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ORIGINAL ARTICLE

Surgical closure of spinal cerebrospinal fluid leaks improves symptoms in patients with superficial siderosis

Amir El Rahal[1,2] | Benedikt Haupt[1] | Christian Fung[1] | Debora Cipriani[1] | Levin Häni[1,3] | Niklas Lützen[4] | Tomas Dobrocky[5] | Eike Piechowiak[5] | Oliver Schnell[1] | Andreas Raabe[3] | Katharina Wolf[1] | Horst Urbach[4] | Luisa Mona Kraus[1] | Florian Volz[1] | Jürgen Beck[1]

[1]Department of Neurosurgery, University Medical Center Freiburg, Freiburg, Germany

[2]Department of Neurosurgery, Faculty of Medicine of Geneva, Geneva University Hospital, Geneva, Switzerland

[3]Department of Neurosurgery, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[4]Department of Diagnostic and Interventional Neuroradiology, University Medical Center Freiburg, Freiburg, Germany

[5]Institute of Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Correspondence
Jürgen Beck, Department of Neurosurgery, University Medical Center Freiburg, Breisacher-Str. 64, 79106 Freiburg, Germany.
Email: j.beck@uniklinik-freiburg.de

Abstract

Background and purpose: Spinal cerebrospinal fluid (CSF) leaks may cause a myriad of symptoms, most common being orthostatic headache. In addition, ventral spinal CSF leaks are a possible etiology of superficial siderosis (SS), a rare condition characterized by hemosiderin deposits in the central nervous system (CNS). The classical presentation of SS involves ataxia, bilateral hearing loss, and myelopathy. Unfortunately, treatment options are scarce. This study was undertaken to evaluate whether microsurgical closure of CSF leaks can prevent further clinical deterioration or improve symptoms of SS.

Methods: This cohort study was conducted using data from a prospectively maintained database in two large spontaneous intracranial hypotension (SIH) referral centers in Germany and Switzerland of patients who meet the modified International Classification of Headache Disorders, 3rd edition criteria for SIH. Patients with spinal CSF leaks were screened for the presence of idiopathic infratentorial symmetric SS of the CNS.

Results: Twelve patients were included. The median latency between the onset of orthostatic headaches and symptoms attributed to SS was 9.5 years. After surgical closure of the underlying spinal CSF leak, symptoms attributed to SS improved in seven patients and remained stable in three. Patients who presented within 1 year after the onset of SS symptoms improved, but those who presented in 8–12 years did not improve. We could show a significant association between patients with spinal longitudinal extrathecal collections and SS.

Conclusions: Long-standing untreated ventral spinal CSF leaks can lead to SS of the CNS, and microsurgical sealing of spinal CSF leaks might stop progression and improve symptoms in patients with SS in a time-dependent manner.

KEYWORDS
neurosurgery, SIH, spontaneous intracranial hypotension, superficial siderosis, surgical closure, ventral CSF leak

INTRODUCTION

Spinal cerebrospinal fluid (CSF) leaks cause spontaneous intracranial hypotension (SIH) [1]. The incidence of SIH is estimated to be 5/100,000. Its most common presentation is as an orthostatic headache. Nonetheless, in practice, a broad range of manifestations like visual symptoms, nausea, vestibulocochlear symptoms, cognitive dysfunction (so-called "brain fog"), fatigue, and chronic subdural hematomas can occur [1–4]. Superficial siderosis (SS) is a condition that is characterized by hemosiderin deposition in the subpial layers of the brain and spinal cord, with an estimated prevalence of 1 in 10 million [5]. Patients usually take several years to become symptomatic and classically present with cerebellar ataxia, myelopathy, and bilateral hearing loss [6, 7]. It is thought to be caused by continuous or recurrent bleeding into the subarachnoid space. Etiologically, this has been described in the context of amyloid angiopathy, neurosurgical procedures, and recurrent episodes of subarachnoid hemorrhage, and in patients with a spinal CSF leak [7–13].

The association between spinal CSF leaks and SS has been postulated for more than a decade. Spinal longitudinal extrathecal collections (SLECs) are frequently observed in patients with SS [5, 6, 8, 11]. In addition, SLECs are a consistent indicator of ventral CSF leaks [14]. SS is primarily associated with ventral spinal CSF leaks, although other types of leaks have also been described [4, 15]. It has been reported that spinal CSF leaks are found in one third of patients with SS and that SS develops in the presence of a long-standing untreated ventral CSF leak [4, 11, 13, 15–19]. The exact source of bleeding is still under debate. Nonetheless, two significant mechanisms in the context of spinal CSF leaks have been highlighted. One is that those friable epidural vessels along the dural defect are responsible for the bleeding [16]. Another proposed mechanism is that brain sagging, commonly observed in patients with spinal CSF leaks, causes rupture or occlusion of the cerebellar bridging veins with subsequent bleeding due to venous stasis [4]. Previous case reports have shown that surgical sealing of a spinal CSF leak stabilizes or improves SS symptoms [16, 20, 21]. Although an intriguing finding, larger cohorts are required to substantiate this observation.

Therefore, we reviewed all cases of spontaneous spinal CSF leaks assessed at our specialized neurosurgical SIH centers for SS. The study aimed to analyze the effect of surgery on symptoms of SS.

METHODS

Patient population

This cohort study was conducted using data from a prospectively maintained database of patients who meet the modified International Classification of Headache Disorders, 3rd edition criteria for SIH [22]. The patient population consisted of a consecutive group of patients with SIH and persistent spinal CSF leaks. The study was performed following the STROBE statement and guidelines [23]. We screened consecutive patients treated for spontaneous spinal CSF leaks in the Departments of Neurosurgery, Freiburg University Hospital, Germany, and Bern University Hospital, Switzerland, two centers with extensive expertise in treating spinal CSF leaks. We included patients from February 2016 to December 2020 with spinal CSF leaks and hemosiderin deposits of the central nervous system (CNS) seen on magnetic resonance imaging (MRI). Demographic, clinical, functional, and imaging studies were extracted from patients' medical records and databases. Imaging and functional studies were independently reviewed by a board-certified neuroradiologist and a board-certified neurosurgeon.

Both centers' ethical committees approved the study (Freiburg: 357/20, Bern: 2020–00645).

Patient inclusion and workup

Patients screened for SIH

Patients underwent a standardized diagnostic workup consisting of imaging procedures, including MRI of the brain and spine, dynamic digital subtraction myelography, and/or dynamic computed tomography myelography [1, 24–27]. Additionally, functional diagnostic modalities were used, such as sonography of the optic nerve sheath diameter and lumbar infusion testing.

The diagnosis of a spinal CSF leak was made using previously established clinical and radiological diagnostic criteria. It consisted of extrathecal contrast accumulation seen on myelography, CT myelography, or MRI and microsurgical identification of the leak [1].

Patients screened for SS

The diagnosis of SS was made using radiological hemosiderin deposits of the CNS according to prespecified radiological criteria defined as typical blooming artifacts along the pial layer on T2 or blood-sensitive sequences (T2* gradient echo or susceptibility-weighted imaging) [6].

Patients underwent a neurological workup with primary respect to the presence of typical symptoms of infratentorial siderosis (i.e., cerebellar gait ataxia, bilateral hearing loss, and spinal symptoms such as myelopathy). Nevertheless, with respect to other confounding neurological diseases causing similar symptoms, care was taken to exclude these. The authors also documented previous intracranial bleeding events that might have caused SS. Symptoms were only ascribed as being due to SS if they were progressive in nature and manifested at least 6 months subsequent to the onset of SIH symptoms. The clinical manifestations of each patient were meticulously assessed by two board-certified neurosurgeons or board-certified neurologists. Patients with symmetric infratentorial SS without a previously known intracranial bleeding event in the medical history and a confirmed spinal CSF leak were included.

TABLE 1 Patients with superficial siderosis who were surgically treated for ventral spinal CSF leaks.

Case	Sex	Age at surgery, years	Age at onset of orthostatic headaches, years	Age at onset of SS, years	SS symptoms	Latency, orthostatic headaches—SS, years	Latency, SS—surgery, years	SLEC	CSF leak level	Location SS deposits	Clinical follow-up	Radiological follow-up
1	M	56	47	54	Gait unsteadiness, bilateral hearing loss	7	2	C5-T3	T2/3	Bilateral infratentorial, spine	Gait unsteadiness and orthostatic headaches improved	SLEC-
2	M	42	31	40	Gait unsteadiness	9	2	C2-L4	T11/12	Brainstem, cerebellum bilateral	Gait unsteadiness and orthostatic headaches improved	SLEC-
3	M	49	29	39	Bilateral hearing loss with cochlear implant	10	10	C5-T7	T 7/8	Bilateral infratentorial	Orthostatic headaches improved	SLEC-
4	F	73	36	65	Gait unsteadiness, bilateral hearing loss, Imbalance	29	8	C5-T3	C7/T1	Bilateral infratentorial, spine	Orthostatic headaches improved	SLEC -
5	M	60	None	48	Gait unsteadiness, bilateral hearing loss with cochlear implant, lower limbs weakness	/	12	C5-T9	T3/4	Bilateral infratentorial Spine	Symptoms remained stable	SLEC-
6	F	83	None	80	Slurred speech, hearing loss, gait unsteadiness	/	3	C7-T10	T2/3	Bilateral infratentorial, cerebellum, brainstem	Gait unsteadiness, slurred speech, and myelopathy improved	SLEC-
7	F	64	None	64	Slurred speech, gait unsteadiness	/	0	C7-T4	T2/3	Bilateral infratentorial	Gait unsteadiness and slurred speech improved	SLEC-
8	M	55	None	54	Gait unsteadiness, hearing loss	/	1	C2-T7	T2/3	Bilateral infratentorial	Gait unsteadiness and hearing loss improved	SLEC-
9	F	51	None	51	Gait unsteadiness	/	0	C7-L1	T11/12	Brainstem, cerebellum	Gait unsteadiness improved	SLEC-

Case	Sex	Age at surgery, years	Age at onset of orthostatic headaches, years	Age at onset of SS, years	SS symptoms	Latency, orthostatic headaches—SS, years	Latency, SS—surgery, years	SLEC	CSF leak level	Location SS deposits	Clinical follow-up	Radiological follow-up
10	M	61	46	[a]	Gait unsteadiness	/	/	C5-T12	T1/2	Brainstem, cerebellum bilateral	Gait unsteadiness and orthostatic headaches improved	SLEC-
11	F	55	55	[b]	None	/	/	C7-T10	T6/7	Cerebellum	Orthostatic headaches improved	SLEC-
12	F	57	55	[b]	None	/	/	T1-5	T4/5	Cerebellum bilateral	Orthostatic headaches improved	SLEC-

Abbreviations: /, does not apply; CSF, cerebrospinal fluid; F, female; M, male; SLEC, spinal longitudinal extrathecal collection; SLEC-, full regression of SLEC; SS, superficial siderosis. [a]Insufficient historical data to determine the onset of symptoms and the corresponding latency period.
[b]No report of SS symptoms.

Statistical analysis

Analyses were performed using the R software (version R 4.0.4) through the studio interface version 1.4.1106. We used Fisher exact test to determine whether there was a statistically significant association between the time since siderosis symptom onset and symptom improvement. First, patients were categorized into two groups based on the time since siderosis symptom onset: early presenters (≤3 years) and late presenters (>3 years). Then, we constructed a 2×2 contingency table, crossing the two groups of patients with their binary outcomes (improved symptoms or stable symptoms). To investigate the association between the presence of SLECs and progression to SS, we conducted a Fisher exact test. Probability values of <0.05 were considered statistically significant.

RESULTS

Patient identification

Of 142 patients treated for SIH at both institutions during the inclusion period, 95 had a ventral spinal CSF leak, and in total, we identified 12 patients with SS. Among them, six were female (Table 1, Figure 1). All patients had predominantly infratentorial hemosiderin

FIGURE 1 Study flow chart. Twelve patients with hemosiderin deposits were identified from two neurosurgical centers, 10 of whom had classical superficial siderosis symptoms (gait unsteadiness, bilateral hearing loss, and limb weakness). CSF, cerebrospinal fluid; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; MRI, magnetic resonance imaging.

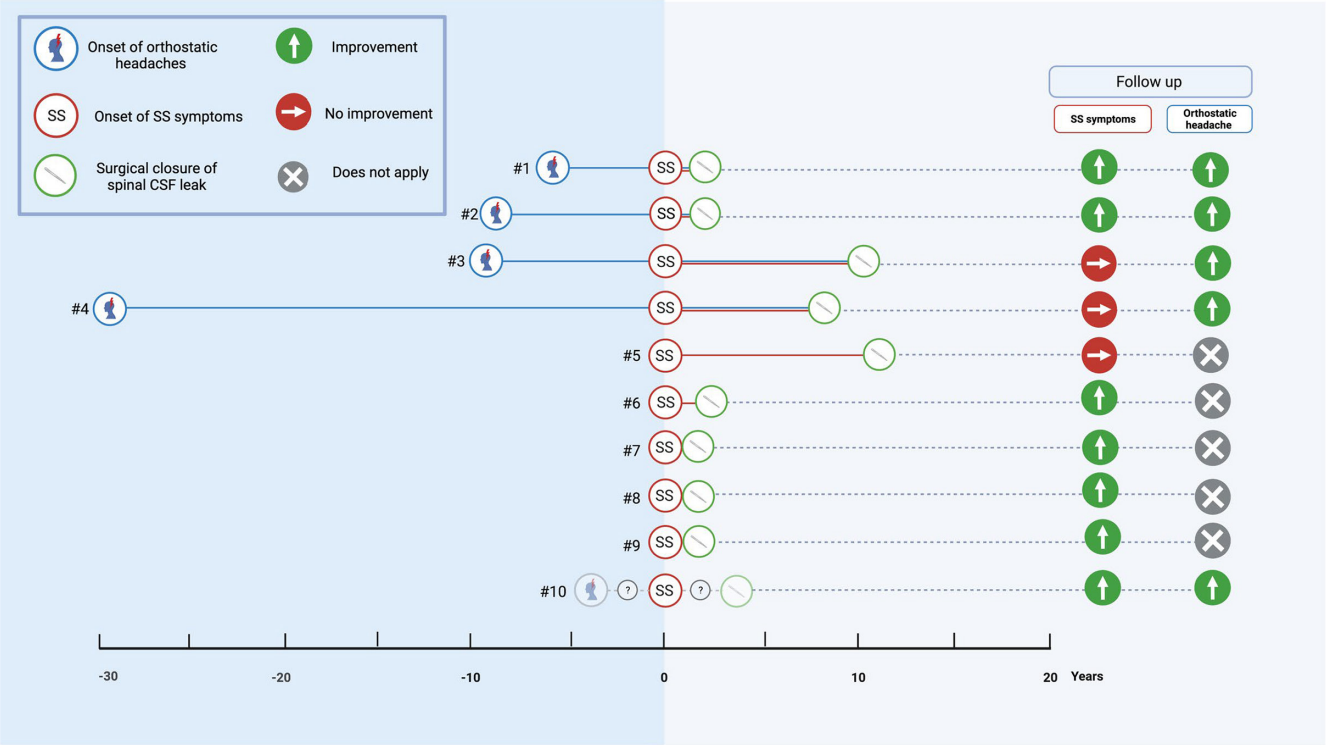

FIGURE 2 Timeline of events in patients with spontaneous ventral spinal cerebrospinal fluid (CSF) leaks and superficial siderosis (SS) of the central nervous system (for Case 10, insufficient historical data were available to calculate the latency times accurately; the patient did, however, report a history of orthostatic headaches and SS; he improved in both after surgery). Note the long latency time between the onset of orthostatic headaches and the beginning of SS symptoms (7–29 years, median = 9.5 years). All but three patients (Cases 3–5) improved in terms of SS symptoms after surgery. Patients who improved presented within 1–3 years after the onset of SS symptoms, and patients lacking clinical improvement presented after 8–12 years. Orthostatic headaches improved in all patients, independent of prior symptom duration. Patients 11 and 12 (Table 1) are left off due to lack of SS symptoms. Created with BioRender.com.

deposits. In addition, all patients demonstrated an SLEC due to a ventral spinal CSF leak caused by discogenic microspurs. All ventral spinal CSF leaks were intraoperatively confirmed and microsurgically sealed. The mean age at surgical closure was 59 years. No significant comorbidities were reported in the whole cohort.

Clinical features

Ten patients reported one or multiple classical symptoms attributed to SS (i.e., gait unsteadiness, imbalance, hearing loss). Two patients had hemosiderin deposits without reporting any typical symptoms of SS (Table 1, Cases 11 and 12). Seven patients reported a history of orthostatic headaches; in four patients, we had sufficient historical data to calculate the latency between the onset of orthostatic headaches and the onset of typical symptoms of SS; the median latency was 9.5 years (7–29 years). The graphical representation in Figure 2 visualizes the latency period between the onset of orthostatic headaches and the beginning of classical SS-related symptoms (Figure 2, Cases 1–4).

The average follow-up after surgery was 6.8 months. Seven of the 10 symptomatic patients reported improvement of SS-related symptoms. Three patients reported stable symptoms (Table 1, Figure 2, Cases 3–5). The two patients with asymptomatic hemosiderin deposits on brain MRI did not develop symptoms. Patients who improved presented between 1 and 3 years after the onset of symptoms of SS, as opposed to patients who presented between 8 and 12 years, who did subsequently not improve (Table 1, Figure 2). Clinical neurological examination and assessment found improvement in ataxia and gait in seven of 10 patients at the follow-up. Hearing loss was stable regarding audiometry in seven of 10 patients.

With the microsurgical closure of the spinal CSF leak, orthostatic headaches of all symptomatic patients improved (Table 1, Figure 2). On follow-up spinal MRI imaging, epidural CSF collections (i.e., SLECs) ultimately resolved in all patients (Table 1).

In one patient, serial MRI imaging showed the development of SS in the presence of an untreated spinal CSF leak (Figure 3). The patient initially had orthostatic headaches and extradural fluid collections on MRI and was treated with multiple blood patches at other institutions, which did not provide long-term improvement. No further actions were taken, and 7 years later, the patient developed gait unsteadiness, imbalance, and falls, which were found to reflect cerebellar gait ataxia during the neurological examination, upon which SS was discovered on imaging, and SLECs were still present. Eventually, a ventral spinal CSF leak was diagnosed at our institution and treated microsurgically. The patient's symptoms improved after surgery (Figure 3).

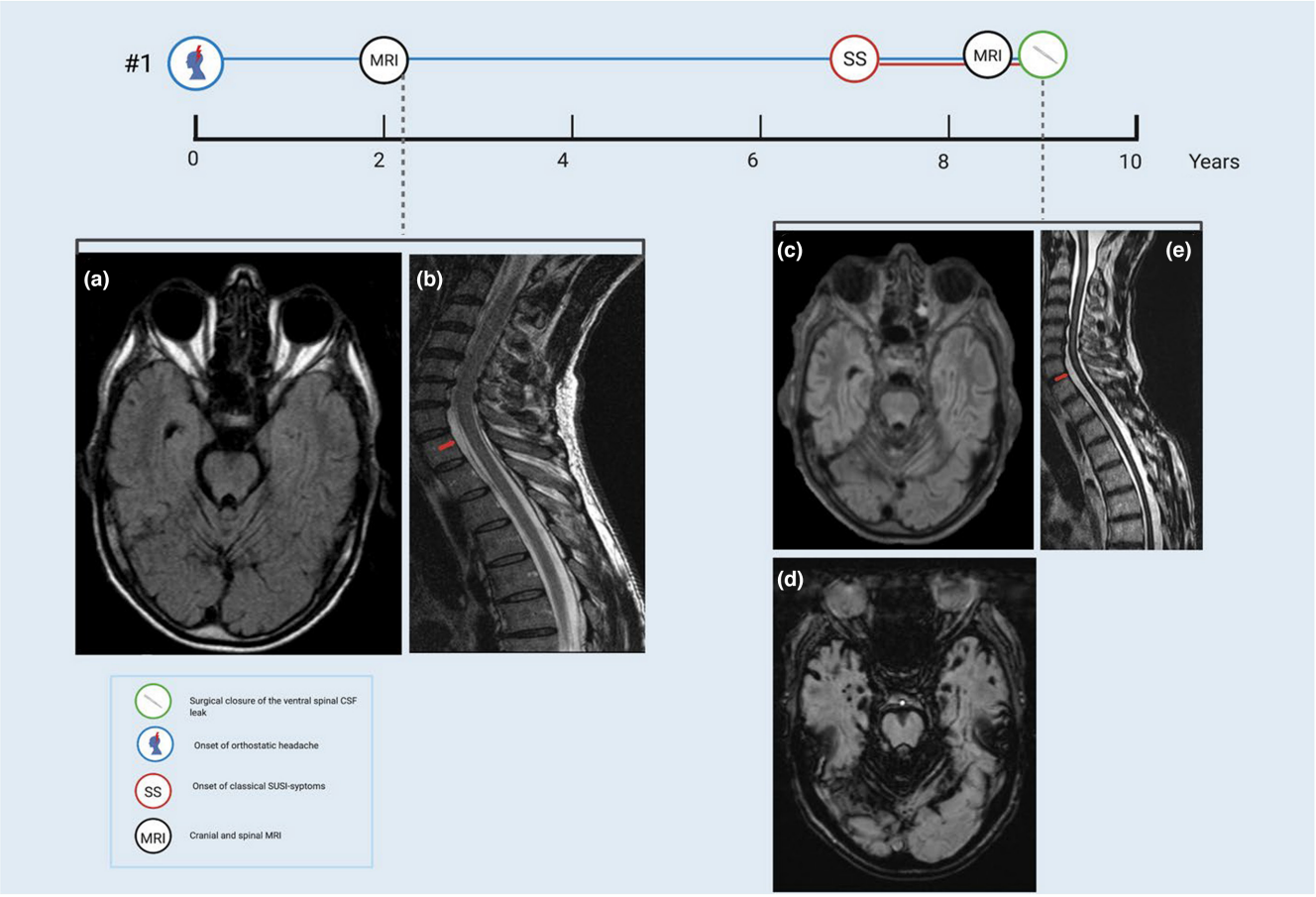

FIGURE 3 Timeline of events in one prototypical patient with a long-standing untreated ventral spinal cerebrospinal fluid (CSF) leak (Table 1, Figure 2, Case 1). Consecutive magnetic resonance imaging (MRI) shows the development of superficial siderosis (SS) in the presence of a ventral spinal CSF leak. This patient developed orthostatic headaches at the age of 47 years and was seen to have spinal longitudinal fluid collections (SLECs) on MRI without signs of hemosiderin deposits (a, b). He was treated with multiple epidural blood patches, none of which had a lasting effect on his symptoms. By the age of 54 years, he started to suffer from gait ataxia. Infratentorial hemosiderin deposits were noted on the newly obtained MRI (c–e). SLECs were still present and unchanged. During workup at our institution, a ventral spinal CSF leak was identified and microsurgically closed. This case illustrates the development of SS in the presence of an untreated spinal CSF leak. Created with BioRender.com.

Fisher exact test yielded a *p*-value of 0.01, a statistically significant association between the time since symptom onset and symptom improvement in patients with SS who underwent surgical closure of spinal CSF leaks. These findings suggest that patients presenting earlier in the disease course are more likely to experience improvements in their symptoms following the surgical intervention.

Whereas all patients (100%) with SS were SLEC-positive and had a surgically proven spinal ventral CSF leak, only 95 of 130 SS-negative patients were SLEC-positive. Fisher exact test revealed a statistically significant association between the presence of SLECs and the development of SS in our patient cohort ($p = 0.03$).

DISCUSSION

As shown by this surgical series, representing a large cohort of patients with both SS and ventral spinal CSF leaks, surgical closure of spinal CSF leaks is a potentially highly effective treatment of SS. The chronological events found in our cohort support the hypothesis that long-standing, untreated ventral spinal CSF leaks can lead to SS. Additionally, in the presence of an untreated ventral spinal CSF leak, we exhibited a case of spinal CSF leak and the gradual emergence of SS on follow-up brain MRI (Figure 3). We provide evidence that even long-standing symptoms of SS are improved by surgical closure of spinal CSF leaks (70%) or the clinical decline can be stopped (30%). On the other hand, surgical closure of the leak improved patients only if performed early, based on this series, that is, no longer than 2 years after the diagnosis of SS.

Our findings imply that all SS patients without solid evidence of other causes need to be scrutinized for spinal CSF leaks with subsequent surgical closure of respective ventral spinal CSF fistulas.

Additionally, we assume that surgery should not be delayed, because there might be a threshold beyond which some symptoms may not be fully reversible. Finally, due to the rarity of the disease, our treatment paradigm should be evaluated in a prospective multicenter study.

That spinal CSF leaks are causally linked to SS has been proposed for several years [4, 11, 13, 15–17]. A recent comprehensive study by Schievink et al. in 2023 elucidated that infratentorial SS can develop in almost 3.6% of a CSF leak cohort [28]. A recent review by Kumar describes CSF leaks as a significant etiology of SS [29]. We observed latency of several years between the onset of orthostatic headaches and the onset of SS (Figure 2). Additionally, in the presence of an untreated ventral spinal CSF leak, we demonstrated the gradual emergence/development of SS on follow-up brain MRI (Figure 3). The chronological events found within this surgical series of 12 patients supports the hypothesis that long-standing, mostly over several years, untreated ventral spinal CSF leaks can lead to SS.

Single case reports have shown that SS symptoms improved after surgical sealing of a spinal CSF leak [16, 18, 21]. We investigated this claim in our surgically treated cohort and showed that SS symptoms improved after surgery or did not progress during follow-up. The latency between the onset of SS symptoms and the timepoint of surgery seems to be very important, because only patients with a relatively short time interval from diagnosis (approximately 1 year) of SS to surgery improved (Figure 2). This observation was especially striking in patients who were treated a couple of months after the onset of SS symptoms (Figure 2, Cases 7–9). We can only speculate on the possible pathophysiological mechanisms behind this. The clinical improvement of SS coincides with the normalization of the MRI with respect to SLECs and brain sagging. We think that SS is a late sequela of a persisting spinal CSF leak and, therefore, SIH. SS represents a continuum of the same pathophysiology.

The hypothesis regarding the development of SS in CSF leak patients involves iterative minor intrathecal bleeding arising from the dura due to the presence of a spinal CSF leak. The bleeding may be due to tearing of the spinal dura at the leak level, causing the formation of small new vessels at the tear site and probably repetitive minor bleeding, leading finally to SS. Our findings support the hypothesis that SLECs, as an indicator of ventral CSF leaks, are closely associated with the development of SS. This mechanism may stop once the spinal pathology is surgically repaired. A recent comprehensive study by Schievink et al. in 2023 came to the same conclusion. Although infratentorial SS can develop in various types of spinal CSF leaks, it predominantly emerges from chronic ventral CSF leaks [28].

We do not have data yet on whether this improvement will last, because the free iron products that are already present will most likely continue to exert their toxic effects on the CNS [5]. Thus, despite finding intriguing results, we need to await long-term follow-up from a prospective multicenter trial.

Our surgical results compare favorably to other treatments of SS, like iron chelators such as deferiprone. Clinical response to deferiprone in small observational case series was mixed, with ongoing clinical progression in up to 37% of patients despite treatment [5, 30, 31]. Moreover, deferiprone was poorly tolerated, with up to 40% of patients withdrawing from treatment [32, 33].

Our results also reflect SS's slowly progressive disease course [7]. Despite having classical hemosiderin deposits seen as blooming pial artifacts on gradient echo MRI, two of our patients were asymptomatic (Figure 2, Cases 11 and 12). One hypothesis might be that hemosiderin deposits seen on gradient-echo MRI are formed from ferritin and iron, and we do know that neurotoxicity comes mainly from free iron [34, 35]. The latter occurs when the glial cells no longer produce enough ferritin to bind the free iron. Early CSF leak treatment may have stopped repeated minor bleeding and allowed the glial cell to clear the free iron without symptom development.

As illustrated in Figure 2 and Table 1, some patients did not report orthostatic headaches. In SIH, some patients commonly complain only of a brief period of orthostatic headaches, which may subside [36–40]. There are additional oligosymptomatic patients not reporting orthostatic headaches with subtle symptoms of brain fog or cognitive decline that need to be actively asked for [7, 41].

It is noteworthy to highlight that the understanding regarding the emergence of SS from spinal CSF leaks has historically stemmed from the research at specialized CSF leak referral centers, notably the work of Schievink et al. in 2023 [28]. Our study provides a robust validation of these earlier insights focusing on the outcome of patients after CSF leak treatment. As unveiled in our research, the prevalence of SS in patients with spinal leaks is remarkable. Recognizing the simultaneous presentation of both conditions is vital and stresses the need for the medical community to be vigilant of the intertwined nature of these diseases.

The current results corroborate previous reports that long-standing untreated ventral spinal CSF leaks can lead to SS of the CNS. The risk of developing severe long-term sequelae is significant among patients with a persistent ventral spinal CSF leak. For the first time in a larger cohort, we were able to show that microsurgical sealing of spinal CSF leaks might stop progression or even might improve symptoms in patients with SS in a time-dependent manner.

LIMITATIONS

All the constraints of retrospective studies apply. These cohorts, consisting of patients with spontaneous intracranial hypotension, are from referral centers and, therefore, highly selected. Incidence may be overstated, limiting the generalization of results. Despite being the largest series, the number of patients with this rare disease remains limited. Follow-up studies with more significant numbers of patients and extended follow-up periods are needed to substantiate our hypothesis, as well as prospective multicenter trials.

CONCLUSIONS

We strongly recommend searching for spinal CSF leaks in all patients with SS with a thorough workup. Based on the current findings, we

conclude that early treatment of ventral spinal CSF leaks is justified in patients with and without SS.

AUTHOR CONTRIBUTIONS

Benedikt Haupt: Conceptualization; investigation; writing – original draft; writing – review and editing; data curation. **Christian Fung:** Conceptualization; methodology; resources; writing – review and editing; project administration; supervision. **Debora Cipriani:** Writing – review and editing; data curation. **Levin Häni:** Investigation; writing – review and editing; data curation. **Tomas Dobrocky:** Writing – review and editing; data curation. **Oliver Schnell:** Writing – review and editing; data curation; supervision. **Andreas Raabe:** Writing – review and editing; data curation; supervision; resources. **Katharina Wolf:** Writing – review and editing; data curation. **Horst Urbach:** Writing – review and editing; resources. **Luisa Mona Kraus:** Writing – review and editing; data curation. **Florian Volz:** Writing – review and editing; project administration. **Jürgen Beck:** Writing – review and editing; project administration; resources; supervision; conceptualization; methodology.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Amir El Rahal https://orcid.org/0000-0002-8250-5883
Levin Häni https://orcid.org/0000-0001-7892-7138
Katharina Wolf https://orcid.org/0000-0003-1468-3634
Florian Volz https://orcid.org/0000-0001-7274-519X
Jürgen Beck https://orcid.org/0000-0002-7687-6098

REFERENCES

1. Beck J, Fung C, Ulrich CT, et al. Cerebrospinal fluid outflow resistance as a diagnostic marker of spontaneous cerebrospinal fluid leakage. *J Neurosurg Spine*. 2017;27(2):227-234. doi:10.3171/2017.1.SPINE16548
2. Mokri B. Spontaneous intracranial hypotension. *Continuum (Minneap Minn)*. 2015;21(August):1086-1108. doi:10.1212/CON.0000000000000193
3. Beck J, Ulrich CT, Fung C, et al. Diskogenic microspurs as a major cause of intractable spontaneous intracranial hypotension. *Neurology*. 2016;87(12):1220-1226. doi:10.1212/WNL.0000000000003122
4. Schievink WI, Maya MM, Nuño M. Chronic cerebellar hemorrhage in spontaneous intracranial hypotension: association with ventral spinal cerebrospinal fluid leaks. *J Neurosurg Spine*. 2011;15(4):433-440. doi:10.3171/2011.5.SPINE10890
5. Kessler RA, Li X, Schwartz K, Huang H, Mealy MA, Levy M. Two-year observational study of deferiprone in superficial siderosis. *CNS Neurosci Ther*. 2018;24(3):187-192. doi:10.1111/cns.12792
6. Wilson D, Chatterjee F, Farmer SF, et al. Infratentorial superficial siderosis: Classification, diagnostic criteria, and rational investigation pathway. *Ann Neurol*. 2017;81(3):333-343. doi:10.1002/ana.24850
7. Kumar N. Beyond superficial siderosis: Introducing "duropathies". *Neurology*. 2012;78(24):1992-1999. doi:10.1212/WNL.0b013e318259e272
8. Kumar N. Neuroimaging in superficial siderosis: an in-depth look. *Am J Neuroradiol*. 2010;31(1):5-14. doi:10.3174/ajnr.A1628
9. Kumar N, Cohen-Gadol AA, Wright RA, Miller GM, Piepgras DG, Ahlskog JE. Superficial siderosis. *Neurology*. 2006;66(8):1144-1152. doi:10.1212/01.wnl.0000208510.76323.5b
10. Linn J, Herms J, Dichgans M, et al. Subarachnoid hemosiderosis and superficial cortical hemosiderosis in cerebral amyloid angiopathy. *Am J Neuroradiol*. 2008;29(1):184-186. doi:10.3174/ajnr.A0783
11. Kumar N, Miller GM, Piepgras DG, Mokri B. A unifying hypothesis for a patient with superficial siderosis, low-pressure headache, intraspinal cyst, back pain, and prominent vascularity. *J Neurosurg*. 2010;113(1):97-101. doi:10.3171/2009.10.JNS091125
12. Hoxworth JM, Patel AC, Bosch EP, Nelson KD. Localization of a rapid CSF leak with digital subtraction myelography. *Am J Neuroradiol*. 2009;30(3):516-519. doi:10.3174/ajnr.A1294
13. Holle D, Sandalcioglu IE, Gizewski ER, et al. Association of superficial siderosis of the central nervous system and low pressure headache. *J Neurol*. 2008;255(7):1081-1082. doi:10.1007/s00415-008-0822-x
14. Schievink WI, Maya MM, Jean-Pierre S, Nuño M, Prasad RS, Moser FG. A classification system of spontaneous spinal CSF leaks. *Neurology*. 2016;87(7):673-679. doi:10.1212/WNL.0000000000002986
15. Schievink WI, Maya MM. Spinal meningeal diverticula, spontaneous intracranial hypotension, and superficial siderosis. *Neurology*. 2017;88:2-4.
16. Takai K, Komori T, Niimura M, Taniguchi M. Superficial siderosis of the central nervous system associated with intraspinal hemorrhage from ventral thoracic epidural veins and a ventral spinal CSF leak: case report. *J Neurosurg Spine*. 2017;26(6):751-753. doi:10.3171/2016.11.SPINE16488
17. Schievink WI, Wasserstein P, Maya MM. Intraspinal hemorrhage in spontaneous intracranial hypotension: link to superficial siderosis? Report of 2 cases. *J Neurosurg Spine*. 2016;24(March):454-456. doi:10.3171/2015.6.SPINE15428.454
18. Schievink WI, Maya M. Regression of infratentorial superficial siderosis following surgical repair of a spontaneous spinal CSF leak. *Neurol Clin Pract*. 2021;11(3):e359-e360. doi:10.1212/cpj.0000000000001068
19. Schievink WI, Maya M, Moser F, Nuño M. Long-term risks of persistent ventral spinal CSF leaks in SIH: superficial siderosis and bibrachial amyotrophy. *Neurology*. 2021;97(19):E1964-E1970. doi:10.1212/WNL.0000000000012786
20. Takai K, Taniguchi M. Superficial siderosis of the central nervous system associated with ventral dural defects: bleeding from the epidural venous plexus. *J Neurol*. 2021;268(4):1491-1494. doi:10.1007/s00415-020-10319-2
21. Kumar N, Lane JI, Piepgras DG. Superficial siderosis: sealing the defect. *Neurology*. 2009;72(7):671-673. doi:10.1212/01.wnl.0000342457.22536.af
22. Olesen J. Headache classification committee of the international headache society (IHS) the international classification of headache disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211. doi:10.1177/0333102417738202

23. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12(12):1495-1499. doi:10.1016/j.ijsu.2014.07.013
24. Dobrocky T, Grunder L, Breiding PS, et al. Assessing spinal cerebrospinal fluid leaks in spontaneous intracranial hypotension with a scoring system based on brain magnetic resonance imaging findings. 2019;76:1-8. doi:10.1001/jamaneurol.2018.4921
25. Häni L, Fung C, Jesse CM, et al. Insights into the natural history of spontaneous intracranial hypotension from infusion testing. *Neurology*. 2020;95(3):E247-E255. doi:10.1212/WNL.0000000000009812
26. Piechowiak EI, Pospieszny K, Haeni L, et al. Role of conventional dynamic myelography for detection of high-flow cerebrospinal fluid leaks. *Clin Neuroradiol*. 2020;31:633-641. doi:10.1007/s00062-020-00943-w
27. Fichtner J, Ulrich CT, Fung C, et al. Sonography of the optic nerve sheath diameter before and after microsurgical closure of a dural CSF fistula in patients with spontaneous intracranial hypotension—a consecutive cohort study. *Cephalalgia*. 2019;39(2):306-315. doi:10.1177/0333102418793640
28. Schievink WI, Maya MM, Harris J, Galvan J, Taché RB, Nuño M. Infratentorial superficial siderosis and spontaneous intracranial hypotension. *Ann Neurol*. 2023;93(1):64-75. doi:10.1002/ana.26521
29. Kumar N. Superficial siderosis: a clinical review. *Ann Neurol*. 2021;89(6):1068-1079. doi:10.1002/ana.26083
30. Cossu G, Abbruzzese G, Forni GL, et al. Efficacy and safety of deferiprone for the treatment of superficial siderosis: results from a long-term observational study. *Neurol Sci*. 2019;40(7):1357-1361. doi:10.1007/s10072-019-03847-x
31. Cummins G, Crundwell G, Baguley D, Lennox G. Treatment of superficial siderosis with iron chelation therapy. *BMJ Case Rep*. 2013;2013(jul08 2):bcr2013009916-bcr2013009916. doi:10.1136/bcr-2013-009916
32. Sammaraiee Y, Banerjee G, Farmer S, et al. Risks associated with oral deferiprone in the treatment of infratentorial superficial siderosis. *J Neurol*. 2020;267(1):239-243. doi:10.1007/s00415-019-09577-6
33. Flores Martin A, Shanmugarajah P, Hoggard N, Hadjivassiliou M. Treatment response of deferiprone in infratentorial superficial siderosis: a systematic review. *Cerebellum*. 2021;20(3):454-461. doi:10.1007/s12311-020-01222-7
34. Regan RF, Panter SS. Neurotoxicity of hemoglobin in cortical cell culture. *Neurosci Lett*. 1993;153(2):219-222. doi:10.1016/0304-3940(93)90326-G
35. Rosen AD, Frumin NV. Focal epileptogenesis after intracortical hemoglobin injection. *Exp Neurol*. 1979;66(2):277-284. doi:10.1016/0014-4886(79)90080-3
36. Kranz PG, Gray L, Amrhein TJ. Spontaneous intracranial hypotension: 10 myths and misperceptions. *Headache*. 2018;58(7):948-959. doi:10.1111/head.13328
37. Mea E, Chiapparini L, Savoiardo M, Franzini A, Bussone G, Leone M. Headache attributed to spontaneous intracranial hypotension. *Neurol Sci*. 2008;29(S1):164-165. doi:10.1007/s10072-008-0914-5
38. D'Antona L, Jaime Merchan MA, Vassiliou A, et al. Clinical presentation, investigation findings, and treatment outcomes of spontaneous intracranial hypotension syndrome. *JAMA Neurol*. 2021;78(3):329. doi:10.1001/jamaneurol.2020.4799
39. Amrhein TJ, McFatrich M, Ehle K, et al. Patient experience of spontaneous intracranial hypotension (SIH): qualitative interviews for concept elicitation. *J Patient Rep Outcomes*. 2023;7(1):82. doi:10.1186/s41687-023-00625-4
40. Callen AL, Pattee J, Thaker AA, et al. Relationship of Bern score, spinal elastance, and opening pressure in patients with spontaneous intracranial hypotension. *Neurology*. 2023;100(22):e2237-e2246. doi:10.1212/WNL.0000000000207267
41. Häni L, Fung C, Marvin C, et al. Outcome after surgical treatment of cerebrospinal fluid leaks in spontaneous intracranial hypotension—a matter of time. *J Neurol*. 2021;269:1439-1446. doi:10.1007/s00415-021-10710-7

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