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REVIEW ARTICLE

Spontaneous intracranial hypotension: review and expert opinion

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Abstract
Spontaneous intracranial hypotension (SIH) results from spinal cerebrospinal fluid (CSF) leaking. An underlying connective tissue disorder that predisposes to weakness of the dura is implicated in spontaneous spinal CSF leaks. During the last decades, a much larger number of spontaneous cases are identified and a far broader clinical SIH spectrum is recognized. Orthostatic headache is the main presentation symptom of SIH; some patients also have other manifestations, mainly cochlear–vestibular signs and symptoms. Differential diagnosis with other syndromes presenting with orthostatic headache is crucial. Brain CT, brain MR, spine MRI, and MRI myelography are the imaging modalities of first choice for SIH diagnosis. Invasive imaging techniques, such as myelography, CT myelography, and radioisotopic cisternography, are progressively being abandoned. No randomized clinical trials have assessed the treatment of SIH. In a minority of cases, SIH resolved spontaneously or with only conservative treatment. If orthostatic headache persists after conservative treatment, a lumbar epidural blood patch (EBP) without previous leak identification (so-called "blind" EBP) is a widely used initial intervention and may be repeated several times. If EBPs fail, after the CSF leak sites identification using invasive imaging techniques, other therapeutic approaches include: a targeted epidural patch, surgical reduction of dural sac volume, or direct surgical closure. The prognosis is generally good after intervention, but serious complications may occur. More research is needed to better understand SIH pathophysiology to refine imaging modalities and treatment approaches and to evaluate clinical outcomes.

Keywords Orthostatic headache · Spontaneous intracranial hypotension · CSF leak · Cerebrospinal fluid · Epidural blood patch

Introduction

Spontaneous intracranial hypotension (SIH) is an uncommon cause of headache related to low cerebrospinal fluid pressure (CSF) [1, 2]. SIH aroused a lot of interest two decades ago when Baharam Mokri published the first report on pachymeningeal gadolinium enhancement, one of the MRI features of SIH. In Western countries, SIH prevalence and incidence have been estimated at 1:50,000 and 2–5:100,000 people per year, respectively, with the higher in large-scale comprehensive hospital and the lower in local health centre [3]. Female are affected twice to fifth as often as males. The peak incidence is in 30–50 years, although it also occurs in children and the aged [4]. Several conditions can cause intracranial hypotension (Table 1). Approximately 500 mL (0.3–0.6 mL/min) of CSF is daily produced by choroid plexus/ependymal capillaries and absorbed by arachnoid villi into the cerebral venous system [5]. In the horizontal position, CSF pressures at lumbar, cisternal, and presumably intracranial or vertex levels are equal (60–250 mm of H_2O in adults), with daily fluctuations related to variable factors [6]. CSF pressure is related to body mass index (BMI) [4]. In the vertical position, CSF pressure diverges: the vertex pressure becomes negative, while lumbar pressure increases. In healthy individuals, sitting greatly increases CSF pressure with CSF opening pressure values ranging from 320 to 630 mm H_2O [7]. The prevailing pathophysiological hypothesis suggests that SIH results from spinal CSF leak through small spinal dural tears. Spinal leaks can be singular or multiple, and are predominantly found in the cervical or upper thoracic regions. Skull-base leaks are rare in SIH. Leakage causes a decrease in CSF volume [6]. Decrease in

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Table 1 Causes of reduced intracranial pressure

Spontaneous intracranial hypotension (SIH)
Unknown cause
Meningeal diverticula
Connective tissue disorders: Marfan's syndrome, Ehlers–Danlos syndrome, hyperflexible joints, unclassified connective tissue disorder
Spondylitic dural tear
Trivial trauma
Secondary intracranial hypotension
True hypovolemic state (reduced total body water)
CSF shunt over drainage
Traumatic CSF leaks
After surgical procedure
After dural puncture

CSF volume is the SIH core pathogenetic factor (independent variable), while CSF pressures and clinical and imaging changes are dependent variables on CSF volume. CSF opening pressure is normal in a substantial minority of patients [4]. The decrease in CSF volume is balanced by an increase in intracranial venous blood volume and subdural collection. These changes cause pachymeningeal thickening, pituitary hyperaemia, venous engorgement, endolymph hypotension, and brain displacement, with sagging of the cerebellar tonsils and brainstem and brain structures stretching. In the 10–60% of patients without an identifiable CSF leak, SIH might be tentatively attributed to undetectable slow-flow leaks, increased compliance of the lower spinal CSF space, or increased CSF drainage towards epidural veins [6].

Aetiology

Cerebrospinal fluid leakage is the most common feature of intracranial hypotension, and substantial majority of cases had cervical or thoracic localization of CSF leakage, while the specific aetiology of underlying spontaneous CSF leaks remains largely undetermined. Various dural weaknesses, either congenital or contrived (ranging from simple dural tears to multi-level complex meningeal diverticula), allow CSF to leak into the epidural space. Above all, patients with symptomatic intracranial hypotension with a history of dural puncture should be first consideration. Minor trauma, mainly refer to tumble, is reported in 80% patients. In rare case, SIH can be caused by a connective tissue disorders such as Marfan syndrome, polycystic kidney disease, Ehlers–Danlos syndrome Type II, hyperflexible joints (Fig. 1), neurofibromatosis, and Lehman syndrome [8]. Attention should be paid on vertebral osteophytic spur, which can result in dural puncture reported [4]. Bariatric surgery is another possible risk factor for SIH [4]. In addition, other relevant factors include malnutrition, short stature [3]. The triggers for the symptoms can be trivial or minor: coughing, sneezing, coitus, physical exertion, suffocation, exercise and sports, objects collection from the ground even if small, changes in position, insignificant falls, rollercoaster, and neck chiropractic manipulation [9]. Precipitating events were recorded in about 30% of the patients. However, in many cases, a clear triggering factor has not been identified.

Clinical features and diagnosis

Headache is the main and most common symptom of SIH. Pain usually progresses rapidly over a few hours. Thunderclap headache occurs in 15% of cases [10]. The typical headache is bilateral (but headache can be unilateral), gravative, generally occipital–nuchal, orthostatic, and identical to the headache of post-lumbar puncture syndrome. Pain intensity varies from "mild" to "severe", making it impossible for the patient to stand up. The pain gets worse during the Valsalva manoeuvre and during head shaking. Orthostatic headache might worsen after a few seconds/minutes or several hours of the patient being upright, and might improve or disappear after a few seconds/minutes/hours of rest in supine position. The orthostatic nature might become less obvious over time. Some patients with SIH, with the condition becoming chronic, may have chronic daily headache with associated anxiety and/or depression. Occasionally, anxiety may occur for several months after SIH resolution. In rare cases, headache may not be postural but continuous. In our series (over 400 cases), we observed seven patients who had as a single symptom headache induced by Valsalva manoeuvre. Some patients, especially those older than 45 years, report no headache and present with other, mainly cochlear–vestibular, manifestations. In at least 50% of cases, headache is associated with nausea/vomiting, neck stiffness, and cochlear–vestibular signs, which can be triggered/worsened by orthostatic position.

The cochlear–vestibular signs include tinnitus, ear fullness, echoing, or distortion of sounds, hypoacusia, dizziness, or even rotational vertigo. Hearing change is present in our case series in about 70% of patients [11, 13], and, in very rare cases, may be the only SIH symptom or preceding the orthostatic headache onset by a few days.

Less common manifestations include interscapular pain, transient diplopia by oculomotor cranial nerve palsy [13], bilateral retro-orbital pain exacerbated by eye movements (symptom not described in literature and present in about 10% of our cases), numbness or facial pain, weakness or facial spasm, and dysgeusia [6]. Rare manifestations include galactorrhoea [12], central diabetes insipidus (unpublished observed case), interscapular pain, radiculopathy, quadriplegia, involuntary movements, cognitive manifestations

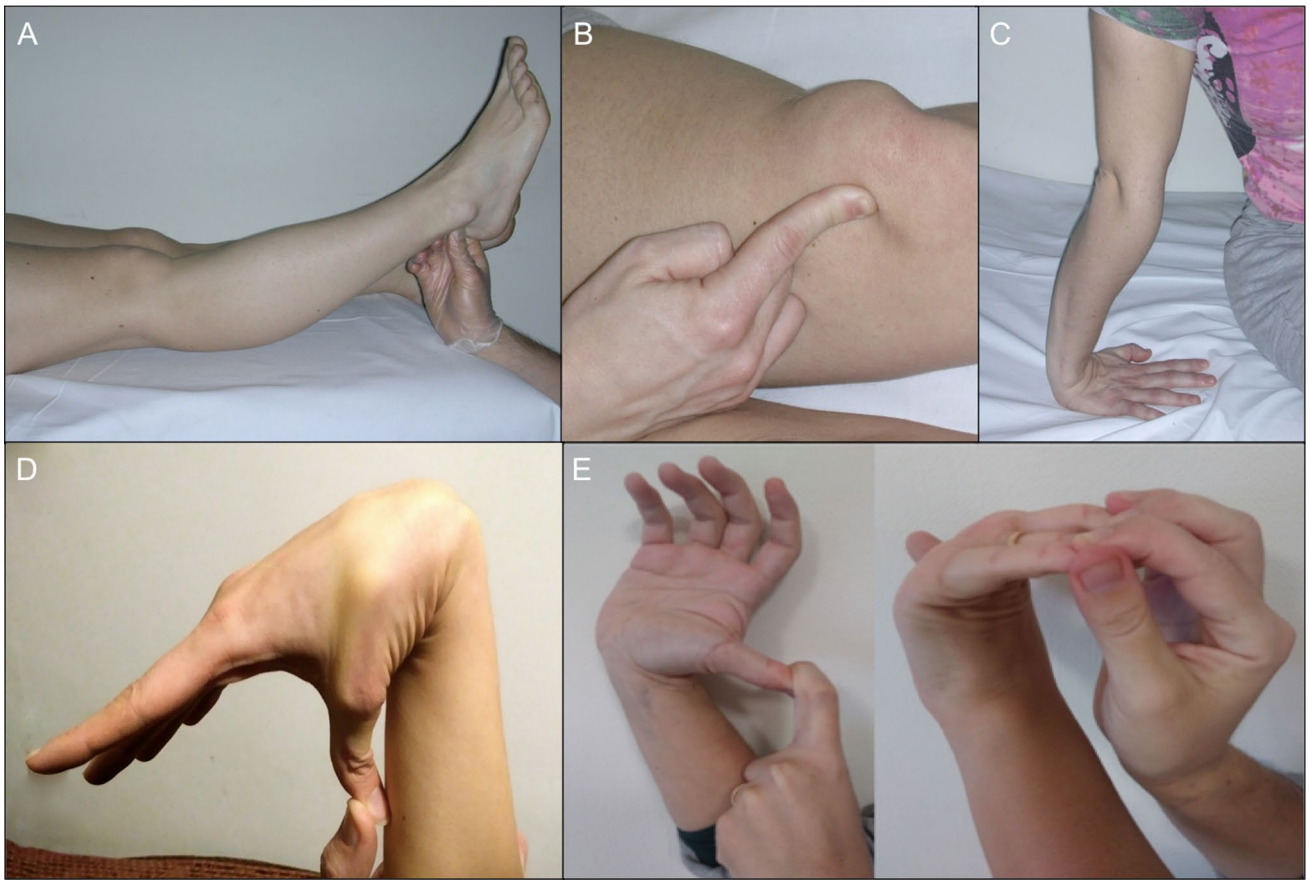

Fig. 1 Joints hypermobility in three different SIH patients. **a** Knee hyperextension. **b** Kneecap displacement. **c** Elbow hyperpronation. **d** Wrist hyperflexion "swan-necked like", the thumb can be bent to touch the forearm. **e**, **f** Fingers hypermobility

[15], epilepsy, and cortical superficial hemosiderosis [16, 28]. Severe brain sagging can also infrequently cause diencephalic herniation with decreased level of consciousness, encephalopathy, or coma [17–27].

One consequence of a decrease in CSF volume by CSF leakage is sinking of the brain. This leads to traction or distortion of the anchoring/supporting pain-sensitive brain/cervical structures (V–IX–X cranial nerve and III cervical nerve included) and, therefore, to headache with orthostatic features [6]. According to Monro–Kellie hypothesis, the CSF leakage reduces the CSF volume and CSF pressure and may give rises to a venous dilatation which likely also plays a role in causing the orthostatic headache via meningeal traction and subdural effusions, hematomas via the rupture of bridging veins [18]. Traction, distortion, or compression of some of the cranial nerves, the brain lobes, brainstem, mesencephalon, and diencephalon are thought to be responsible for the non-headache SIH manifestations. Cochlear vestibular manifestations (e.g., tinnitus, hearing change, and dizziness) may be related to traction of the VIII cranial nerve, but an alternative and more plausible mechanism could be the alteration of pressure in the perilymphatic/endolymphatic inner ear fluid by alteration of the pressure gradient between CSF and perilymphatic fluid that are in contact at the level of the acoustic aqueduct. This would cause an endolymphatic hydrops such as Menière's syndrome [6]. Clinical history alone is often highly suggestive of the diagnosis. Brain MRI with gadolinium is mandatory to confirm the diagnosis. Spinal MRI with MRI myelography sequences may be useful for locating the site of CSF loss. SIH diagnostic criteria have undergone several revisions since 2004 to date. The most recent are described in the third edition of the international classification of headaches (ICHD) [19].

Brain neuroimaging

Brain CT

Brain computed tomography (CT) is often normal and is generally less useful than cerebral MRI, but may show some of SIH signs of SIH, such as engorged transverse venous sinuses, bilateral fluid collections (hygromas or subdural hematomas), small ventricles, obliteration of

the prepontine cistern, and hyperdensity at the level of tentorium or sylvian fissure (subarachnoid pseudo-haemorrhage) [20].

Brain MRI

Brain MRI often shows indirect signs of SIH. These suggestive signs are: diffuse pachymeningeal enhancement (symmetrical and linear), subdural fluid collections, engorgement of venous structures, pituitary hyperaemia, and sagittal sagging. All these features are consistent with the Monro–Kellie hypothesis and are attributable to a loss of CSF volume and a diminution of the normal CSF pressure equilibrium. Brain MRI is normal in about 20% of cases [2].

Pachymeningeal gadolinium enhancement

Diffuse pachymeningeal gadolinium enhancement (Fig. 2a, b) is the most common neuroimaging finding in SIH (80% of cases) and is caused by dural venous engorgement. The enhancement pattern typically spares leptomeninges and is seen diffusely in both the supratentorial and infratentorial spaces. The expansion of the subdural space can also be seen on fluid-attenuated inversion recovery imaging without gadolinium [2].

Subdural fluid collections

Subdural fluid collections occur in about 50% of cases; about 3/5 of these are hygromas and 2/5 are hematomas (Fig. 2c). In particularly severe cases, subdural hematomas may exert a

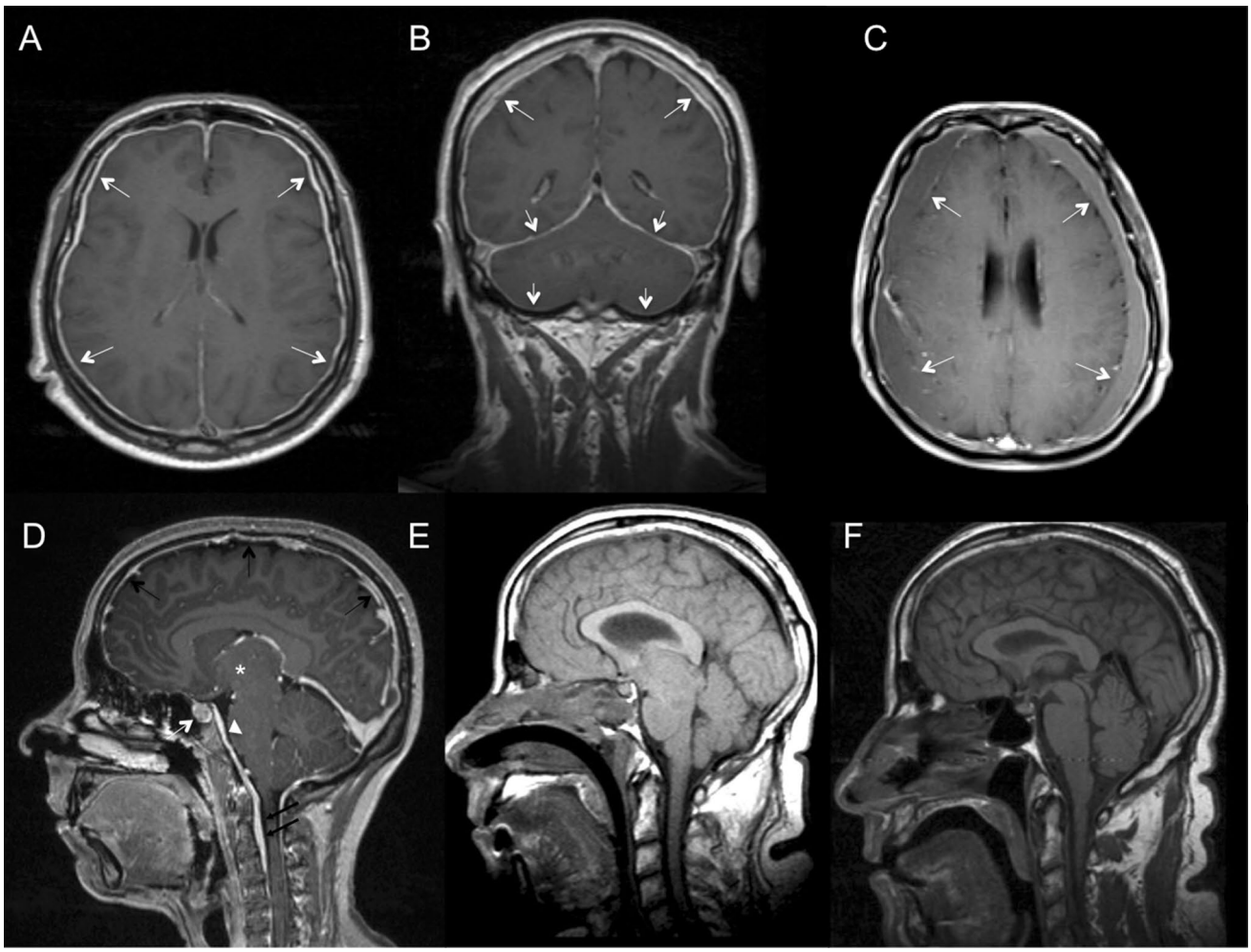

Fig. 2 Brain neuroimaging. Axial (**a**) and coronal T1-weighted (**b**) brain MRI with gadolinium showing diffuse pachymeningeal enhancement (arrows). **c** Axial T1-weighted brain MRI with gadolinium showing bilateral subdural hematomas (arrows). **d** Sagittal T1 weighted brain MRI with gadolinium showing pituitary gland hyperaemia (withe arrow), diffuse cerebral and cervical pachymeningeal enhancement (black arrow), flattening of the pons against the clivus with obliteration of the prepontine cistern (arrowhead), and descent of hypothalamic structures (star). Sagittal T1 weighted brain MRI pre- (**e**) and post-EBP (**f**) in a patient treated at our centre

significant mass effect, prompting neurosurgical evacuation. Fluid collections may also occur in the retro-clival space or overlying the cerebellar convexities [2].

Venous engorgement

Venous engorgement seen in SIH can be subtle. Often, with the exception of the transverse sinus dilatation already visible in the diagnostic phase, it is only retrospectively appreciable when comparing pre- and post-treatment neuroimages. In a neuroimaging study, 93% of SIH patients had a convex inferior border of the dominant transverse sinus, and this resolved to being concave in 100% of those seen at follow-up [2].

Pituitary gland hyperaemia

Pituitary gland hyperaemia (Fig. 2d) leading to imaging enlargement to a height of 8–11 mm may occur and can easily be mistaken for an adenoma. Care must be taken not to confuse this sign with physiologic enlargement as can be seen with pregnancy [2].

Sagittal sagging signs

Signs of sagittal sagging include ventricular collapse, bowing of the optic chiasm, flattening of the pons against the clivus with obliteration of the prepontine cistern (Fig. 2d), drooping of the corpus callosum, and cerebellar tonsillar descent. The degree of sagittal sag is greater than what would be expected from mass effect from the subdural collections [2].

Optic nerve sheath diameter and thickness

Significantly reduced optic nerve sheath diameter (ONSD) and thickness have been shown in SIH. Measured on MRI brain coronal T2 sequences, patients with SIH have a mean ONSD of approximately 3.4 mm (normal is 4.4 mm). The ONSD normalizes after successful treatment. Similar results have been shown with transorbital ultrasonography, making ONSD a promising surrogate for intracranial pressure in this population [2].

Magnetic resonance angiography (MRA)

Magnetic resonance angiography is generally normal; rarely, it can show evidence of reversible cerebral vasoconstriction syndrome (RCVS) [29] or cerebral venous thrombosis.

Spine neuroimaging

Spinal MRI

Spinal MRI might show abnormalities, even in patients with SIH who have normal brain. These abnormalities include cervical pachymeningeal enhancement (Fig. 2d), non-compressive spinal epidural collection (Fig. 3b), fluid collection in soft tissues near the C1 and C2 vertebrae (it could be sometimes a CSF leak false localization sign), meningeal diverticula, dilated nerve root sleeves, and engorgement of epidural venous plexus (Fig. 3h). The main usefulness of a spinal MRI is to identify an area of CSF collection in the epidural space, suggestive of the site of CSF leak. Identification of a CSF leak is often challenging.

Whole spinal MRI from the cranial–cervical junction to the sacrum with T2 fat suppression sequences is a safe, non-invasive, and sensitive technique to identify a spinal CSF leaks. This technique called MRI myelography (Fig. 3c) should be performed as a first-line clinical investigation whenever possible. Invasive imaging techniques that need a dural puncture for injection of contrast media or radioactive tracer are progressively being abandoned. Invasive imaging techniques should be reserved for patients without identified leak on spinal MRI, who have failed to respond to two or three EBPs performed "blindly" and in whom a treatment targeted (EBP or surgery) at the site of a leak is being considered. CT cisternography is now occasionally used in complex cases [7].

Myelography and CT myelography

Myelography (Fig. 3a) and CT myelography may show several abnormalities:

1. Extra-arachnoid fluid that is focal or extending across several vertebral levels (in extreme cases, from cervical all the way to the lumbar level).
2. Meningeal diverticula (single or multiple, various sizes, different levels) may or may not be the site of CSF leakage (Fig. 3g) even when large.
3. Extradural egress of contrast extending into the paraspinal soft tissues (Fig. 3f).
4. Spinal CSF-venous fistula, a new recognized entity [30, 31].

CT myelography is the most reliable test to show the exact site of leak. It also provides an opportunity to measure the CSF opening pressure. The rate of CSF leak may range from very slow to very fast. The two extremes of

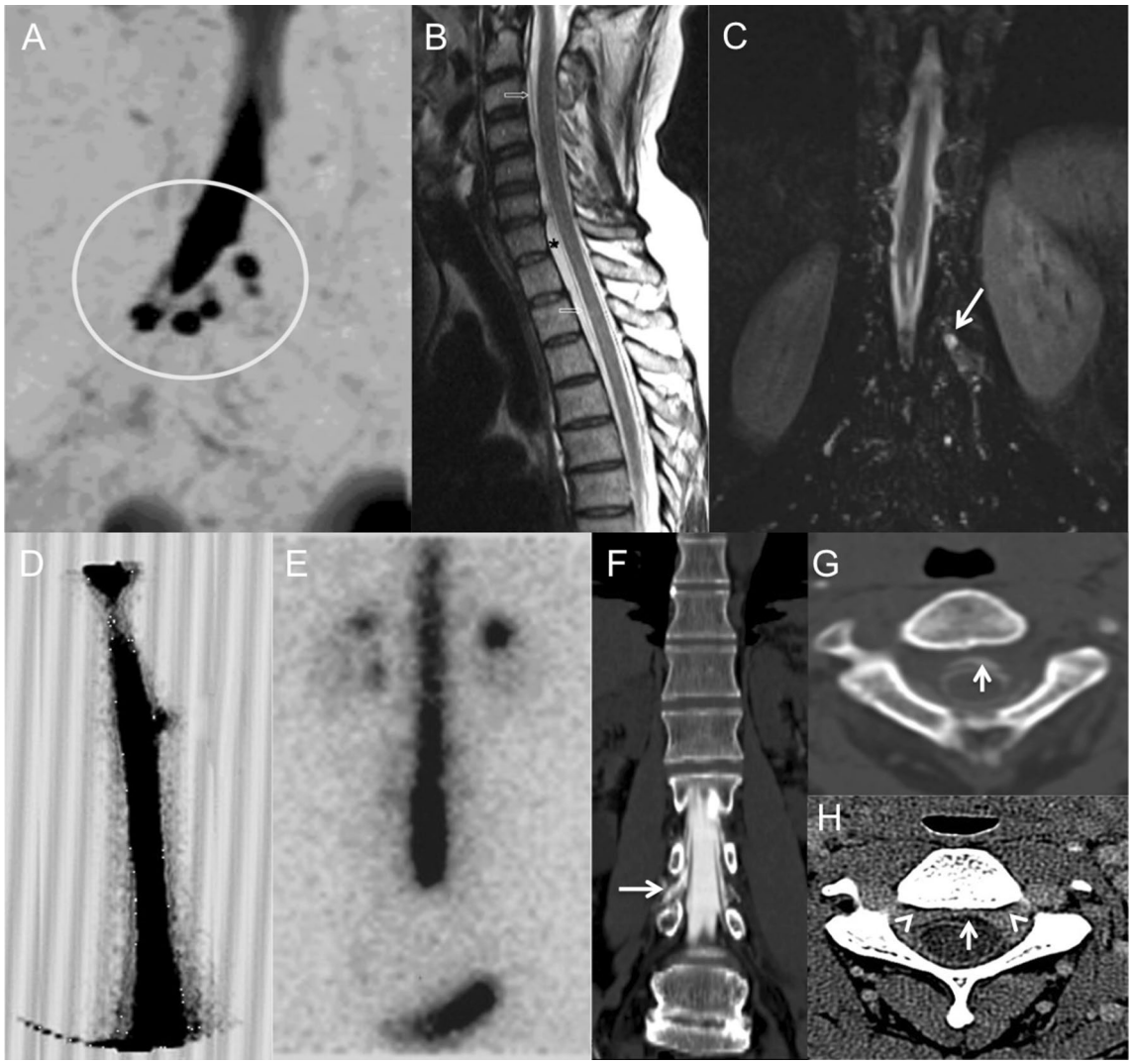

Fig. 3 Spine neuroimaging. **a** Myelography showing multiple sacral nerve roots cysts (within the circle). **b** Sagittal T2-weighted spinal MRI showing CSF epidural collection from C2 to T11 (star). The white empty arrows show the dura mater. **c** MRI myelography showing lumbar CSF leak (arrow). **d** Radioisotope cisternography showing paradural activity at cervico-thoracic junction, site of the CSF leak. **e** Radioisotope cisternography after 4 h showing early appearance of radioactivity in the kidneys and the urinary bladder. **f** Coronal CT Myelography showing extradural egress of contrast extending into the right paraspinal soft tissue at L2 level (arrow). **g** Axial CT Myelography showing cervical CSF leak (arrow). **h** Axial spinal CT with iodinated contrast media showing epidural venous plexus engorgement (arrowheads) and cervical CSF leak (arrow)

rapid flow or slow flow present substantial challenges in locating the actual site of the leak. In rapid-flow leaks, the obstacle may be dealt with by proceeding with high-speed CT scanning of the spine immediately after the intrathecal injection of contrast, bypassing the myelographic portion of the study.

This technique, known as dynamic CT myelography, and its variations have been very helpful in locating the site of the leakage in rapid-flow leaks, as has digital subtraction myelography. In slow-flow CSF leaks, several procedures have been tried, including: (a) delayed CT scanning; (b) intrathecal injection of fluid to elevate CSF pressure from low to normal levels before injection of contrast to increase the likelihood of CSF-contrast extravasation, which the author has referred to as positive pressure myelography. Results have been variable and not strong enough to generate significant enthusiasm; and (c) gadolinium myelography, which is essentially a spine MRI after intrathecal injection of gadolinium. This is sometimes helpful in detecting the site of a slow-flow CSF leak but not as much as initially hoped. This is an off-label use of gadolinium and should be considered only when the diagnosis of CSF leak is highly suspected and when the site of CSF leak has not been detected by other diagnostic techniques such as

CT myelography. Locating the site of slow-flow CSF leaks frequently remains problematic and sometimes quite frustrating for both the patient and the physician. Considering the broad, and growing, clinical spectrum of spontaneous CSF leaks and substantial variability in many of its various aspects, a ''what to do'' algorithm is both important and complex, and will likely become even more complex in the future. Nonetheless, it can still prove useful [7]. In the light of our 25 year experience in the treatment of SIH (over 400 cases treated), we propose an algorithm for diagnosis and managing of SIH (Fig. 4).

Radioisotopic cisternography

Indium-111 is the radioisotope of choice when conducting radioisotope cisternography (Fig. 3d). It is introduced intrathecally via a lumbar puncture, and its dynamic flow is followed by sequential scanning done at predetermined intervals up to 24 or even 48 h. normally by 24 h, but often even earlier, abundant radioactivity is detected over the cerebral convexities.

Early appearance, before the sixth hour, of radioactivity in the kidneys and the urinary bladder is an indirect sign indicating CSF loss (Fig. 3e), as well as the absence of radioactivity over the cerebral convexities at 24 h, which is the most common anomaly during cisternography in CSF loss.

Differential diagnosis

Not all orthostatic headaches are due to a CSF leak. Postural orthostatic tachycardia syndrome (POTS), a form of dysautonomia, can present with orthostatic headache as the most noticeable symptom [32]. Furthermore, there is a possible relation between POTS and Ehlers–Danlos syndrome, because patients affected by Ehlers–Danlos syndrome appear to be at increased risk of both POTS and spinal CSF leaks, and can have both. Diagnosis of POTS is made with

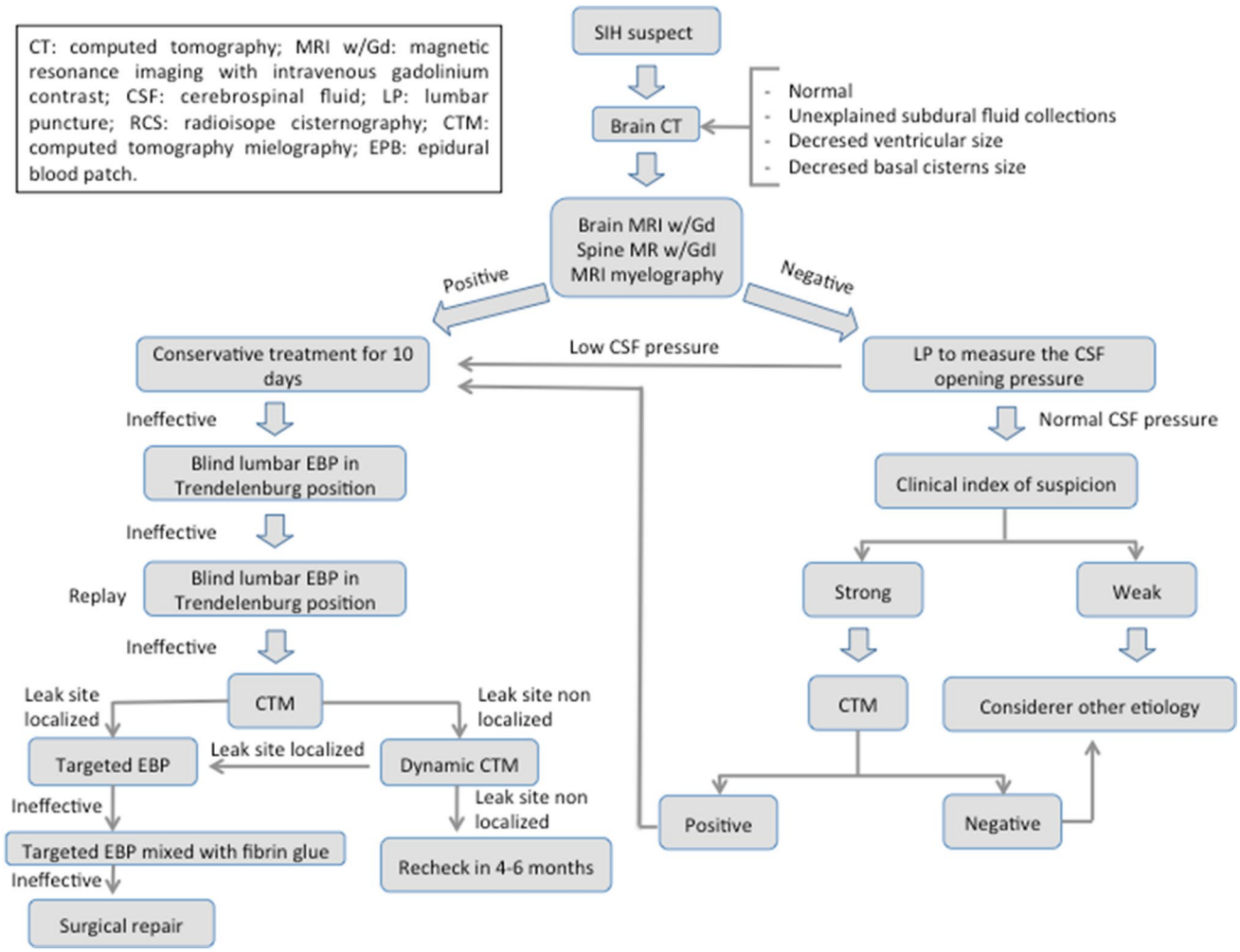

Fig. 4 Algorithm for diagnosis and managing of spontaneous intracranial hypotension (SIH)

autonomic testing. Positional headache may be part of clinical picture in diabetes insipidus, cervicogenic headache, and in post-decompression surgery for Chiari malformation without CSF leak. Moreover, we report few cases with anxiety and/or depression suffering with orthostatic headache [32].

Treatment

No randomized clinical trials have assessed the treatment of SIH, management of SIH relies on observational data and expert opinion [26]. All patients need initial symptomatic management (based on bed rest) to alleviate orthostatic headache and potentially encourage spontaneous closure of a CSF leak [7]. Overhydration is a further usually recommended measure. The corticosteroids efficacy for symptom control is effective, but often partial and with uncertain durability. Considering the potential side effects of prolonged corticosteroid therapy, this does not seem to be a long-term therapeutic solution [4].

Caffeine and theophylline are sometimes used to increase the CSF production, without a proof of efficacy. Compressive abdominal binders, which are thought to reverse the gradient between CSF and venous spaces, are also used without proof of efficacy. In 15–30% of cases, SIH is resolved spontaneously or with only conservative treatment measures within a period of 1–2 weeks from the symptom onset [7]. In our view, when the orthostatic headache persists after 14 days of absolute bed rest, the main treatment option for SIH is a lumbar EBP (Fig. 2e, f). Because the diagnosis is often delayed, many patients have already exhausted the conservative approaches. Since most patients with compelling clinical–radiological signs of SIH have no demonstrable CSF leaks, an EBP can reasonably be performed without previous identification of a leak (so-called "blind" EBP) whenever headache is orthostatic, and after exclusion of another headache trigger [4, 21–23]. The effect of EBP is twofold: (1) an early (sometimes almost immediate) effect related to volume replacement and (2) a latent effect resulting from sealing of the leak. In spontaneous leaks, the success rate for each EBP is variable from 30 to 90% for complete immediate response and no relapse within 6 months. Different approaches to EBP are used, based on local practices, without evidence from randomized controlled trials to prospectively compare these procedures. Blood volumes used range from small (10 mL) to large (50 mL).

When the first EBP does not result in clinical benefit, it is possible to perform one or two additional patches at least 7 days apart from each other. We usually perform "blind" EBP under fluoroscopic guidance with an autologous blood volume ranging from about 30–50 mL mixed with 5 mL of iodinated contrast agent [23, 24]. The volume of blood varies according to patient's anatomy and is mainly limited by local or radicular pain or headache. In our experience, the success of an EBP depends on the adequate volume of blood injected, which has to be sufficient to fill the epidural space, and a on strict bed rest in Trendelenburg position for at least 8 h after the procedure, to allow blood to ascend from the lumbar regions to the CSF leak. After about 20 min after the procedure, we perform a spiral dorso-lumbar CT to visualize the EBP and confirm its correct execution. After discharge, patients are advised to refrain, for about 7 days, from intense physical exercise, Valsalva manoeuvers (forced evacuation or coughing) and long journeys, because a sudden increase in intracranial pressure or vibrations in sitting position might dislodge a stable clot formed [14]. Other therapeutic approaches include blind EBP with mixed blood and fibrin sealant, targeted epidural patch with fibrin glue, surgical reduction of dural sac volume, or direct surgical closure. EBP has a well-documented efficacy for the SIH treatment and the consequent serious complications are rare. Until studies demonstrating clinical efficacy of other therapeutic procedures will not be available, we recommend performing lumbar EBP for SIH treatment after a short period of absolute bed rest and overhydration. Targeted EBP in thoracic or upper cervical regions or surgical approaches could be useful if two or three attempts at a lumbar epidural blood patch of adequate volume, done by a trained operator, and followed by a strict 24 h bed rest, have failed. Such cases should also be submitted to careful multidisciplinary reassessment of the diagnosis [4].

Management of serious complications

Early complications of SIH should be suspected in any patients reporting changes in headache, such as the pain becoming non-postural, which may suggest intracranial hypertension. Cerebral venous thrombosis affects 1% of patients with SIH. In these cases, we suggest to first treat SIH with EBP to remove the cause of thrombosis and subsequently to use oral anticoagulant therapy. Subdural hematomas are not an infrequent complication of SIH, and they are commonly chronic, with or without an acute haemorrhagic component. Subdural hematomas in SIH are generally well tolerated, but evolve unpredictably and have the potential risk of acutely worsening. Cerebral infarction in the basilar artery territory has been described after craniotomy for a subdural hematoma in SIH. In the absence of concomitant treatment for SIH, subdural hematoma can often recur even after surgical evacuation. Therefore, SIH should be treated primarily, or in close temporal relationship with the evacuation surgery [4, 25]. An awareness that serious complications such as coma can arise from SIH is important

so that urgent treatment of the CSF leak can be undertaken [6, 10, 11].

Conclusion

Spontaneous intracranial hypotension is commonly misdiagnosed in clinical practice; patients may have headaches for decades before the diagnosis is considered. Although the most common presenting symptom is orthostatic headache, SIH should be suspected in patients with headaches that are daily from onset and refractory to every medical treatment. Since, in our case series, over 90% of SIH patients reported the exact day when the orthostatic headache started (observed unpublished data), we suggest considering this finding among the SIH criteria. Diagnostic work-up is crucial for both establishing the diagnosis and localizing spinal CSF leaks, to guide the management. Brain MRI with contrast enhancement should be performed in all patients as first-line diagnosis tool, because it may reveal one or more typical neuroimaging features in 90% of SIH cases. However, CT myelography, MR myelography, and digital subtraction myelography are the modalities of choice to identify spinal CSF leaks. Treatments for spinal CSF leaks include conservative approaches, epidural patching with autologous whole blood or fibrin sealant, and surgery. It is, however, known that bed rest, overhydration, and a single blood patch are sufficient to treat the majority of SIH patients. The SIH prognosis is generally good after successful treatment of leaks. However, leaks can recur and/or new leaks may develop in different sites, particularly in patients with connective tissue disorders. In our case series of 400 patients, of which 300 treated using EBP, we reported 15 leaks relapses, of which two cases suffering with connective tissue disorders. We also observed a long-term SIH relapse after 25 years (observed unpublished cases).

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Compliance with ethical standards

Conflict of interest Enrico Ferrante declares that he has no conflict of interest. Michele Trimboli declares that he has no conflict of interest. Fabio Rubino declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent N/A.

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