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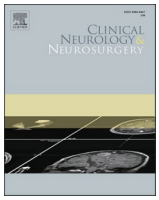

Patient-reported symptomatology and its course in spontaneous intracranial hypotension – Beware of a chameleon

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ABSTRACT

Objective: Although orthostatic headache is the hallmark symptom of spontaneous intracranial hypotension (SIH), patients can present with a wide range of different complaints and thereby pose a diagnostic challenge for clinicians. Our aim was to describe and group the different symptoms associated with SIH and their course over time.

Methods: We retrospectively surveyed consecutive patients diagnosed and treated for SIH at our institution from January 2013 to May 2020 with a specifically designed questionnaire to find out about their symptomatology and its course.

Results: Of 112 eligible patients, 79 (70.5%) returned the questionnaire and were included in the analysis. Of those, 67 (84.8%) reported initial orthostatic headaches, whereas 12 (15.2%) denied having this initial symptom. All except one (98.7%) patients reported additional symptoms: most frequently cephalic pressure (69.6%), neck pain (68.4%), auditory disturbances (59.5%), nausea (57%), visual disturbances (40.5%), gait disturbance (20.3%), confusion (10.1%) or sensorimotor deficits (21.5%). Fifty-seven (72.2%) patients reported a development of the initial symptoms predominantly in the first three months after symptom onset. Age and sex were not associated with the symptomatology or its course ($p > 0.1$).

Conclusion: Although characteristic of SIH, a relevant amount of patients present without orthostatic headaches. In addition, SIH can manifest with non-orthostatic headaches at disease onset or during the course of the disease. Most patients report a wide range of associated complaints. A high degree of suspicion is crucial for an early diagnosis and targeted treatment.

1. Introduction

Spontaneous intracranial hypotension (SIH) is an important cause of disabling headaches that can lead to long periods of sick leave, high socioeconomic burdens, and impaired health-related quality of life [1–5].

Orthostatic headaches are the most prominent symptom of SIH. They usually appear when in an upright position within fifteen minutes and improve after lying down [5–7]. Many patients report additional symptoms, such as visual or vestibulocochlear manifestations [8,9]. During the course of the disease, the typical orthostatic character blurs into a more diffuse pattern of chronic, non-orthostatic headaches [10,11]. This course of chronification of symptoms is accompanied by changes in cerebrospinal fluid (CSF) dynamics [10]. Additionally, SIH can have a wide range of other clinical presentations ranging from Parkinsonism, ataxia, dementia and bulbar weakness to coma [12–20]. Although surgical treatment can improve symptoms, patients may develop rebound high-pressure headaches, which can prolong the recovery process [21].

The estimated incidence of SIH is 5/100,000 per year [2]. However,

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the dark figure is probably higher due to the diverse clinical presentations and difficult diagnosis. Whereas patients presenting typical symptoms are easily recognized, those with less specific, often chronic complaints pose a diagnostic challenge for clinicians. In addition, the literature on patient-reported symptoms of SIH is scarce. The aim of our study was to assess the symptomatology and the course of symptoms in patients with SIH due to a spinal CSF leak more comprehensively.

2. Material and methods

2.1. Study design

We conducted a retrospective, observational cohort study. Patients diagnosed with SIH due to a spinal CSF leak were surveyed using a specifically designed questionnaire. Approval from the local ethics committee of the canton of Bern, Switzerland, was obtained for this study (2020–00645). We excluded patients who declined to give general consent for the use of their health-related data.

2.2. Patient selection

We included consecutive patients with proven SIH diagnosed and treated at our institution between January 2013 and May 2020. Diagnosis of SIH was based on the criteria of the International Classification of Headache Disorders (ICHD-3) [11] and the demonstration of a spinal CSF leak, but with a minor modification. This consisted of including patients without headaches if imaging was consistent of an active CSF leak and their symptoms were best explained by SIH [22]. We excluded patients whose intracranial hypotension had non-spontaneous causes, such as postoperative CSF leakage or following a previous lumbar puncture, from the analyses. We also excluded all patients without valid contact information.

2.3. Diagnostic work-up, treatment and follow-up

All patients with suspected SIH underwent a stepwise and standardized diagnostic work-up at our institution, as reported previously [23–25]. The diagnostic work-up started with non-invasive imaging such as magnetic resonance imaging (MRI) of the head and spine, and optic nerve sheath ultrasound.

If non-invasive imaging showed brain sagging or signs of a spinal CSF-leak or patients presented with typical symptomatology, more invasive techniques were utilized. In patients with proven spinal longitudinal epidural collection (SLEC+) dynamic myelography, or dynamic computed tomography (CT) myelography were performed to localize the exact site of the leakage. In patients with cranial imaging signs of SIH [26] and no spinal longitudinal epidural collection (SLEC-), a CSF-venous fistula as the most probable cause was searched using lateral decubitus digital subtraction myelography and postmyelography CT.

The brain (Bern) SIH-Score (bSIH-Score) was calculated according to Dobrocky et al. [26]. It is a quantitiave score of cranial MRI signs reflecting the possibitliy to find a CSF-leak ranging from 0 to 9 (higher values are associated with higher possibilities of finding a CSF leak). The bSIH-Score was quantified by two board-certified neuroradiologists, who were blinded to the symptomatology.

Treatment consisted of conservative measures such as bedrest, oral caffeine and/or epidural lumbar blood patching [27]. In patients with persisting symptoms and with a proven spinal CSF leak, we performed surgical closure of the leak as described previously [28,29]. All patients were followed up after two months, including an MRI-study of the head and spine and a clinical examination.

2.4. Study-specific questionnaire and data collection

We designed a study-specific questionnaire with open, numeric and multiple-choice questions. The questions covered the symptomatology, its duration and course, previous treatments and post-treatment changes, treatment success, and the effects on the patient's social life and work capacity before and after treatment. Patients were asked to report their initial symptoms and the changes over time. We only included symptoms reported by at least two different patients for final analysis.

Parts of the questionnaire and the results reported by the surgically treated patients have been presented in previous publications [1,30]. All patients who met the inclusion criteria received the questionnaire by mail. If no response was received, we tried to contact the patient three times by phone and asked them to complete a digital version of the questionnaire. Thereafter, we considered the data as missing and excluded these patients from the analysis.

The patient-specific data, as well as data regarding the surgery, radiological findings and the perioperative course have been collected in our SIH database and was retrospectively analyzed.

We grouped CSF-leaks according to the classification proposed by Schievink et al. [31] with minor modifications [30]:

- Type 1a: Ventral dural tear with visible CSF egress. These tears are often caused by a bony microspur penetrating the ventral dura [29].
- Type 1b: Lateral dural leak with visible CSF egress. Often these tears occur in the axilla of the nerve root and are associated with prolapsing arachnoid (meningeal diverticulum). "Nude" nerve roots with visible CSF egress were also classified as type 1b [32].
- Type 2: Meningeal diverticulum without visible egress of CSF. Surgical techniques in these cases included ligation of large meningeal diverticula. Cases with a clear dural tear, visible CSF egress and prolapsing arachnoid were classified as type 1b [33].
- Type 3: CSF-venous fistula.
- Type 4: Indeterminate. This category includes cases with active egress of CSF seen on surgical exploration, but where the site of leakage cannot be identified. Surgical techniques in such cases included augmentation of dura.

2.5. Statistics

Statistical analysis was performed using the statistical software SPSS (IBM, Armonk, NY, USA, version 28). Descriptive data included calculation of the mean and standard deviation (SD) for all groups. Data was tested for normal distribution. For the comparison between groups, the Mann-Whitney U-test was used for continuous not normally distributed variables, and Fisher's exact test or the chi-squared test for categorical variables. A logistic regression analysis was used to test the association between continuous variables and a categorical outcome. Missing values were addressed first by re-analyzing the data, and, if the values were not retrievable, by pairwise deletion. Statistical significance was set at a p-value less than 0.05.

3. Results

3.1. Patient characteristics

Between January 2013 and May 2020, 118 patients were treated at our institution for SIH or a spinal CSF leak. Six patients were excluded because the initiating event was a lumbar puncture. Three additional patients were excluded as they had no valid contact information. The remaining 109 patients were eligible for participation and received the study-specific questionnaire. Thirty of them did not return the questionnaire. Therefore, the data from the remaining 79 patients (70.5%), who returned the questionnaire, were analyzed (Fig. 1).

The mean age was 47.7 ($\pm$ 12.6) years and 53 (67.1%) of the patients were female. The site of the leak was localized in the cervical spine in four (5.1%) cases, at the cervicothoracic junction in one (1.3%) case, in the thoracic spine in 59 (74.7%) cases, at the thoracolumbar junction

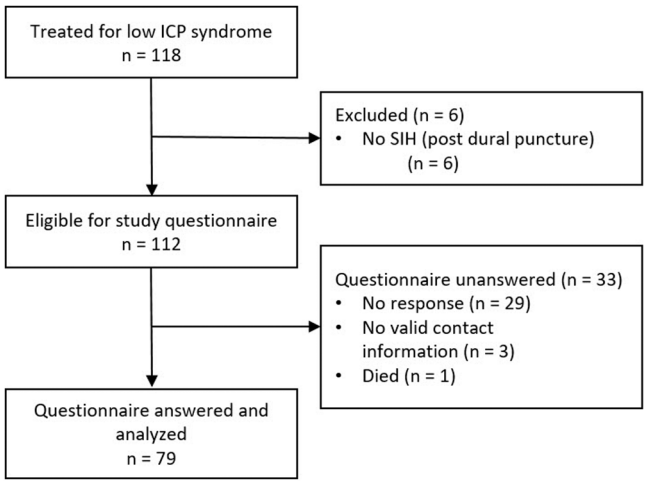

Fig. 1. : Flow diagram of patients included in the study.

in seven (8.9%) cases and in the lumbar spine in one (1.3%) case. In seven patients, the exact location of the leak remained unknown, although a spinal CSF leak was proven. A ventral leak (Type 1a) was identified in 49 (62%) patients. A lateral dural leak (Type 1b) was found in 17 (21.5%) of patients. Five (6.3%) patients had a meningeal diverticulum without CSF egress (Type 2) as a triggering lesion. No CSF leak despite the presence of extradural CSF (Type 4) was found in eight (10.1%) patients (including one patient whose leak was located radiologically but in whom the exact spot could not be found intraoperatively). No CSF-venous fistula (Type 3) was detected in our cohort.

Mean duration from symptom onset until treatment was 47 (± 92.2; range: 1–619) weeks. Out of the 79 patients, 69 (87.3%) were treated surgically and 10 (12.7%) were treated conservatively including non-targeted epidural blood patching. Out of the 69 surgically treated patients, 53 (76.8%) received an epidural lumbar blood patch before surgery.

For 66 patients, a lumbar CSF opening pressure was available. The mean lumbar opening pressure was 85 (± 60) mm CSF. In 38 (57.6%) patients, it was higher than 60 mm CSF.

3.2. Initial symptoms and orthostatic character

Orthostatic headache was reported as the initial symptom by 67 (84%) patients, 12 (15.2%) patients denied having this initial symptom. Twenty-nine (36.7%) patients reported non-orthostatic headache at disease onset. Regarding position dependent symptoms, 33 patients (41.8%) reported symptoms immediately after a change to the upright posture, 19 (24.1%) after 1 to 5 min, and 15 (19.0%) patients reported an onset after more than 5 min. For twelve (15.2%) patients, there was no temporal-positional relationship. In 35 (44.3%) cases, symptoms improved directly or within the first five minutes after lying down, while 15 (19.0%) patients reported improvement after 5 to 15 min, and 13 (16.5%) patients reported improvement only after more than 15 min.

Thirty-three (41.8%) patients reported remembering the exact date of first onset of symptoms. Neither age ($p > 0.1$) nor sex ($p > 0.1$) were associated with the initially presenting symptoms. We found a significant difference in the frequency of initial presentation with orthostatic headaches associated with different types of CSF leaks ($p = 0.046$). A post-hoc test demonstrated less frequent orthostatic headaches in patients with lateral leaks (type 1b) ($p = 0.009$, Bonferroni correction).

3.2.1. Additional symptomatology

All except one (1.3%) of our patients (98.7%) reported additional symptoms besides headaches. The most frequent non-headache symptoms were cephalic pressure (69.6%), neck pain (68.4%), auditory disturbances (59.5%), nausea (57%) and visual disturbances (40.5%) (Fig. 2, Table 1). No patient reported incontinence as a symptom. Additionally, there was a difference among patients reporting the additional symptom “neck pain” associated with different types of CSF leaks ($p = 0.021$; post-hoc test with Bonferroni correction not significant).

3.3. Temporal evolution of symptoms

Fifty-seven (72.2%) patients reported an alteration of their symptoms over the course of the disease: 27.9% (19/68) of patients reported reduced intensity of complaints, 33.8% (23/68) of patients reported increasing cephalic pressure and 29.4% (20/68) of patients reported other new symptoms or other alterations of the initial symptoms (Table 2). These developments occurred in the majority of patients within the first three months after symptom onset (Fig. 3). Again, there was no association of the temporal evolution of symptoms with sex ($p > 0.1$) and age ($p > 0.1$).

3.4. Clinical and radiological correlation

The bSIH-Score was available for 77 (97.5%) patients. The median bSIH-Score was 7 points. While 56 (72.7%) patients had high probability (>4 points) for CSF leak, 12 (15.6%) patients had an intermediate probability (3–4 points) and nine (11.7%) had a low probability for CSF leak (<3 points). Patients with an intermediate or high bSIH-Score tended to report more frequently orthostatic headache at onset compared to patients with a low bSIH-Score (88.2% vs. 66.7%, $p = 0.113$).

4. Discussion

Although characteristic of SIH, an important number of patients deny having orthostatic headaches at the onset of disease. In addition, many patients report non-orthostatic headaches. Associated complaints, such as neck pain, nausea, visual and auditory disturbances are often also prevalent among SIH patients. This variable symptomatology could mislead physicians and obscure the diagnosis, thus precluding prompt treatment of affected patients.

Importantly, around 15% of patients in our cohort reported that they had never experienced the typical hallmark symptom of orthostatic headaches. These patients are particularly difficult to diagnose, and a high index of suspicion is necessary [26]. Similar to our results, Mea et al. [34] reported that 24% of patients in their SIH cohort had non-orthostatic headaches. In addition, second-half-of-the-day headaches or chronic daily headaches have been described as a symptom of SIH in the literature [35–39]. However, the affected patients might have had orthostatic headaches initially, which changed over the course of the disease. Such a temporal evolution was frequently observed in our cohort. Not only is SIH not always characterized by orthostatic headaches, but also not all orthostatic headaches are associated with SIH, since there are other diseases like postural orthostatic tachycardia syndrome that are known to cause orthostatic headache as well [40,41]. In contrast, a recent meta-analysis suggested that 97.7% of patients suffer from orthostatic headache. This discrepancy might be the result of more restrictive inclusion criteria in previous studies selecting only patients with orthostatic headaches. Nevertheless, the authors acknowledge that a significant minority of patients may have non-orthostatic headaches [42].

The change in clinical presentation over time is accompanied by a change in the pattern of CSF fluid dynamics in SIH patients [10]. Patients presenting early with typical symptoms display a clear pathological profile of CSF fluid dynamics, whereas patients with long-standing complaints frequently present with atypical symptoms and a normalized profile of CSF fluid dynamics. Therefore a normal lumbar opening pressure does not rule out the diagnosis of SIH and lumbar puncture is

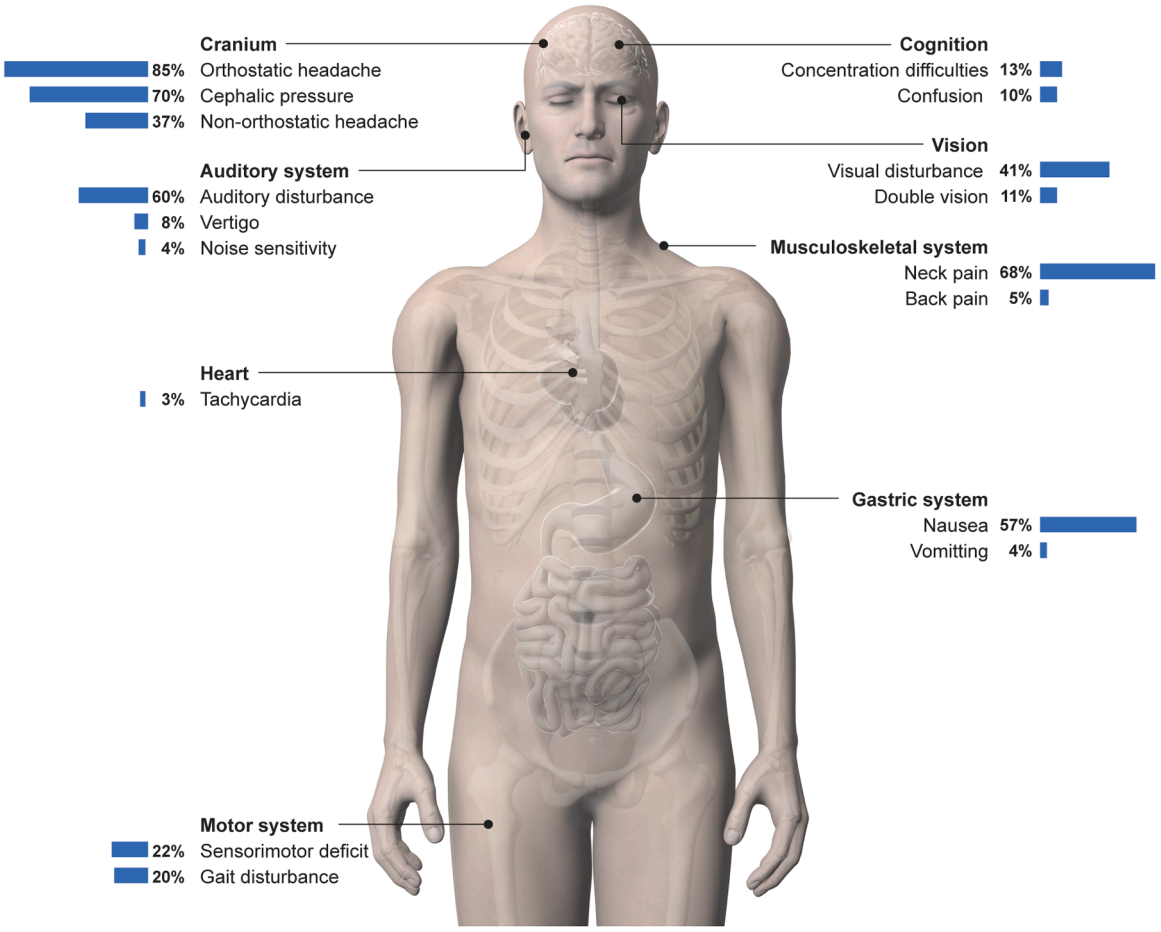

Fig. 2. : Patient-reported symptomatology of spontaneous intracranial hypotension. (Printed with permission by Inselspital, Bern University Hospital, Dept. of Neurosurgery).

Table 1
Self-reported initial symptoms of spontaneous intracranial hypotension (SIH) sorted by frequency of mention* .

Symptoms	Frequency of mention (%)
Orthostatic headache	85
Cephalic pressure	70
Neck pain	68
Auditory disturbance	60
Nausea	57
Visual disturbance	41
Non-orthostatic headache	37
Sensorimotor deficit	22
Gait disturbance	20
Concentration difficulties	13
Double vision	11
Confusion	10
Vertigo	8
Back pain	6
Noise sensitivity	4
Vomiting	4
Tachycardia	3

*Symptoms are only listed if mentioned at least twice.

Table 2
Self-reported new symptoms or course of symptoms of spontaneous intracranial hypotension (SIH) sorted by frequency of mention* .

Change of initial symptoms	Frequency of mention (%)†
(Progressive) cephalic pressure	34
Less orthostatic	29
Less intensive	28
Progression of initial symptoms	7
Depressive mood	4
Fatigue	4
Concentration difficulties	3
Immobilizing intensity	3
Vertigo	3
Undulating character	3
New tinnitus	3

*Symptoms/changes are only listed if mentioned at least twice.
† Percentage of the 68 patients who mentioned a change in symptomatology.

not necessary in all cases to make the diagnosis. Interestingly, in our cohort, this change in symptomatology was reported within the first 3 months of symptoms, which coincides with the change observed in the pattern of CSF fluid profile. Thus, the character of symptoms at disease onset needs to be explored when taking the history of a patient with chronic, non-orthostatic headaches.

The mechanism responsible for the wide range of associated complaints, such as neck pain, nausea, visual and auditory disturbances, remains obscure. Capizzano et al. [17] described an atypical presentation of SIH with a more chronic character, more severe brain sagging and a lower rate of clinical responses. They assumed that more severe brain sagging with a greater midbrain involvement may help to explain atypical symptoms like gait disturbance, movement disorders, daytime somnolence or imbalance. This could be an explanation for some of the supplementary symptoms. Additionally, the brain sagging may lead to more tension of other cranial nerves resulting in their involvement as well as symptoms like double vision, visual or auditory disturbances. In accordance with our results, D'Antona et al. reported on a similar wide

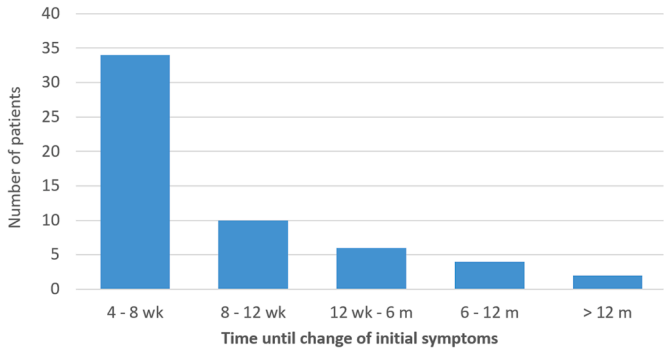

Fig. 3. : Time until change of symptoms. Patients were asked how long after first onset their initial symptoms changed. (wk: weeks; m: months).

range of associated signs and symptoms [42].

Houk et al. showed a low correlation of bSIH-Score with headache severity [43]. While there was a negligible tendeny of higher bSIH-Scores with typical orthostatic headache at onset in our cohort, our findings are generally in line with their findings indicating limited clinical relevance.

Many patients have seen several different specialists before the final diagnosis is made [1]. Additionally, a significant number of patients are initially misdiagnosed with migraine or psychogenic disorders [6]. Our results underscore this difficulty: not only was there little awareness among clinicians in the past, but patients can also present with a wide range of symptoms, sometimes non-specific, which easily misleads physicians. This is reflected by the long delay of almost one year on average, before patients in our cohort were referred for specialized management. Since treatment is more effective early after symptom onset [30], it is crucial to identify patients with SIH expeditiously and refer them for appropriate diagnostic work-up and treatment. Additionally, the probably high number of undiagnosed SIH patients may interfere with our results. Therefore, there might be an even higher number of patients with uncommon symptomatology, e.g. non-orthostatic headaches, which are never diagnosed.

5. Limitations

Several limitations apply to our analysis. Firstly, the data were obtained retrospectively in a single-center study. The analysis included exclusively patients referred to our institution for specialized care and/or surgical management. Patients with a favorable response to conservative treatment or spontaneous resolution are thus likely to have been underrepresented in our cohort. Therefore, the generalizability of the results is limited to a certain degree. Secondly, the questionnaires were sent to the patients on average two years after the treatment. Thus, this analysis is prone to a recall bias. Patients might not accurately remember all their initial symptoms and their course. They might also attribute symptoms to SIH that might have been present for another reason. Thirdly, there are probably many patients, which are not diagnosed correctly and are not included in our analysis. Therefore, there may be a selection bias in our study.

6. Conclusion

SIH can present with a wide range of symptoms. Although characteristic of SIH, some patients present without orthostatic headaches. In addition, SIH can manifest with non-orthostatic headaches at disease onset or during the course of the disease. Even when present at disease onset, orthostatic headaches can change over the course of the disease and blur into non-specific, chronic symptoms. Most patients report a wide range of associated complaints. Rising awareness about the disease among clinicians and a high index of suspicion is crucial for an early diagnosis and targeted treatment.

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CRediT authorship contribution statement

Fung Christian: Conceptualization, Project administration, Writing – review & editing. **Schankin Christoph J.:** Methodology, Writing – review & editing. **Piechowiak Eike Immo:** Data curation, Writing – review & editing. **Dobrocky Tomas:** Data curation, Project administration, Writing – review & editing. **Ulrich Christian T.:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Jesse Christopher Marvin:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing, Investigation. **Häni Levin:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing. **Raabe Andreas:** Supervision, Writing – review & editing. **Beck Jürgen:** Methodology, Supervision, Writing – review & editing. **Goldberg Johannes:** Methodology, Writing – review & editing. **Schär Ralph T.:** Conceptualization, Supervision, Writing – review & editing.

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Disclosures

All authors declare that they have no conflict of interest.

Supplementary Data:

Suppl. Data 1: Questionnaire german.

Appendix B. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2023.108087.

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