Spontaneous intracranial hypotension: The quest for the CSF leak

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Abstract:

Spontaneous intracranial hypotension (SIH) is caused by loss of CSF at the level of the spine. The most frequent symptom is orthostatic headache, which increases in the upright position and subsides after laying down. Neuroimaging plays a crucial role in diagnosing and monitoring SIH, as it provides objective (albeit often subtle) data in the face of variable clinical syndromes and often normal lumbar puncture opening pressure. Spinal imaging aims to classify and localize the site of CSF leakage as a ventral dural leak, leaking spinal nerve root diverticulum, or direct CSF-venous fistula. Searching for this leak can be very difficult, scrutinizing the entire spine for a dural breach often the size of pin. Precisely locating the site of CSF leakage is fundamental to successful treatment, which includes a targeted epidural patch or surgical closure when conservative measures fail to provide long-term relief. Increased awareness of SIH among clinicians highlights the need for dedicated diagnostic and therapeutic guidelines.

Introduction:

Spontaneous intracranial hypotension (SIH) is a debilitating medical condition caused by loss of CSF from the spinal canal. Despite not being considered a serious or life-threatening disease by many, SIH may cause considerable morbidity, result in significant long-term disability, and in rare cases leads to decreased level of consciousness and coma. [1–3]

Our knowledge about SIH has significantly increased over the past decade, and the underlying pathological mechanisms have been elucidated. Nonetheless, there remains some debate with regards to diagnostic criteria and optimal work-up. For example, according to the International Classification of Headache Disorders (ICHD-3), a low opening pressure on lumbar puncture (<6cm CSF) or typical radiological signs of intracranial hypotension (either direct on spinal imaging or indirect on brain imaging) are required for the diagnosis of SIH.[4] Low opening pressure is, however an unreliable marker of the disease since only one-third of patients with confirmed SIH have low opening pressure.[5,6] Neuroimaging is more useful in the diagnostic work-up of patients with suspected SIH. As such, the clinician and radiologist must be familiar with the typical brain and spine imaging findings of SIH, as well as the strengths and weaknesses of the various imaging modalities that may be used at each stage of managing this condition.

In this Review, we provide an update on SIH and its management. We describe the use of brain MRI and spinal work-up for localisation of CSF leaks and highlight challenges that might be encountered. Finally, we evaluate a three-tier therapeutic consensus approach with increasing levels of invasiveness that has been proposed for SIH.

Epidemiology and Clinical presentation:

The estimated incidence of SIH is 5 cases per 100 000 person-years, though growing recognition among health care practitioners and more sensitive diagnostic tests point to a higher true incidence.[7,8] Women are more often affected than men, with a female-male ratio of approximately 2:1.

Most patients with SIH present acutely with classic orthostatic headache, which increases in intensity in the upright position and decreases after laying down. The orthostatic character may become less apparent over time, and more than a third of patients with a longer duration of illness will have non-orthostatic, non-headache complaints, making correct diagnosis more challanging.[6] Non-orthostatic forms of headache include thunderclap, non-positional, exertional, cough-related, and "second-half-of-the-day" phenotypes.[9] Thus, during clinical work-up, characteristics of the initial headache phenotype should be evaluated, and any patient with unexplained chronic headache should be evaluated for potential SIH.

The table includes potential differential diagnoses for patients presenting with orthostatic headache and key clinical clues. SIH was misdiagnosed in up to 94% of patients in the early 2000s, most commonly as migraine, meningitis, psychological disorder, or even malingering.[10] Patients with SIH often suffer severe impairment of quality of life and/or psychological distress, and often they have been referred to several physicians prior to accurate diagnosis and effective treatment.[11]

The clinical manifestations of SIH are thought to result from increased efflux of CSF in the upright position, leading to traction on pain-sensitive fibers within the dura mater. Additional symptoms such as diplopia, dysgeusia, and vestibulo-cochlear disturbances may also occur and are related to brain sagging and traction on the cranial nerves. This phenomenon is due to the decrease in buoyant force normally provided by the CSF, which under physiological conditions reduces downforce of the brain and uplifts the structures despite gravity.[12]

Alternatively, vestibulo-cochlear disturbances may result from negative intracranial pressure transmitted through the patent cochlear aqueduct and perilymph leading to endolymphatic hydrops and Meniere's disease. Additionally, enlargement of the pituitary gland or the pituitary venous plexus, hyperprolactinaemia, galactorrhea, and other endocrine disorders have been reported in patients with SIH.[13]

Although the clinical and imaging findings may be similar, the distinction between SIH and iatrogenic forms of intracranial hypotension (including surgical interventions, lumbar punctures, and spinal anesthesia) is important since the clinical course and management differ.

Causes and risk factors

Three types of CSF leak have been described (figure 1). Type 1 leaks are typically ventrally located dural slits due to an osteodiscogenic microspur (calcified disc protrusion or spondylophyte) penetrating the thecal sac. Type 2 leaks are leaking spinal nerve diverticula. Type 3 leaks are direct CSF-venous fistulas (CSFVF).[14] Type 1 and 2 leaks typically lead to CSF effusion from the intrathecal into the epidural compartment resulting in a spinal longitudinal extradural CSF collection (SLEC) [15], whereas CSF-venous fistulas typically do not.[14]

The site of CSF leakage remains occult in some patients with typical signs of intracranial hypotension on brain imaging despite multimodal spine investigations. Much of this discrepancy likely reflects incompletely sensitive myelographic techniques, though hypercompliance of the thecal sac, CSF hyperresorption, and thrombosis of the inferior vena cava have been proposed as possible alternative pathomechanisms for SIH in some patients.[16] There is no evidence for an association between SIH and CSF leaks at the level of the skull base.[17] Under physiologic circumstances, the CSF pressure in the intracranial compartment is less than the atmospheric pressure in the upright position. Consequently skull base defects are aggravated by lying down, and usually do not leak when the patient is upright.[18]

Patients with genetic connective tissue disorders, such as Marfan syndrome or Ehlers-Danlos syndromes, are at higher risk of spontaneous spinal CSF leaks.[19,20] In the absence of disease-modifying treatments for the connective tissue abnormalities, most SIH referral centers do not routinely perform genetic testing in patients with SIH.

Associated morbidity

There is increasing evidence for associations between SIH and other morbidities initially not thought to be linked. For example, intracranial hypotension may lead to formation of subdural hematomas, most likely due to injury of bridging veins that have been stretched by the sagging brain.[21] While decompressive craniotomy might be required in severe cases, it will not treat the underlying cause and repeat craniotomy will often be necessary. Closure of the underlying CSF leak, in contrast, often leads to resolution of the subdural fluid collections. Especially when (bilateral) subdural hematomas are discovered in non-geriatric patients or those with no history of trauma, SIH should be high on the differential diagnosis and spine MRI should be performed as part of the search for a spinal CSF leak.

On rare occasions, SIH patients might present with decreased level of consciousness eventually leading to coma.[22] The mechanisms proposed in the literature include transtentorial herniation with compression of the diencephalon and traction on cerebral sinuses resulting in deep venous thrombosis.

A link between SIH and superficial siderosis has been reported by several authors.[23,24] The proposed mechanisms include stretching and bleeding of bridging veins or, in the presence of extradural CSF in the spine, repeated intraspinal hemorrhage at the level of the dural dehiscence. A long-standing history of untreated SIH seems to be present in most patients, with a mean time between symptom onset and imaging evidence of superficial siderosis of 19.6 years.[25]

Ventral herniation of the spinal cord may occur on the basis of a ventral dural defect secondary to a calcified disc protrusion, as in some spinal CSF leaks, with the result being a transdural protrusion of the adjacent spinal cord.[26] Other associated morbidities include non-convulsive status epilepticus, or cognitive decline (frontotemporal brain sagging syndrome).[27,28]

Diagnosis

A careful diagnostic evaluation of patients who are clinically suspected to have SIH is crucial, noting that imaging abnormalities are central to the ICHD-3 criteria/definition (efigure 1). The armamentarium of diagnostic tools may be divided according to degree of invasiveness (non-invasive vs. invasive), imaging modality (MRI, CT, fluoroscopy, ultrasound), and whether the study provides direct (spine) or indirect (brain, optic nerve, renal pelvis opacification) evidence of leakage. Brain MRI which is usually performed first in patients presenting with new onset headaches, followed by spinal imaging to detect and localize a CSF leak (Figure 3). Additional diagnostic tools include lumbar infusion testing, optic nerve sheath ultrasound and intrathecal gadolinium enhanced spine MRI.

Brain MRI

Several abnormalities may be observed on brain imaging of patients with SIH. These generally result from intracranial CSF loss and compensatory increase in the blood compartment, resulting in hyperemia.[15,16] Typical findings include subdural fluid collections, enhancement of the pachymeninges, engorgement of venous structures, pituitary hyperemia, and sagging of the brain (known as SEEPS).[10]

However, the number of brain imaging signs required for the diagnosis of SIH has not been clearly defined, and reliable cut-off values for quantitative signs are lacking.[29] Although smooth generalized dural enhancement is almost pathognomonic in a patient, no single imaging sign is specific for SIH. Pituitary enlargement is an unreliable sign of SIH, since the gland size varies according to age and sex or an underlying infiltrative process, such as hypohysitis or adenoma.[30] A particularly important distinction is the low-lying cerebellar tonsils Chiari malformation (a congenital condition that may be treated by posterior fossa decompression) versus that of SIH (an acquired condition too often made worse when Chiari surgery is inappropriately pursued).[31] Low-lying cerebellar tonsils are a possible imaging feature of SIH (usually in very severe mid brain sagging) but can be unreliable. For instance,

in a study including 56 SIH patients with a proven CSF leak, on average the cerebellar tonsils were 5.5 mm above the McRae line (instead of below), indicating the poor prognostic value of this sign.[32] In addition, patients with Chiari malformation have other very important imaging features, are usually diagnosed at a much younger age (type II-IV), and present with different clinical symptoms compared to SIH patients.

A 9-point, brain MRI-based SIH score (bSIH) has been proposed that would allow stratification of the likelihood of finding a spinal CSF leak in patients with clinically suspected SIH (efigure 2).[32,35] The score comprises 3 major and 3 minor signs. The major signs (scoring 2 points each) are pachymeningeal enhancement, engorgement of venous sinus, and effacement of the suprasellar cistern (≤4.0 mm) (eFigure 1). The minor signs (scoring 1 point each) are subdural fluid collection, effacement of the prepontine cistern (≤5.0 mm), and reduced mamillopontine distance (≤ 6.5mm). (eFigure 1) Although the specificity and sensitivity of the score to correctly identify patients with a high likelihood for a CSF leak has been reported to be 81.8% and 88.9%, respectively it is by no means absolute, and some patients with proven spinal CSF have no abnormalities whatsoever on brain MRI.[33]

The bSIH score helps determine if more spinal imaging is warranted, as not every patient with orthostatic headache should be subjected to multiple myelograms with their attendant invasiveness, potential for adverse reactions to intrathecal contrast, relatively high radiation exposure, and burden on the health care system. The bSIH score may also serve as a reliable and quantitative tool for monitoring response to therapy. A recent study showed a decrease in bSIH score after surgical closure of the underlying spinal dural leak (6.9 vs 1.3, $P < .001$), implying recovery of an equilibrium within the CSF compartment.[34]

Spine imaging

Identification and precise localization of a CSF leak is the main goal of spinal imaging. Although most leaks have been reported in the thoracic spine and at the cervico-thoracic

junction, the leak can occur anywhere from the skull base to the sacrum, and thus the entirety of the spinal canal must be scrutinized for a dural breach that may be only the size of pin. Multiple imaging modalities may be utilized during the spinal diagnostic work-up. Each has its strengths (spatial/temporal resolution) and shortcomings (radiation exposure, patient positioning/cooperation).

If SIH is suggested on brain imaging, the next step should be non-enhanced MRI of the entire spine.[15] The study should include a heavily T2-weighted, fat suppressed, high resolution, 3D sequence (Figure 2) to visualize the dura and screen for the presence of SLEC (SLEC +) vs no SLEC (SLEC –), which guides further diagnostic steps. A static spine MRI has no localizing value and does not replace dynamic imaging. Independent of the MRI sequence, even for experienced readers, the accuracy for CSF leak localization is poor mostly relying on indirect signs (accuracy less than 40%).[35] This lack of localization will prevent an epidural blood patch from being truly targeted, and it precludes consideration of any open surgical repair. The reasons for poor accuracy of leak localization on spine MRI are multiple. First, in SLEC+ patients, the extensive epidural CSF collection usually spans several vertebral levels and cannot be pinpointed to a specific level. Second, apparent CSF collection at the cervico-thoracic junction is a false localizing sign that rarely reflects the actual site of the dural tear.[36] Third, multiple levels suspicious for leak are encountered in most patients, including multiple disc protrusions and nerve root cysts, even though our experience indicates there is only a single site of leakage in the overwhelming majority of patients. Fourth, MRI lacks temporal resolution, even when intrathecal gadolinium (Gd) is used. This is because, between intrathecal Gd application and scan acquisition, the contrast agent has spread or pooled within the epidural compartment and usually spans several vertebral levels. Thus, the diagnostic yield of intrathecal Gd for leak localization is low. Intrathecal use of Gd remains off-label and

has been associated with major adverse outcomes.[37] It should be reserved for highly selected patients when alternative modalities are not available.

The necessity for precise CSF localization arises in case of intractable SIH, not responding to conservative therapy or non-targeted epidural blood patch (ntEBP). In these patients, the next therapeutic options include a targeted epidural blood patch (tEBP) or microsurgical exploration and closure of the dural breach. To have a precise EBP target, and to minimize the extent of the surgical field, pinpointing the site of dural tear to one vertebral level using dynamic imaging modalities with high temporal resolution is mandatory. Conspicuous disc protrusions or large spinal nerve root cysts do not always correlate with the level of CSF leakage, and thus do not obviate the need for dynamic imaging.

SLEC+ indicates a high-flow leak, typically type 1 or 2, and the need for an imaging modality with high temporal resolution. In high-flow leaks, contrast extravasation and pooling in the epidural compartment occur rapidly, extending across multiple vertebral levels within a few seconds after the initial spill. Three dynamic myelography techniques have been described: conventional dynamic myelography (CDM), digital subtraction myelography (DSM), and dynamic CT myelography (DCTM).[38] While the intrathecal administration of contrast and ionizing radiation is common to all techniques, there are important differences. In most dedicated centers, CDM or a DSM is the first dynamic modality of choice, while a few perform primary DCTM.[15,39] With all techniques the moment that contrast first exits the intrathecal space and enters the epidural compartment forming a double contour must be captured in order to confidently localize the level of leakage. (Figure 4, video 1) Briefly, after lumbar puncture iodinated contrast media is applied in the intrathecal compartment. To facilitate caudo-cranial flow of the intrathecal contrast agent, the table is actively tilted into the Trendelenburg position during CDM. (eFigure 3) Alternatively, the patient`s hips are

elevated on a foam pad or pillow to eliminate the lumbar lordosis and allow contrast flow during DSM, DCTM.[40] Images are acquired during contrast injection. The level at which the intrathecal contrast agent starts filling the epidural compartment is the level of the dural dehiscence. Patient positioning may be adapted according to the findings of the previous spinal MRI, prone for suspected ventral osteo-discogenic microspur (type 1 leak) or lateral decubitus for suspected rupture of a spinal nerve root cyst (type 2 leak). If the initial examination fails to demonstrate the precise site of CSF leakage, it may help to narrow down the region of presumed leakage (e.g. excluding the more caudal and well visualized levels) and alter patient positioning during a repeat exam.

A postmyelography CT (PMCT) confined to the level of leakage should be performed immediately after CDM or DSM to identify underlying osseous pathology such as bony spurs of the vertebral endplates or calcified disc protrusions. Because of the time required to transfer a patient from myelogram table to CT scanner, the temporal resolution of PMCT is low and does not generally allow for precise leak localization. PMCT may also provide indirect evidence of CSF leakage. Recent studies have shown renal pelvic opacification on PMCT in patients with a CSF leak or CSFVF compared to non-SIH patients. [41,42] This finding likely indicates increased spinal CSF resorption from the epidural space in SLEC+ patients and direct flow of intrathecal contrast (and CSF) to the bloodstream via CSFVF in SLEC– patients. When postmyleography CT clearly demonstrates leakage of contrast into the epidural compartment, while CDM or DSM fails to localize the site of leakage, DCTM is an important technique and should be considered for leak localization. [43,44] DCTM is particularly helpful in the cervicothoracic junction, where superimposition of bony structures reduces image quality on CDM or DSM. Briefly, during DCTM the region of interest is repeatedly scanned during intrathecal contrast agent injection. (Figure 4)

In patients with SIH but no SLEC (SLEC–), a CSFVF should be considered. CSFVF was first described by Schievink at al. in 2014 and represents a connection between the intrathecal space and a spinal epidural vein that allows CSF efflux directly into the vascular system.[45] Regarding the underlying pathomechanism, the rupture or failure of a spinal arachnoid granulation (SAG), located on the dorsal nerve root sleeve, leading to unregulated CSF resorption into an adjacent radicular vein has been proposed.[46] CSFVF were associated with a nerve root diverticulum in 82% of patients, consistent with this theory.[47] The main imaging modality used for the diagnosis of CSFVF is DSM.[48] Lateral decubitus positioning during DSM has recently been reported to provide a five-fold increase in detection rate of CSFVF.[49] Likewise, lateral decubitus CTM may make CSFVF more conspicuous.[50] Increased diagnostic yield in lateral decubitus is believed to be due to increased contrast concentration in the dependent portion of the thecal sac, including the spinal nerve root cysts where the fistulous connection is usually located. [49,51] Acquiring images during the inspiratory phase of the respiratory cycle has also been suggested to increase the conspicuity of CSFVF. [52] This is likely due to increased venous return to the heart during inspiration ("suction effect") that is transmitted down the inferior vena cava and creates an increased pressure gradient between the intrathecal compartment and the epidural venous plexus. A CSFVF may be appreciated as a tubular opacified structure ("hyperdense paraspinal vein sign") extending from a nerve root sleeve cyst or the thecal sac into the paravertebral space on PMCT. [45,48,53]

Additional diagnostic tools

While lumber puncture opening pressure is an unreliable sign of SIH, lumbar infusion testing may add valuable insight into the dynamics of the CSF compartment. Lumbar infusion was first described by Katzman et al. in the early 1970s, and the technique has since been adapted by others.[54] Briefly, following lumbar puncture, a spinal needle is connected via a 3-way tap to an infusion pump and pressure transducer. The CSF pressure is constantly monitored

during continuous sterile saline infusion. The acquired pressure curves in patients with a CSF leak are distinct from those without SIH, including a lower baseline pressure, lower amplitude, slower rise, and delayed and lower plateau pressure.[55] The presence of a CSF leak by definition implies a low resistance to CSF outflow (R_{CSF}). Beck et al. reported that $R_{CSF} \leq$ 5 mm Hg/(ml/min) was predictive of a spinal CSF leak that could later be proven by imaging.[55] This finding has been validated in a larger cohort with a sensitivity and specificity near 80% in the acute phase (symptom duration <10 weeks).[56] With increasing duration of disease, the profile of CSF fluid dynamics normalizes. This process seems to be accompanied by an evolution of the clinical picture into a less violent, atypical headache. Lumbar infusion testing has no localizing value and does not replace imaging studies.

The optic nerve sheath diameter (ONSD) is related to the intracranial pressure and has previously been used to estimate intracranial hypertension.[57] Fichtner et al. proposed a non-invasive dynamic method of measuring the change in optic nerve sheath diameter from the supine to the upright position on ultrasonography—optic nerve sheath ultrasound.[58] With this method, a significant reduction in ONSD by 10.0% was recorded when patients with SIH and orthostatic headache moved from supine to standing, a change not seen in individuals without a CSF leak. Fichtner et al. attributed this "collapse" of the optic nerve sheath to increased CSF loss in the upright position.[61]

Intrathecal administration of gadolinium was first reported in 1999 by Zeng et al,[59] but remains an off-label indication not currently approved by the US Food and Drug Administration. In a study of 103 patients with suspected SIH, intrathecal gadolinium enhanced spine MRI did not significantly improve diagnostic accuracy for detection of

epidural CSF and thus should not be included in routine SIH work-up.[35] As with other non-dynamic spinal imaging methods, this method lacks temporal resolution and is not suited for localization of high-flow leaks. Individual case reports suggest this technique may be useful in refractory cases when other imaging methods fail to localize a low-flow leak or CSFVF.[60]

Considerations for diagnosis in low-resource settings

In countries of low and middle income (LMICs), where advanced imaging techniques might not be available, the important message is for clinicians to consider SIH in the differential diagnosis. Several techniques used during the diagnostic work-up of patients with suspected SIH are widely available and are not cost-intensive, such as optic nerve sheath ultrasound, conventional fluoroscopy, and standard iodine-based contrast agents.

Treatment:

SIH patients should be treated in a multidisciplinary setting by neurologists, neuroradiologists and neurosurgeons. A three-tier therapeutic consensus approach has been proposed for treatment of SIH patients, with an increasing level of invasiveness and reliance on precise leak localization. This approach—in order of increasing invasiveness—includes conservative treatment (bed rest or caffeine), percutaneous treatment with epidural patching (targeted or non-targeted), and surgical or endovascular closure of the CSF leak or fistula. Local practice may vary according to institutional expertise. Moreover, in LMICs, where advanced surgical options might not be available, percutaneous treatment with epidural blood patching could provide relief, is not costly, and can be performed in an outpatient setting.

Conservative treatment:

Anecdotally, bed rest, oral hydration, theophylline, and oral caffeine administration have been proposed for non-invasive treatment of SIH.[61,62] Even though a few small studies have reported symptomatic improvement after conservative management, our clinical experience suggests that the conservative approach is unlikely to provide long-term relief to patients with SIH.

Percutaneous techniques:

Percutaneous therapy is performed often enough to be considered standard of care in SIH. Despite almost half a century of experience with epidural patching technique, there have been no large randomized controlled trials. Moreover, the mechanism of effect remains unclear and of doubtful durability. The efficacy varies significantly depending on the amount and type of

injected substance (autologous blood, fibrin), number of levels injected, and the method of delivery (targeted vs. non-targeted), with response rates ranging from 29% to 90%.[63–67] In addition, inconsistency in patient selection, including patients without spinal imaging, contributes to the inconsistent results.[66] Reports on imaging signs predictive of a good response to epidural blood patching have shown conflicting results[64,66,68]

The efficacy of EBP is related to a "patch effect" suggesting that the injected blood coagulates and forms a plug, sealing the dural hole, thus preventing further CSF leakage.[69] Second, the "pressure effect" when increased pressure in the epidural compartment, elevates subarachnoid CSF pressure by compressing the dura, most likely leading to the immediate effect of EBP. Although some studies claim to perform a target EBP, the method of localizing the level of spinal leakage is not always reliable because of the low accuracy for CSF leak localization on any static spine imaging, including MRI or postmyelogram CT. This poor accuracy is mainly due to lack of temporal resolution and the fact that usually multiple suspicious lesion are encountered, although leakage almost exclusively occurs in a single location.[35] In addition, an extensive CSF collection in the epidural compartment usually spanning several vertebral levels (“false localizing sign”) renders the targeted approach impossible.

A recently published meta-analysis by Signorelli at al. on factors affecting the outcome of epidural blood patching in SIH, including 500 patients from six retrospective studies reported a good response defined as complete remission of symptoms within 48 h after the first EBP in 300 patients.[70] Among various variables available for analysis, none was demonstrated to be statistically significant in affecting the efficacy of EBP. The authors conclude that the current knowledge about EBP in SIH patients is scarce, the existing literature is contradictory, and thus insufficient to provide solid evidence in clinical practice

Most studies reporting on the effectiveness of EBP neglect spinal imaging and merely rely on clinical findings. Currently, there is a lack of evidence demonstrating a permanent sealing of a

spinal CSF leak after an EBP (targeted or non-targeted). However, due to the low rate of adverse effects, easy access, EBP is the first invasive treatment with proven clinical benefit.[66,71]

There are two randomized controlled trials on EBP in SIH patients. The first, comparing CT Fluoroscopy-guided Targeted Autologous Blood and Fibrin Glue Patch with a sham procedure in SIH patients. (clinicaltrials.gov, NCT03276975) Overall, 15 patients were included (8 treatment arm, 7 control arm). Primary outcome was Change in Median (Headache Impact Test-6) HIT-6 Score from Baseline. All patients at the four month time point in the simulated patching arm had crossed over to the EBP arm.

A second study investigated the superiority of the trendelenburg position compared to supine position during 24 hours after an EBP for a SIH. (clinicaltrials.gov, NCT02261792) Overall, 64 patients were randomized, and the results are yet to be published.

Epidural blood patching is less effective for patients with CSFVF. In one series, only 3 of 22 patients with a CSFVF reported symptomatic relief from a combination of autologous blood and fibrin glue at the level of the fistula.[48] In a larger series of 40 patients with CSFVF who underwent blood or fibrin patching, only 1 had a durable response.[72] In contrast, surgical ligation of the CSFVF has been reported to provide immediate symptom relief, but it is much more invasive.[73,74] Brinjikji et al. recently described a novel transvenous approach for CSFVF treatment. Superselective catheterization of the periradicular vein draining the CSFVF, previously identified on DSM, was performed via the azygos/hemiazygos vein. (eFigure 4) The authors embolized the draining vein with a liquid embolic material. Even though the long-term results are not yet available, the technique seems a prudent way to approach

CSFVF. The preliminary results in 5 patients indicated clinical and radiological improvement.[75]

Surgical techniques:

The surgical treatment of SIH depends on the type of CSF leak and, critically, on the ability to pinpoint the site of spinal CSF leakage. Ventral dural leaks (type 1), pose the challenge of accessing the anterior dura. For surgical closure the site of CSF leakage is accessed through a posterior approach. The posterior dura is exposed in a standard fashion by a midline incision, subperiosteal dissection and a subsequent hemilaminotomy. After a dorsal durotomy, the dentate ligament is cut, thereby releasing the spinal cord and allowing a gentle rotation by grasping the free ends of the ligament. After identification of the ventral dural slit, any causative osseous spur penetrating the dural membrane is removed. The dura is sutured and occasionally augmented with an artificial or autologous graft.[76,77] (eFigure 5) Intraoperative neuromonitoring is an important surgical adjunct. In the case of a lateral CSF leak, the dura can usually be sutured via an extrathecal approach, hence a durotomy is not necessary. Prolapsed arachnoid in the axilla of the nerve root is reduced, and the dura is sutured and buttressed with an extradural wrap. Several studies have demonstrated the efficacy of surgical closure of CSF leaks with a symptomatic improvement in up to 95% of cases.[76,78] In cases without clearly localized CSF leaks or CSFVF, palliative surgical approaches have been described, including clipping of large meningeal diverticula, surgical sacrifice of the nerve root and complex vascular vein ligation, and reduction of the lumbar dura.[79,80]

Conclusion and future directions:

Awareness of SIH is growing amongst neurologists, neuroradiologists, and neurosurgeons. The most common symptom of SIH is orthostatic headache, but myriad clinical and radiographic presentations are possible and lead to considerable diagnostic delay and psychological burden. Despite the widely recognized name of the syndrome, CSF hypotension is not a reliable marker of SIH. A rational and meticulous evaluation aims to confirm the presence of spinal CSF leakage, define the type and precise location of such leakage, and provide effective therapy. The key points of this review are summarized in panel 1.

Ongoing research in the field of SIH has increased our understanding of the underlying mechanisms and clarified several future directions. Increased awareness of SIH among clinicians highlights an unmet need for dedicated diagnostic and therapeutic guidelines. A non-invasive tool for CSF leak localization would be desirable, as current diagnostic work-up includes invasive myelography with intrathecal application of contrast agents and ionizing radiation. A randomized trial of EBP for SIH, including SLEC+ patients, could inform the treatment of many patients. Finally, there should be a comparison of early versus delayed treatment of spinal CSF leaks on quality of life. Additional important research questions will undoubtedly surface as our ability to recognize and treat patients with SIH advances.

Panel 1 - Key points:

(1) Low lumbar puncture opening pressure is not a reliable marker of SIH.

(2) The brain SIH (bSIH) score is 9-point, brain MRI-based scale that stratifies the likelihood of finding a spinal CSF leak in patients with clinically suspected SIH.

(3) distinction between SIH and other forms of iatrogenic induced intracranial hypotension (e.g. post-lumbar puncture) is important

(4) Non-enhanced MRI of the entire spine with fat suppression is important to screen for spinal longitudinal extradural CSF collection (SLEC) and guide further diagnostic steps

(5) Most spinal CSF leaks are due to one of three etiologies: (1) ventrally located dural slit due to an osteodiscogenic microspur (calcified disc protrusion or spondylophyte), (2) leaking spinal nerve diverticulum, (3) CSF-venous fistula.

(6) Spinal CSF leaks do not always occur at the level of prominent disc protrusions or from large nerve root

(7) conventional spine MRI has no localizing value, so a dynamic myelography technique with intrathecal contrast is generally required for leak localization

(8) intrathecal enhanced spine MRI is an off-label indication and should only be used for highly selected patients when alternative modalities are not available

(9) bSIH score can be used as a quantitative measure of therapeutic outcome

(10) rapid decrease in bSIH after surgical closure of the underlying spinal dural breach indicates restoration of an equilibrium within the CSF compartment

(11) Epidural blood patching in patients with SIH often fails to provide permanent relief

(12) Surgical repair of spinal CSF leaks can be curative but requires precise pre-operative leak localization

(13) Spinal CSF-venous fistulas typically do not resolve with blood patching and instead

require surgical obliteration or endovascular embolization

(14) consider a spinal CSF-leak in non-geriatric patients with non-traumatic (bilateral) subdural hematoma

Search strategy and selection criteria

We searched PubMed, MEDLINE, PsycInfo, and Embase databases for papers published between Jan 1, 2014, and January 1, 2021, using the search terms “spontaneous intracranial hypotension”, “CSF leak”, “CSF loss”, “CSF venous fistula”. There were no language restrictions. We also identified articles through citations and reference lists, review articles, and the authors’ own publications. The final reference list was generated on the basis of the relevance of papers to the topics that are discussed in this Review.

Conflict of interest statement

The authors declared no conflicts of interest.

Contributors section

TD, LH, JKCG were involved in the drafting of the first version of the manuscript. TD and EIP performed the literature research. The manuscript draft was critically reviewed and edited by all authors.

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Tables:

Alternative Diagnosis	**Clues**
Traumatic CSF leak	History of lumbar puncture, peridural anesthesia, spinal or cranial surgery
Postural tachycardia syndrome (POTS)	Excessive heart rate acceleration and symptoms of cerebral hypoperfusion (not merely headache) upon standing
Migraine	Headache improves with supine position but never goes away within minutes
Benign exertional headache	Precipitated by exertion
Intracranial neoplasm, including colloid cysts	May block CSF flow in the brain, resulting in a major change in CSF pressure when upright
Cerebral venous thrombosis (CVT)	Thromboembolic risk factors MR-Venography and D-Dimer
Cervicogenic headache	Worse with upright posture and head movement
Headache due to sinusitis	Particularly anterior, worsened with Valsalva and bending forward, and may be exacerbated by other changes in position
Idiopathic intracranial hypertension (IIH)	Female predominance, overweight, visual field defects

Figure legends

Figure 1: Three types of CSF leaks. Type 1: typically ventrally located dural slit due to an osteodiscogenic microspur (calcified disc protrusion or spondylophyte) penetrating the thecal sac. CSF leaking into the epidural space Type 2: leaking spinal nerve root cyst. Type 3: direct CSF–venous fistula.

Figure 2: SIH patient presenting with spinal longitudinal extradural CSF collection (SLEC+). (A) Sagittal, T2 weighted image demonstrating a hyperintense signal in the dorsal epidural space, which is difficult to differentiate from epidural fat. (B, C) Sagittal, and transverse, T2 weighted fat-saturated image clearly demonstrating extensive CSF collection in the dorsal epidural space in the thoracic spine and ventral epidural CSF (arrow) in the lower cervical spine. The posterior dura is visible on the sagittal and axial images (dashed arrows).

Figure 3: Flow-chart diagnostic work-up in SIH patients. SLEC - spinal longitudinal extradural CSF collection. CSFVF – cerebrospinal venous fistula. DSM – digital subtraction myelography.

Figure 4: Dynamic CT myelographic image with the patient in prone position. For temporal reference (A+C) unenhanced, (B+E) acquired 15 seconds, and (C+F) 30 seconds after intrathecal contrast agent injection. (B+E) A dural breach on the ventral aspect of the thecal sac at the level T5/6 is demonstrated (arrow). Contract leakage into the epidural space is demonstrated forming a double line. (C+F) 30 seconds after injection, the contrast has already spread within the epidural space spanning several vertebral levels, making allocation in the late phase impossible. Note, the patient has had previous surgery at the wrong level (dashed arrow) one segment cranial to the actual leak point.