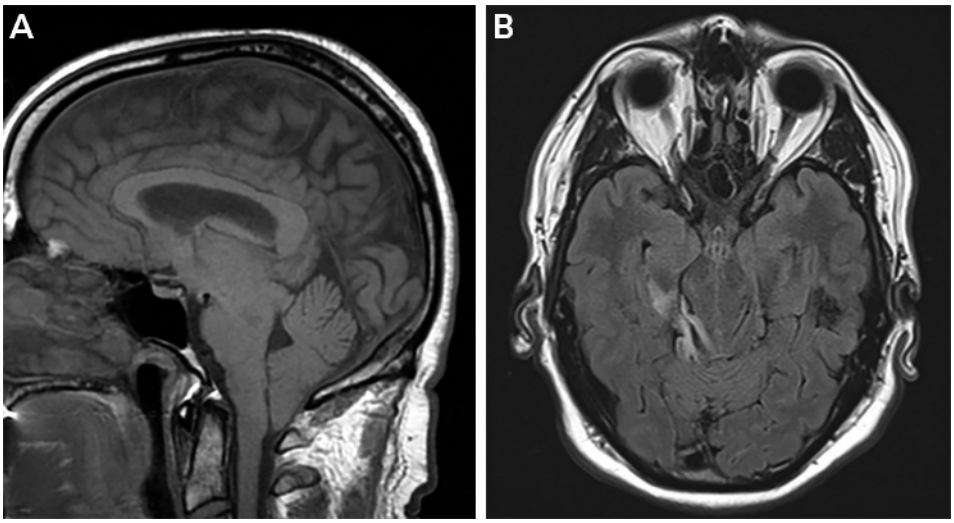

FIGURE 6-2
Imaging findings of spontaneous intracranial hypotension. A 61-year-old man, who worked as a high-level financial executive, underwent neuroimaging for a 3-year history of cognitive decline, which had progressed to the point that he missed paying his bills and could not recall the day of the week. *A*, T1-weighted sagittal MRI showed pronounced brain sag with tonsillar descent, flattening of the anterior pons, midbrain collapse, downward displacement of the posterior corpus callosum, obliteration of the third ventricle, and straightening of the optic chiasm. *B*, Axial fluid-attenuated inversion recovery (FLAIR) image showed marked distention of the midbrain with abnormal high signal in the right hippocampal formation indicating partial herniation. No abnormal pachymeningeal enhancement was seen on the postcontrast images (not shown). The patient had minimal improvement with blood patches and ultimately required surgical repair of his spinal CSF leak, resulting in significant improvement in his cognition. This case illustrates that symptoms other than headache may be predominant in spontaneous intracranial hypotension.

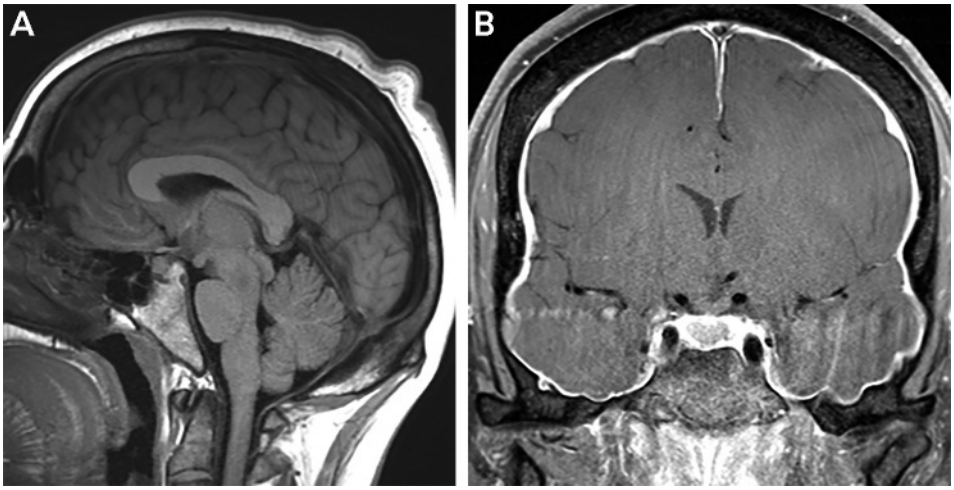

FIGURE 6-3
Spontaneous intracranial hypotension. A 30-year-old man developed a severe orthostatic headache, intense vomiting, vertigo, blurred vision, and neck pain. Imaging 2 weeks later revealed mild flattening of the anterior pons and pituitary enlargement on T1-weighted sagittal MRI (*A*). Despite the relatively normal precontrast images, meningeal thickening and enhancement is seen on the postcontrast T1-weighted coronal MRI (*B*).

nerve root sleeves and are often large and irregular in contour. Degenerative changes, such as osteophytes and calcified disk protrusions, can directly tear the dura and are most commonly located ventrally in the lower cervical or thoracic spine.[20] CSF venous fistulas are identified in a small percentage of patients. The anatomy of a leak may be complex, and localizing the exact leak site or sites may be elusive. In 46% to 55% of cases, including those with slow or intermittent leaks and those caused by CSF venous fistulas, the leak site cannot be found.[21,22]

In fast (high-flow) leaks, a pool of contrast material extravasates into the epidural space surrounding the thecal sac. It may be extensive in some cases, arising at multiple levels and tracking into the paraspinal soft tissues.[3] An extensive leak may impede exact localization of the leak site, which requires high resolution and rapid imaging after the administration of contrast. A large pool of epidural contrast is usually absent with slow (low-flow) leaks. Slow leaks generally occur around nerve root sleeves and are easier to treat than fast ventral leaks. However, if the leak is quite slow or intermittent, identification of the leak site is difficult. Delayed imaging may be helpful. One strategy is to inject the contrast material for the CT and MRI simultaneously after injecting a bolus (approximately 15 mL) of intrathecal saline or artificial CSF to increase the CSF volume. The patient is immediately imaged with CT, followed by delayed imaging using MRI. Both techniques are invasive, and the use of gadolinium for intrathecal injection is off-label. Radiation dose must always be considered with CT.

Digital subtraction myelography is performed under fluoroscopy and allows the real-time visualization of the contrast agent traversing along the spine to identify the site of the leak.[3] The leak appears as a split in the column of contrast material creating a parallel track in the epidural space. The resolution is excellent, but there is a limit to the area of coverage possible, so the lower cervical and thoracic spine are generally scanned unless a leak is suspected elsewhere. The patient must be absolutely immobile, which may require general anesthesia. This technique is performed in the angiography suite and is not widely available.

Spinal MRI with heavily T2-weighted images and fat suppression is a noninvasive technique that best identifies the presence (but not necessarily the location) of high-flow leaks. A retrospinal fluid collection at C1-C2 seen with this technique does not indicate the site of the leak and is a false localizing sign.[23] Disadvantages of this technique are the lower spatial resolution, higher rate of artifacts, decreased likelihood of localizing the leak, and the need for very homogeneous fat suppression.[19] This imaging technique is not generally included in standard MRI software and may require additional programming.

Radionuclide cisternography incorporates an iodinated tracer (indium 111 diethylenetriamine pentaacetic acid [^{111}InDTPA]), which is injected intrathecally with image acquisition immediately and at 1, 2, 4, 24, and sometimes 48 hours after injection. It may show direct or indirect evidence of a leak. Unilateral or bilateral focal areas of increased activity within paraspinal tissues indicate direct evidence.[13] Indirect signs include early uptake in the kidneys and bladder within 4 hours, absence of activity along cerebral convexities at 24 hours (similar to normal pressure hydrocephalus), and rapid loss of spinal activity. Cisternography has only modest sensitivity and specificity, and the cost of the tracer is sometimes prohibitive. False-positive and false-negative results may occur.

KEY POINTS

- Patients with spontaneous intracranial hypotension may be asymptomatic or experience visual, vestibulocochlear, and cognitive problems, as well as an altered level of consciousness, movement disorders, and intracranial hemorrhage.
- Patients who have a typical headache pattern or abnormal brain imaging are generally identified early. The lack or subtle nature of orthostatic symptoms coupled with normal brain imaging leads to considerable delay in diagnosis, sometimes for decades. Spontaneous intracranial hypotension should be considered in patients with headaches of any phenotype that are refractory to conventional headache therapies.
- Brain sag may be erroneously diagnosed as a Chiari malformation type I, leading to unnecessary surgery that may make the patient worse.
- In cases of spontaneous intracranial hypotension, the leak site cannot be identified in about half of cases, and intermittent leaking may occur, which can make identification of the leak site challenging.
- Nerve sheath diverticula and osseous changes are indirect signs of a potential leak site.
- In cases of spontaneous intracranial hypotension, a large pool of epidural contrast suggests a high-flow leak.

Treatment

Conservative treatments may be attempted but are generally unsuccessful (TABLE 6-5); the refractory nature of spontaneous intracranial hypotension headaches to typical headache medications is a clue that the patient may have a secondary disorder. Occasionally, leaks will resolve spontaneously.

A nontargeted, autologous, high-volume epidural blood patch is often the first step in management, and each attempt is successful approximately 30% of the time.[21] A disagreement exists regarding whether this procedure should be tried empirically or whether patients should be evaluated to determine the leak site first. Even transient relief of symptoms supports the diagnosis of spontaneous intracranial hypotension, so the procedure also has diagnostic value in suspected cases with normal brain imaging. Symptoms may subsequently recur, requiring additional blood patches, and at least 5 days are recommended between procedures.[26]

"Nontargeted" midline epidural blood patches are generally performed at one or more spinal levels from T12-L1 through L4-L5, and multilevel patches may be done in one session. The success rate is potentially enhanced by pretreating the patient with acetazolamide (250 mg orally given at 18 and 6 hours prior to the procedure) to decrease CSF volume and allow a higher volume of blood to be injected in the epidural space and placing the patient in the Trendelenburg position during and immediately after the procedure.[27] A volume of 10 mL to 20 mL of autologous blood is initially injected, which may be increased as tolerated in subsequent attempts. The amount of blood injected is generally determined by the patient's level of procedure-related pain or anatomic constraints limiting the volume of injection.

Another technique employs a single puncture in the lower thoracic or lumbar space, passing a guidewire into the epidural space, and advancing in a 4-French vertebral catheter superiorly into the dorsal epidural space. After confirming epidural placement with contrast administration, the guidewire is removed, and autologous blood is injected into the epidural space while slowly withdrawing the catheter to the access site.[28]

The mechanism of epidural blood patches leading to improvement is uncertain and may be related to tamponade and sealing of the leak, restriction of

TABLE 6-5 **Strategies for Conservative Management of Spontaneous Intracranial Hypotension**

- Bedrest (patients can be bedbound because of their symptoms)
- Elevate the foot of the bed (home Trendelenburg position)
- Caffeine, theophylline (often helpful but may produce anxiety and insomnia)
- Abdominal binder
- Analgesics
- Corticosteroids (2- to 4-week gradual prednisone taper starting with 50 mg/d)[24]
- Bilateral greater occipital nerve blocks[25]
- Overhydration
- Time

CSF egress into the epidural space, mild compression of the thecal sac by the epidural blood and secondary increased CSF pressure rostral to the injection, or decreasing the elasticity of the thecal sac. Aspirin, anticoagulant therapy, and nonsteroidal anti-inflammatory drugs all interfere with blood clotting and should be temporarily limited in the periprocedural period, if possible. Detailed postprocedure instructions (TABLE 6-6) are recommended to prolong the duration of relief, although they have not undergone rigorous study.

If leak site(s) or potential leak site(s) are identified, targeted epidural blood patches with percutaneous placement of fibrin sealant ("glue") have the best chance of alleviating the patient's symptoms.[26] This procedure is generally performed with CT guidance and conscious sedation.

Surgery may be needed in cases of a calcified disk or osteophyte causing a dural defect. Leaking meningeal diverticula can be ligated or clipped. Larger dural defects are closed with a muscle or fat pledget, with gelatin sponge and fibrin sealant, or sutured.[26] Suturing may be less successful in patients with thin and friable dural composition. Lumbar dural reduction surgery is occasionally employed in otherwise refractory cases.[29] Transient rebound intracranial hypertension is possible after successful closure of a spinal leak and can generally be managed medically. Intrathecal saline or artificial CSF infusion is a temporizing measure that is incorporated in patients with coma or a decreased level of consciousness, indicative of brain herniation.[30]

Prognosis

Once a leak has been successfully treated, the prognosis is generally good. However, leaks can recur, and new leaks may develop, particularly in patients with underlying connective tissue disorders.

Postprocedure Instructions Following Epidural Blood Patches TABLE 6-6

Bedrest and light activity only for 24–48 hours after the procedure

Unless medically necessary, avoid nonsteroidal anti-inflammatory drugs for at least 48 hours

Patients requiring anticoagulation who were transitioned to enoxaparin sodium may resume enoxaparin sodium 12 hours after the procedure

For the first 4 weeks:

- No lifting more than 4.5 kg (10 lb)
- Avoid straining to have a bowel movement; patients who are prone to constipation should take a stool softener (sennosides, docusate sodium, fiber supplementation)
- Do not bend over to lift objects, tie your shoes, or pick something up; either ask someone else to help you or, if you must bend over, do so from the knees rather than the waist
- Avoid activities that cause twisting of the trunk, such as golf, tennis, canoeing, kayaking, yoga, martial arts, mopping, vacuuming, or contact sports
- If you engage in sexual activity, you should be on the bottom

After 4 weeks, you may gradually increase your activity level as tolerated; however, activities that require heavy lifting, straining, or trunk rotation (see above) may increase your risk of developing another leak and should be kept to a minimum if possible

Chiropractic manipulation or adjustment and similar procedures should be avoided indefinitely as they can tear the dura; massage is acceptable after the first week

KEY POINTS

- CT myelography performed immediately after the instillation of intrathecal contrast is the preferred technique for detecting fast leaks in cases of spontaneous intracranial hypotension; delayed MRI myelography is more sensitive for detecting slow leaks.
- Close collaboration with a neuroradiologist who is experienced in the diagnostic imaging modalities, interpretation of findings, and interventional treatments of spontaneous intracranial hypotension is imperative.
- A retrospinal fluid collection at C1-C2 is a false localizing sign of a spinal CSF leak.
- A nontargeted lower thoracic or lumbar high-volume epidural blood patch is successful in alleviating symptoms in about 30% of patients with spontaneous intracranial hypotension. However, the symptoms may recur over time.
- Of the neurointerventional procedures for spontaneous intracranial hypotension, targeted epidural blood patches with fibrin sealant have the best chance of alleviating the patient's symptoms.
- Headache is the most common symptom of pseudotumor cerebri syndrome and may persist after other symptoms resolve and the CSF pressure normalizes.

PSEUDOTUMOR CEREBRI SYNDROME

The pseudotumor cerebri syndrome primarily affects children and adults younger than age 50. Boys and girls are equally affected until puberty, when the female preponderance manifests.[31] For the most part, the clinical presentation in teenage girls with pseudotumor cerebri syndrome is similar to adult women with the disorder. The etiology is unknown.[32] Many secondary causes have been associated with pseudotumor cerebri syndrome such as exogenous agents, obstruction to cerebral venous outflow, endocrine disorders, obstructive sleep apnea, and head trauma (TABLE 6-7).[34] When no secondary cause is identified, the syndrome is termed idiopathic intracranial hypertension (IIH), which most commonly affects women of childbearing age who are obese. As pseudotumor cerebri syndrome potentially causes blindness, early recognition and treatment are essential. Headache is the most common presenting symptom of pseudotumor cerebri syndrome and often persists for years after the other symptoms resolve and the CSF pressure normalizes.[35–37]

Clinical Features

The diagnostic criteria of pseudotumor cerebri syndrome are listed in TABLE 6-8. A definite diagnosis requires the presence of papilledema, normal level of consciousness, normal MRI (including ventricular size) except for signs referable to intracranial hypertension, and a lumbar puncture with an opening pressure measurement and normal CSF composition confirming the diagnosis. In the absence of papilledema or an abducens palsy, the diagnosis can only be suggested if neuroimaging criteria are met.

Headache is the most common symptom, present in approximately 80% to 90% of patients at diagnosis, and is frequently the initial symptom. No distinguishing characteristics of the headache occur, although it often represents a new or different headache and may be quite severe. In the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) that prospectively studied 165 patients newly diagnosed with papilledema and mild visual field loss from IIH (perimetric mean deviation from –2 dB to –7 dB on Humphrey automated perimetry), headache was present in 84% at the baseline visit.[38] Headache phenotypes, characterized using the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria,[39] were migraine (52%), probable migraine (16%), tension-type headache (22%), probable tension-type headache (4%), and unclassifiable (7%). Of the participants, 68% described frontal pain that was either pressurelike or throbbing, but many also experienced posterior (39%), ocular (47%), and neck pain (47%); 36% reported global pain, and 30% had unilateral pain. Migraine-associated symptoms were common and included photophobia (70%), phonophobia (52%), nausea (47%), vomiting (15%), and worsening with routine physical activity (50%). Participants indicated substantial to severe headache disability as measured by the six-item Headache Impact Test (HIT-6) questionnaire, and concurrent photophobia significantly worsened the HIT-6 score. The mean headache frequency was 12 days in the month prior to study entry, with 23% having constant, daily head pain.[40]

Most enrollees in the IIHTT with headache also had other symptoms suggesting a secondary cause, such as constant visual loss (34%), transient visual obscurations (68%), diplopia (22%), and dizziness (53%). However, 14% of those with headache had none of those symptoms despite having papilledema. Of all enrollees, intermittent or daily pulse-synchronous tinnitus occurred in

Causes of Pseudotumor Cerebri Syndrome and Commonly Associated Conditions[a]

TABLE 6-7

Primary Pseudotumor Cerebri Syndrome

- **Idiopathic intracranial hypertension**

Secondary Pseudotumor Cerebri Syndrome

- **Cerebral venous abnormalities**
  - Cerebral venous sinus thrombosis
  - Jugular vein obstruction
- **Decreased CSF absorption from previous intracranial infection or subarachnoid hemorrhage**
  - Increased right heart pressure
  - Superior vena cava syndrome
- **Associated with systemic venous hypertension**
- **Medications and exposures**
  - Antibiotics (tetracycline family, fluoroquinolones, nalidixic acid)[33]
  - Vitamin A and retinoids (including isotretinoin, all-transretinoic acid, hypervitaminosis A)
  - Hormones
    - Human growth hormone
    - Thyroxine (in children)
    - Leuprorelin acetate
  - Anabolic steroids
  - Withdrawal from chronic corticosteroids
  - Lithium
  - Chlordecone
- **Medical conditions**
  - Endocrine disorders (Addison disease, hypoparathyroidism)
  - Hypercapnia (sleep apnea, pickwickian syndrome)
  - Anemia
  - Renal failure
  - Turner syndrome
  - Down syndrome

CSF = cerebrospinal fluid.

[a] Modified with permission from Friedman DI, et al, Neurology.[34] © 2013 American Academy of Neurology.

52% of patients and was most frequently bilateral (66%).[37] Daily nonpulsatile tinnitus occurred in 23% of patients. Back pain, including radicular pain, was experienced by 53% of the study cohort. Occasionally, IIH is diagnosed in asymptomatic patients (often children) when papilledema is discovered during a routine ophthalmic examination.[41]

Headaches arising from pseudotumor cerebri syndrome may cause nocturnal awakening and may worsen in high altitude or in recumbence. Young children with pseudotumor cerebri syndrome may not be able to articulate their symptoms, which must be inferred by manifestations such as behavior change, decline in school performance, malaise, withdrawal, light avoidance, apparent inability to see well, decreased appetite, or vomiting.

Papilledema from pseudotumor cerebri syndrome may be asymmetric and is sometimes difficult to discern with direct ophthalmoscopy, so ophthalmologic consultation is recommended. However, misdiagnosis is possible even using more sophisticated techniques of evaluating the optic nerve.[2] The diagnosis of pseudotumor cerebri syndrome in patients without papilledema is challenging

TABLE 6-8 **Diagnostic Criteria for the Pseudotumor Cerebri Syndrome**[a]

1 Required for Diagnosis of Pseudotumor Cerebri Syndrome[b]

- **A** Papilledema
- **B** Normal neurologic examination except for cranial nerve abnormalities
- **C** Neuroimaging: normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used
- **D** Normal CSF composition
- **E** Elevated lumbar puncture opening pressure (≥250 mm CSF in adults and ≥280 mm CSF in children [≥250 mm CSF if the child is not sedated and not obese]) in a properly performed lumbar puncture

2 Diagnosis of Pseudotumor Cerebri Syndrome Without Papilledema

- **A** In the absence of papilledema, a diagnosis of pseudotumor cerebri syndrome can be made if B–E from above are satisfied and, in addition, the patient has a unilateral or bilateral abducens nerve palsy
- **B** In the absence of papilledema or sixth nerve palsy, a diagnosis of pseudotumor cerebri syndrome can be suggested but not made if B–E from above are satisfied and, in addition, at least three of the following neuroimaging criteria are satisfied:
  - **i** Empty sella
  - **ii** Flattening of the posterior aspect of the globe
  - **iii** Distention of the perioptic subarachnoid space with or without a tortuous optic nerve
  - **iv** Transverse venous sinus stenosis

CSF = cerebrospinal fluid; CT = computed tomography; MRI = magnetic resonance imaging.
[a] Reprinted with permission from Friedman DI, et al, Neurology.[34] © 2013 American Academy of Neurology.
[b] A diagnosis of pseudotumor cerebri syndrome is definite if the patient fulfills criteria A–E. The diagnosis is considered probable if criteria A–D are met but the measured CSF pressure is lower than specified for a definite diagnosis.

and potentially problematic. Papilledema may not be present in patients with preexisting optic atrophy, in cases of recurrence, or in patients with mild disease who were not evaluated for disc edema at symptom onset (which may have been years prior).

Of the 165 participants in the IIHTT, 67 had a self-reported history of migraine, which is more than twice the expected prevalence in the general population.[37,38] This may ultimately lead to uncertainty about the etiology of headaches in patients with pseudotumor cerebri syndrome in the long-term. However, the visual disturbances of pseudotumor cerebri syndrome are different from those that occur in migraine.

Transient obscurations of vision are brief episodes of visual loss in one or both eyes that are often precipitated by arising after bending over. They may also be provoked by eye movement or occur spontaneously. The visual loss may be complete ("black out" or "white out") or partial, often described as cloudy or foggy. The episodes last seconds to a few minutes (shorter than typical migraine aura) and may occur many times during the day. These episodes were one of the most disabling symptoms reported by participants in the IIHTT, likely because of their unpredictability.[42] Diplopia in pseudotumor cerebri syndrome is binocular, meaning that the patient sees double only when viewing from both eyes simultaneously. Reflecting abducens palsy, most patients with double vision experience horizontal diplopia that is worse at a distance and is usually constant. It is extraordinarily uncommon for diplopia to occur in the absence of papilledema in the initial presentation of this condition. Other visual symptoms include subjective visual loss (eg, blurred vision, scotomas, dimness, decreased peripheral vision) and visual distortion (if associated macular edema is present). Flashes of light (photopsia) lasting seconds to hours may be similar to those experienced by patients with migraine and are generally provoked by headache, postural change, darkness, fatigue, eye closure, or watching television.[43] The daily occurrence of photopsia was more common in patients with pseudotumor cerebri syndrome than in controls.[43] However, patterned positive visual phenomena, such as fortification spectra or scintillating scotomata, do not occur in pseudotumor cerebri syndrome. Eye pain does not reliably distinguish pseudotumor cerebri syndrome from migraine or controls.[43] Functional (psychogenic) visual loss may occur and, in one study, was more common in patients with IIH who did not have papilledema.[44,45]

Other symptoms of pseudotumor cerebri syndrome may be quite similar to those of spontaneous intracranial hypotension. Tinnitus can occur with either condition, although pulse-synchronous tinnitus suggests pseudotumor cerebri syndrome. Hearing loss or a "high altitude" sensation, neck pain, dizziness, and back pain are common to both disorders.

Prolonged elevated intracranial pressure from pseudotumor cerebri syndrome may cause bony erosion at the skull base with a subsequent empty sella and CSF rhinorrhea or otorrhea. Because patients with skull base CSF leaks from pseudotumor cerebri syndrome have largely "self-decompressed," their CSF pressures tend to be only minimally elevated prior to intervention, and papilledema is absent.[46,47] Similarly, rupture of spinal diverticula from increased intracranial pressure may lead to spontaneous intracranial hypotension, which reverts to a high-pressure syndrome when the spinal leak is repaired (CASE 6-2).

KEY POINTS

- When present, the headache of pseudotumor cerebri syndrome is heterogeneous in phenotype, severe, and disabling.
- The presence of pulse-synchronous tinnitus and transient obscurations of vision supports a diagnosis of pseudotumor cerebri syndrome.
- A history of migraine was over twice as common in participants in the Idiopathic Intracranial Hypertension Treatment Trial as in the general population.
- Elevated CSF pressure in patients with pseudotumor cerebri syndrome may lead to skull base CSF leaks or intracranial hypotension.

CASE 6-2

A 46-year-old woman presented with a history of orthostatic headaches that had begun at least 10 years prior to her initial evaluation. The headaches occurred after being upright for 6 to 7 hours and gradually increased to a 7 out of 10 in severity. The pain was located at the top of her head, was sharp in quality, and was associated with nuchal aching; it was daily and constant, relieved only with sleep and traveling to high altitude. Associated symptoms included phonophobia, constant tinnitus, and pulsatile tinnitus (whooshing) when arising in the morning. She also experienced occipital headaches with intrascapular tension and a burning neck pain. The previous year, she had woken up 2 days in a row with a "wet ear" with a halo of blood and clear liquid on the pillowcase. Her headaches worsened after this, although no CSF leak was found on imaging. She took topiramate 100 mg/d for headache prevention.

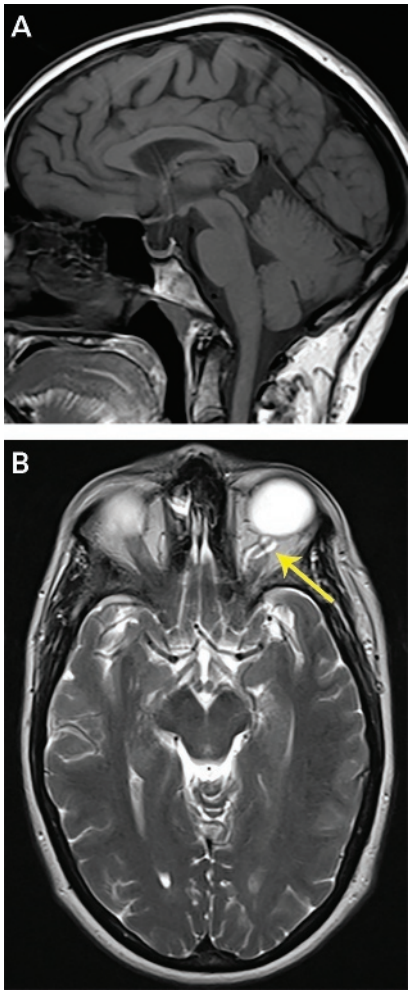

FIGURE 6-4
MRI of the patient in CASE 6-2. *A*, Sagittal T1-weighted image shows an expanded and partially empty sella. *B*, Axial T2-weighted image reveals flattening of the posterior sclerae and a tortuous optic nerve (*arrow*) with distention of the perioptic subarachnoid space (*left eye shown*).

Lumbar puncture 5 years prior for suspected intracranial hypotension showed an opening pressure of 17 cm CSF. A CT myelogram showed multiple perineural cysts but no CSF leak; her headaches resolved for a month after a nontargeted lumbar epidural blood patch. MRI 2 years prior to her current evaluation had shown an expanded and partially empty sella, flattening of the posterior sclerae, and distension of the perioptic subarachnoid space with normal ventricles and brain parenchyma (FIGURE 6-4). She had Ehlers-Danlos syndrome type A.

Examination revealed a body mass index of 28 kg/m^2 and normal fundi with spontaneous venous pulsations. The Trendelenburg test reduced the headache severity from a 7 out of 10 to a 5 out of 10 in 10 minutes.

An epidural blood patch was performed to target a large perineural cyst at T10-T11 (FIGURE 6-5) with short-lived relief. Topiramate was discontinued for potentially exacerbating intracranial hypotension. She had subsequent blood patches with relief for 5 to 9 weeks. However, 10 days after her last blood patch, she developed a different headache that worsened when lying flat. She awakened with a headache that resolved within 10 to 15 minutes of being upright, then the previous orthostatic headache began 4 hours later. She had gained weight (13.6 kg [30 lb]) after stopping topiramate and related a "lifelong" history of transient visual obscurations upon standing.

Her examination showed mild bilateral papilledema (FIGURE 6-6) with absent spontaneous venous pulsations. A trial of acetazolamide was somewhat helpful although poorly tolerated with nausea and cognitive dysfunction, and therapeutic lumbar punctures were required. She was not a candidate for optic nerve sheath fenestration because of good vision, and shunting was undesirable because of its general limitation for headache treatment and potential for increased complications related to Ehlers-Danlos syndrome. Magnetic resonance venography (MRV) revealed a dominant right transverse sinus with a focal narrowing or arachnoid granulation. The left transverse sinus was small with a focal stenosis. Venous manometry showed a gradient of more than 20 mm across the stenotic area in the right transverse sinus, which was successfully stented, albeit with difficulty due to a congenital fenestration in the sinus. She improved considerably after the procedure, but she continued to have mild symptoms of both high and low CSF pressure during the day.

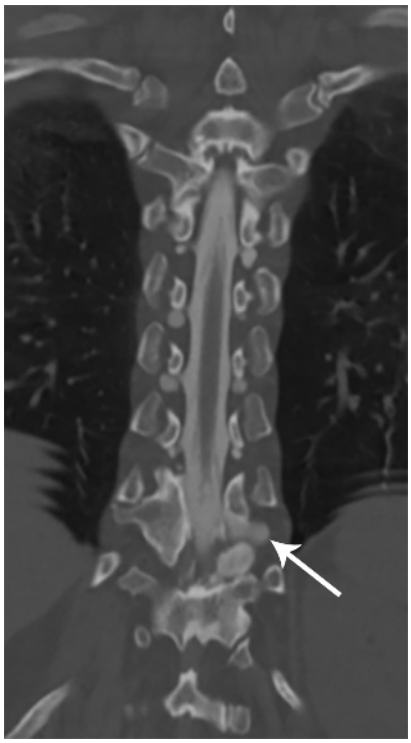

FIGURE 6-5
CT myelography of the patient in CASE 6-2 showing a large, irregular nerve sheath diverticulum at T10-T11 on the left side (*arrow*).

CONTINUED ON
PAGE 1084

Diagnosis

The diagnosis of pseudotumor cerebri syndrome is based on the presence of papilledema or abducens nerve palsy, neuroimaging findings, lumbar puncture opening pressure, and CSF analysis. The status of the patient's vision helps determine the appropriate therapy.

VISION EVALUATION. The importance of visual assessment in pseudotumor cerebri syndrome cannot be overemphasized. Any patient with headache and visual symptoms needs, at a minimum, a measurement of visual acuity in each eye, assessment of visual fields, pupil examination to look for an afferent pupillary defect or poor pupillary reaction, and a fundus examination. Patients with suspected pseudotumor cerebri syndrome should have a complete ophthalmologic evaluation with a stereoscopic viewing of the optic discs and perimetry. Fundus photography, optical coherence tomography, and fluorescein angiography or orbital ultrasound (if the diagnosis of papilledema is uncertain) are helpful to document the disc appearance for subsequent comparison.

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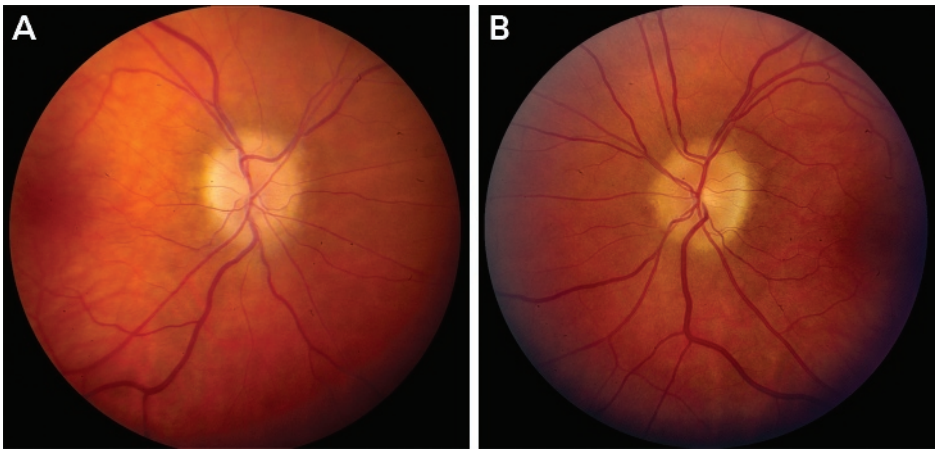

FIGURE 6-6
Fundus image of the patient in CASE 6-2 shows mild optic disc edema in both eyes (*A, right eye; B, left eye*).

COMMENT

This complex case has features of both intracranial hypotension and intracranial hypertension. Considering her brain MRI findings, most likely, the patient's initial problem was intracranial hypertension, with a secondary self-limited skull base leak (otorrhea) and spinal manifestations of intracranial hypotension. Ehlers-Danlos syndrome predisposed her to developing spinal diverticula and a CSF leak. She initially had a good response to epidural blood patches, but her weight gain after discontinuing topiramate caused the intracranial hypertension to recur, producing a "mixed" CSF pressure headache syndrome.

NEUROIMAGING. MRI of the brain with contrast is the imaging test of choice.[48] Orbital images are helpful, although most intraorbital findings can be seen on a high-quality brain image. The T1-weighted midline sagittal images may demonstrate an expanded/empty sella or tonsillar descent. T2-weighted axial images best show flattening of the posterior sclerae, which is assessed at the level where the optic nerves exit the globe. Other findings include distention of the optic nerve sheath complex with enlargement of the perioptic subarachnoid space, tortuosity of the optic nerves, protrusion of the optic nerve head into the vitreous cavity (papilledema), and widening of the foramen ovale. Skull base CSF leaks with meningoceles and meningoencephaloceles may occur.[48]

Brain magnetic resonance venography (MRV) is usually performed simultaneously with MRI to exclude venous sinus thrombosis and determine whether venous sinus stenosis is present. In urgent settings or if MRI is unavailable or contraindicated, contrast-enhanced brain CT with CT venography may be performed.[49]

LUMBAR PUNCTURE. A lumbar puncture is required for the diagnosis. CSF pressure–lowering agents should be discontinued for 24 to 36 hours prior to the lumbar puncture. For the most accurate reading, the opening pressure should be measured with the patient in the lateral decubitus position with the legs at least partially extended; studies in both children and adults suggest that the leg position does not appreciably alter the opening pressure in most cases, but the difference of approximately 10 mm CSF may be meaningful in some patients who have pressures at the upper end of normal.[50]

CSF pressures of 250 mm or greater in adults or 280 mm or greater in children are considered abnormal.[51] Body mass index has a negligible effect on CSF opening pressure, but sedation and Valsalva maneuvers may significantly increase it.[51] Valsalva maneuvers performed during a lumbar puncture can double the opening pressure, which is applicable to patients who are anxious or crying during the procedure.[52] Deeper levels of sedation can also increase the opening pressure, possibly related to hypercapnia, and sedation should be avoided whenever possible in adults and older children.[51] A low-dose benzodiazepine or anxiolytic is preferred if sedation is needed. In children requiring sedation, performing the lumbar puncture immediately after a sedated MRI helps to reduce the number of times that sedatives are administered.[51] No studies support the concept that headache relief following CSF removal proves that intracranial hypertension is the etiology. Also, no evidence suggests that a "large volume" lumbar puncture is warranted, and it may instead cause a spinal headache. A reasonable strategy is to remove enough CSF to achieve a closing pressure in the middle of the normal range.

OTHER TESTS. An evaluation for sleep apnea is recommended in all patients with pseudotumor cerebri syndrome who are obese. As sleep apnea can also occur in individuals of a normal weight, inspection of the pharynx (Mallampati score) and employing a standardized questionnaire to assess sleep apnea risk are also recommended for patients who are not obese and in whom an underlying cause is not identified.

A thorough medical and medication history is needed that specifically inquires about weight gain; medications taken prior to symptom onset (eg, retinoids, tetracycline and related compounds, lithium, treatment for

KEY POINTS

- A comprehensive ophthalmic examination, including perimetry, is of prime importance for patients with suspected or confirmed pseudotumor cerebri syndrome. Confrontation visual field testing is inadequate to detect subtle defects, but the presence of a visual field abnormality on confrontation testing is highly concerning for significant visual loss.
- Body mass index has a negligible effect on lumbar puncture opening pressure.
- The position of the legs during a lumbar puncture has little impact (approximately 10 mm CSF) on the opening pressure, although the most accurate measurement is produced with the patient relaxed and legs extended.
- Sedation and Valsalva maneuvers can substantially increase the CSF opening pressure during a lumbar puncture.
- If the CSF pressure is elevated, remove enough CSF to achieve a closing pressure in the mid-normal range.
- Evaluate patients with pseudotumor cerebri syndrome for obstructive sleep apnea. This process may include screening questionnaires, asking the patient (and bed partner) about sleep apnea symptoms, assessing the Mallampati score, and polysomnography. Treatment of sleep apnea often helps lower the intracranial pressure.

malignancy); and a history of anemia, thyroid disease, or renal disease (TABLE 6-7). Women are evaluated for manifestations of polycystic ovary syndrome, which may warrant an endocrinology consultation. One series showed a high percentage of laboratory abnormalities in patients with IIH such as elevated C-reactive protein (51%), thrombophilia (31%), increased plasma cortisol levels (29%), and elevated lactate dehydrogenase (20%).[53]

Treatment

Patients with asymptomatic papilledema and normal visual function may be followed closely once the diagnosis is established. Causes of pseudopapilledema, such as tilted optic nerves and optic disc drusen, should be excluded. Weight loss is recommended for appropriate patients, and the papilledema usually resolves over time.

The IIHTT demonstrated that acetazolamide was superior to placebo in improving the visual field, papilledema grade, visual quality of life, and general quality of life in adults with IIH and mild visual field loss. The medical regimen was combined with a weight loss program with a goal of losing at least 6% of a patient's body weight.[54] Thus, acetazolamide initiated at 500 mg twice daily and gradually increasing the dosage to 2000 mg twice daily as needed/tolerated is recommended for treatment of such patients.

Other diuretics (not studied in the IIHTT) may be employed in patients who cannot tolerate acetazolamide, including methazolamide, furosemide, bumetanide, or thiazide diuretics. Spironolactone, ethacrynic acid, or triamterene may be used in patients who are allergic to carbonic anhydrase inhibitors, loop diuretics, and thiazide diuretics. Small case series support the use of IM octreotide to induce remission of IIH.[55] Although pregnant women were excluded from participation in the IIHTT, clinical experience supports the use of acetazolamide during pregnancy.[56]

Patients with more extensive visual field loss than was studied in the IIHTT may need additional treatments to reverse visual loss. Therapies may include optic nerve sheath fenestration, a temporary lumbar drain, shunting (ventriculoperitoneal shunting is preferred over lumboperitoneal shunting because of a lower rate of failure and complications), or venous sinus stenting.[57–59] Currently, no evidence-based guidelines recommend one treatment over another, although a randomized trial comparing optic nerve sheath fenestration, maximal medical management, and ventriculoperitoneal shunting is expected to commence in 2018 and is listed on *ClinicalTrials.gov*.[60,61] Other options for patients with sight-threatening disease include IV acetazolamide, IV furosemide, and corticosteroids as temporizing agents. More than one modality may be needed for patients with progressive visual loss or fulminant disease.[62] Weight loss, which may include bariatric surgery, is recommended for long-term management in patients who are obese.[63]

While headache disability improved overall in the IIHTT, no benefit of acetazolamide with regard to headache disability was found compared to placebo. Moreover, no correlation was found between the lumbar puncture opening pressure and headache disability.[38] Therefore, additional treatments may be needed for headache management. No evidence-based guidelines exist for headache treatment in pseudotumor cerebri syndrome, so strategies are similar to those used for primary headache disorders based on the headache phenotype.[64] Among preventive treatments, topiramate and zonisamide have the

potential benefit of facilitating weight loss and have mild carbonic anhydrase activity. Their concurrent use with acetazolamide is generally well tolerated, although symptomatic hypocarbia sometimes occurs. Some enrollees in the IIHTT were treated with a low dose of amitriptyline (up to 50 mg/d) for headache prevention, which did not impede their overall weight loss during the trial; the small number of participants precluded analysis of effectiveness.[38] Medications with weight gain or fluid retention as common side effects must be used with caution and close monitoring. OnabotulinumtoxinA treatment may be useful for patients with a chronic migraine phenotype. No role exists for long-term corticosteroid treatment as corticosteroids result in weight gain, may increase the risk of venous sinus thrombosis, and their discontinuation provokes rebound intracranial hypertension.[65] Most patients will also require acute headache treatments. Indomethacin has a modest CSF pressure–lowering effect but may have intolerable gastrointestinal side effects.[66] Among the nonsteroidal anti-inflammatory drugs, those with a longer duration of action may be less likely to cause medication overuse headache (eg, naproxen, diclofenac). Opioids are occasionally needed initially, but are best avoided in the long-term. Triptans may be used for migrainous headaches.

Medications associated with the development of pseudotumor cerebri syndrome should be discontinued. However, discontinuation alone may not be enough to reverse the process, and therapies to lower the CSF pressure are recommended.[67]

Follow-up and Prognosis

The clinical team caring for patients with pseudotumor cerebri syndrome includes, at a minimum, a neurologist and an ophthalmologist, or a neuro-ophthalmologist. Other disciplines may be involved, such as neurosurgeons, oculoplastic surgeons, neuroradiologists, neurointerventionalists, dietitians, endocrinologists, sleep medicine specialists, headache medicine specialists, and gynecologists. Ongoing communication between team members and the patient's primary care physician facilitates a unified treatment approach. After the initial diagnosis is made, patients need close visual monitoring to incorporate testing mentioned in the diagnosis section of this article. Office visits gradually become less frequent as the patient improves or stabilizes.

Most patients have a good visual outcome, but severe visual loss may occur in up to 10% of patients.[68] In the IIHTT, male sex, high-grade papilledema (often with optic disc hemorrhages), frequent transient obscurations of vision, decreased visual acuity at baseline, and treatment assignment to placebo were associated with a poor prognosis.[69–71] Other poor prognostic factors include profound anemia, renal failure, uncontrolled systemic hypertension, and elevated inflammatory markers. Optic neuropathy with or without coexisting outer retinal changes in the macula (chorioretinal folds, hyperopic shift, hemorrhages, macular edema, subretinal fluid, or neovascularization) as measured by optical coherence tomography correlated with a poor visual outcome in patients with baseline acuity of 20/25 or worse in one study.[71] Transverse sinus stenosis and other MRI changes have no predictive value.[72] Recurrence is possible and is associated with weight gain.[73,74]

Persistent headaches are a major source of morbidity and contribute greatly to decreased quality of life in patients with pseudotumor cerebri syndrome.[42] Both vision-specific and overall quality of life was impaired in

KEY POINTS

- A randomized treatment trial comparing maximal medical therapy with and without ventriculoperitoneal shunting or optic nerve sheath fenestration was funded by the National Eye Institute and is expected to begin enrollment in 2018.
- Although headache disability improved overall in the Idiopathic Intracranial Hypertension Treatment Trial, no benefit of acetazolamide treatment was shown compared to placebo in Headache Impact Test-6 scores. Lowering the CSF pressure does not always result in improvement in headaches; no correlation existed between Headache Impact Test-6 score and lumbar puncture opening pressure at baseline or at 6-month follow-up.
- Many patients with pseudotumor cerebri syndrome require headache treatment in addition to intracranial pressure–lowering therapies. Preventive therapies should be selected based on headache phenotype with attention to side effect profile.
- A team approach is needed for the management of patients with pseudotumor cerebri syndrome, with a neurologist (or neuro-ophthalmologist) directing the coordination of care.

KEY POINTS

- **The visual prognosis in patients with pseudotumor cerebri syndrome is generally good, but up to 10% of patients have permanent severe visual loss. Male sex, high-grade papilledema, profound anemia, renal failure, and uncontrolled systemic hypertension are risk factors associated with a poor visual outcome. Patients who present with loss of visual acuity require aggressive treatment.**

- **Headaches may persist after the CSF pressure is controlled and pseudotumor cerebri syndrome seems otherwise quiescent. This may be related to central sensitization occurring early in the course.**

patients in the IIHTT who had only mild visual impairment prior to the initiation of treatment. Blurred vision, diplopia, transient obscurations of vision, neck pain, a high risk of obstructive sleep apnea, and interference with driving all contributed to reduced visual quality of life in the study. Depression and anxiety are more common in patients with IIH than in age- and weight-matched controls, are frequent comorbid conditions with headache, and may need to be addressed.[75] Thus, a patient-centered, individualized, and multifaceted approach to management is needed.

CONCLUSION

Spontaneous intracranial hypotension is likely underdiagnosed in practice, particularly when the disorder is long-standing and the typical clinical and neuroimaging features recede; patients may have headaches for decades before the diagnosis is considered. Neurologists and headache specialists are more likely to encounter such patients in practice, as individuals with classic symptoms and abnormal imaging are frequently diagnosed and treated by other specialists (eg, neurosurgeons, neuroradiologists). Careful inquiry regarding the onset of symptoms for potential minor trauma, aspects of the headache and other associated symptoms vis-à-vis a postural or circadian component, worsening with Valsalva maneuvers, and assessment of joint hypermobility may be enlightening. In addition to those who have a classic clinical presentation, spontaneous intracranial hypotension should be suspected in patients with headaches that are daily from onset, refractory to "everything," and in those with chronic headaches that do not fit a particular phenotype. The management of patients with spontaneous intracranial hypotension requires collaboration with neuroradiologists and neurosurgeons with expertise in the disorder. Identification of the leak site is often elusive, and the treatment is challenging.

Pseudotumor cerebri syndrome remains a sight-threatening disorder that continues to be missed acutely because fundoscopy was not performed, emphasizing the need for ophthalmoscopic evaluation of all patients being evaluated for headache. A recent study from a large neuro-ophthalmology center indicated that misdiagnoses of IIH are common, largely related to misinterpretation of the fundus findings; as with spontaneous intracranial hypotension, patient care requires a team approach.[2]

The IIHTT provided evidence supporting the use of high-dose acetazolamide, up to 4 g/d, in patients with mild visual field loss. However, data from the IIHTT also indicate that controlling the intracranial pressure alone may not improve headache disability, so neurologists have an important role to play in the management of this symptom that so greatly impacts quality of life. The upcoming surgical trial for patients with moderate to severe visual loss from IIH will be a welcome addition to our evidence base for treatment.

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DISCLOSURE

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