Headache associated with low CSF pressure
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Introduction

This article includes discussion of headache associated with low CSF pressure, aliquorrhea, CSF hypovolemia, CSF volume depletion, hypoliquorrhea, intracranial hypotension headaches, low cerebrospinal fluid pressure headaches, Schaltenbrand headaches, and spontaneous intracranial hypotension. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

In this article, the author reviews new concepts in spontaneous intracranial hypotension. He discusses the role of CSF volume depletion and addresses the substantial variability in the clinical aspects, imaging findings, and CSF abnormalities related to this disorder. Preexisting dural defects, likely related to disorders of the connective tissue matrix, are sometimes seen and contribute to the often complex anatomy of these spontaneous leaks, presenting therapeutic challenges far beyond the expected management of post-lumbar puncture or even post-epidural catheterization CSF leaks. An update with special emphasis on recent advances of the imaging techniques to localize CSF leaks and treatment options is provided.

Key points

• Spontaneous intracranial hypotension is characterized by an orthostatic headache accompanied by neck stiffness, tinnitus, hypacusia, photophobia, or nausea.
• Spontaneous intracranial hypotension is caused by spontaneous spinal cerebrospinal fluid leaks, resulting in intracranial hypotension or “hypovolemia.”
• Spinal CSF leaks can be localized with heavily T2-weighted magnetic resonance myelography, computed tomographic myelography, radionuclide cisternography, or gadolinium-enhanced magnetic resonance myelography.
• The treatment of choice is epidural blood patches, preferably delivered at the level of spinal CSF leaks; fibrin sealant injection and surgical repair are reserved for intractable cases.

Historical note and terminology

Schaltenbrand, a German neurologist, introduced the term “aliquorrhea,” a disorder associated with low, unobtainable or even negative CSF pressures and clinically marked by orthostatic headaches and other features that are now recognized as the clinical picture of intracranial hypotension (Schaltenbrand 1938).

From the 1960s to the 1990s, radionuclide cisternography (Front and Penning 1973; Labadie et al 1976) and conventional myelography emerged as useful and reliable diagnostic tools to demonstrate CSF leaks and help with the study of CSF dynamics. Pachymeningeal enhancement and additional MRI abnormalities in intracranial hypotension were subsequently reported (Sable and Ramadan 1991; Hochman et al 1992; Fishman and Dillon 1993; Pannullo et al 1993). Magnetic resonance imaging of the head and spine has truly revolutionized the diagnosis of spontaneous intracranial hypotension and CSF leaks. Furthermore, it has been realized that an overwhelming majority of, if not all, cases of spontaneous intracranial hypotension result from spontaneous CSF leaks. It has been hypothesized that the main culprit in spontaneous CSF leaks is loss of CSF volume (Mokri 1999). Therefore, terms such as “CSF hypovolemia” or “CSF volume depletion” as well as “spontaneous CSF leaks” have appeared in the literature and have been used interchangeably with spontaneous intracranial hypotension (Mokri 1999; Chung et al 2000; Miyazawa et al 2003). It has been pointed out, however, that “CSF hypovolemia” is a misnomer because hypovolemia denotes a decrease in blood volume (Schievink 2008).
Clinical manifestations

Presentation and course

An orthostatic headache relieved by recumbency is the cardinal symptom of intracranial hypotension (Schaltenbrand 1953; Schievink 2008). This may be a throbbing headache, but often it is nonthrobbing. It may be frontal, fronto-occipital, occipital, or holocephalic. It is often aggravated by Valsalva-type maneuvers and is typically bilateral but sometimes may be unilateral. Indeed, variability is considerable (Mokri 2004). Sometimes, the headaches may have an acute thunderclap-like onset and mimic a subarachnoid hemorrhage (Schievink et al 2001; Famularo et al 2004). Rarely, a paradoxical postural headache may occur and is present in recumbency and relieved in an upright position (Mokri et al 2004). Occasionally, the headaches are primarily or entirely exertional (Mokri 2002a; Wang and Fuh 2005).

In some patients, a “second-half-of-the-day” headache may be seen. These patients are typically headache free in the morning, but by late morning or early afternoon, an increasing headache develops if the patient continues to be up and about. These headaches may have clear or vague orthostatic features (Mokri 2004; Leep Hunderfund and Mokri 2012).

Sometimes, despite documented CSF leaks, low CSF opening pressures, and the presence of typical MRI abnormalities of the disorder, patients have no headaches at all (Mokri et al 2000). On the other hand, not all orthostatic headaches are due to CSF leak or spontaneous intracranial hypotension. For example, orthostatic headache may sometimes be the dominant clinical presentation of postural tachycardia syndrome (Mokri and Low 2003).

Of note, a change in headache pattern should alert the physician to the possibility of development of complications, such as subdural hematoma or cerebral venous thrombosis (Lai et al 2007b; Schievink and Maya 2008).

Clinical vignette

A 37-year-old woman was referred due to an acute orthostatic headache. She had had no known systemic disease and had not been taking any medication on a regular basis. She experienced an acute onset of severe headache after she got up from bed one morning 2 weeks prior to her presentation. It was described as a persistent dull ache in the occipital region and was associated with neck stiffness and muffled hearing. The symptoms were relieved soon after she lay supine and recurred within 5 minutes after she sat erect. There was no photophobia, phonophobia, nausea, vomiting, tinnitus, nasal congestion, or other upper respiratory tract infection symptoms, and she denied having trauma, surgery, or lumbar puncture before the onset. After unsuccessful treatment as migraine or tension-type headache by her family physician, she went to the neurology service of another hospital for help. Spontaneous intracranial hypotension was suspected, although the initial brain MRI did not show the characteristic diffuse pachymeningeal enhancement. She was treated with hydration with intravenous fluids, and generous caffeine intake was recommended. There was little improvement, and she was, thus, referred to our institute. The neurologic examination was unremarkable except for mild neck stiffness. A second brain MRI with contrast on admission revealed characteristic findings suggestive of intracranial hypotension. Heavily T2-weighted MR myelography demonstrated multiple CSF leaks in the cervico-thoracic junction and the upper thoracic regions. An epidural blood patch of 20 ml was delivered at the level of T1-2 and resulted in substantial improvement of her symptoms. She still had a mild to moderate orthostatic headache after the procedure. A follow-up heavily T2-weighted MR myelography demonstrated residual CSF leaks at the level C7-T1, and another targeted epidural blood patch was carried, which resulted in complete and sustained resolution of her symptoms.

This case was selected to demonstrate the following:

- The characteristic presentation of an orthostatic headache relieved with recumbency in the absence of previous trauma or lumbar puncture should alert the physician to the possibility of spontaneous intracranial hypotension and prompt a search for spinal CSF leaks.

- Characteristics of brain MRI findings can be trivial and can be easily overlooked. If the initial brain MRI does not provide objective evidence supporting the clinical diagnosis, imaging procedures to demonstrate spinal CSF leaks, such as heavily T2-weighted MR myelography, CT myelography, or radionuclide cisternography, and a lumbar puncture to measure the CSF opening pressure should be considered.
• Heavily T2-weighted MR myelography is useful in localizing spinal CSF leaks. It is non-invasive and radiation-free, and it may be a good alternative to CT myelography to guide placement of targeted epidural blood patches.

**Biological basis**

**Etiology and pathogenesis**

A substantial minority of the patients report a history of trivial trauma, such as coughing, pushing, trivial falls, lifting, sports activities, and the like. That weakness of the dural sac leads to meningeal diverticula; subsequent spinal CSF leaks is an attractive hypothesis, and patients with Marfan syndrome and meningeal diverticula developing spontaneous intracranial hypotension have been reported (Davenport et al 1995; Schrijver et al 2002). A minority of the patients with spontaneous CSF leaks display stigmata of the disorders of a connective tissue matrix (Marfanoid features, hyperflexible joints, hyperextensible skin, etc.) (Mokri et al 2002). However, only dolichostenomelia (disproportionately long limbs), but not the other above-mentioned stigmata, was more common among patients with spontaneous intracranial hypotension (Liu et al 2011). The common belief that meningeal diverticula is more common in such patients has been challenged (Kranz et al 2013). Moreover, it has been shown that the majority of patients do not harbor mutations in \textit{FBN1} gene, encoding fibrillin 1, or in \textit{TGFBR2} gene, encoding transforming growth factor-beta receptor 2 (Schrijver et al 2002; Chung et al 2007; Schievink et al 2008b).

Uncommonly, a dural tear from a spondylotic spur (Vishteh et al 1998; Eros et al 2002; Binder et 2005) or disc herniation (Winter et al 2002; Rapport et al 2003) may cause dural defect and CSF leak.

The majority, if not all, cases of spontaneous intracranial hypotension result from spinal spontaneous CSF leaks, which leads to CSF volume depletion (CSF hypovolemia) (Mokri 1999). That depletion of CSF volume is the sole cause of spontaneous intracranial hypotension has been questioned, as CSF rhinorrhea or otorrhea, which may also cause CSF volume depletion, has rarely, if ever, been associated with typical symptoms and brain imaging findings (Schievink 2008). It was also suggested that even in the presence of cranial CSF leaks, a spinal source should be sought in patients with orthostatic headaches (Schievink et al 2012). Changes that follow CSF volume depletion are responsible for the clinical and MRI abnormalities noted in CSF volume depletion.

**Table 1. Mechanisms of Clinical Manifestations in CSF Volume Depletion**

<table>
<thead>
<tr>
<th>(1) Headaches</th>
<th>Headaches that are often orthostatic are attributed to sinking of the brain and, thus, stretching and distortion of the pain sensitive suspending structures of the brain (Fay 1937; Miyazawa et al 2003; Mokri et al 2004). Nevertheless, a study involving 6 patients failed to demonstrate any difference between supine and upright brain MRIs (Schievink and Tourje 2007). These are thought to result from stretching or compression of the related cranial nerves (Ferrante et al 1998; Grueb et al 2005).</th>
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<tr>
<td>(2) Diplopia</td>
<td>These have been attributed to compression or vascular congestion of the intracranial portion of the optic nerve (Horton and Fishman 1994).</td>
</tr>
<tr>
<td>(3) Visual blurring and visual field cuts</td>
<td>These have been attributed to stretching of the eighth nerve or pressure changes in the perilymphatic fluid of the inner ear (Portier 2002; Oshiro and Fukushima 2003).</td>
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<tr>
<td>(4) Dizziness and change in hearing, decreased hearing, deafness, tinnitus, orthostatic tinnitus</td>
<td>These are attributed to distortion of the pituitary stalk as a result of sinking of the brain (Yamamoto et al 1993).</td>
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<tr>
<td>(5) Galactorrhea and increased serum prolactin level</td>
<td>Headaches that are often orthostatic are attributed to sinking of the brain and, thus, stretching and distortion of the pain sensitive suspending structures of the brain (Fay 1937; Miyazawa et al 2003; Mokri et al 2004). Nevertheless, a study involving 6 patients failed to demonstrate any difference between supine and upright brain MRIs (Schievink and Tourje 2007). These are thought to result from stretching or compression of the related cranial nerves (Ferrante et al 1998; Grueb et al 2005).</td>
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Radicular upper limb symptoms These are attributed to stretching of the cervical nerve roots as the result of sinking and downward displacement of the brain or irritation of the nerve root by dilated epidural venous plexus (Albayram 2002; Mokri 2004).

Encephalopathy, stupor, and coma These have been attributed to diencephalic compression (Beck et al 1998; Pleasure et al 1998; Evans and Mokri 2002).

Cerebellar ataxia and parkinsonism and bulbar manifestations These have been attributed to compression of posterior fossa and deep mid-line structures (Pakiam et al 1999).

Frontotemporal dementia This has been attributed to the compression of frontal and temporal lobes (Hong et al 2002).

Gait disorder This has been attributed to spinal cord venous congestion (Nowak et al 2003), cord distortion, or deformation (Miyazaki et al 1998).

Table 2. Mechanisms of MRI Abnormality

CSF volume depletion leads to the following:

1. Collapse of the ventricles, which may be obvious or subtle.

2. Sinking of the brain that, on MR imaging, is manifested by descent of the cerebellar tonsils (sometimes mimicking Chiari I malformation), a decrease in the size of the prepontine and perichiasmatic cisterns, flattening of the optic chiasm, and crowding of the posterior fossa.

3. Intracranial venous hypervolemia and subdural fluid collections. According to the Monro-Kellie Doctrine (Mokri 2001), given the fact that an intact skull is not compressible and that the brain is not expected to expand, loss of CSF volume has to be somehow compensated. This is accomplished by engorgement of cerebral venous sinuses and dilation of meningeal veins. The latter is the cause of diffuse pachymeningeal enhancement. Engorgement of the pituitary vessels is responsible for pituitary enlargement.

4. Another consequence of CSF volume depletion is partial collapse of the spinal dura, which in turn leads to a compensatory dilation of epidural venous plexus.

Epidemiology"

The actual incidence and the prevalence of the disorder have not been determined. According to a community-based study, the prevalence was estimated at 1 per 50,000 (Schievink et al 1998). An emergency-based study reported an estimated annual incidence of 5 per 100,000 (Schievink et al 2007b). The disorder can occur at any age but is rare in childhood (Schievink et al 2013). The vast majority of patients are adults (peak incidence at about age 40), and there is a female preponderance (female to male ratio of about 2 to 1) (Schievink 2006).

Prevention

Because the pathogenesis has not yet been fully clarified, little is known about prevention.

Differential diagnosis

A patient presenting with a chief complaint of an orthostatic headache relieved with recumbency should alert the physician to the possibility of spontaneous intracranial hypotension. The differential diagnosis could include post-lumbar puncture headache, traumatic CSF fistula, and other primary or secondary headache disorders.

Diagnostic workup

CSF examination may reveal important information. However, considerable variability should be expected (Mokri et al 1995). Opening pressure is typically low (sometimes atmospheric and unmeasurable, occasionally even negative) (Schaltenbrand 1953) but may be consistently within the limits of normal (Mokri et al 1998). However, a correct
diagnosis can usually be made based on characteristic clinical presentation and typical findings on noninvasive MRI techniques, and the need for a spinal tap has been greatly reduced.

Overall a head CT scan is of little help in the diagnosis of this disorder. It is typically negative. Sometimes subdural fluid collections or increased tentorial enhancement may be seen (Pavlin et al 1979; Sipe et al 1981).

Magnetic resonance imaging has truly revolutionized the diagnosis and follow-up of patients with spontaneous intracranial hypotension. Typical brain MRI findings in spontaneous intracranial hypotension include:

1. Diffuse pachymeningeal enhancement
2. Imaging evidence of sinking of the brain
   - Descent of the cerebellar tonsils
   - Decrease in the size of preoptic or perichiasmatic cisterns
   - Crowding of the posterior fossa
3. Subdural fluid collections
4. Engorgement of cerebral venous sinuses
5. Enlargement of the pituitary gland
6. Decrease in the size of the ventricles
7. Elongation of brain stem in anteroposterior plane
8. Collapse of superior ophthalmic veins

Diffuse pachymeningeal enhancement (sparing the leptomeninges) is the most common MRI abnormality. It is diffuse, uninterrupted, non-nodular, and involves the supratentorial and intratentorial pachymeninges. Typically, it is thick and obvious but sometimes is thin (Hochman et al 1992; Fishman and Dillon 1993; Pannullo et al 1993). It has been reported that a normal initial cranial MRI was predictive of poor outcome (Schievink et al 2005). However, it was also found that the timing of brain MRI, rather than the outcome, was associated with this finding, and brain MRI performed later in the course (about 3 weeks after onset) tended to have a higher positive rate (Fuh et al 2008). The mechanism is still unknown. “A fairly thin zone of fibroblasts and thin-walled small blood vessels in an amorphous matrix” on the subdural aspect or pachymeningeal fibrosis and intra- and perivascular granulocyte infiltrate may be found on microscopic examination of biopsy specimens (Mokri et al 1995).

Sinking of the brain, “sagging,” or “descent of the brain” is manifested by descent of the cerebellar tonsils mimicking a type I Chiari malformation, as well as sinking of the opening of the third ventricle aqueduct (“iter”) to a level below the incisural line (Kasner et al 1995; Lin et al 2002). Furthermore, descent of the brain may lead to a decrease in the size of the preoptic and perichiasmatic cisterns, crowding of the posterior fossa, inferior displacement, and flattening of the optic chiasm. It is proposed that decreased mamillopontine distance (< 5.5 mm) and reduced pontomesencephalic angle (< 50˚) may provide supportive clues for diagnosis (Shah et al 2013).

Subdural fluid collections are typically bilateral but may be unilateral and appear over the cerebral convexities. These fluid collections are usually hygromas that may reveal variable signal intensity depending on the concentration of protein in the fluid, although subdural hematoma may sometimes develop and cause significant mass effects (Lai et al 2007b).

Engorgement of cerebral venous sinuses is frequently noted (Bakshi et al 1998). The venous distension sign, distension of the midportion of the dominant transverse sinus with a convex appearance on T1-weighted sagittal MRI, is useful in the detection of intracranial hypotension (Farb et al 2007). The diameter of the superior ophthalmic vein on contrast-enhanced T1-weighted coronal MRI was reported to be correlated with intracranial pressure (Lirng et al 2003), and collapsed superior ophthalmic veins might provide additional clues for intracranial hypotension (Chen et al 2003).

Enlargement of the pituitary gland can be obvious and may mimic pituitary adenoma or pituitary hyperplasia (Alvarez-Linera 2000). Decreased intersheath space of the optic nerve has been reported as well and probably also results from
reduced CSF content (Rohr et al 2010), and a similar finding has been demonstrated with sonography (Dubost et al 2011).

Conventional spinal MRI abnormalities include the following:

(1) Extra-arachnoid or epidural fluid collections
(2) Meningeal diverticula
(3) Spinal pachymeningeal enhancement
(4) Engorgement of spinal epidural venous plexus

Extra-arachnoid or epidural fluid collections, when present, indicate the presence of CSF leakage (Chiapparini et al 2002). However, such fluid collections often extend across several levels and, thus, do not reveal the exact site of the CSF leakage.

Extravasation and extension of fluid into the paraspinal soft tissues are infrequently seen, and may represent the actual location of CSF leakage. However, when these are seen in the high retro-cervical region, it is claimed that they may not represent the actual site of the leak and may be a false localizing sign (Schievink et al 2004b).

Spinal pachymeningeal enhancement may also be seen, although not as frequently as intracranial pachymeningeal enhancement (Moayeri et al 1998).

Engorgement of epidural venous plexus may be seen at any level of the spine, but typically it is more prominent in mid-thoracic and low thoracic as well as lumbar levels (Chen et al 2002; Chiapparini et al 2002). Generally, although a conventional spinal MRI is helpful in revealing abnormalities that might suggest a CSF leak, it is only occasionally that it reveals the actual site of the leakage of the CSF.

CT myelography has been the gold standard in localizing spinal CSF leaks. This test may show the following:
- Extra-arachnoid leakage of fluid
- Extradural extravasation of contrast (and, therefore, CSF) and its extension into the paraspinal soft tissues
- Meningeal diverticula
- The actual site of the CSF leakage

CT myelography is carried out by performing a myelogram with water-soluble contrast, followed by CT scanning. Slices are typically obtained at each spinal level or at a more selected region if the myelogram itself or a previous cisternography or spinal MRI has revealed clues for potential leakage sites. Under typical circumstances, one would expect to locate the site of the CSF egress and CSF leakage. However, the rate of leakage of CSF may provide special challenges.

A delayed scan may be helpful for slow-flow leaks, and dynamic CT myelography may allow detection of fast-flow leaks (Leutmer and Mokri 2003; Luetmer et al 2012).

Radionuclide cisternography, involving intrathecal injection of indium-111, is useful in establishing a diagnosis of CSF leak. The dynamics of injected radionuclide are followed by subsequent scanning at various intervals of up to 24 or 48 hours. Normally by 24 hours but often earlier, abundant radioactivity is detected over the cerebral convexities. When there is CSF leakage, the radioactivity often does not extend much beyond the basal cisterns. Therefore, on 24-hour or 48-hour images, there is the absence or paucity of activity over the cerebral convexities (Molins et al 1990; Benamer et al 1998; Bai et al 2002).

A more desirable but much less common abnormality is detection of “parathecal” or “paradural” activity, pointing to the site or approximate level of CSF leak. Meningeal diverticula may assume a similar appearance, and they can be confused with actual leakage sites. Multiple parathecal radioactivities do not necessarily correspond to multiple spinal CSF leaks (Mokri 2004).

Another cisternographic finding in CSF leaks is the early appearance of radioactivity in the kidneys and urinary bladder
Normally, such activity is noted at the 6 to 24 hours after the intrathecal introduction of radioisotope. When there is a CSF leak, activity in the kidneys and urinary bladder may be seen in less than 4 hours.

Contrast-enhanced MR myelography or gadolinium-enhanced MR cisternography involves obtaining MRI of the spine after intrathecal gadolinium administration; immediate and delayed images are obtained. This technique might be helpful in the detection of the so-called "slow-flow leaks" (Tali et al 2002; Albayram et al 2008) and might be sensitive and accurate enough to be an alternative to CT myelography (Vanopdenbosch et al 2011). However, it should be noted that none of the gadolinium-containing contrast medium has been approved for intrathecal use.

Exposure to radiation is a concern for radionuclide cisternography and CT myelography, especially for the latter. For patients receiving dynamic CT myelography, which involves multiple scans, the dose of radiation is even higher. The cumulative risk of oncogenicity should be carefully weighed against the benefits because most of these patients are young or middle-aged adults who have a considerable life expectancy (Berrington de Gonzalez et al 2009; Smith-Bindman et al 2009). One study reported evidence of iatrogenic lumbosacral CSF leakage on MR myelography after radionuclide cisternography in a substantial proportion of patients (Sakurai et al 2010). The results indicated that iatrogenic CSF leaks could be a potential pitfall for imaging studies involving a lumbar puncture, such as radionuclide cisternography and, perhaps, CT myelography and gadolinium-enhanced MR myelography/cisternography.

Heavily T2-weighted MR myelography is a non-invasive MRI technique useful in localizing spinal CSF leaks and has emerged as a good alternative to invasive imaging techniques, such as radionuclide cisternography and CT myelography, in the diagnosis and follow-up of patients with spontaneous intracranial hypotension (Wang et al 2005; Katramados et al 2006; Tsai et al 2007). Neither lumbar puncture nor contrast medium administration is needed. The principle of heavily T2-weighted MR myelography is to exaggerate the contrast between the signal of CSF, which appears bright, and those from other tissues, which are either invisible or barely visible, and unlike that on conventional spinal MRI, extravasated CSF in heavily T2-weighted MR myelography is readily discerned from the background. Axial slices throughout the entire spine can provide excellent spatial resolution comparable to CT myelography. It is also a time-efficient technique, for a single-shot fast spin-echo pulse sequence is used, and the entire spine can be imaged in both axial and longitudinal planes within 15 minutes (Tsai et al 2007). As in CT myelography, heavily T2-weighted MR myelography can demonstrate 3 major types of CSF leakages:

1. CSF leaks along the nerve roots: These are the presumed location of dural defects. Extravasated CSF leaks out of the spinal canal along the nerve roots and at times extends into the paraspinous soft tissues. The leaks appear as bright signals extending from the flanks of “sunny side up,” which represent signals from the intradural CSF and the cord, through the neuroforamina. They assume a band- or thread-like appearance and sometimes look like a fimbria, spreading out at the end. They are most commonly seen in the cervicothoracic junction or the upper thoracic spine, and multiple leaks are not uncommon.

2. Epidural CSF collections: Some of the extravasated CSF stays within the spinal column and appears as bright signals alongside the periphery of the “sunny side up.” Epidural CSF collections usually extend for several spinal segments and are not necessarily located in the vicinity of CSF leaks along the nerve roots. The distribution might represent compliance with gravity and can be misleading in localizing the actual location of dural tears.

3. High-cervical extraspinal CSF collections: They appear as patchy bright signals, which may be confluent or scattered, outside the spinal canal in the high cervical region. They are mostly on the dorsal side of the “sunny side up,” but occasionally extension to the lateral or even ventral side can be seen. These are well-known false localizing signs and have nothing to do with the actual leakage sites.

It has been demonstrated that heavily T2-weighted MR myelography was comparable to CT myelography in localizing spinal CSF leaks and was a good alternative to CT myelography prior to targeted epidural blood patching. However, its applicability for other targeted treatments, such as injection of fibrin sealant or surgical repair, is yet to be determined (Tsai et al 2008; Wang et al 2009).

Management

Various treatment modalities have been advocated for patients with spontaneous CSF leaks. Some are based on prior experience with post-lumbar puncture headaches, rather than direct experience with spontaneous CSF leaks. These include the following:
There is an intuitive and reasonable tendency to treat the patient initially with conservative measures. Fortunately, many patients recover spontaneously. Bed rest has been traditionally advocated.

Hydration or overhydration, recommended in some of the older studies (Tourtellote et al 1964), is frequently practiced, but its effectiveness has not been definitely established.

Caffeine and theophylline are used by some experts, but most of the evidence derived from studies on postlumbar puncture patients (Feuerstein 1986; Jarvis et al 1986; Camann et al 1990), and the effectiveness is often not impressive.

Although many patients show no improvement with corticosteroids, some do (Gentile et al 2004). Considering the potential serious side effects of long-term corticosteroid therapy, then, this would hardly seem to be a solution to the patient's problem.

Epidural blood patch has emerged as the treatment of choice for those patients who fail an initial conservative management (Gormley 1960; DiGiovanni and Dunbar 1970; Crawford 1985; Szeinfeld et al 1986; Seebacher et al 1989; Berroir et al 2004), and it has been suggested that early epidural blood patching is helpful in the majority of patients (Berroir et al 2004). The effect of epidural blood patch is essentially two-fold. The immediate effect is simply related to volume replacement by compression of the dura. The latent effect is related to the sealing of the dural defect by triggering a focal tissue reaction (Duffy and Crosby 1999). Sometimes, the patient may obtain a near-immediate and lasting effect soon after the procedure. On the other hand, some patients note an almost immediate improvement followed by the recurrence of symptoms and then a latent improvement after days or a few weeks. Moreover, repeated large-volume epidural blood patches may be necessary to achieve symptomatic relief on rare occasions (Mehta and Tarshis 2009). Overall, the efficacy of epidural blood patch in spontaneous CSF leaks is approximately 30% to 35% (Sencakova et al 2001), which is less satisfactory than in intracranial hypotension syndrome following lumbar puncture or epidural or spinal anesthesia (Vilming 1993). This discrepancy is likely attributed to the fact that epidural blood patches are delivered exactly to the site or the vicinity of the dural defects in treating post-lumbar puncture headaches, whereas in spontaneous intracranial hypotension, the blood patches are usually delivered at the lumbar region instead of the CSF leakage sites, especially when the CSF leaks could not be localized. In addition, the anatomy of dural defects in spontaneous intracranial hypotension is more complex. However, some evidence suggests that targeted epidural blood patches, ie, directly placed at the level of identified spinal CSF leaks, may double the response rates as compared to traditionally nontargeted lumbar epidural blood patches (Sencakova et al 2001; Wang et al 2009; Cho et al 2011). With the advent of non-invasive heavily T2-weighted MR myelography, targeted epidural blood patches may be considered as the first-line treatment, directed at the identified spinal CSF leaks in the hope of hastening recovery and limiting development of complications, although more studies are needed before the spectrum of applicability is determined.

Reports on epidural injections of fibrin glue and fibrin sealant are encouraging (Gerritse and van Dongen 1997; Crul et al 1999; Schievink et al 2004a), especially for patients who failed epidural blood patching. However, there have been 2 patients experiencing anaphylactic reactions after fibrin sealant injection in treating spontaneous intracranial hypotension (Schievink et al 2008a).
Epidural infusion of saline has produced various results (Rice and Dobbs 1950; Usubiaga et al 1967; Gibson et al 1988). One might consider this with limited expectations in some of the patients who have failed epidural blood patches and when other measures such as epidural injection of fibrin glue or surgery are not viable options.

Similarly, the experience with intrathecal infusion of fluid in spontaneous CSF leaks is limited. However, on the rare occasions that patients show obtundation or impending coma, this technique may prove helpful in improving the level of consciousness and allowing time to search for the site of the leak and establish a more definitive treatment if no lasting effect is obtained (Binder et al 2002; Weisfelt et al 2002). One would be concerned about potential complications of continuous epidural or intrathecal infusions such as infection.

Surgery in well-selected cases often proves helpful. It may be considered in those patients who have failed less invasive treatment modalities. It is essential that the actual site of the CSF egress be determined by neuroradiological studies before surgery is undertaken. Because the anatomy of the spontaneous leak may be complex, the surgery may not always be straightforward. Sometimes, a surgeon may encounter the CSF that has leaked but may not be able to locate the exact site of the leak. In this type of case, he or she may pack the area with blood-soaked gel foam, muscle, etc. and hope for the best. Sometimes, dural defects are encountered with so markedly attenuated a border that it may not yield to suturing. Other times, meningeal diverticula or dural defects are encountered that surround 1 or more nerve roots and create technical challenges (Schievink 1998). It was recently reported that minimally invasive surgery to correct the leaking meningeal diverticulum may be considered an alternative to conventional open surgical repair, although it is yet to be determined whether this approach is feasible for most patients (Farhat et al 2011).

Outcomes

Many patients with spontaneous CSF leaks make a complete recovery either spontaneously or with conservative management. Many, however, require more invasive therapeutic approaches such as epidural blood patch, epidural injection of fibrin glue, or even surgery. Recurrences may occur in a minority.

A major complication of spontaneous CSF leak is the development of unilateral or bilateral subdural hematomas. As many as 20% of patients may develop subdural hematomas, which may be asymptomatic, or they can increase in size and become symptomatic and create significant therapeutic challenges (Augustin et al 2003; de Noronha et al 2003; Praline et al 2003; Tsai et al 2005; Lai et al 2007b). There have been reports that such subdural hematomas can lead to transtentorial herniation resulting in bilateral posterior circulation infarcts and Duret hemorrhage (de Noronha et al 2003; Chi et al 2007). Drainage or decompressive surgery is not always helpful as paradoxical herniation may occur, and treatment for spinal CSF leaks should be considered before surgical interventions are undertaken (Vogel et al 2010; Ghavanini et al 2013).

Cerebral venous thromboses occur in 2.1% of patients with spontaneous intracranial hypotension, and the majority (85%) involve dural venous sinuses (Berroir et al 2004; Schievink and Maya 2008). Isolated cortical vein thrombosis has also been reported in spontaneous intracranial hypotension (Lai et al 2007a; Lan et al 2007; Wang et al 2007), as well as in intracranial hypotension syndrome following unsuccessful epidural anesthesia (Albayram et al 2009). These patients may have a change in headache pattern (40%), venous infarction, seizure, dural arteriovenous fistula, or even cortical subarachnoid hemorrhage.

Sometimes following treatment of spontaneous CSF leaks, whether by surgery or by epidural blood patch, a symptomatic syndrome of intracranial hypertension may develop (Mokri 2002b). This is usually a self-limiting syndrome that resolves within several weeks or months.

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**References especially recommended by the author or editor for general reading.

**Former authors**

Stephen D Silberstein MD (original author) and Bahram Mokri MD

**Profile**

**Age range of presentation**

02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

**Sex preponderance**

female>male, >1:1
female>male, >2:1

**Family history**

none

**Heredity**

none

**Population groups selectively affected**

none selectively affected
Occupation groups selectively affected

none selectively affected

**Differential diagnosis list**

orthostatic headache
orthostatic hypotension
intracranial hypotension
dural puncture
migraine
subarachnoid hemorrhage
meningitis
idiopathic Chiari I malformation
foramen magnum tonsillar herniation
pituitary tumor
hyperplasia
tension-type headache

**Associated disorders**

Cerebrospinal fluid rhinorrhea
Chiari malformation
Dural tear
Subdural hematoma
Traumatic avulsion

**Other topics to consider**

Activity-related headache
Headache associated with increased intracranial pressure
Headache associated with neurologic deficits and cerebrospinal fluid lymphocytosis

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