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Cerebrospinal fluid biomarkers of superficial siderosis in patients with spontaneous intracranial hypotension

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ABSTRACT

Background:

Spontaneous intracranial hypotension (SIH) is an important etiology of infratentorial superficial siderosis (iSS) of the central nervous system (CNS).[1–7] However, the prevalence of iSS among patients with SIH is unknown and the imaging findings of iSS might represent a late stage of disease. We aimed to identify cerebrospinal fluid (CSF) biomarkers of iSS in patients with SIH.

Methods:

We included consecutive patients evaluated for SIH at our institution between 05/2017 and 01/2019. Lumbar CSF samples were analyzed for the presence of ferritin and bilirubin. MRI was assessed for the presence of iSS.

Results:

We included 24 patients with SIH. CSF samples were positive for bilirubin in 2/19 (10.5%). CSF ferritin was elevated in 7/23 (30.4%). Signs of iSS on imaging were present in four patients (16.7%). All patients with imaging signs of iSS demonstrated elevated CSF ferritin. Ferritin level was significantly higher among patients demonstrating iSS compared to those without (median 45.0 versus 11.0 µg/l; p=0.003). Symptom duration was longer in patients with iSS than in patients without iSS (median 40 months versus 9 months, p=0.018).

Conclusion:

CSF alterations indicative of iSS are prevalent among patients with SIH. We speculate that a preclinical phase without symptoms or imaging signs, but during which elevated biomarkers of the disease are apparent from CSF analysis, might exist. We suggest

incorporating measurement of CSF ferritin in the work-up of patients with SIH to identify those at risk of developing iSS.

INTRODUCTION

Infratentorial superficial siderosis (iSS) of the central nervous system is a rare disorder presenting with ataxia and hearing loss. It is caused by chronic leakage of small amounts of blood into the cerebrospinal fluid (CSF).[1,8] Heme breakdown results in free iron and bilirubin. Free iron is bound to form ferritin and subsequently hemosiderin.[1,2] Dural pathologies have been recognized as the most important etiology of classical (type 1) infratentorial superficial siderosis (iSS).[1,2] Among them, ventral dural tears associated with spontaneous intracranial hypotension (SIH) are prevalent.[3–7,9] SIH is an important cause of incapacitating headache with an estimated incidence of 5/100'000.[10] The majority of patients with SIH suffers from a spinal CSF leak. Using dedicated neuroimaging techniques, the site of CSF leakage can be precisely determined in 71.3 - 87.0% of patients with SIH.[11,12]

However, the prevalence of iSS among patients with SIH is unknown and imaging findings of iSS might represent a late stage of disease. Therefore, we aimed to identify potential biomarkers of iSS by analyzing the CSF of consecutive patients with SIH.

METHODS

Standard protocol approvals

We conducted a retrospective study, which was approved by the local ethics committee of the canton of Bern, Switzerland (2020-00645). Informed consent for further use of

healthcare data was provided by the patients using the general consent form. The study data are available and will be shared upon reasonable request.

Patient population

We included consecutive patients diagnosed with SIH and a confirmed spinal CSF leak treated at our institution between 05/2017 and 01/2019. CSF leaks were confirmed by dynamic myelography and computed tomography (CT)-myelography. Routine clinical testing for SIH involves lumbar puncture, either for exclusion of differential diagnosis, measurement of CSF pressure, lumbar infusion testing and/or myelography. In this context, CSF samples were drawn and analyzed for blood breakdown products. We excluded patients without a CSF sample and patients who had undergone intradural spinal or cranial surgery within the past five years.

The diagnosis of SIH was based on the International Classification of Headache Disorders,[13] with a minor modification. The modification consisted of including patients without headaches, if imaging was consistent and their symptoms best explained by SIH.[5]

Data analysis

CSF spectrophotometry of net bilirubin absorbance (NBA) and net oxyhemoglobin absorbance (NOA) was assessed according to Cruickshank et al.[14] Spectrophotometry was considered positive for bilirubin if NBA >0.007 and NOA >0.020. If the absorbance of oxyhemoglobin was high enough to interfere with NBA measurement, the result was considered inconclusive in accordance with the guidelines.[14] CSF ferritin was estimated by electrochemiluminescence immunoassay on a Cobas 8000 analyzer

(Roche Diagnostics, Rotkreuz, Switzerland) and values > 15 µg/l were considered positive.[15]

Superficial siderosis was defined as bilateral, symmetrical low signal on blood-sensitive sequences (T2* or susceptibility weighted MRI [SWI]) or, if unavailable, T2 sequences over the superficial regions of the brainstem and/or cerebellum.[2] We graded superficial siderosis on imaging as mild (purely infratentorial on SWI/T2*, no or only thin rim on T2), moderate (supra- and infratentorial on SWI/T2*, thin rim on T2) or severe (supra- and infratentorial on SWI/T2*, thick rim on T2).[2] Intensity of headaches was rated on the numeric rating scale (NRS) 0-10 in the upright position.

Statistics

Statistical analysis was performed using the statistical software SPSS (IBM, Version 25.0). We compared continuous variables with a Mann-Whitney U test and nominal variables with a chi squared test. We assessed the association between variables and siderosis grading as dependent, ordinal variable, by performing a univariate ordinal logistic regression analysis. Model fitting was assessed using a Likelihood Ratio Chi-Square statistic. We addressed missing data, if no value was retrievable, by pairwise deletion.

RESULTS

Patient population

During the study period, 33 patients undergoing a diagnostic work up at our institution were diagnosed with SIH. We excluded three patients due to previous spinal or cranial surgery, five due to lack of CSF samples, and one patient because no myelography was performed to determine the presence of a CSF leak. Thus, our study group

comprised 24 patients with SIH with a confirmed spontaneous spinal CSF leak. Mean age was 44.8 years (± 8.5) and 15 patients (62.5%) were female. All except one patient complained initially of orthostatic headache (95.8%). Nine patients (37.5%) reported tinnitus or hearing disturbances and five patients (20.8%) reported subjective gait imbalance. Clinical examination was unremarkable in all except one patient, who demonstrated bibrachial amyotrophy with bilateral arm abduction weakness. Table 1 displays demographic and clinical features of the study population. Four patients (16.6%) were treated with epidural blood patch (EBP) only, while three patients (12.5%) were treated solely surgically and 17 (70.8%) underwent surgical closure of the CSF leak after failure of EBP. Thirteen patients (54.2%) had an EBP before CSF analysis with a median time interval of 2 months.

CSF and imaging analysis

CSF spectrophotometry of NBA and NOA was available for 19 patients. The results indicated the presence of bilirubin in two patients (10.5%). Four patients (21.1%) had inconclusive spectrophotometry results. CSF ferritin measurements were available for 23 patients. Samples from seven of them (30.4%) demonstrated an elevated ferritin level. Red blood cells (RBC) in the CSF were analyzed in 21 patients and found in 14 of them (66.7%).

On imaging, four patients (16.7%) exhibited findings of iSS (figure 1). While three of them demonstrated a moderate degree, one demonstrated a mild degree of siderosis. All four of these patients had elevated ferritin. Furthermore, ferritin level was significantly higher among patients demonstrating iSS compared to those without (median 45.0 versus 11.0 µg/l; p=0.003, figure 2). Among the four patients with iSS on imaging, three demonstrated RBC in the CSF, and RBC were not measured in the

fourth patient. The amount of RBC did not differ between patients with and without iSS (p=0.471), and between patients with and without elevated CSF ferritin (p=0.131).

Symptom duration was longer in patients with iSS than in patients without iSS (median 40 months versus 9 months, p=0.018). When analyzing only patients with elevated ferritin levels, those with iSS also tended to present with a longer duration of symptoms compared to those without iSS (median 40 months versus 1 month, p=0.100). When analyzing symptom duration and siderosis grading in an ordinal regression analysis, a non-significant trend towards higher degree of siderosis with longer symptom duration was obtained (p=0.067, figure 3). Likewise, a trend towards higher CSF pressure with increasing siderosis grade was found, but no significant model was obtained (p=0.079, figure 3).

Both patients who were positive for CSF bilirubin also demonstrated elevated CSF ferritin but had no imaging signs of iSS. Interestingly, they both reported a short duration of SIH-related symptoms of only one month.

Performance of an EBP before CSF sampling had no influence on ferritin levels (p=0.393)

DISCUSSION

Our results showed evidence of blood breakdown products in the CSF in 30.4% of patients with SIH. However, only half of them demonstrated iSS on brain imaging. Patients with iSS on imaging presented with a longer symptom duration. We speculate that CSF alterations might precede the appearance of radiological signs of iSS.

Because iSS frequently develops several years after an untreated spinal CSF leak, the radiological features might represent a late stage of the disease.[5] Hemosiderin

deposits have to accumulate in the CSF to become apparent in brain MRI. Thus, there could be a preclinical phase without symptoms or imaging signs of iSS, but during which biomarkers of the disease evident on CSF analysis are already elevated. Because iSS is a progressive disorder, and heme and free iron could lead to irreversible neuronal damage, early recognition and treatment of affected patients could offer an opportunity to prevent further clinical deterioration. If untreated, the cumulative neurotoxic effect of heme and free iron has the potential to result in neurodegeneration.

CSF ferritin is more sensitive than bilirubin for the detection of recurrent hemorrhages, because CSF ferritin remains elevated for up to a several months after hemorrhage, whereas CSF bilirubin levels normalize within weeks.[16] After subarachnoid hemorrhage, CSF ferritin levels peak between day 7 and day 11.[17,18] Our study did not include a healthy control group. But, using the same assay as in our study, Barateau et al. reported a median and maximal CSF ferritin level of 4.9 and 12 µg/l among 38 healthy patients referred for non-specific sleepiness complaints.[19] The cut-off of 15 µg/l for CSF ferritin is fairly specific, even though false-positives occur in patients with other conditions such as encephalitis, meningitis and tumors.[15,20]

We found a non-significant trend towards higher siderosis grading on imaging with increasing CSF pressure. A longer symptom duration in patients with iSS might explain this finding, because a longer symptom duration is associated with a higher CSF pressure in patients with SIH.[21] In turn, one could speculate that normalization of CSF pressure over time might reduce brain sagging. This would support the hypothesis that blood in the CSF in patients with SIH does not originate from tearing of cerebellar veins, but rather originates from the site of spinal CSF leakage.[6]

It is important to note that lumbar puncture is not mandatory for the diagnosis of SIH. The opening pressure is within normal range in 44-62% of cases and its measurement therefore of limited value.[21–24] Nevertheless, many patients undergo lumbar puncture either to exclude differential diagnosis, or for diagnostic myelography.

Interestingly, one patient with iSS on imaging also developed bibrachial amyotrophy in our study. It is unclear, whether bibrachial amyotrophy is a consequence of SIH per se or develops in relation to iSS. It has been suggested, that bibrachial amyotrophy in patients with SIH is caused by stretching of the cervical nerve roots over the extradural CSF collection, or by chronic dynamic pressure upon the ventral cervical spinal cord by the extradural fluid collection.[5,25] However, Schievink et al. and Driver-Dunckley et al. reported two cases suffering from bibrachial amyotrophy and concomittand iSS.[5,26] Consequently, one could speculate that the association between bibrachial amyotrophy and iSS is not coincidental, but causal. The neurotoxic effect of heme and free iron might damage cervical nerve roots and thereby produce symptoms of bibrachial amyotrophy. However, further studies are necessary to explore this association.

Our analysis has some important limitations. We obtained the results in a single center retrospective study on a limited number of patients. Untreated SIH per se might produce complaints similar to iSS, such as hearing disturbances and gait imbalance. However, Schievink et al. reported the occurrence of hearing loss and ataxia among patients who developed iSS in the context of untreated SIH over many years.[5] These authors reported that symptomatic patients demonstrated a more extensive burden of hemosiderin deposits than asymptomatic patients who developed iSS.[5] In line with this finding, the patient with the longest duration of symptoms in our cohort presented with iSS and concomitant bibrachial amyotrophy. Nevertheless, patients with SIH with iSS

differ in clinical presentation from classical iSS without SIH. We speculate that the accumulation of neuronal damage caused by chronic heme and free iron burden might produce symptoms only after a long period of exposure. Because of incapacitating headaches and a remarkable impact on the quality of life[27], patients with SIH might seek medical attention earlier. Consequently, diagnosis and/or treatment ensues before classical symptoms of iSS, such as deafness and myelopathy, occur.

Our findings have several clinical implications. Firstly, in patients with SIH with a spinal CSF leak and minimal or no symptoms, closure of the leak can be considered in order to prevent the development of iSS. Measurement of CSF ferritin can reinforce this decision, if elevated. Secondly, measurement of CSF ferritin should be integrated into the work-up of patients with SIH in order to identify individuals at risk of developing iSS. In patients with elevated baseline CSF ferritin, a prolonged follow-up and repeat measurement of CSF ferritin after treatment might be prudent, in order to identify non-responders who should be considered for further diagnostic or therapeutic interventions. Thirdly, clinicians should search and treat a spinal CSF leak in patients with iSS, even in the absence of typical orthostatic headaches. For patients with SIH, closure of the CSF leak represents a causal and definitive treatment.[28] Evidence concerning the impact of closure of the CSF leak on iSS and CSF ferritin is limited.[29,30] A case report by Lobo et al. demonstrated a marked reduction of CSF ferritin after surgical treatment of SIH in a patient with iSS.[31]

To conclude, our results suggest that CSF alterations indicative of iSS are prevalent among patients with SIH and might precede the radiological appearance of signs of iSS. We suggest integrating the measurement of CSF ferritin into the work-up of patients with SIH and building an international database to identify patients who are potentially at risk of developing iSS.

CONTRIBUTORS

Designed and conceptualized study: LH, CF, JB

Data acquisition: LH, CMJ, CS, EIP, TD

Analyzed the data: LH, CF

Interpreted data: LH, CF, AR, JB

Drafted manuscript: LH, CF, JB

Revised manuscript for intellectual content: CMJ, CS, EIP, TD, AR

Disclosure/conflict of interest:

The authors report no disclosures or conflict of interests relevant to the manuscript.

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The statistical analysis was performed by Levin Häni (Department of Neurosurgery, Bern University Hospital, Bern Switzerland).

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subarachnoid bleeding in classical infratentorial superficial siderosis. Neurol Sci. 2022;Epub 2022 Jun.

FIGURE LEGEND

Figure 1

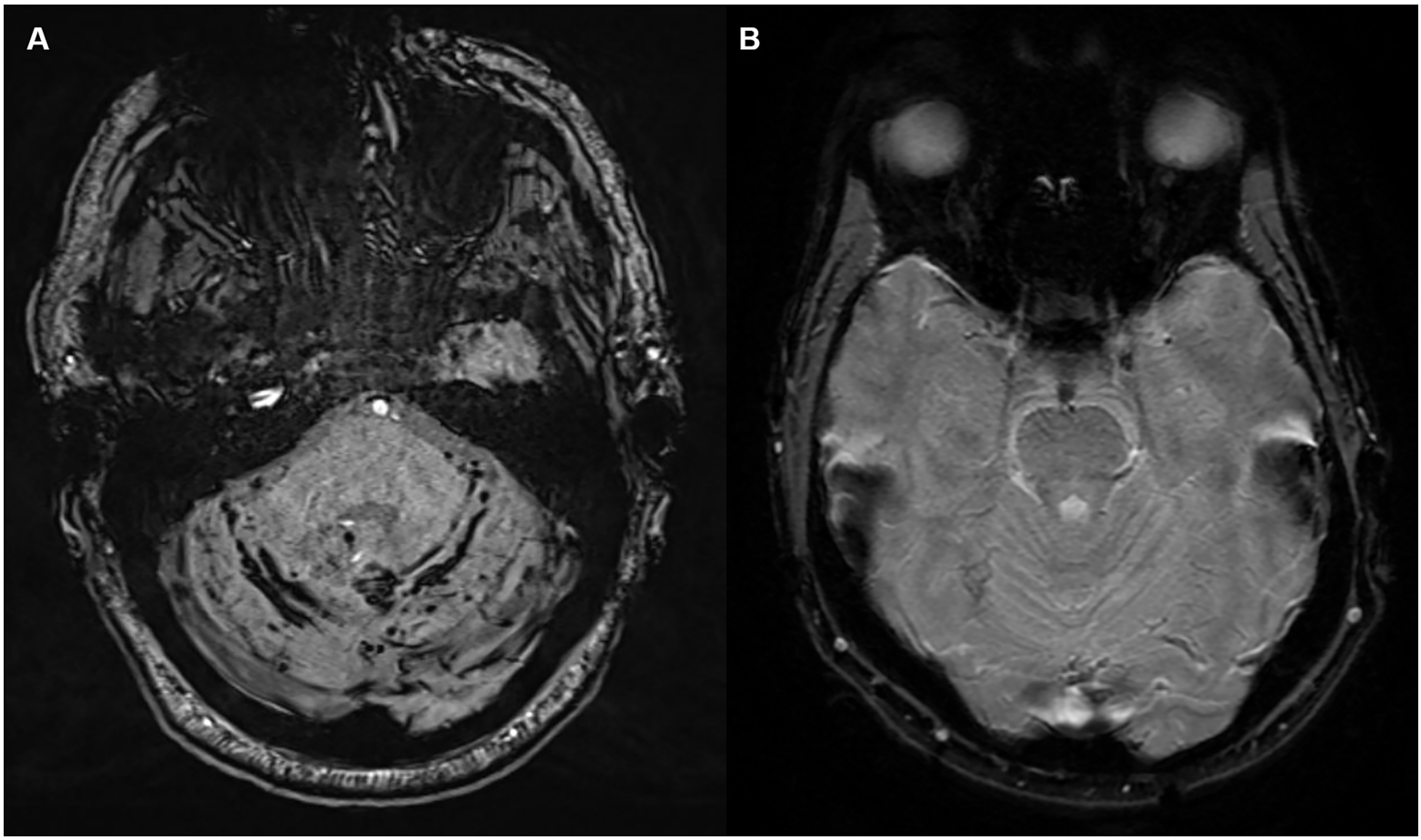
A: Patient 22 demonstrating superficial siderosis on SWI with preponderance over the cerebellar vermis. CSF ferritin level was 36 µg/l. B: No signs of siderosis on T2* imaging are evident in patient 1, despite a symptom duration of 54 months. CSF ferritin level was 11 µg/l.

Figure 2

Comparison of CSF ferritin levels among patients with SIH with and without infratentorial superficial siderosis on imaging. The solid line indicates the median. The horizontal line indicates the cut-off of 15 µg/l. The box covers the interquartile range from the first to the third quartile. T-bars display minimum and maximum values, whereby outliers (more than 1.5× interquartile range from the first or third quartile) are displayed separately. Ferritin levels were significantly higher among patients who exhibited iSS on imaging compared to those who did not (median 45.0 versus 11.0 µg/l; p=0.003).

Figure 3

Boxplots displaying association between siderosis grade and symptom duration (A) as well as between siderosis grade and CSF pressure (B). On imaging, we graded superficial siderosis as none (n=20), mild (purely infratentorial on SWI/T2*, no or only thin rim on T2; n=1), moderate (supra- and infratentorial on SWI/T2*, thin rim on T2; n=3) or severe (supra- and infratentorial on SWI/T2*, thick rim on T2; n=0). CSF pressure was measured lumbar in the lateral decubital position. The median is indicated by a horizontal bar. The box covers the interquartile range from the first to the third quartile. Whiskers display minimum and maximum values, whereby outliers (more than 1.5x interquartile range from first or third quartile) are displayed separately.



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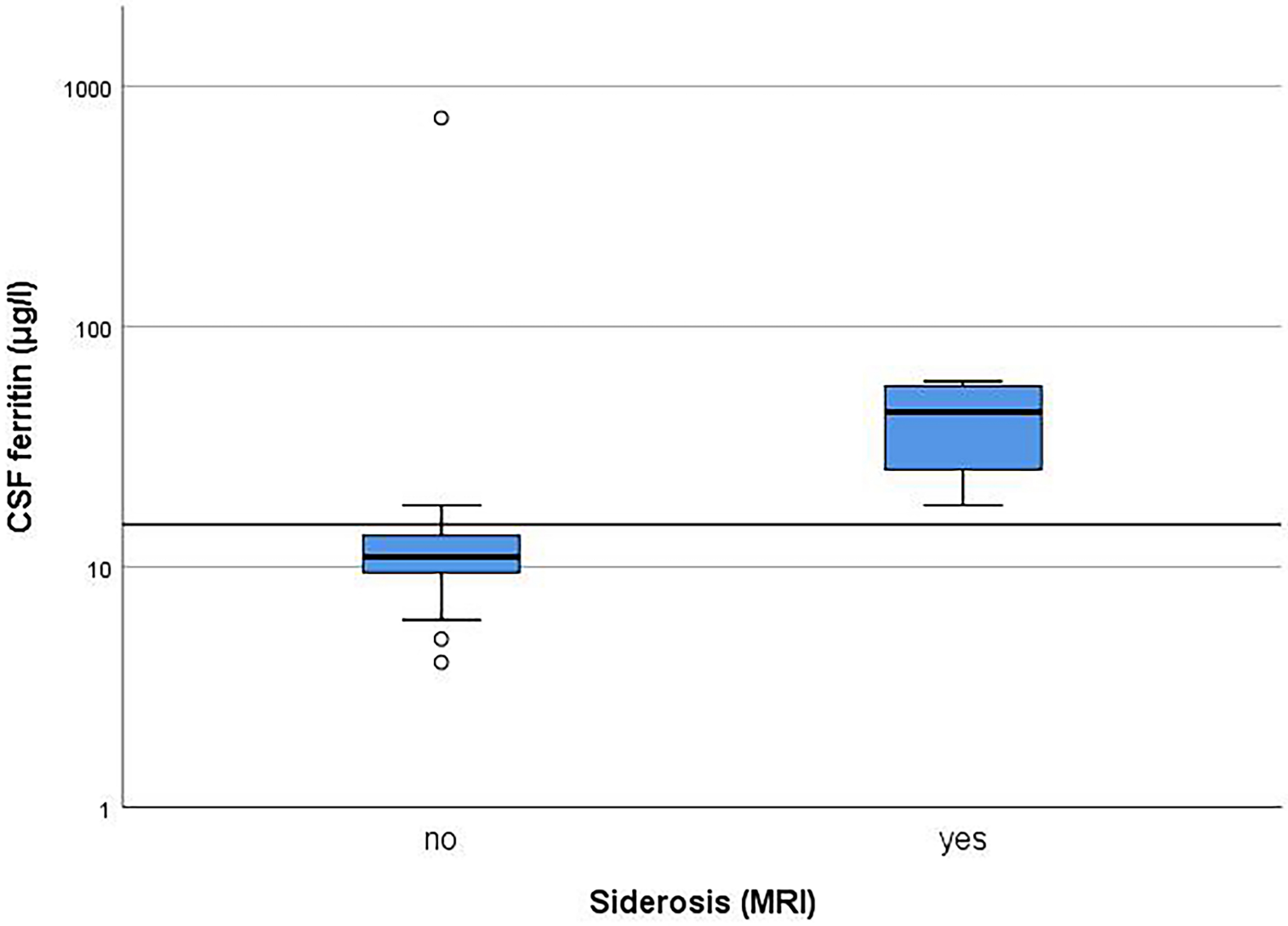

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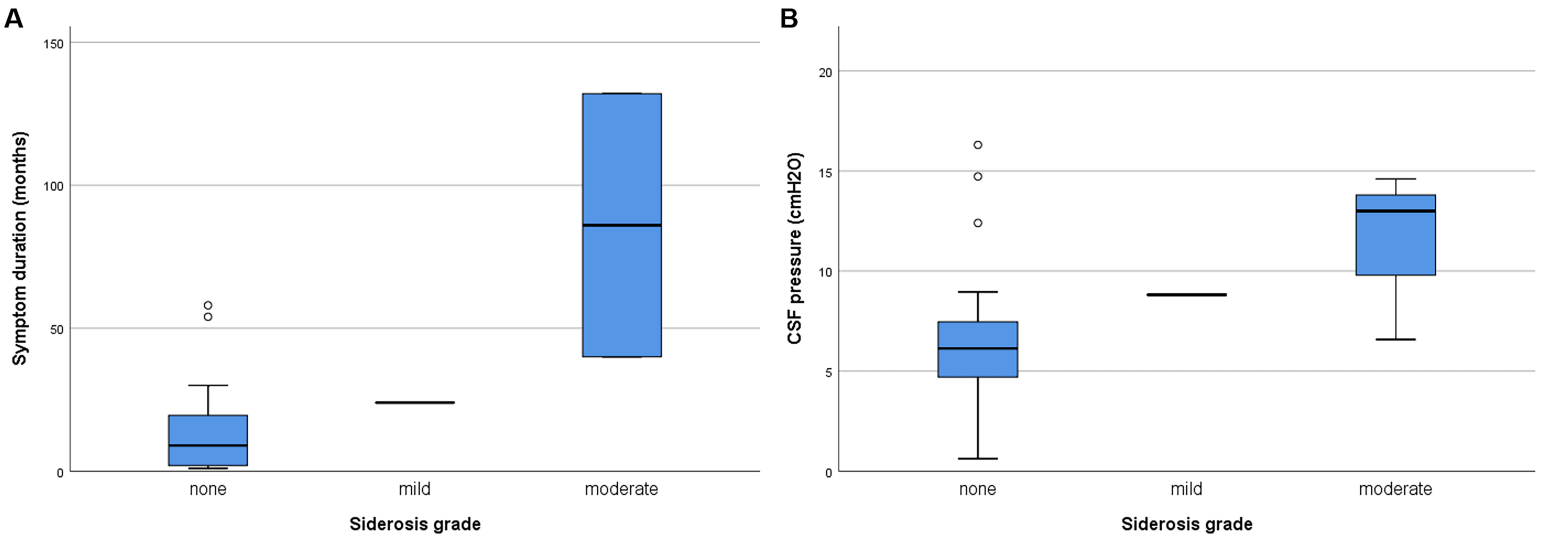

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Table 1: Demographic and clinical features of consecutive patients with spontaneous intracranial hypotension

Patient	Sex	Age (years)	Symptoms†	Headache intensity (NRS)	Symptom duration (months)	CSF pressure (cmH_2O)‡	CSF ferritin (µg/l)	CSF bilirubin	CSF RBC (per µl)	Siderosis on imaging§
1	m	43	h	m/v	54	7.5	11	no	m/v	no
2	f	48	h	8	5	14.7	14	no	1'000	no
3	m	39	h	m/v	1	0.6	736	yes	448'000	no
4	m	42	h	10	3	7.1	17	inconcl.	<1	no
5	f	57	h, g, a	10	24	8.8	18	no	10	mild
6	m	42	h, g, amyotr.	m/v	132	14.6	54	inconcl.	5'000	moderate
7	m	44	h, a	10	1	5.8	m/v	inconcl.	4'000	no
8	f	40	h, a	m/v	58	16.3	9	no	30	no
9	f	55	Vertigo	0	m/v	6.6	59	no	m/v	moderate
10	f	43	h	8	24	5.3	9	no	10'000	no
11	f	32	h	7	13	12.4	5	no	<1	no
12	f	60	h, a	9	1	2.0	18	yes	104'000	no
13	m	37	h, g	9	4	4.7	13	no	110	no
14	f	39	h, a	6	23	2.9	6	no	620	no
15	f	36	h	8	15	7.3	11	no	<1	no
16	f	50	h, g	8	16	6.5	11	inconcl.	770	no
17	m	47	h	4	30	m/v	13	no	40	no
18	f	36	h, g	10	2	5.0	15	no	<1	no
19	m	43	h	10	2	7.0	11	no	<1	no
20	f	63	h, a	8	1	2.8	13	m/v	<1	no
21	f	30	h	m/v	15	9.0	4	m/v	30	no
22	m	53	h, a	8	40	13.0	36	m/v	980	moderate
23	f	50	h, a	5	15	5.1	11	m/v	<1	no
24	f	47	h, a	8	3	m/v	10	m/v	m/v	no

† = symptoms are self-reported by patients, clinical examination was unremarkable in all except one patient with bibrachial amyotrophy; ‡ = CSF opening pressure was measured lumbar in the lateral decubital position in all patients; § = siderosis on imaging was graded as mild (only infratentorial on SWI or T2*, no or only thin rim on T2), moderate (supra- and infratentorial on SWI or T2*, thin rim on T2), severe (supra- and infratentorial on SWI or T2*, thick rim on T2); a = acoustic disturbances (tinnitus, hearing disturbances); amyotr. = bibrachial amyotrophy; f = female; g = gait imbalance; h = headache; inconcl. = inconclusive; m = male; m/v = missing value; NRS = numeric rating scale; RBC = red blood cell count.

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