Hindawi
Acta Neurologica Scandinavica
Volume 2024, Article ID 9355884, 10 pages
https://doi.org/10.1155/2024/9355884

Research Article

Spontaneous Intracranial Hypotension: Long-Term Follow-Up

Vlasta Vukovic-Cvetkovic,[1] **Henrik W. Schytz**,[1] **Emil Andonov Smilkov**,[2] **and Rigmor H. Jensen**[1]

[1]*Danish Headache Center, Department of Neurology, The Rigshospitalet-Glostrup, University of Copenhagen, Denmark*
[2]*Department of Radiology, The Rigshospitalet-Glostrup, University of Copenhagen, Denmark*

Correspondence should be addressed to Vlasta Vukovic-Cvetkovic; vlasta.vukovic@uclmail.net

Received 10 August 2023; Revised 28 November 2023; Accepted 6 December 2023; Published 27 January 2024

Academic Editor: Carlo Colosimo

The outcome of spontaneous intracranial hypotension (SIH) years after onset is largely unknown. The objective of our study was to describe our clinical experience and long-term outcomes in a case series of patients with SIH. From March 2007 to March 2022, demographic variables, clinical symptoms, neuroimaging findings, and response to treatment were retrospectively analyzed in patients with confirmed SIH and in a subgroup of patients with clinical symptoms but not confirmed by MR or LP, probable SIH (pSIH). We have included 37 SIH and 13 pSIH patients. The average age at onset was 44 years, and 59% (pSIH 46%) were women. All patients presented with a new-onset orthostatic headache. In the SIH group, brain MRI showed signs of intracranial hypotension in all patients, spinal MR was performed in 70%, and pathological findings were identified in 73%. The range of EBP was 1-8 (average 2.2). Good outcome after single or 2 EBPs had 42% (pSIH 46%) of patients. At follow-up, 81% (pSIH 54%) of patients had a favorable outcome. Relapse occurred in 16% of patients in the SIH group and none in the pSIH group. The mean follow-up time was 60 months. EBP is an effective and minimally invasive treatment, and efficacy seems independent of disease duration. The long-term prognosis is favorable in 80% of SIH patients and in half of pSIH patients. Despite the lack of MRI signs of low intracranial pressure on neuroimaging, pSIH patients should also be offered EBP, and more awareness of SIH is needed.

1. Background and Objectives

The recognition of spontaneous intracranial hypotension (SIH) has increased in recent years. Although the incidence is estimated at 5 per 100,000, it is likely to be more common since the disease is often underdiagnosed [1]. SIH results from spinal cerebrospinal fluid (CSF) leaks, which mostly occur at the thoracic level or at the cervicothoracic junction [2]. Spinal MRI scans showing so-called spinal longitudinal extradural fluid (SLEC) are suggestive of ventral dural tears (type 1 leak) often caused by a calcified ventral osteophyte, leaking nerve root sleeves are typically associated with meningeal diverticula (type 2 leaks), and the third cause is CSF-venous fistulas (type 3 leaks). Type 2 leaks are SLEC-positive if the tear is proximal and SLEC-negative if it is distal, and type 3 leaks are always SLEC-negative [3]. SIH typically manifests as orthostatic headache that resolves shortly after patients return to a recumbent position. Magnetic resonance imaging (MRI) abnormalities are found in most, but not all, and include diffuse pachymeningeal gadolinium enhancement (PGE), brain sagging, subdural hygroma, venous distension signs, and pituitary engorgement [2, 4].

Orthostatic headache may disappear with time, but after months/year, patients may present with a chronic headache (migraine, tension type, or new daily persistent headache) [2, 5]. A meta-analysis suggests that the following can occur in SIH: absence of orthostatic headache, normal imaging findings, or normal opening pressure at lumbar puncture (LP) in up to 25% of cases [2]. Epidural blood patch (EBP) is considered the treatment of choice for patients unresponsive

to conservative or pharmacologic treatment [6, 7], but repeated, preferably targeted EBPs are sometimes needed and relapses are not uncommon [6, 7].

As there are relatively few long-term follow-up studies on SIH patients, the purpose of this study was to describe our clinical experience and long-term outcomes in our patient cohort with SIH and in a subgroup of patients with clinical symptoms but not confirmed by MR or LP, probable SIH (pSIH).

2. Methods

In this case series, a retrospective review of the medical records of 50 patients suspected of having SIH was conducted from March 2007 to March 2022. All referred patients were evaluated at our neurological department and/or in the outpatient clinic at the Danish Headache Center (DHC), which is a tertiary headache center, connected to the Department of Neurology, Rigshospitalet-Glostrup, University of Copenhagen, where the diagnostic work-up and follow-up was conducted. The study was done in accordance with the Declaration of Helsinki with later revisions. The study was approved by the Neuroscience Center at Rigshospitalet-Glostrup as a quality assurance study and approved as such by the Regional Ethics Committee (H-18008942), which determined that participant consent was not required as the study collected information from patients undergoing usual treatment and evaluation. The study was conducted in accordance with Danish data laws. This is the primary analysis of these data. The patients were identified when given the diagnostic ICD-10 code (DG96.0) and/or when identified by the authors or colleagues at the Danish Headache Center.

2.1. Inclusion Criteria. We included patients who were available for follow-up at least 6 months after establishing the diagnosis and whose medical records contained sufficient and relevant data for the study. Patients were included if medical charts contained data on headache characteristics at onset, frequency, and intensity; MR imaging; treatment with EBP; and sufficient data on headache characteristics at follow-up.

Patients with orthostatic headaches whose diagnosis was confirmed by positive MRI findings or low CSF pressure were included in the SIH group.

Patients with a clear history of orthostatic headache (with or without other symptoms) at the onset but with a negative brain MRI or normal CSF pressure were included in the probable SIH (pSIH) group. Because the primary purpose of this study was to follow-up patients in the long term, we thought it would be interesting to also review the outcomes of patients with a negative MRI. The inclusion of these MRI negative patients was based on the observation that an MRI may be negative 4 months after the onset of the condition [4]. The SIH and pSIH groups were analyzed separately.

2.2. Exclusion Criteria. Patients with previous head or spinal trauma, lumbar punctures, and/or spinal anesthesia were excluded from the study. By neuroimaging modalities (MRI, CT/MR angiography), possible causes for an orthostatic headache such as colloid cyst of the third ventricle, intracranial neoplasm, sinusitis, and cerebral venous thrombosis were excluded. Overview of inclusion and exclusion criteria are shown in Table 1.

2.3. Data Collection. The following data were collected and analyzed: demographic variables, comorbidities, and precipitating factors at onset. Headache frequency and intensity at onset and follow-up was collected at an interview and based on the patient headache diary. In addition, we obtained the neuroimaging descriptions (brain MRI, spine MRI, CT, and myelography), the number of EBPs performed, response to pharmacological treatment and EBPs, and relapse rate and time to relapse. In order to reflect the clinical daily practice, we obtained all the initial imaging descriptions by experienced neuroradiologists. In case of doubt or unclear descriptions, our neuroradiologist (ES) reassessed the images.

At our headache center, we do not routinely use LP to diagnose SIH, because LP pressures are often normal in SIH [7] and to avoid trauma to the connective tissue [8, 9].

However, LP has been performed in several patients to rule out other diagnoses. Spinal MRI and CT myelography were not performed on all patients; however, they were used in those whose initial treatment with EBP was unsuccessful.

2.4. Follow-Up Data. All patients enrolled in the study were followed up for at least 6 months. They were included if they could provide sufficient data on at least 2 follow-up visits after the last treatment. In cases where EBP was ineffective and a new treatment and/or diagnostic plan were required, patients were instructed to self-refer to the outpatient clinic after 2-3 weeks.

2.5. Outcome. On follow-up, it was noted that either no headaches (or additional symptoms) were present or, if headaches were present, the frequency was reported as episodic (1-14 days per month) or chronic (15 days or more per month). Patients were asked to define their headache using the visual analog scale (VAS), and the intensity was then reported as mild (VAS 1-3), moderate (VAS 4-7), or severe (VAS 8-10) (Tables 2 and 3).

2.6. Treatment. Depending on the clinical data, patients were offered treatment (in most cases, nontargeted EBP in the lumbar region) followed by additional investigation if needed (Appendix). The EBP was performed as follows: the patient was placed lying in the left lateral position. A standard epidural kit and an 18-gauge or 20-gauge angiocatheter was used to draw autologous blood in a sterile fashion. The epidural space was identified in the standard fashion using loss-of-resistance to air or saline. Once the placement of the needle tip of the epidural needle was confirmed, approximately 20-40 mL of autologous blood was injected slowly (30 to 60 seconds) into the patient's epidural space to create the blood patch.

Patients were discharged from our clinic if they were symptom-free for at least 6 months after the last EBP treatment. Patients who experienced a relapse of symptoms were

Table 1: Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
(i) Spontaneous intracranial hypotension patients confirmed by MRI or low CSF pressure on spinal tap (ii) Probable intracranial hypotension patients with a clear history of orthostatic headache (iii) Patients with follow-up data at least six months after the diagnosis and medical charts containing data on headache characteristics at onset, frequency, and intensity; MR imaging; and treatment with EBP	(i) Patients with previous head or spinal trauma (ii) Patients with lumbar punctures and/or spinal anesthesia (iii) Patients with possible causes for an orthostatic headache such colloid cyst of the third ventricle, intracranial neoplasm, sinusitis, cerebral venous thrombosis

treated with repeat EBP and managed according to the above discharge criteria.

A successful outcome was defined as no headache after the last treatment at 6-month follow-up or mild headache in some cases associated with physical activity but not requiring additional treatment. Persistent chronic headache (≥15 days per month) of moderate or severe intensity was considered a poor outcome. These outcome measures are somewhat more stringent than those used in similar studies, in which a good response is defined as having achieved at least a 50% reduction in the VAS score within 48 hours of the intervention and persisting for at least 6 months [7].

2.7. Statistical Analysis. This is an observational descriptive study in which data is presented as frequencies, percentages, means, and ranges. The SPSS statistics software was used to calculate descriptive data.

3. Results

3.1. Demographics. The study included 50 patients, 37 in SIH and 13 in the pSIH group. In the SIH group, 22/37 (59%) were women and in the pSIH 6/13 (46%). The average age of symptom onset was 44 years for the SIH group and 42 years for the pSIH group (range 19-75 years): in the SIH group, 41 years in men and 47 years in women (range 19-75) and in the pSIH group, 48 years in men and 32 years in women (range 22-72). The time from onset to diagnosis was 6.5 months (range 1-41). In 20/37 (54%) of the patients, the diagnosis was established within 3 months.

3.2. Follow-Up. The mean follow-up time was 60 months (range 6-178 months). The number of cases was low in 2007, at the beginning of our inclusion period. This was due to very limited focus on that disorder. In recent years, there have been much more interest in the condition, in line with better diagnostics and treatment possibilities, which has resulted in an increasing referral rate.

The clinical data, diagnostic work-up, treatment, and follow-up for both groups are presented in Tables 2 and 3.

3.3. Clinical Findings. All patients presented with a new-onset orthostatic headache. Five patients in the SIH group and 3 in the pSIH group with a previous migraine noticed a new type of headache that was clearly distinguishable from their migraine attacks. Overall, 96% of patients complained of moderate-to-severe headaches when they were in the upright position. Over time, all patients developed a daily unremitting tension headache of mild-to-severe intensity, with an additional orthostatic feature. All patients had at least one associated symptom: cochleovestibular manifestations (tinnitus, phonophobia, and hearing loss) (62%), nausea (52%), neck pain (47%), dizziness (41%), interscapular pain (23%), paresthesia in the arms (21%), stabbing headache (12%), photophobia in patients without known migraine (8%), and cranial nerve palsies (abducens paresis) (1 patient).

The presenting symptoms did not differ between the SIH and pSIH groups.

3.4. Diagnostic Work-Up

3.4.1. SIH Group. Brain MRI showed signs of intracranial hypotension in all SIH patients, and all but 1 had diffuse PGE. Additional signs of intracranial hypotension on brain MRI were identified in 51% of patients: subdural hygroma (38%), brain sagging (16%), pituitary engorgement (14%), and venous distension sign (8%). Spine MRI was performed in 70% of the patients and revealed pathological findings in 73% of these. CT myelography revealed pathologic findings in 70% of the patients.

Pathologic findings on spinal MR or CT myelography were as follows: epidural fluid (42%), spinal root cysts (23%), PGE (15%), herniated discs (12%), osteophytes (12%), meningeal diverticula in 1 patient, and thoracic cerebrospinal fluid venous fistula in 1. In 7/37 (19%) of patients, a lumbar puncture was performed to exclude neuroinfections or xanthochromia in the spinal fluid, and in all cases, the pressure was low (Table 2).

3.4.2. pSIH Group. In all 13 patients, the brain MRI was normal, with no signs of intracranial hypotension. Spine MRI was performed in 31%, revealing a perineural cyst in 2 patients; one also had a herniated disc. Lumbar puncture was performed in 2 patients showing normal CSF pressure (Table 3).

Overall, CT myelography has been performed only in 10% of the patients, and this is due to 2 reasons: (1) this was a retrospective study with a primary aim to assess the long-term outcome of the patients with SIH; the majority of patients was included before our center began with the routine use of CT myelography; (2) if the patients had good outcome after the EBP, we did not proceed with further investigations.

Table 2: Patients with spontaneous intracranial hypotension (SIH) and positive MR signs for intracranial hypotension.

	N	M/F	Age at onset (range)	Relapse (*N*)	Comorbidity (*N*)	Diagnostic				Work-up		Treatment	
						MR brain		MR spine/CT-myelography		LP (*N*) (cm CSF)	Epidural blood patch (mean *N* per patient)	Other treatment (*N*)	
No headache	16	7/9	39 (19-62)	1	Leiden V Endometriosis Migraine	1 2 2	PGE Hygroma BS PE VDS	16 8 2 2 1	Not performed Normal PGE Perineural cysts Epidural fluid Disc herniation M. diverticula Osteophyte CSVF Dural defect	8 1 2 1 4 0 0 0 1 1	3 (4, 7, 8)	2.4 *Patient with 8 EBPs was not included	Surgical removal of hygroma Surgery for CSVF	2 1
Exertional headache/ mild chronic headache	14	7/7	44 (23-75)	4	Arterial hypertension Atrial fibrillation Irritable bowel sy	2 1 1	PGE Hygroma BS PE VDS	14 5 2 2 3	Not performed Normal PGE Perineural cysts Epidural fluid Disc herniation M. diverticula Osteophyte CSVF Dural defect	2 3 2 2 7 2 0 0 1 1	3 (0, 6, 5)	1.8	Surgery for dural defect	3
Moderate-to-severe headache	7	1/6	50 (36-65)	1	Arterial hypertension Migraine	1 3	PGE Hygroma BS PE VDS Normal	6 1 1 1 0 1	Not performed Normal PGE Perineural cysts Epidural fluid Disc herniation M. diverticula Osteophyte Dural defect	1 3 0 2 2 0 1 1 1	1 (8)	2.8	0	
Total	37	15/22	44	6	—	—		—		7	2.3	—	

Table 3: Patients with probable spontaneous intracranial hypotension (pSIH) but without MR signs for intracranial hypotension.

	N	M/F	Age at onset (range)	Relapse (*N*)	Comorbidity (*N*)	Diagnostic		Work-up			Treatment	
							MR brain	MR spine/ CT-myelography		LP (*N*) (cm CSF)	Epidural blood patch (mean *N* per patient)	Other (*N*)
No headache	3	2/1	48 (34-72)	0	Migraine	1	Normal	Normal Not performed	1 2	0	1.8	0
Exertional headache/ mild chronic headache	4	2/2	38 (33-44)	0	Migraine	1	Normal	Normal Not performed Perineural cysts Disc herniation	1 3 1 2	0	1.3	0
Moderate-to-severe headache	6	3/3	42 (22-63)	0	Arterial hypertension Migraine	1 1	Normal	Normal Not performed Perineural cysts	0 4 1	2 (11, 15)	1.5	0
Total	13	7/6	42	0	—		—	—		2	1.5	0

M: male; F: female; LP: lumbar puncture; PGE: pachymeningeal gadolinium enhancement; BS: brain sagging; PE: pituitary engorgement; VDS: venous distension sign; M. diverticula: meningeal diverticula; CSVF: cerebrospinal venous fistula.

3.5. Treatment

3.5.1. Conservative Treatment. All patients were instructed to have a high fluid intake including caffeine-containing drinks. All patients were offered simple analgesics, and those whose headache was lasting more than 1 month were offered preventive treatment. A total of 17/50 (34%) of patients had <50% effect on intensity after commencement of conservative treatment (simple analgesics in 4 patients, indomethacin in 5, amitriptyline in 3, and caffeine in 3 patients), while codeine achieved relief in one and cannabis tablets in another patient. The conservative treatment was stopped after 2-6 weeks if there was no response or in the presence of side effects or was continued until the patients received the EBP. As the conservative treatment was not satisfactory in most patients, they were offered EBP.

There was no medication overuse.

3.5.2. Epidural Blood Patch. In the SIH group, all but one patient was treated with EBP in a range from 1 to 8 (average 2.3) per patient. Only one patient received 8 EBPs with short-lasting but significant improvement in her clinical symptoms (severe headache and cognitive decline) and was eventually successfully treated surgically for a small thoracic CSF venous fistula.

Multilevel targeted EBP was performed in 3 patients, and the remaining patients underwent single-level nontargeted EBP in the lumbar region by injection of autologous venous blood. In the pSIH group, all but one patient were treated with EBP from 1 to 6 (average 1.5).

3.5.3. Surgical Treatment. Before the SIH diagnosis was established, 2 patients underwent surgery for cerebral subdural fluid collection, with symptoms temporarily worsening in one patient. Three patients underwent surgery for a dural defect in the spine, with 2 patients being successful and the third with partial improvement.

3.6. Follow-Up of Patients

3.6.1. SIH Group. After one or two EBPs, 15/36 (42%) of patients had a good outcome and another 13/36 (36%) after multiple EBPs. One patient did not receive EBP but had a spontaneous remission of symptoms. At follow-up, 81% of patients had a good outcome. In this group, 16/37(44%) of patients had no headache, 10/37 (27%) had only episodic/exertional headache, and 4/37 (10%) of patients had chronic but mild headache that required no further treatment. Chronic headaches of moderate or severe intensity were noted in 7/37 (19%) of patients.

During the follow-up period, 6/37 (16%) of patients experienced a relapse of SIH after symptoms had previously resolved completely for at least 3 months.

After relapse, 4/6 patients were successfully treated with repeated EBP. One patient was left with chronic moderate headache after unsuccessful repeated EBPs twice. One patient had remission after surgery for a dural defect and suffered only occasional exertional headaches. Relapses occurred over a period of 3 to 41 months (mean, 16 months).

Overall, the effect of EBP was good, even when patients were treated several months or even years after headache onset. A single patient had not received EBP because she had a good effect of pharmacologic treatment (Table 2).

No difference in response to EBP was found between men and women with respect to age or the presence of MRI findings.

3.6.2. pSIH Group. 7/13 (54%) of patients had a good outcome. After a single or two EBPs, 6/13 (46%) of patients had a good outcome. Relapse occurred in none of the patients in this group (Table 3).

Two women became pregnant after being diagnosed with SIH. No change in symptom pattern was observed during pregnancy, and both women delivered healthy babies without further complications.

4. Discussion

Our study is among very few long-term follow-up studies that analyzed the clinical and neuroimaging findings, treatment, and outcomes in patients with SIH diagnosed according to the ICHD-3 criteria [10]. However, this is the first study that analyzed long-term follow-up in a subgroup of patients with probable SIH based on symptomatology but with a normal brain MRI. Our study showed that overall, 80% of our SIH patients and over half of the pSIH patients had a good outcome at long-term follow-up after treatment with EBP. Although studies have shown that up to 25% of patients with suspected SIH can have a negative MRI, the long-term follow-up of these patients was unknown. Our study however suggests that this subgroup should be treated as patients with evidence of low intracranial volume on MRI and should be offered the same treatment as even 50% has a good outcome. As in most other cases, conservative therapy is unspecific and insufficient, so patients with suspected SIH should be offered an EBP [7, 11, 12], even after several months to years after onset.

Treatment with EBP usually needs to be repeated, as only 1/3 of the patients respond well after the first EBP and up to half of the patients who receive three or more EBPs respond well [7, 12]. The outcome after treatment with EBP in our series of patients showed that remission of symptoms occurred in one-third of patients after a single EBP. Compared with a similar study in which a good response was defined as achieving at least a 50% reduction in the VAS score within 48 hours of the procedure and persisting for at least 6 months, the relatively poorer outcome in our study may be explained by more stringent outcome measures of frequency reduction [7].

One of the most important findings of our study is that the beneficial effect of EBP was not related to the duration of the disease; thus, some patients were successfully treated months and years after the onset of the disease. This is encouraging and proves that EBP should be tried in all patients with suspected SIH, no matter how late after the onset of symptoms.

Furthermore, a recent systematic review and meta-analysis has shown, interestingly, that no differences in terms

of outcome have been reported concerning targeted versus nontargeted EBP [13]. This finding has significant implications, as nontargeted EBP is much easier to perform and can be performed at most hospitals as an efficient treatment, thus sparing the time and resources.

As Kranz et al. point out, when diagnosing SIH, one should keep in mind that SIH is not always characterized by orthostatic headache, a negative MRI of the brain does not rule out SIH, the opening pressure may be normal, and an epidural blood patch does not immediately cure SIH [14].

In reality, the IHCD-III diagnostic criteria [9] for headaches attributed to low CSF volume are difficult to apply in clinical practice because the temporal relationship can be very difficult to determine, there is often no direct trauma or procedure to relate to, the opening pressure may be normal and thus misleading, and the clinical presentation may be vague over time.

There are few studies addressing long-term follow-up of patients with SIH, and most are case reports. In a large series of patients in which the median follow-up was 60 months, the overall response rate after EBP (injection of 10 mL of autologous venous blood fibrin glue and contrast agent) was 68.3% at the 6-month follow-up, with a reduction in pain scores of at least 50%. Symptoms recurred in 31.7%; of these patients who underwent a second procedure, the overall response rate at the last follow-up was 89.1% [7].

A series of 11 patients in whom 3-year follow-up was available showed that 83% were completely free of clinical symptoms and 8.3% had sporadic orthostatic headache [15]. A retrospective analysis of 31 patients showed that EBP resulted in significant improvement of headache in 77% of patients [16].

Recurrent spontaneous spinal CSF leaks are not uncommon and can occur at any time after the initial CSF leak. Our results showed that recurrence occurred in 16% of patients over an average period of 16 months, two-thirds of whom were successfully treated with repeat EBP. Recurrence was also observed in up to one-third of patients in other long-term follow-up studies [7, 17, 18], which is a higher recurrence rate than in our study.

A retrospective analysis of 30 patients found that 50% achieved dramatic symptom relief after the first EBP and symptoms recurred in 6 patients [19]. In another study, symptoms recurred in 32 patients (31.7%) after successful EBP. These patients underwent a second intervention, and the response rate at 6-month follow-up was 78.1%. Seven patients did not improve after a third procedure and remained symptomatic [7].

One study showed that recurrent spinal CSF leak developed in 5 of 13 patients who underwent surgical repair, compared with none of the five patients who had been treated nonsurgically. The recurrent leak occurred between 10 and 77 months after the initial spinal CSF leak, but in all patients, it occurred within 2 or 3 months after successful surgical repair of the leak [18].

Of our SIH patients, 38% had subdural cerebrospinal fluid collection on brain MRI, two were exposed to surgery, and one experienced transient clinical deterioration. Surgical removal of subdural cerebrospinal fluid collections should be avoided because patients do not experience lasting neurologic improvement and some even deteriorate [20]. More than half of these patients experienced recurrence of hematomas due to neglected treatment of the spinal CSF leak [21].

The onset of SIH headache is usually sudden and may appear in the form of a thunderclap headache [22] without obvious trauma. Thereafter, the main clinical feature of SIH is an orthostatic headache that occurs immediately after a change to an upright position and resolves within minutes after a change to a recumbent position. In cases where the diagnosis is delayed, the clinical presentation of headache often lacks the orthostatic character. Over time, most patients develop a continuous headache that is no longer orthostatic or a delayed response to postural changes. The headache worsens after several hours in an upright position but does not necessarily improve after the patient has been in a recumbent position for an extended period. This has led to the term "second-half-of-the-day headache," which is probably a manifestation of a slow-flowing CSF leak [23, 24].

In our group, 26% of patients (SIH+pSIH) had a chronic headache that was no longer orthostatic but could worsen during the day. Most patients presenting to specialized headache clinics have chronic headaches and may not remember the characteristics of the headache (i.e., orthostatic) at baseline. Therefore, they may be misclassified as chronic migraine or new daily persistent headache. Headaches in the second half of the day have low sensitivity and specificity because they may also resemble a TTH. In cases where the headache starts abruptly, leading to a definite orthostatic headache that changes over time to a chronic headache that no longer has orthostatic features but worsens in the afternoon, this observation should raise the suspicion of underlying SIH during history taking.

Therefore, to raise awareness of SIH, it is essential to specifically ask patients about the onset of headache and any orthostatic components and to offer them a blood patch in suspected cases. In some cases, SIH may mimic benign exertional headache [25]. In our study, 27% of patients had exertional headache as the sole sequela of a previous SIH at follow-up.

In all our patients, we found symptoms other than orthostatic headache, which are likely due to traction of the meninges and other brain structures. This is consistent with observations from other clinical studies [2, 26, 27]. Therefore, it is important to ask about cochleovestibular manifestations, neck pain, nausea, interscapular pain, and upper extremity paresthesia in the history. In our study, almost 1/3 of patients developed SIH after a specific activity. Therefore, the history should include information about events that may be associated with SIH, such as mild trauma, sneezing, airplane travel, sudden body flexion, another type of physical activity, or even activities such as yoga [28]. We did not find any reports of pregnant women diagnosed with SIH in the literature. The two patients who were pregnant during follow-up in our study experienced no changes in clinical symptoms during pregnancy and gave birth to healthy infants. Although it is not possible to draw definitive conclusions based on only two patients, our observation is

that pregnancy may not pose risks in women previously diagnosed with SIH.

There is no clear diagnostic algorithm for the diagnostic approach in a patient with suspected SIH. Clinical features and neurologic imaging findings remain the most important criteria for diagnosis [2, 27–31]. However, a recent meta-analysis showed that brain MRI findings were normal in 19% of patients [2]. When we combined our SIH and pSIH groups, 26% of patients had normal MRI of the brain. As 54% of pSIH patients had a good outcome after treatment with EBP, we suggest that patients with a clear history of orthostatic headache should be offered standard treatment, even if there is no evidence of low intracranial pressure on neuroimaging.

A neuroimaging study has shown that a significantly shorter latency between the time of MRI examination and the time of headache onset was observed in patients with a negative initial MRI examination compared with patients with a positive PGE. It is estimated that PGE becomes apparent approximately 7-10 days after headache onset in most patients and may resolve as early as 25 days after headache onset [5].

The presence of an underlying cause of SIH can sometimes be difficult to detect; these include these included perineural cysts, osteophytes, meningeal diverticula, and cerebrospinal fluid venous fistula [2, 27, 29–33]. Various neuroimaging techniques have been proposed [26]. Most investigators suggest standard and heavily T2-weighted MR imaging and/or a CT myelogram [4, 29, 34]. The advantage of CT myelography is that it can detect both disc osteophyte spurs and CSF venous fistulas [29, 35]. Depending on the neuroimaging method chosen, leaks due to high flow/high volume and slow flow or intermittent leak can be captured [28], but it can be time-consuming and repeated examinations are often required. We suggest that spinal MRI and CT myelography should be part of the work-up in patients with probable SIH as recent studies have shown an improved sensitivity with improved MR technique [2]. This would be of clear advantage in the pSIH group, which might be underdiagnosed regarding the spinal CSF leak, since they all improved by the treatment.

4.1. Methodological Considerations. The study covers a period of 15 years, and as the Capital Region has 1.5 million citizens, it would be expected to see 75 new patients alone per year. The reason why we only identified 50 patients in the current study are due to several factors: less awareness about the diagnosis years ago and insufficient data in the medical charts leading to patients being excluded. Since the study was retrospective, we included only patients with sufficient data for this study. In addition, there is a risk of recall bias and a certain number of patients were probably not identified. For the entire group of patients studied, there may also have been inclusion bias because they were enrolled from a tertiary center.

The diagnostic work-up was primarily based on clinical outcome, i.e., response to the first two EBPs, and therefore, not all patients underwent spinal MRI or CT myelography. Because of the relatively small number of patients included, we cannot draw definitive conclusions, especially in the pSIH group.

However, because few published studies of SIH include long-term follow-up, our clinical observations may help physicians identify and treat patients with SIH for decision-making and prognostic evaluation.

One of the most important findings of our study is that the beneficial effect of EBP was not related to the duration of the disease, such that some patients were successfully treated months and years after the onset of the disease. Another finding is that 54% of pSIH patients responded positively to treatment with EBP, raising the question whether the current ICHD-3 criteria for SIH should be reevaluated and include this group of patients.

4.2. Conclusions. The clinical picture of SIH is more typical in the early stages of the disease and is characterized by orthostatic headache. However, as this feature may disappear over time, a detailed history of disease onset is crucial. Signs of intracranial hypotension on MRI are common but absent in some cases. Even in cases where there is a significant delay in diagnosis, we recommend offering treatment with one or more EBPs even in pSIH patients. Long-term recurrences may occur, so follow-up is required. However, the long-term prognosis is good in most patients and more awareness of SIH is needed.

Appendix

A.1. Management Algorithm of SIH Based on the Literature and Our Experience

(1) History taking

  (i) Circumstances and time since the activity and headache onset (physical activity, yoga, trauma, etc.)

  (ii) Presence of a positional headache at onset (the patient will not necessary bring it up, especially longer time after headache onset)

  (iii) Ask whether the headaches disappear after being in a recumbent position/in the morning/or about the presence of the "second-half-of-the-day headache"

(2) The "48-hour flat test" can be performed in doubtful cases (courtesy of Dr. Ian Caroll, developed at Stanford University; to be published)

(3) Clinical picture speaks in favor of SIH (orthostatic headache, tinnitus, paresthesia, interscapular pain, and dizziness)

(4) Evidence of low intracranial pressure on MR (gadolinium): PGE, engorgement of venous structures, pituitary hyperemia, sagging of the brain, and bilateral subdural hematoma

  (i) Positive findings confirm the diagnosis

(ii) Negative findings do not rule out the diagnosis

(5) Opening pressure by lumbar puncture is not necessary for the diagnosis; best avoided

(6) Epidural blood patch (preferably targeted). Can be repeated in cases of partial or no effect

(7) In case of persistent symptoms after 1-2 EBP, further diagnostic work up

(i) MR of the whole spine for signs of fluid, dural defect, microspurs, and disc protrusions

(8) If EBP is ineffective and/or spinal MR is negative, proceed to CT myelography in lateral decubitus digital subtraction myelography (requires an experienced neuroradiologist). CT myelography is the diagnostic method of choice if the patient proceeds to have clear signs of SIH

(9) In cases of positive findings (dural defect, microspurs, and fistulas), refer to surgeon

(10) All patients with moderate-to-severe headache who are under diagnostic work-up and nonresponsive to simple analgesics may be offered a trial with prophylactic treatment such as indomethacin, amitriptyline, or caffeine tablets

Data Availability

The datasets used and analyzed during the current study are available from the corresponding author at the reasonable request.

Ethical Approval

Because this was a retrospective study based on medical records and the analyzed data were used for the purposes of safety analysis at the Neurology Department, an approval by the ethics committee in Denmark was not required. The study is compliant with the principles of the Declaration of Helsinki.

Conflicts of Interest

The authors declare that they have no competing interests.

Acknowledgments

We have used the "48-hour flat test," courtesy of Dr. Ian Caroll, developed at Stanford University (to be published).

References

[1] W. I. Schievink, "Spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension," *JAMA*, vol. 295, no. 19, pp. 2286–2296, 2006.

[2] L. D'Antona, M. A. Jaime Merchan, A. Vassiliou et al., "Clinical presentation, investigation findings, and treatment outcomes of spontaneous intracranial hypotension syndrome: a systematic review and meta-analysis," *JAMA Neurology*, vol. 78, no. 3, pp. 329–337, 2021.

[3] N. Luetzen, P. Dovi-Akue, C. Christian Fung, J. Beck, and H. Urbach, "Spontaneous intracranial hypotension: diagnostic and therapeutic workup," *Neuroradiology*, vol. 63, no. 11, pp. 1765–1772, 2021.

[4] P. G. Kranz, T. P. Tanpitukpongse, K. R. Choudhury, T. J. Amrhein, and L. Gray, "Imaging signs in spontaneous intracranial hypotension: prevalence and relationship to CSF pressure," *AJNR. American Journal of Neuroradiology*, vol. 37, no. 7, pp. 1374–1378, 2016.

[5] J. L. Fuh, S. J. Wang, T. H. Lai, and S. S. Hseu, "The timing of MRI determines the presence or absence of diffuse pachymeningeal enhancement in patients with spontaneous intracranial hypotension," *Cephalalgia*, vol. 28, no. 4, pp. 318–322, 2008.

[6] G. L. Pagani-Estévez, J. K. Cutsforth-Gregory, J. M. Morris et al., "Procedural predictors of epidural blood patch efficacy in spontaneous intracranial hypotension," *Regional Anesthesia & Pain Medicine*, vol. 44, no. 2, pp. 212–220, 2019.

[7] V. Levi, N. E. Di Laurenzio, A. Franzini et al., "Lumbar epidural blood patch: effectiveness on orthostatic headache and MRI predictive factors in 101 consecutive patients affected by spontaneous intracranial hypotension," *Journal of Neurosurgery*, vol. 132, no. 3, pp. 809–817, 2019.

[8] P. G. Kranz, T. P. Tanpitukpongse, K. R. Choudhury, T. J. Amrhein, and L. Gray, "How common is normal cerebrospinal fluid pressure in spontaneous intracranial hypotension?," *Cephalalgia*, vol. 36, no. 13, pp. 1209–1217, 2016.

[9] L. L. Yao and X. Y. Hu, "Factors affecting cerebrospinal fluid opening pressure in patients with spontaneous intracranial hypotension," *Journal of Zhejiang University. Science. B*, vol. 18, no. 7, pp. 577–585, 2017.

[10] Headache Classification Committee of the International Headache Society (IHS), "The International Classification of Headache Disorders," *Cephalalgia*, vol. 381–211, 2018.

[11] J. W. Wu, S. S. Hseu, J. L. Fuh et al., "Factors predicting response to the first epidural blood patch in spontaneous intracranial hypotension," *Brain*, vol. 140, no. 2, pp. 344–352, 2017.

[12] D. Sencakova, B. Mokri, and R. L. McClelland, "The efficacy of epidural blood patch in spontaneous CSF leaks," *Neurology*, vol. 57, no. 10, pp. 1921–1923, 2001.

[13] F. Signorelli, V. M. Caccavella, M. Giordano et al., "A systematic review and meta-analysis of factors affecting the outcome of the epidural blood patching in spontaneous intracranial hypotension," *Neurosurgical Review*, vol. 44, no. 6, pp. 3079–3085, 2021.

[14] P. G. Kranz, L. Gray, and T. J. Amrhein, "Spontaneous intracranial hypotension: 10 myths and misperceptions," *Headache*, vol. 58, no. 7, pp. 948–959, 2018.

[15] A. Franzini, G. Messina, V. Nazzi et al., "Spontaneous intracranial hypotension syndrome: a novel speculative physiopathological hypothesis and a novel patch method in a series of 28 consecutive patients," *Journal of Neurosurgery*, vol. 112, no. 2, pp. 300–306, 2010.

[16] M. McCann, K. Kelly, D. Sokol, and M. A. Hughes, "Management of spontaneous intracranial hypotension: a series of 31 cases over 15-years with a challenging outlier," *British Journal of Neurosurgery*, vol. 35, no. 3, pp. 251–253, 2021.

[17] D. S. Kong, K. Park, J. I. Lee, J. S. Kim, W. Eoh, and J. H. Kim, "Clinical features and long-term results of spontaneous intracranial hypotension," *Neurosurgery*, vol. 57, no. 1, pp. 91–96, 2005.

[18] W. I. Schievink, M. M. Maya, and M. Riedinger, "Recurrent spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension: a prospective study," *Journal of Neurosurgery*, vol. 99, no. 5, pp. 840–842, 2003.

[19] S. H. Yoon, Y. S. Chung, B. W. Yoon, J. E. Kim, S. H. Paek, and D. G. Kim, "Clinical experiences with spontaneous intracranial hypotension: a proposal of a diagnostic approach and treatment," *Clinical Neurology and Neurosurgery*, vol. 113, no. 5, pp. 373–379, 2011.

[20] J. J. Loya, S. A. Mindea, H. Yu, C. Venkatasubramanian, S. D. Chang, and T. C. Burns, "Intracranial hypotension producing reversible coma: a systematic review, including three new cases," *Journal of Neurosurgery*, vol. 117, no. 3, pp. 615–628, 2012.

[21] K. Takahashi, T. Mima, and Y. Akiba, "Chronic subdural hematoma associated with spontaneous intracranial hypotension: therapeutic strategies and outcomes of 55 cases," *Neurologia Medico-Chirurgica (Tokyo)*, vol. 56, no. 2, pp. 69–76, 2016.

[22] E. Ferrante and A. Savino, "Thunderclap headache caused by spontaneous intracranial hypotension," *Neurological Sciences*, vol. 26, Supplement 2, pp. s155–s157, 2005.

[23] A. N. L. Hunderfund and B. Mokri, "Second-half-of-the-day headache as a manifestation of spontaneous CSF leak," *Journal of Neurology*, vol. 259, no. 2, pp. 306–310, 2012.

[24] P. G. Kranz, T. J. Amrhein, K. R. Choudhury, T. P. Tanpitukpongse, and L. Gray, "Time-dependent changes in dural enhancement associated with spontaneous intracranial hypotension," *AJR. American Journal of Roentgenology*, vol. 207, no. 6, pp. 1283–1287, 2016.

[25] B. Mokri, "Spontaneous CSF leaks mimicking benign exertional headaches," *Cephalalgia*, vol. 22, no. 10, pp. 780–783, 2002.

[26] B. Mokri, "Spontaneous low pressure, low CSF volume headaches: spontaneous CSF leaks," *Headache*, vol. 53, no. 7, pp. 1034–1053, 2013.

[27] C. Li, H. K. Raza, T. Chansysouphanthong, J. Zu, and G. Cui, "A clinical analysis on 40 cases of spontaneous intracranial hypotension syndrome," *Somatosensory & Motor Research*, vol. 36, no. 1, pp. 24–30, 2019.

[28] M. N. Haider, J. J. Leddy, A. L. Hinds et al., "Intracranial pressure changes after mild traumatic brain injury: a systematic review," *Brain Injury*, vol. 32, no. 7, pp. 809–815, 2018.

[29] T. J. Amrhein and P. G. Kranz, "Spontaneous intracranial hypotension: imaging in diagnosis and treatment," *Radiologic Clinics of North America*, vol. 57, no. 2, pp. 439–451, 2019.

[30] P. Martineau, S. Chakraborty, K. Faiz, and J. Shankar, "Imaging of the spontaneous low cerebrospinal fluid pressure headache: a review," *Canadian Association of Radiologists Journal*, vol. 71, no. 2, pp. 174–185, 2020.

[31] P. G. Kranz, L. Gray, M. D. Malinzak, and T. J. Amrhein, "Spontaneous intracranial hypotension: pathogenesis, diagnosis, and treatment," *Neuroimaging Clinics of North America*, vol. 29, no. 4, pp. 581–594, 2019.

[32] S. J. Cheng, I. Hakkinen, P. Zhang, and S. Roychowdhury, "Paradoxical headache in a case of chronic spontaneous intracranial hypotension and multiple perineural cysts," *Headache: The Journal of Head and Face Pain*, vol. 61, no. 8, pp. 1291–1294, 2021.

[33] W. Sivakumar, V. M. Ravindra, A. Cutler, and W. T. Couldwell, "Intracranial hypotension in the setting of concurrent perineural cyst rupture and subarachnoid hemorrhage," *Journal of Clinical Neuroscience*, vol. 21, no. 6, pp. 1063–1065, 2014.

[34] Y. F. Wang, J. F. Lirng, J. L. Fuh, S. S. Hseu, and S. J. Wang, "Heavily T2-weighted MR myelography vs CT myelography in spontaneous intracranial hypotension," *Neurology*, vol. 73, no. 22, pp. 1892–1898, 2009.

[35] P. G. Kranz, P. H. Luetmer, F. E. Diehn, T. J. Amrhein, T. P. Tanpitukpongse, and L. Gray, "Myelographic techniques for the detection of spinal CSF leaks in spontaneous intracranial hypotension," *AJR. American Journal of Roentgenology*, vol. 206, no. 1, pp. 8–19, 2016.