Intracranial hypotension (IH) is an uncommon, benign, and usually self-limiting condition caused by low cerebrospinal fluid (CSF) pressure, usually due to CSF leakage. The dominant clinical finding is an orthostatic headache. Other common clinical features include fever, nausea, vomiting, and tinnitus.

Magnetic resonance imaging (MRI) plays an important role in the diagnosis and follow-up of patients with IH. Specific MRI findings include intracranial pachymeningeal enhancement, sagging of the brain, pituitary enlargement, and subdural fluid collections.

Intracranial hypotension can mimic other conditions such as aseptic meningitis or pituitary adenomas. Differential diagnosis is important, because misdiagnosis may lead to unnecessary procedures and prolonged morbidity.

MeSH Keywords:  Cerebrospinal Fluid Pressure • Headache • Intracranial Hypotension • Magnetic Resonance Imaging • Meningitis, Aseptic • Pituitary Gland

Background

Intracranial hypotension (IH), first described in 1938 by Schaltenbrand [1], is an important condition with characteristic clinical and magnetic resonance imaging (MRI) findings. It is an uncommon disease, with an estimated incidence of 5 per 100,000 per year [2], and it usually affects young to middle-aged adults, with a female predominance [3].

Intracranial hypotension is of either primary (spontaneous intracranial hypotension – SIH) or secondary origin, e.g. iatrogenic or traumatic. Spontaneous intracranial hypotension is believed to occur as a result of trivial trauma and weakness in the dural sac due to spontaneous dural dehiscence and dural tears caused by degenerative causes. There is also an association with connective tissue disorders such as Marfan and Ehlers-Danlos syndromes [2,4,5]. Secondary intracranial hypotension may be caused by injury of the dura mater, e.g. following cranial or spinal surgery, lumbar puncture, spinal anaesthesia, placement of ventriculo-peritoneal shunts, and craniospinal trauma [2,4].

The aim of this review is to describe clinical, laboratory, and radiological features of patients with IH and to discuss the differential diagnosis and available treatments.

Clinical Features

Intracranial hypotension (IH) is caused by a low pressure of cerebrospinal fluid (CSF), usually due to CSF leakage. On lumbar puncture, the opening CSF pressure is usually low in patients with IH (<50 mmHg), the protein level is elevated, and the levels of glucose and electrolytes are normal [6]. Notably, there is also a rare form of intracranial hypotension in which CSF pressure is normal. For instance, Spero et al. described a woman with IH who had typical clinical and MRI findings and normal CSF pressure [7].
The main symptom of intracranial hypotension is an orthostatic headache that worsens in an upright position, on coughing, laughing, and the Valsalva manoeuvre. It is also resistant to analgetics [4]. Kranz et al. reported that the pattern of headache may change from orthostatic to atypical and constant in patients with chronic IH (average symptom duration: 45.3±59.0 [SD] weeks) [8]. Among other clinical features, there may be impairment of hearing, tinnitus, dizziness, fever, anorexia, nausea, vomiting, photophobia, diplopia, visual field defects, cranial nerve palsies, backache, and neck pain [4,6].

Furthermore, intracranial hypotension may be accompanied by hormonal abnormalities, mainly hyperprolactinemia (usually 20–85 ng/ml, rare >100 ng/ml). According to Schievink et al., elevated prolactin levels might be detected in up to 24% patients with IH. The authors measured pituitary hormone levels in patients with IH, but only the level of prolactin was elevated in more than a single patient, and hyperprolactinemia was detected in 24% patients. Following effective treatment of IH (improvements in clinical and MRI findings), hyperprolactinemia resolved in all patients. According to Schievink et al., hyperprolactinemia in patients with IH is not associated with pituitary enlargement, which occurred in only 29% of patients with elevated prolactin levels (in other studies 6–100%), but it is related to the presence of sagging of the brain [3,9].

A stalk effect hypothesis puts forward that sagging of the brain, which develops due to the loss of buoyant force of CSF, results in stretching of the pituitary stalk and/or hypothalamic region, thereby leading to impaired dopamine delivery to the anterior pituitary and increased prolactin levels. This hypothesis is confirmed by the fact that hyperprolactinemia resolved soon after resolution of clinical symptoms and brain MRI findings in the treated patients with IH [3,10].

It should be stressed also that pituitary hyperaemia or pituitary haematomas can lead to the above-mentioned endocrine disorders [4].

In IH, the loss of buoyant force of CSF, venous engorgement, and sagging of the brain, which lead to traction on cerebral and cerebellar veins, meninges, and cervical nerves, cause headaches. A descent of the brain and venous engorgement are exacerbated in an upright position, which explains the orthostatic pattern of headache [4]. Another theory states that headaches may be caused by secretion of neurotransmitters from the hypothalamus due to sagging of the brain (e.g. orexin) [3,11].

Traction of the bridging veins may cause their rupture and bleeding into CSF, which explains the presence of erythrocytes, high protein level, and pleocytosis in CSF [4].

Disorders of hearing and balance may be explained by a reduction in perilymph volume due to low CSF pressure [12]. Moreover, traction on the cranial nerves may lead to hearing impairment and dizziness (8th cranial nerve), weakness of facial muscles (7th cranial nerve), vision impairment such as horizontal diplopia (6th cranial nerve), and facial numbness (5th cranial nerve) [4].

Fever in IH can be explained by the action of pyrogenic cytokines that are released by endothelial cells and astrocytes following breakdown of the blood-brain barrier due to the loss of CSF pressure or an impaired thermoregulation by the hypothalamus secondary to venous engorgement and mechanical distractions in the diencephalic region and cavernous sinuses [12].

**Diagnostic Imaging**

Typically, IH is caused by leakage of CSF through the spinal dural sac [13]. CSF leakage is broadly divided into three commonly observed patterns: fast leaks, slow leaks, and cases in which no leak is visible despite the presence of other clinical and imaging signs of IH [5]. The majority of leakages are detected in the thoracic region. Active leaks may be identified by radioisotope cisternography; however, it is not a very sensitive procedure. Also, computed tomography myelography (CTM) may indicate the level and the site of leaks. Sensitivity of CT myelography is greater than that of radioisotope cisternography and spinal magnetic resonance imaging (MRI), but this examination is invasive, time-consuming, and more harmful to patients. Therefore, radioisotope cisternography or conventional spinal MRI might be used as guides to determine adequate CT myelography scanning levels [4].

In recent years, an increasing experience has been gathered with respect to MR myelography using intrathecal gadolinium, which combines the benefits of CT myelography with the excellent contrast resolution of conventional MRI. Kranz et al. reported that MR myelography is more sensitive for slow or intermittent leaks than CT myelography, with CSF leaks identified in approximately 20% of patients with no leakages identified on prior CTM. Intrathecal gadolinium administration is an off-label procedure and is not currently approved by the U.S. Food and Drug Administration. In general, it is well tolerated; however, several cases of overdosage resulting in acute neurotoxicity were reported, and the long-term safety of intrathecal gadolinium is unknown. Therefore, intrathecal gadolinium should be used cautiously, and should be reserved for cases in which other myelographic techniques are insufficient [5].

Magnetic resonance imaging in patients with IH reveals brain and spinal abnormalities caused by low CSF pressure. The main MRI finding is a characteristic diffuse pachymeningeal enhancement (Figure 1), which, along with other symptoms such as a headache, fever, nausea, and vomiting, raises a suspicion of e.g. meningitis [12]. To exclude inflammatory causes of pachymeningeal enhancement in IH, meningeal biopsy was performed in 1993 for the first time and revealed no evidence of inflammation but only fibroblasts and small thin-walled blood vessels in an amorphous matrix [14].

Apart from diffuse intracranial pachymeningeal enhancement, MRI may also show sagging of the brain (Figure 2), pituitary enlargement [4], (Figure 3) subdural fluid collections (usually hygromas, less commonly haematomas) (Figure 4), posterior lobe pituitary haematomas, diffuse dural enhancement of the spinal canal, spinal epidural fluid collection (Figure 5) [7], distension of the spinal epidural venous plexus, and abnormal intensity around the root sleeves [13].
In 2004, IH criteria were included in the International Classification of Headache Disorders. To confirm the diagnosis of IH, at least 1 of the following signs must be present: low CSF pressure, evidence of CSF leakage (on CT myelography, conventional myelography or radionuclide cisternography), or diffuse pachymeningeal enhancement on brain MRI imaging [13,15]. However, this classification does not include leakage of CSF through the spinal dural sac, which is the most common cause of IH.

Moreover, a recent retrospective study performed in patients with SIH, who underwent pre-treatment brain MRI, revealed that diffuse intracranial pachymeningeal enhancement may no longer appear in patients suffering from prolonged headaches [8].

The fluid-attenuated inversion recovery MRI sequence (FLAIR) is a noninvasive and convenient alternative to magnetic resonance imaging with gadolinium. FLAIR imaging allows visualization of such anatomic details as brain surface sulci or lesion differentiation in areas close to CSF.
Intracranial liquid collections are one of the major signs of IH. However, in many cases, they cannot be seen on CT or conventional MRI, since they are thin and demonstrate similar signal to CSF in most MRI sequences [16].

Tosaka et al. performed a retrospective study in a small group of patients with IH, in which they focused on FLAIR imaging. The authors noticed a good differentiation of thickened pachymeninges that are hyperintense on FLAIR from CSF that is hypointense on FLAIR. Also, on FLAIR, hyperintense bilateral subdural effusions/haematomas can be easily distinguished from hypointense CSF. Diffuse pachymeningeal enhancement (DPME) is more sensitive than pachymeningeal hyperintensity on FLAIR; however, the latter does not require the use of contrast agents and therefore may be performed in patients with contraindications to contrast agents such as renal insufficiency, allergy, asthma, and pregnancy. Similarly, it is convenient for follow-up after IH treatment [16].

Another consequence of low CFS pressure is the so-called sagging of the brain, whereby effacement or depletion of perichiasmatic and prepontine cisterns, inferior displacement of cerebellar tonsils or optic chiasm, descent of the...
cerebral aqueduct, and effacement of subarachnoid spaces are seen on brain MRI [14].

Due to sagging of the brain, bridging veins in subdural spaces may rupture, resulting in subdural hematomas [4].

Another effect of low CSF pressure and consecutive increase in venous intracranial blood volume is pituitary gland enlargement, which was first described in 1993 by Shimazu et al. [17]. However, there is a considerable discrepancy between different reports, which may arise from differences in the applied criteria and methods. Measurement of the pituitary height can be even more difficult because of gender and age differences and the small size of the gland. Coexistence of pituitary gland enlargement and IH in different studies ranges between 8 and 100% [2].

Pituitary gland height varies from 4.2 to 4.8 mm in healthy, adult, postpubertal, nonpregnant women and is up to 3.5 mm in men. Alvarez-Linera et al. considered gland enlarged when the mean height of the gland was 1.5 times greater than the above-mentioned values [18], while Forghani et al. revealed that pituitary enlargement co-occurs with IH in approximately 43% of cases [2]. According to Sainani et al., it reverses earlier than pachymeningeal enhancement during recovery [4].

Furthermore, there are reports of cases with IH in which small liquid collections in the gland [18] and pituitary haemorrhages were observed, which was first described in an enlarged pituitary gland in 2011 by Spero et al. Haemorrhage is likely caused by rupture of venous vessels, and it may be dangerous by causing certain hormonal disorders [3,19].

Pathology

The typical abnormalities that are found in IH can be explained by the Monro-Kellie hypothesis, which states that the sum of volumes of the brain tissue, CSF, and intracranial blood is constant in an intact cranium [20].

Therefore, low CSF pressure can be compensated for by an increase in the intracranial blood volume through enlargement of dural arteries or dilatation of cortical and medullary veins and dural venous sinuses [4], including the inferior intercavernous sinus [21]. This causes non-nodular enhancement of pachymeninges and sometimes also of dura mater of the spinal cord without leptomeningeal involvement. When compensatory dilatation of blood vessels is insufficient, contrast enhancement of pachymeninges may not occur [4].

Unless enlargement of vessels is sufficient to maintain balance of the intracranial volume, subdural effusions may appear, and they occur most commonly in the fronto-parietal region, are bilateral, crescentic, thin, and do not cause a mass effect. They arise due to CSF extravasation through permeable microvessels of the dura mater [4].

Venous vessels of the spine region are also likely to participate in maintaining balance of the intracranial volume, since they may dilate in IH to compensate for CSF leakage [22]. Distension of spinal epidural venous plexuses, extradural fluid collections, and abnormal intensity around the root sleeves on MRI were already described in the early 2000s [13,22,23].

Watanabe et al. detected spinal MRI abnormalities in 94% patients with IH, including 78% cases of spinal epidural vein distension in the anterolateral epidural space of the upper cervical or thoracolumbar regions, 89% cases of

Figure 5. MR examination of the cervical spine in patients with IH. Sagittal (A) and (B) axial T2-weighted images of the spine demonstrate a hyperintense fluid collection (arrow) in the anterior epidural space at the cervical level.

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epidural fluid collections, and 6% cases of fluid collection along the nerve root sleeves in the thoracic region [13].

**Treatment**

Headaches usually resolve after bed rest and conservative treatment. Lying position decreases pressure in the region of CSF leakage and allows recovery at the site of leakage. Blocking the adenosine receptors with oral or intravenous caffeine and theophylline induces arterial contraction and consequently reduces intracranial blood flow and venous engorgement, which relieves symptoms [12].

Intravenous or oral hydration and steroid therapy also lead to positive outcomes (Figure 6). If this is not enough, autologous epidural blood patch may be administered.
intrathecally, which leads to sealing of the site of leakage with a formed clot. Balkan et al. reported that, in most patients with suspicion of IH, the symptoms disappeared up to 72 hours after blood patch treatment, and after 9 to 10 months, pachymeningeal contrast enhancement was not present on MRI [12].

Eventually, a surgical correction of dural tears or other meningeal defects may be performed [4].

**Differential Diagnosis**

Fever, headache, and irritation of the meninges are generally considered as symptoms of meningitis. If CSF examination does not indicate bacterial meningitis, and a headache has an orthostatic pattern, IH should be considered in the differential diagnosis. Aseptic meningitis may have viral or non-infectious aetiology – malignant, autoimmune, or due to IH. MRI findings can help distinguish between viral meningitis and IH [12].

Differential diagnosis of diffuse intracranial pachymeningeal enhancement includes hypertrophic cranial pachymeningitis, which might be idiopathic or secondary to inflammation (HTLV – human T-cell leukaemia, fungal, tuberculosis, syphilis, Lyme’s disease), collagen vascular disorders (rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, granulomatosis with polyangiitis), brain tumours (meningioma, en plaque lymphoma, carcinoma), and other causes, such as intrathecal drug administration, haemodialysis, mucopolisaccharidosi, sarcoidosis, ventricular shunting, craniotomy [4], but in such cases, pachymeninges are often thinner, nodular, and irregular [24].

Balkan et al. established that orthostatic headaches that coexist with pachymeningitis and imaging evidence of CSF leakage (MRI or CT myelography), and show symptom relief within 72 hours after blood patch administration do not indicate aseptic meningitis [12].

Pituitary gland enlargement caused by IH may mimic pituitary adenoma [18,25].

Cases of surgical resection of enlarged pituitary glands in IH due to misdiagnosis of macroadenoma have been reported [19,26].

Leung et al. performed surgery for an enlarged pituitary gland, assumed to be due to a hormonally inactive macroadenoma, despite the fact that prior to the procedure other signs of IH such as pachymeningeal enhancement, sagging of the brain, and extradural fluid collections were present on MRI [19].

Moreover, Luna et al. removed an enlarged pituitary gland suspected to contain a hormonally inactive macroadenoma in a patient with orthostatic headache and optic chiasm compression symptoms, i.e., visual field defects. A histological examination performed after the surgery revealed normal tissue with no features of adenoma [26].

A dilated inferior intercavernous sinus, which may be associated with intracranial hypotension, may also mimic a focal pituitary lesion. A recent study performed in a small group of patients revealed that 50% of patients with IH had a dilated inferior intercavernous sinus. There was no significant difference in the size of the sinuses compared to a control group [21].

Before deciding to remove an enlarged or affected pituitary gland, IH should be considered, since it is an increasingly recognized cause of distension of this gland and may also induce hormonal disorders, which makes a correct diagnosis even more difficult. The characteristic orthostatic headache and MRI findings should delay the decision to operate.

**Conclusions**

Because IH can occur with normal CSF pressure, and symptoms can exacerbate after lumbar puncture, clinicians and radiologists should be aware of characteristic MRI features of IH such as diffuse intracranial pachymeningeal enhancement, sagging of the brain, pituitary enlargement, subdural fluid collections (usually hygromas, less likely haematomas), posterior lobe pituitary haematomas, diffuse dural enhancement of the spinal canal, and spinal epidural fluid collections. However, it is important to be aware of the low prevalence of diffuse intracranial pachymeningeal enhancement in patients with prolonged atypical headaches due to IH. Absence of dural enhancement may exacerbate the problem of underdiagnosis of chronic IH, since the presence of pachymeningeal enhancement is considered as the main imaging feature of this condition.

Although IH is a benign and usually self-limiting condition, it may mimic other, even life-threatening, diseases. Knowledge of the typical clinical symptoms of IH and careful MRI assessment may lead to a correct diagnosis, thus obviating the need for further, especially invasive, procedures.

**Conflicts of interest**

We declare that we have no conflict of interest.
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