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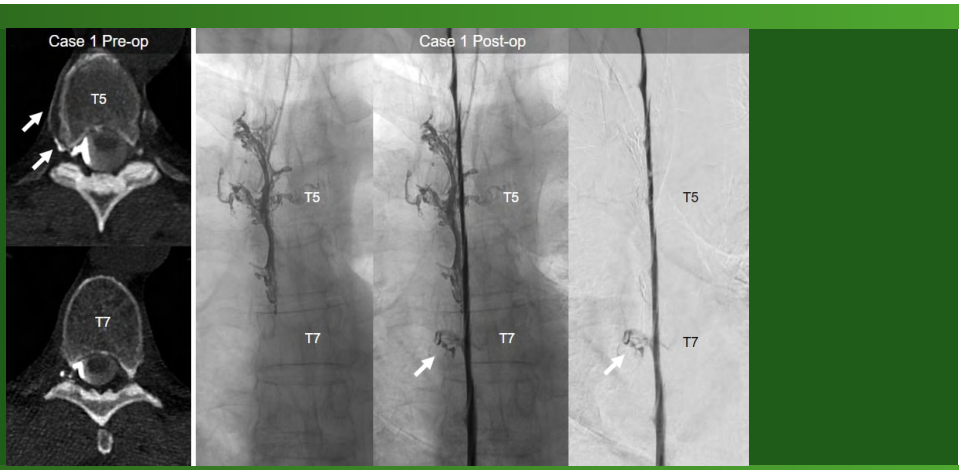

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Leading Topic Editor: Olga P. Fermo, MD, Department of Neurology, Mayo Clinic, Jacksonville, Florida, United States

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Cover photo: Roaa Zayat et al. Pre-embolisation and post-embolisation of T5 CVF. (see figure on page 56)

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LEADING TOPIC

Leading Topic Editor: Olga P. Fermo, MD, Department of Neurology, Mayo Clinic, Jacksonville, Florida, United States

Overlapping challenges of treating cerebrospinal fluid dynamic disorders

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In my role as the guest editor of the current issue of Leading Topics published in the Polish Journal of Neurology and Neurosurgery, I am delighted to introduce a collection of articles on disrupted cerebrospinal fluid (CSF) dynamics (Tab. 1).

The parameters of CSF dynamics include intracranial pressure, volume, resistance to CSF outflow, cerebrospinal compliance, compensatory reserve, and waveform components [1, 2]. Imbalances in these parameters can lead to a variety of disorders of CSF dynamics, primarily encompassing the conditions of hydrocephalus, pseudotumour cerebri syndrome (PTCS), spontaneous intracranial hypotension, Chiari malformation, and syringomyelia. Although each condition typically occurs independently, there can be a striking continuum of abnormalities and 'never right' dynamics when these conditions intersect. This results in considerable challenges in diagnosis, and consequently many treatment dilemmas.

PTCS is nearly always associated with papilloedema [3] which in and of itself confirms pathologically sustained intracranial hypertension. Published criteria for the more rare PTCS without papilloedema exist, relying heavily on a constellation of radiographic stigmata of sustained intracranial hypertension [4]. These diagnostic criteria do not account for the patients who have 'self-decompressed' their pressure through a cranial or spinal CSF leak preventing papilloedema, or preventing the full expected radiographic picture, as we will see in this issue's work by Macedo et al. Such a case is presented and illustrated in Figure 1.

Macedo et al. present a narrative review of the association between PTCS and spontaneous CSF rhinorrhea [5]. Their extensive literature review, encompassing a total of 943 patients, focuses on the commonly identified patient characteristics, clinical presentation, imaging findings and management of spontaneous skull-based CSF leaks caused by intracranial hypertension. Many diagnostic and treatment challenges were

Table 1. Leading Topic articles: disorders of cerebrospinal fluid dynamics; PJNNS 1/2024

Title	Authors
INVITED REVIEW ARTICLES	
Spontaneous rhinorrhea and idiopathic intracranial hypertension: a complex and challenging association	Leonardo Jose Monteiro de Macedo Filho, Carolina Carmona Pinheiro Machado, Gabrielle Brito Bezerra Mendes, Luma Maria Figueiredo Santana, Mauro Emiliano Ruella, Sanjeet Grewal, Kaisorn Chaichana, Alfredo Quinones-Hinojosa, Olga Fermo, Joao Paulo Almeida
Headache associated with intracranial hypotension: diagnostic challenges and difficulties in everyday neurological practice	Magdalena Boczarska-Jedynak, Daniel Stompel
Normal pressure hydrocephalus, or Hakim syndrome: review and update	Philip W. Tipton, Benjamin D. Elder, Petrice M. Cogswell, Neill Graff-Radford
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Neuronal pentraxin 2 correlates with neurodegeneration but not cognition in idiopathic normal pressure hydrocephalus (iNPH)	Megha Patel, Yifan Zhang, Mei-Fang Xiao, Paul Worley, Abhay Mogheka
Recurrence of cerebrospinal fluid-venous fistulas at different spinal levels following transvenous embolisation or blood/fibrin glue patching	Roaa Zayat, Olga P. Fermo, Thien J. Huynh

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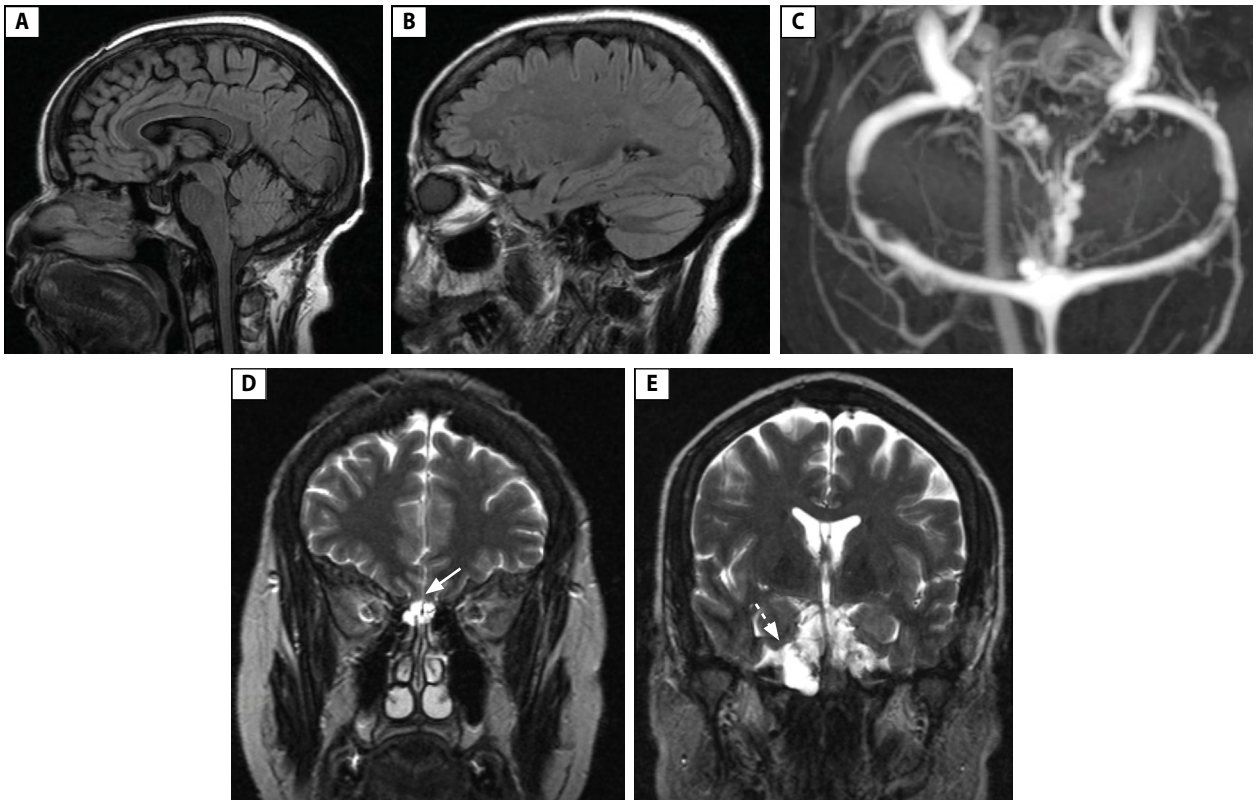

Figure 1. A patient with migraine was evaluated for daily left hemicranial headache after suffering a whiplash injury. History revealed intermittent clear rhinorrhea when bending over of 1–2 years' duration, unrelated to chief concern. Patient was suspected to have pseudotumour cerebri syndrome based on multiple radiographic stigmata of intracranial hypertension. However, lumbar puncture revealed an opening pressure of 8 cmH20 and there was no papilloedema. Image **A**: partially empty, expanded sella turcica; **B**: tortuosity of right optic nerve in vertical plane; **C**: bilateral transverse venous sinus stenosis; **D**: large right cribriform plate defect with meningocele and remodelling of ethmoid trabeculae (solid arrow); **E**: large right petrous apex and clivus osseous defect with meningocele (dashed arrow). Patient underwent endoscopic endonasal repair of right anterior cranial fossa for non-active CSF rhinorrhea one year after images were taken. Bolt intracranial pressure monitoring performed four months after surgery confirmed nocturnal intracranial hypertension (normal pressures while awake) with average overnight intracranial pressure of 26.6 cmH20 and maximum intracranial pressure of 31.38 cmH20. Intracranial pressure normalised after intravenous administration of acetazolamide 500 mg. The most likely aetiology of intracranial hypertension in this case was bilateral primary venous transverse sinus stenosis in combination with untreated sleep apnoea. Patient continued on oral acetazolamide to prevent papilloedema and development of recurrent or new skull-based CSF leak

identified, including difficulty in diagnosing PTCS according to the published criteria during an active leak, and the higher recurrence rate of skull-based CSF leak in the intracranial hypertension population compared to other types of cranial leaks. They identified several significant differences compared to PTCS without cranial leak. These differences included a relatively low incidence of headache as a presenting symptom (20.36% with cranial leak versus ≥ 84% without cranial leak [6]), the frequent absence of papilloedema before leak closure, a lower mean lumbar puncture opening pressure (25.52 cmH20 compared to c.34 cmH20 observed in the population studied in the Idiopathic Intracranial Hypertension Treatment Trial [7]), and a much lower prevalence of common imaging abnormalities. For instance, 42.3% of patients with cranial leak had a partially empty sella, compared to the previously reported 80% of patients with pseudotumour cerebri without papilloedema [3]. Additionally, 2.6% of patients with cranial leak had venous sinus stenosis, in contrast to 78% of patients with pseudotumour cerebri without papilloedema [3]. As highlighted by the authors, the distinct clinical variations between those individuals with intracranial hypertension who experience leaks and those who do not, create a challenge in terms of recognition.

This underlines the importance of a collaborative, multidisciplinary approach to the care of these patients, involving otolaryngologists, neurosurgeons, neurologists, and radiologists. Given that these patients often require multiple diagnostic interventions, such a comprehensive team strategy becomes essential. Moreover, the extended period preceding leak recurrence shown by our authors, c.20.5 ± 13 months, highlights the need for longitudinal team follow-up [5].

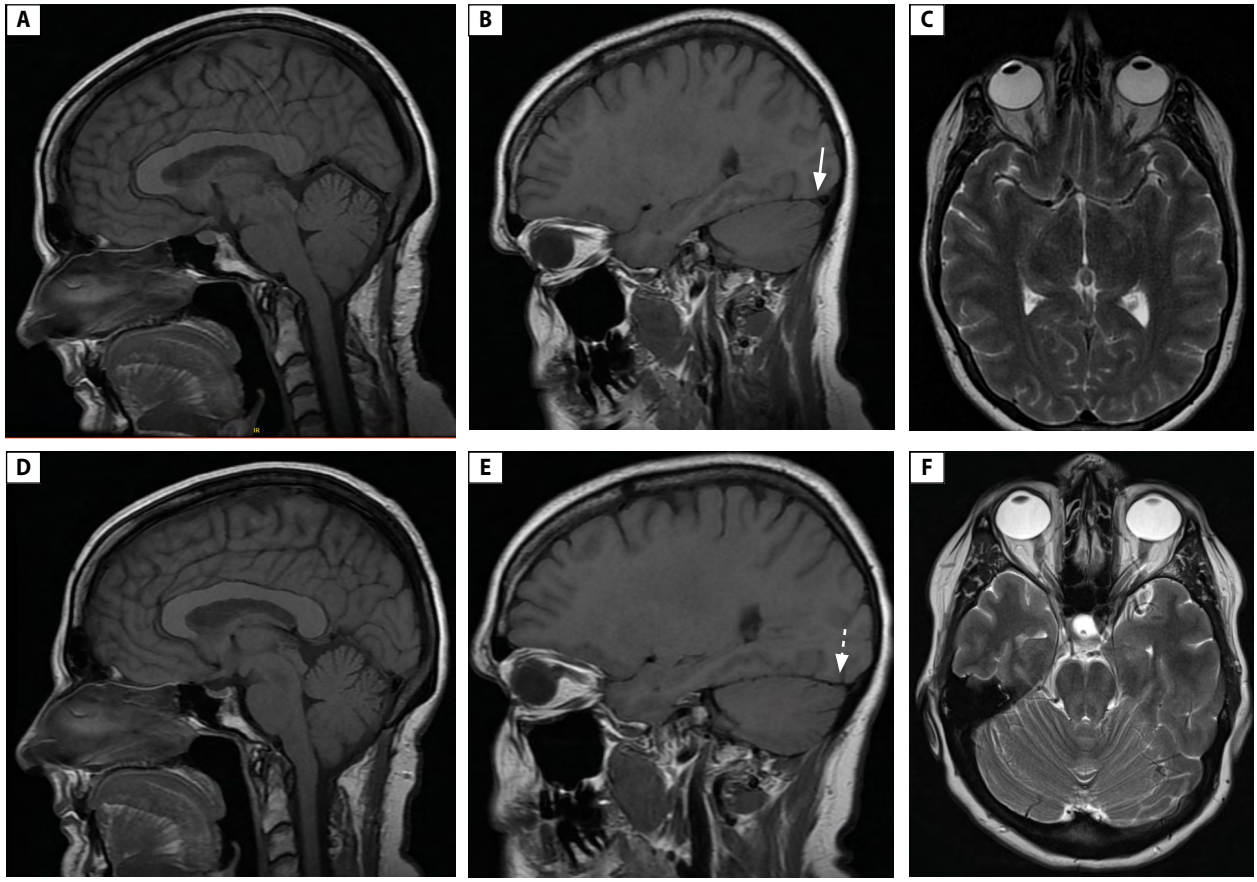

Figure 2. A patient with new daily persistent headache for 30 years was found to have spontaneous intracranial hypotension from a multilevel, ventral, upper thoracic spine, longitudinal epidural fluid collection. There was a history of posterior fossa decompression for a (questionable) Chiari 1 malformation diagnosis 18 years prior to leak discovery. Patient underwent CT-guided fibrin patching to ventral upper thoracic spine 10 months after pre-treatment images (**A, B, C**) were taken, which show classic stigmata of intracranial hypovolemia. **A:** engorged pituitary gland and mild brain sag; **B:** right optic nerve is straight in vertical plane (normal); right transverse venous sinus is engorged (solid arrow); **C:** optic nerves are straight in horizontal plane (normal). Patient developed a headache pattern change and papilloedema with peri--nerve haemorrhage within three weeks of patch. Post-treatment images (**D, E, F**) were taken six weeks after treatment, demonstrating new stigmata of intracranial hypertension. **D:** partially empty sella turcica; **E:** subtle tortuosity of right optic nerve in vertical plane (abnormal), and development of right transverse sinus stenosis (dashed arrow). **F:** bilateral horizontal optic nerve tortuosity (abnormal). Patient ultimately required ventriculoperitoneal shunting for persistent intracranial hypertension despite high-dose oral acetazolamide therapy

In contrast to the *relatively* few patients with cranial leaks experiencing headache, as shown by Macedo et al. [5], headache is overwhelmingly the most common presenting symptom of a spontaneous spinal CSF leak, present in 98.6% of patients [8]. Spontaneous intracranial hypotension from a spinal CSF leak can be misdiagnosed as a Chiari type 1 malformation when subtle imaging findings are overlooked, a problem that Boczarska-Jedynak and Stompel set out to rectify in this issue [9].

To further complicate matters, spontaneous intracranial hypotension from a spinal CSF leak may be caused by underlying intracranial hypertension [10] akin to the cranial leaks described in this issue by Macedo et al. [5], and the treatment of spontaneous intracranial hypotension can result in intracranial hypertension [11]. These problems are illustrated in the case in Figure 2. As pointed out by Boczarska-Jedynak and Stompel in this issue [9], many patients with actively leaking spinal leaks have normal opening pressure, and some even have intracranial hypertension during the leak [12]. Given the strong correlation between a normal opening pressure and a normal brain MRI in the presence of a spinal leak [12], the phenotypic criteria presented in this issue become crucial for maintaining a high level of suspicion for an inconspicuous disorder.

In their review of headache attributable to intracranial hypotension, the authors immediately point out the challenges in diagnosing this clinical syndrome beyond the hypotension dilemma. These challenges also encompass the fact that key symptoms such as headache, neck pain, and vestibulocochlear disturbance are relatively nonspecific. Patients may exhibit signs of meningeal irritation [13], such as photophobia, which can mimic migraine. Additionally, subtle positive diagnostic

imaging findings may be easily overlooked by those without specialised training [9]. They move on to expand on the International Classification of Headache Disorders, 3rd edition diagnostic criteria of Headache attributed to low CSF pressure, the three reviewed conditions being post-dural puncture headache, CSF fistula headache (not to be confused with CSF venous-fistula), and spontaneous intracranial hypotension [14]. Emphasising another aspect of this syndrome's complexity — the variability in clinical presentations—the authors lead us through three distinct scenarios. A sudden, possibly thunderclap-onset, headache when presented in a hospital setting may mimic subarachnoid haemorrhage, acute central nervous system infection, ischaemia, or thrombosis. This is juxtaposed against an indolent chronic headache disorder often misdiagnosed as migraine, tension headache, or cervicogenic headache which persists as medically refractory for years, and in some cases even decades. The authors finish with a description and prevalence of the head imaging abnormalities caused by intracranial hypotension, followed by a discussion of localising spinal imaging findings [9].

Even after overcoming the challenges of diagnosing spontaneous intracranial hypotension, further difficulties emerge. As demonstrated by Zayat et al. [15] in this issue, patients may experience a second leak even after successful treatment of the initial spinal CSF leak. In this original research submission, the authors describe the clinical and radiographic characteristics of 4/42 patients with myelography-proven CSF venous fistulas who developed leak symptoms after successful venous fistula embolisation. These four patients were discovered to have new CSF venous fistulas at spinal levels different from their initially identified fistulas. Notably, three of the four exhibited the persistence or recurrence of intracranial radiographic signs indicative of intracranial hypovolemia before the diagnosis of the recurrent leak. In the fourth patient, a recurrent fistula was discovered despite an improvement in brain imaging, although it remained abnormal. This underlines the importance of post-treatment surveillance brain imaging for assessing treatment response and establishing a new radiographic baseline. Additionally, the worsening Bern score serves as a valuable indicator in confirming the recurrence of a leak after treatment. However, as illustrated in the last case, improving imaging results may provide a false sense of reassurance. Therefore, a high level of suspicion for recurrent leaks should persist, especially when clinical symptoms are present. Regrettably, there is still a significant amount to discover within the realm of spontaneous intracranial hypotension. The precise triggers for spinal CSF leaks remain unclear, and the factors contributing to recurrence are not understood. In this issue's other editorial, Cutsforth-Gregory proposed several possible risk factors for fistula recurrence including regionally abnormal CSF and venous pressure or fluid dynamics or the development of rebound intracranial hypertension [16]. By examining recurrent leaks like Zayat et al., we may advance our understanding of leak origin.

An issue focused on cerebrospinal fluid dynamic disorders would not be complete without a discussion of probably the most studied hydrodynamic anomaly, i.e. normal pressure hydrocephalus. In this issue, Tipton et al. [17] present a comprehensive review of contemporary normal pressure hydrocephalus management. The authors initiate their topic with the proposal that the term 'normal pressure hydrocephalus' is outdated, based on newer evidence that stretches our previous definition of 'normal' intracranial pressure. Considering a more comprehensive understanding of the diverse factors contributing to shunt-responsive hydrocephalus, including congenital, vascular, and absorptive derangements, the authors suggest adopting the term 'Hakim Syndrome' to refer to the combination of gait disorder with cognitive decline and/or urinary dysfunction. The authors emphasise the complexity for several reasons of reaching a diagnosis, including the variable and sometimes asymptomatic clinical presentation, the presence of commonly associated comorbidities, the absence of a consensus definition for a positive response to cerebrospinal fluid diversion, and the lack of proven cerebrospinal fluid biomarkers that could aid in the diagnostic process. With these limitations in mind, the authors recommend a thorough, cautious and systematic methodology to assessing suspected Hakim Syndrome. They conclude with a discussion of the latest approaches to minimising shunt-related complications.

In a further quest to better understand the pathophysiology of normal pressure hydrocephalus, Patel et al. [18] present their original research regarding the diagnostic and prognostic value of the synaptic protein neuronal pentraxin-2 (NPTX2). The authors found that CSF NPTX2 concentrations were not correlated with short-term improvement on the Timed Up and Go Test after temporary CSF removal or long-term improvement after shunt surgery, indicating that NPTX2 cannot be used as a diagnostic or prognostic biomarker for the condition. They also found no correlation between NPTX2 and baseline cognitive performance, implying that mechanisms other than synaptic degeneration are responsible for the cognitive decline seen in some patients with normal pressure hydrocephalus.

One wonders whether the extensive progress made in the understanding of normal pressure hydrocephalus is a precursor to reimagining the other disorders of CSF dynamics. As presented by Tipton et al. [17], normal pressure hydrocephalus is probably best considered a final common pathway for several different congenital or acquired pathologies. Could this same umbrella concept hold true for PTCS and spontaneous intracranial hypotension? Are these actually collections of different disorders with a final common symptomatology? Much work remains to be done.

At the current juncture, the work presented in this issue showcases the plethora of challenges faced when treating disorders of CSF dynamics. On the one hand, this may occur because subtle diagnostic features are overlooked or misinterpreted, such as misdiagnosing a spinal CSF leak as Chiari or failing to recognise that intracranial hypertension can cause tonsillar descent, mimicking Chiari. On the other hand, it may be because the patient genuinely has two competing conditions

that 'cancel each other out', as seen in cases of PTCS leading leak, or when a spinal CSF leak is complicated by post-treatment intracranial hypertension.

The key 'takeaway' from this issue is the importance of a thorough familiarity with all cerebral spinal fluid dynamic disorders. Consider the possibility of cranial leaks in patients with PTCS who do not present with papilloedema. This is not usually an immediate consideration because it is not part of the diagnostic criteria for PTCS. Think about spinal leaks, or postdural puncture headaches in the patients with PTCS who have changing headache patterns. It is suggested that clinicians should protect the patients with cranial CSF leaks from headaches, papilloedema, and leak recurrence by developing a system to check and monitor for intracranial hypertension postoperatively, as in Figure 1. Finally, consider the emergence of intracranial hypertension in the patient with a spinal CSF leak who fails to improve after successful treatment, as in Figure 2, or the patient who continues to develop new spinal leaks.

To gain a comprehensive understanding of each abnormality, it is essential to view them as part of a continuum.

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INVITED EDITORIAL

This Invited Editorial accompanies a Research Paper, see page 54

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Recurrent spinal CSF-venous fistulas

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Spinal CSF-venous fistulas (CVF) are aberrent connections between the spinal subarachnoid space and the paraspinal veins and/or epidural venous plexus that allow unregulated egress of CSF into the venous circulation, effectively reducing CSF volume and causing the broad variety of clinical and radiographic manifestations of spontaneous intracranial hypotension.

In 2024, we mark the 10th anniversary of the first description of spinal CSF-venous fistulas as a distinct type of spontaneous spinal CSF leak [1] and celebrate remarkable advances in our understanding of this complex disorder that now constitutes the majority of CSF leaks encountered at our referral centre. The diagnosis and management of CVF today would in many ways be unrecognisable to experts in this field only a decade ago.

Diagnosis of CVF begins with the clinical history (new daily persistent headache with orthostatic, Valsalva manoeuvre, or second-half-of-the-day worsening is the most common but certainly not the only presentation), that is supported by signs of intracranial CSF volume depletion on brain MRI, and is further suggested by meningeal nerve root sleeve diverticula and no extradural fluid collection on spinal MRI. Finally, advanced myelography performed in the lateral decubitus position, most often digital subtraction myelography or dynamic CT myelography, must be performed with impeccable technique, and a bit of good luck, to capture the fleeting opacification of fistulised spinal veins in order to localise the CVF and provide a target for treatment. Most patients have a single CVF, but two or occasionally even more CVF may be diagnosed simultaneously [2, 3]. The recent introduction of photon counting detector CT has increased the yield of decubitus dynamic CT myelography for CVF, but there is still no technique that detects every CVF [4].

The treatment of CVF is an area of intense research, although neither randomised trials nor head-to-head comparisons of techniques have yet been published. Case series have shown clinical and radiographic improvement in patients with CVF with open spine surgery (ligation of the nerve root, dural sleeve, and associated veins or placement of an aneurysm clip on the neurovascular bundle) [5, 6] and transvenous embolisation of the paraspinal and foraminal veins with Onyx liquid embolic agent [7, 8]. At least short-term success has also been reported with percutaneous administration of blood and fibrin glue [9], but other series have shown dismal odds of enduring relief after blood patching for CVF [10, 11]. In this issue of PJNNS, Zayat et al. add to the short list of publications describing recurrent CVF and their treatment [12].

When patients report persistent or recurrent symptoms after treatment of CVF, the differential diagnoses include incompletely treated CVF, opening of a new CVF, and headache due to another cause. Zayat et al. describe 10 patients with ongoing or relapsed symptoms among 42 treated for CVF. Of these 10 patients requiring retreatment, four were determined to have been initially treated successfully (transvenous embolisation in three, fibrin patching in one) because repeat myelography did not show their original CVF but did show a new CVF at a new level [12]. Recurrence was ipsilateral in every case. Defining the success of prior treatment as disappearance of the initial CVF on repeat myelography is a fraught definition because the sensitivity of CT myelography or digital subtraction myelography for CVF is probably no higher than 75% [2, 3]. Yet that nuance is less important than the main message: that patients may develop CVF at new levels after treatment of initial CVF, meaning that repeat diagnostic testing can be fruitful [12].

Also of interest in Zayat's series are the five patients with residual symptoms whose 'recurrence' was suspected to be at the same level as the original fistula. In other words, a primary treatment failure. A previous, larger study by Brinjikji et al. showed a similar likelihood for recurrent CVF to occur at or near the initial level: of 100 patients treated initially, 17 required retreatment, seven at the same level and five within two

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levels above or below the original CVF [8]. A similar pattern was seen in a 2021 report by Malinzak et al., which included four patients whose CVF were treated surgically and then recurred ipsilaterally at the same or within three levels [13].

That CVF recurrence is likely to occur very near the original CVF has several implications. It may suggest an underlying focal dural weakness that predisposes to CVF formation. It may suggest a loco-regional change in CSF and/or venous fluid dynamics that promotes CVF formation by raising CSF pressure or lowering venous pressure, which could blow or suck open, respectively, a connection between nerve root sleeve and vein. Indeed, the Brinjikji et al. series found rebound intracranial hypertension after transvenous embolisation to be a risk factor for CVF recurrence [8].

Despite major advances in the diagnosis and treatment of CVF in the 10 years since their initial description, we still have much to learn. I commend Zayat et al. for reinforcing the message that recurrence of symptoms or brain MRI signs of CSF volume depletion should prompt consideration of repeat myelography for possible new CVF.

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LEADING TOPIC

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Normal pressure hydrocephalus, or Hakim syndrome: review and update

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ABSTRACT

This review makes the case that idiopathic normal pressure hydrocephalus (iNPH) is an outdated term because new information indicates that the syndrome is less idiopathic and that the cerebrospinal fluid (CSF) pressure of normal individuals is affected by several factors such as body mass index, age, and sex. Our review updates the epidemiology of iNPH and provides a clinical approach to the management of these patients. All the clinical features of iNPH are common in older individuals, and each has many causes, so the diagnosis is difficult. The first step in reaching an accurate diagnosis is to address the possible contributory factors to the gait abnormality and determine what if any role iNPH may be playing. The two best diagnostic tests are neuroimaging and cerebrospinal fluid (CSF) diversion (large volume lumbar puncture or external lumbar drainage) with pre/post gait evaluation. This review provides an update on the growing evidence that vascular disease, impaired CSF absorption, congenital, and genetic factors all contribute to the pathogenesis of iNPH. We suggest replacing the term iNPH with the term Hakim syndrome (HS) in acknowledgement of the first person to describe this syndrome. Lastly, we discuss the improvements in shunt technology and surgical techniques that have decreased the risks and long-term complications of shunt surgery.

Keywords: normal pressure hydrocephalus, dementia, gait impairment, genetics

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Introduction

Adult-onset hydrocephalus can occur secondarily to brain insult (e.g. subarachnoid haemorrhage, meningitis, prior brain surgery, traumatic brain injury) or it can be a primary manifestation without an obvious cause. This is most often referred to as 'normal pressure hydrocephalus' (NPH) or 'idiopathic NPH' (iNPH). However, NPH and iNPH are misnomers. 'Normal pressure' indicates normal intracranial pressure, while 'idiopathic' implies unknown causes. However, the latest evidence supports multiple aetiologies or pathogeneses, and this will be one of the features of this review.

Multiple demographic features, such as body mass index (BMI), age, and sex, can alter CSF pressure at lumbar puncture (LP). A study of 339 individuals indicated that a normal opening pressure for males should be below 30 cm H_2O up to the age of 70 or below 25 cm H_2O if older than 70 [1]. For women, the study suggested a normal opening pressure maximum of 25 cm H_2O but 27.5 cm H_2O for those with a BMI >30. This strengthens the notion that symptomatic hydrocephalus in adults may be a more appropriate term given that 'normal' now appears to be on a continuum with a wide range of pressures. Furthermore, some patients with different hydrocephalus pathogeneses can remain asymptomatic for many years [2].

We suggest that the symptom combination of gait impairment with cognitive decline and/or urinary dysfunction should be referred to as Hakim syndrome (HS) in honour of the first person to describe the syndrome.

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Epidemiology

A recent systematic review reported the prevalence of HS to be 10–22 out of 100,000 individuals across all ages, and 5.9% of individuals ≥ 80 years old [3]. They also found that incidence increases in older age and ranges from 1.8 to 7.3 per 100,000 individuals annually [3]. These epidemiological conclusions are limited because the review included studies applying both Japanese [4] and American/European guidelines [5].

Approach to diagnosis

The approach to diagnosis begins by acquiring a thorough history focused on gait/balance, cognition, and urinary function. Patients with HS experience insidious onset of progressive gait impairment with variable cognitive and/or urinary dysfunction, but only rarely present with the full triad of symptoms, which develop over time [6, 7].

Gait impairment

Gait should be the initial focus when diagnosing HS. The gait pattern of HS has been described as magnetic gait, gait apraxia, frontal gait, and lower body parkinsonism. However, to say that HS has a stereotypical gait pattern is erroneous and we suggest misleading. For example, a clinician may assert that a patient does not have HS only on the grounds that he/she does not have gait apraxia. The current diagnostic criteria for HS require at least two of the following nine features to satisfy gait criteria: decreased step height, decreased step length, decreased cadence, increased trunk sway during walking, widened standing base, external rotation of the feet when walking, retropulsion, *en bloc* turning (>2 steps for 180°) and impaired walking balance (>1 correction on an 8-step tandem walk) [5]. These features are not specific to HS and are seen in many other disorders including parkinsonian syndromes, e.g. Parkinson's Disease (PD) and progressive supranuclear palsy (PSP) [8]. Lim et al. used a pressure-sensing walkway to assess HS-related gait features quantitatively [9]. They found that patients with suspected HS had slower gait velocity, shorter stride length, widened base of support, longer stance phase, increased double-limb support, and increased variability both of stride time and stride length. A retrospective study categorised the gait pattern of 140 patients initially suspected to have HS [10]. Eighty patients were ultimately diagnosed with HS and their gait was categorised as "frontal" (short steps, wide base of support, reduced step height) in 26%, "parkinsonian" in 15%, "other" in 30%, and "normal" in 29%. The prevalence of each gait pattern was not significantly different among patients diagnosed with HS mimic conditions, except for a parkinsonian gait which occurred in 30% of cases. Although some studies have indicated that upper extremity coordination/speeded up tasks may improve following temporary CSF diversion [11, 12], the presence of upper body parkinsonism (e.g. soft voice, decreased facial expression) should dissuade clinicians from diagnosing HS in favour of suspecting PD or PSP.

When evaluating the gait of someone with suspected early HS, one should consider the disease stage. Early gait changes may only manifest as subjective unsteadiness or widened base with increased external feet rotation. As impairment progresses gait velocity slows, but cadence may increase as subtle festination emerges. With further impairment, festination becomes more prominent and gait freezing may occur, especially when turning. In the most advanced stages, the gait pattern is dominated by severe gait freezing that tends to be less responsive to external cueing. HS is more common in elderly populations and co-morbidities commonly contribute to gait impairments. These should be screened for and medically optimised before proceeding with HS testing with temporary CSF diversion.

Cervical spinal stenosis with myelopathy is common and has recently been reported in up to 17% of patients with HS [13]. Even subtle pyramidal tract signs should prompt imaging with an MRI of the cervical spine. Lumbar stenosis can also contribute to gait impairment with forward-leaning postures and symptoms of neurogenic claudication. A recent study by Tominaga et al. found that 33% of patients with HS had lumbar spinal stenosis [14]. After shunting, 81% of these patients experienced fewer gait improvements compared to 90% of patients who did not have lumbar spinal stenosis. There was no difference in improvements of cognition or urinary function.

Additional factors commonly affecting gait include hip and knee osteoarthritis, lower extremity sensory loss such as peripheral neuropathy, and vision impairment. Even patients with adequately corrected vision may have vision-related gait impairment, because it can be difficult to see the ground and one's feet through lenses with multiple focal points (e.g. bifocals and progressive lenses). In addition, vestibular function is critically important to a person's balance. Common conditions, such as benign paroxysmal positional vertigo or ototoxic medications (e.g. aminoglycosides) can impair gait. Impairment of blood pressure regulation, especially orthostatic hypotension, can also affect a person's gait. It is important to assess orthostatic hypotension prior to gait testing because the patient may well be unaware of this [15]. The presence of neurogenic orthostatic hypotension should increase suspicion for a synucleinopathy, e.g. PD or Lewy Body Disease, which may be misdiagnosed as HS [16]. Prior to gait assessment, clinicians should review medications for dopamine blockers, sedatives, alpha blockers, antihypertensives, and other centrally acting medications (e.g. benzodiazepines and opioids), which can disrupt gait. Individuals with gait impairment often become more sedentary, resulting in deconditioning, which may be observed as symmetric hip flexor weakness. Deconditioning is especially important to identify and optimise prior to testing for ambulatory improvements subsequent to temporary CSF diversion.

Cognition in HS

Cognitive impairment usually occurs later than gait and urinary impairment, although the temporal progression of these symptoms can vary. Patients whose presenting symptom is dementia have a lower likelihood of improving with CSF shunting [17, 18]. Patients with dementia of more than two years' duration have a poor prognosis despite shunting [2, 19]. The cognitive profile of HS consists of frontal-subcortical systems dysfunction [20]; however, a recent literature review did not find a well-defined cognitive profile of HS prior to shunting [7]. This may manifest with psychomotor slowing, decreased attention and concentration, executive dysfunction, and apathy.

Aphasia is not a characteristic feature of HS and is a poor prognostic indicator for shunting [2, 21]. In addition to a bedside cognitive screening (e.g. Short Test of Mental Status), we recommend clinicians carefully examine speech and language function, because anomia would suggest cortical involvement and is more characteristic of Alzheimer's Disease (AD) or primary progressive aphasia. Moreover, concurrent AD pathology has been reported in 19–56% of patients with HS [22–25]. If AD is suspected, confirmatory biomarker testing with CSF p-tau/Abeta42 or amyloid PET can inform shunt outcomes.

Urinary function in HS

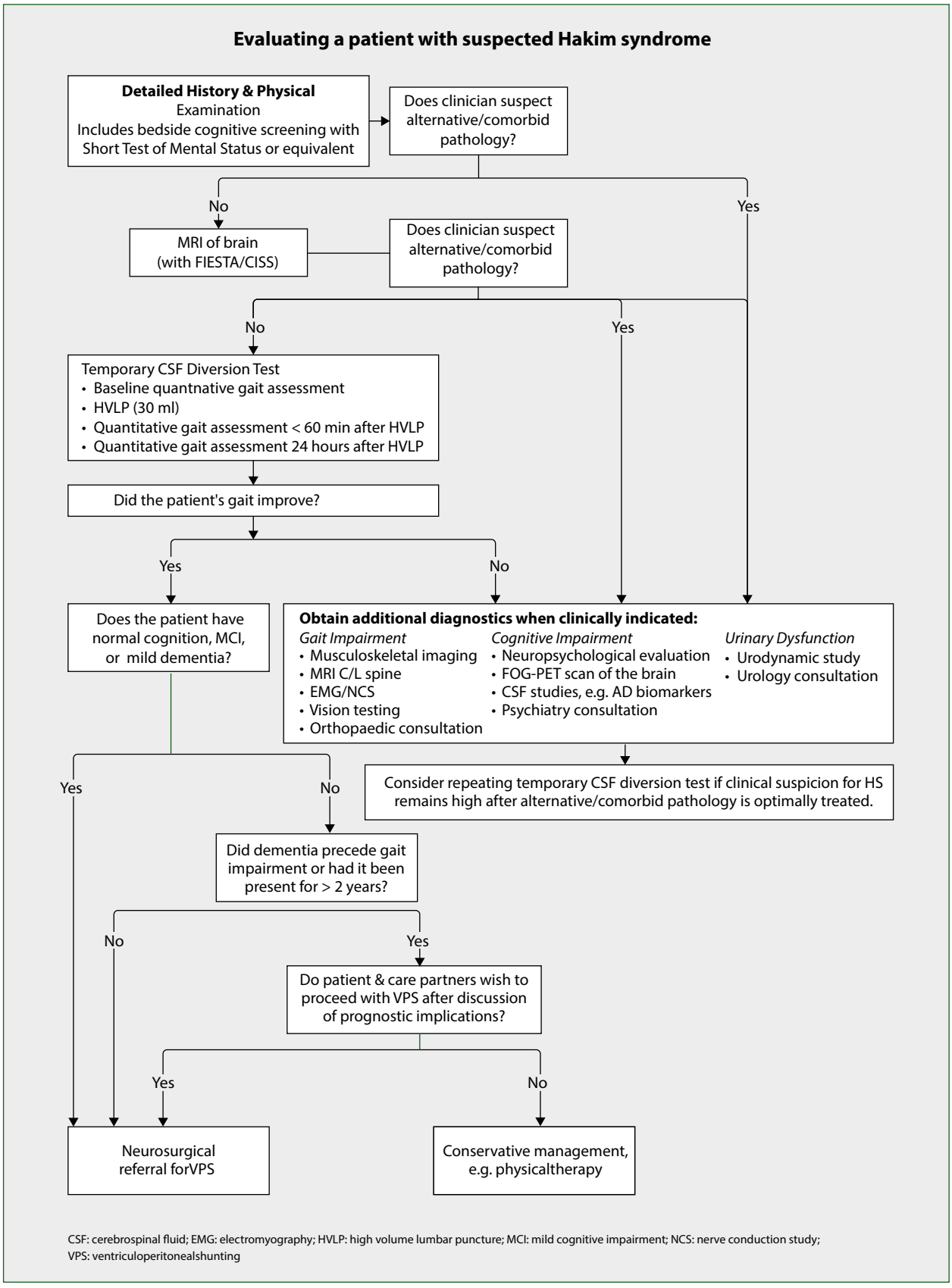
Urinary symptoms of HS most often include urgency and increased frequency leading to incontinence. Given that increased ventricular and extraventricular CSF content often involves the anteromedial frontal lobe, it is not surprising that this pattern of urinary dysfunction is consistent with other reports of frontal lobe incontinence [26]. A recent review identified only four studies with objective testing of urinary function among patients with HS [7]. Of these, three studies using urodynamic testing identified detrusor overactivity in 89% of patients. The fourth study identified predominantly right-sided frontal lobe hypoperfusion with single-photon emission computed tomography in 97 patients with clinico-radiologically definite HS [27]. Urinary symptoms can be caused by a variety of conditions unrelated to HS. Therefore, a urodynamic study and/or urological consultation may be necessary to ensure that urinary symptoms are not incorrectly attributed to HS.

Diagnostic testing

Numerous diagnostic tests for HS have been developed over the years and all have false negative and false positive findings related to shunt outcome. These include cisternography [28], aqueductal flow rates [29], and CSF pressure measurements [2, 30]. One reason for this is that HS has several pathogeneses. For example, a study evaluating CSF absorption found that resistance to CSF outflow (R_{OUT}) correlated with shunt outcome when absorption is impaired, but improvements were also seen among patients with normal R_{OUT} [31]. In contrast, a randomised double-blind study of HS patients demonstrated that patients without CSF malabsorption, but with significant vascular disease, improved after shunting [32]. Because there are different pathogeneses of HS to determine whether a shunt will help, a temporary trial of CSF diversion seems to be the most logical approach to predict whether a shunt will provide clinical benefit. Temporary CSF diversion is accomplished by either an external lumbar drain (ELD) or a high-volume lumbar puncture (HVLP) with 30-40 mL of CSF removed.

There is a paucity of data regarding the sensitivity and specificity of ELD and HVLP in predicting shunt responsiveness, because most studies do not shunt patients who do not improve clinically after temporary CSF diversion. A recent meta-analysis of ELD as a diagnostic test for HS found varying results [33]. The investigators found only four small studies in which patients (n=84) having ELD underwent shunt surgery regardless of the outcome. The sensitivity was 94% (confidence interval (CI) 94–100%) and specificity was 85% (CI 33–100%). Study of HVLP is complicated by the lack of a standardised methodology across medical centres. Patients are usually assessed for gait improvements within the first few hours after CSF diversion because CSF is made at a rate of 0.3 mL/min. At this rate, removal of 30 mL is completely replaced in less than two hours. Nevertheless, patients have often reported improvements delayed by many hours or even days after the HVLP. At our institution, patients are evaluated within 30–60 minutes of the HVLP and again 24 hours later (Fig. 1).

There is no consensus regarding what constitutes a *positive* CSF diversion test, but positivity is typically defined by changes in ambulation rather than cognition or urinary function. Walking speed (i.e. gait velocity) is a reliable and sensitive metric for generally assessing functional status; however, slowed walking speed is non-specific and is altered by myriad conditions [34]. Gait velocity would be an adequate metric in a hypothetically pure HS gait; however, this is unrealistic due to the increased prevalence of comorbidities in older individuals. The CSF diversion test is typically not aiming to confirm the presence of HS. Rather it is intended to determine whether HS is a significant contributor to gait impairment, thereby informing the likelihood of gait improvements from shunting. Therefore, the CSF diversion test should focus on gait features that are expected to improve when HS is treated. Identifying these features has been challenging, and would be best addressed by a study that shunted all individuals regardless of their improvement with temporary CSF diversion. Walchenbach et al. did this in a small cohort, but rated gait impairment and improvement after CSF diversion (HVLP, temporary external lumbar drain (ELD), and ventriculoperitoneal shunting (VPS) using a semi-quantitative functional status scale rather than a quantitative gait metric [35]. They determined that the positive predictive value of the HVLP



CSF: cerebrospinal fluid; EMG: electromyography; HVLP: high volume lumbar puncture; MCI: mild cognitive impairment; NCS: nerve conduction study; VPS: ventriculoperitonealshunting

Figure 1. Evaluating a patient with suspected Hakim syndrome (HS): algorithmic representation of general approach to a patient suspected of having HS

was 100% with a negative predictive value of 32%, while the positive and negative predictive values of the ELD were 88% and 36%, respectively.

Several studies have aimed to identify specific gait metrics that should improve after temporary CSF diversion; however, none can provide positive or negative predictive values because participants who do not "improve" with temporary CSF diversion are typically not shunted. Wikkelso et al. found that a decrease in the number of steps required to walk 18 m linearly correlated with the same metric three months after shunting [36]. Another study found decreases in the time and number of steps required to walk 18 m [37]. The authors reported that improvements of at least 5% in these gait metrics highly correlated (r = 0.99) to improvement after shunting [37].

Neuroimaging

Neuroimaging of the brain, preferably with an MRI, is necessary to evaluate patients with suspected HS. Given the phenotypic variability, MRI may be particularly helpful in refining one's differential diagnosis. Atrophy of the cortex or brainstem may suggest neurodegenerative pathology, such as Alzheimer's Disease (AD) or PSP, respectively. The diagnosis of HS is dependent on the presence of ventriculomegaly, which is often assessed by calculating the Evans Index, which is the ratio of the widest part of the frontal horns of the lateral ventricles to the maximum inner skull diameter at the same level axial imaging (CT or MRI). An Evans Index of greater than 0.3 corresponds to the 20th percentile of ventricle size. The callosal angle is another way of quantifying ventricular enlargement and subsequent displacement of the corpus callosum. Normal callosal angles measure 101–123^{o}, but are significantly lower (52–80^{o}) in HS [38]. A multivariate analysis of 390 subjects found that neither the EI nor the callosal angle could reliably identify individuals with HS [39]. A recent study comparing the diagnostic performance of 15 cross-sectional imaging measures showed that linear measurements of caudocranial alterations of ventricular geometry were more reliable than laterolateral ventricular (e.g. EI) measurements at differentiating HS subjects from healthy controls [40]. Ventricular volume as a ratio of the total intracranial volume is a better measure, but is not readily available [41].

An important radiological feature of HS is disproportionately enlarged subarachnoid hydrocephalus (DESH), which includes tight high convexity and enlarged Sylvian fissures with ventriculomegaly [42]. This is often accompanied by pockets of CSF accumulation indicating disruption of CSF absorption. DESH appears to be a feature of disrupted CSF dynamics and is associated with a good prognostic outcome after shunting [43]. Gunter et al. have developed an automated, machine learning method of detecting high tight cortical sulci [44]. Applying this method to the Mayo Clinic Study of Ageing identified that 6.6% of the population had DESH, which appears to be a feature of disrupted CSF dynamics. A recent study of patients who underwent cisternography showed that DESH was commonly associated with radiotracer accumulation in the ventricles and delayed or absent ascent over the cerebral convexity, suggesting that DESH is a feature of CSF flow or dynamic abnormality [45]. DESH illustrates that in HS there is increased CSF accumulation, both within and outside of the ventricles. CSF collects in the Sylvian fissures and entrapped cortical sulci and is sometimes mistaken for atrophy. After successful shunting for HS these pockets decrease in size and can be helpful in determining whether the shunt is working (Fig. 2).

CSF biomarkers

CSF biomarkers are very useful in diagnosing AD, but have not proved helpful in distinguishing those with HS from those with ventriculomegaly and concomitant AD. Patients with HS typically have low Aβ42 and low phosphorylated tau (pTau) levels, whereas patients with AD have low Aβ42 and high pTau levels [46, 47]. In HS, not only are Ab42 and pTau low, but all the products of the APP protein are low. Jeppsson et al. identified low levels of soluble amyloid precursor protein (sAPP) isoforms (sAPPα, sAPPβ), β-amyloid isoforms (Aβ38, Aβ40, and Aβ42), and tau isoforms (total and phosphorylated) in lumbar and ventricular CSF of patients with HS [48]. Six months after shunting, levels of all metabolites increased, and β-amyloid isoforms increased more among patients who improved clinically after shunting. A hypothetical explanation for this is based on sleep-related brain dynamics. During sleep, neurons shrink by c.50% and the interstitial space expands to facilitate protein waste product clearance via CSF drainage [49]. Brain compression by hydrocephalus may limit the degree of interstitial space expansion during sleep because the brain is tight. This would impede APP protein fragment drainage into the CSF. Shunting decompresses the brain, allowing for expansion of the interstitial space and subsequently improved drainage of protein waste fragments [50].

The diagnostic evaluation for patients suspected of having HS varies even among institutions that regularly treat patients with HS. Our approach begins with a thorough history and physical examination followed by a brain MRI for all patients. If neuroimaging supports a diagnosis of HS, then we obtain baseline quantitative gait metrics prior to a HVLP. The patient undergoes a repeat quantitative gait assessment 30–60 minutes (post1) and 24 hours (post2) after the HVLP. If quantitative comparison (pre vs. post1 and/or pre vs. post2) indicates ambulatory improvement, then the patient is referred to neurosurgery for shunt placement. If there is no or minimal ambulatory improvement following the HVLP, then the patient is counselled based on the Walchenbach study that a subset of patients with a "negative" CSF diversion test will still improve with shunting [35].

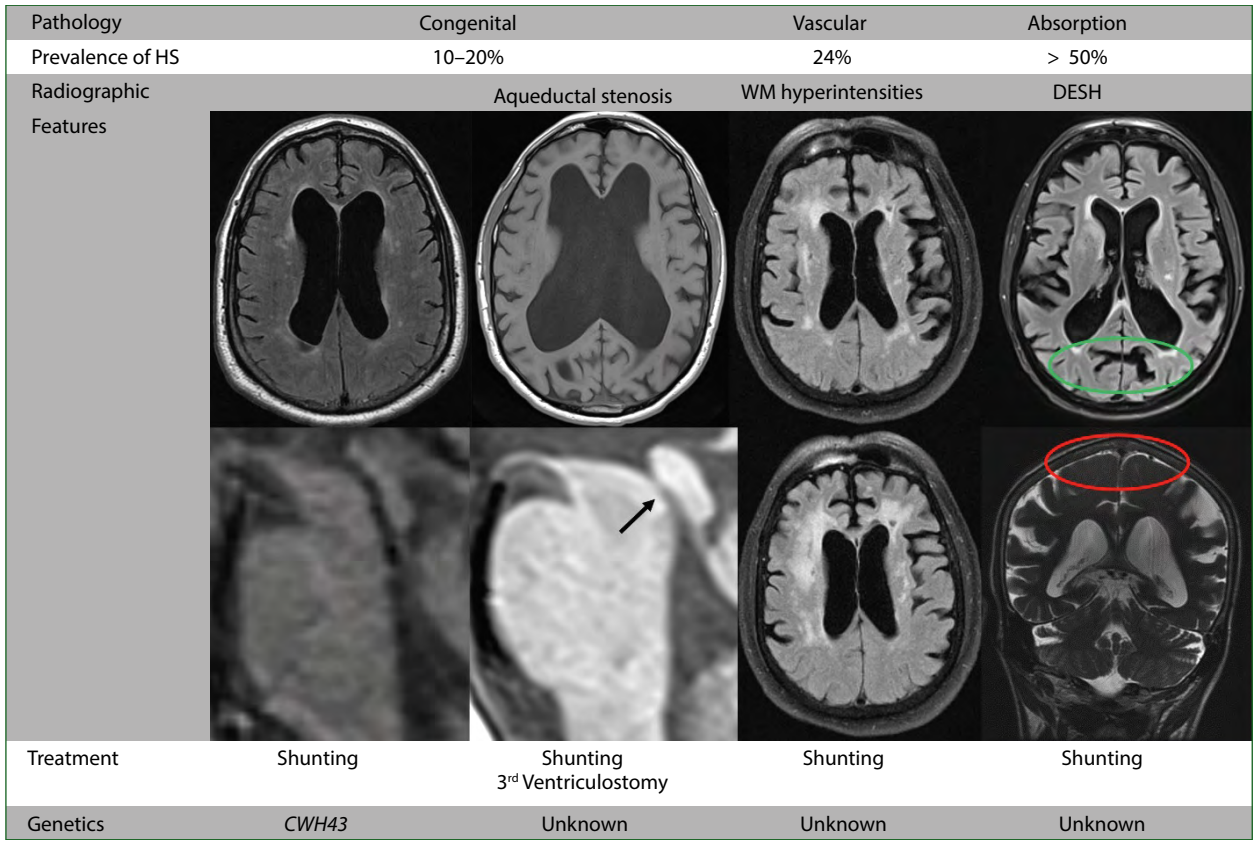


Figure 2. Pathogeneses of Hakim syndrome (HS). Patients with congenital hydrocephalus may or may not have aqueductal stenosis. Hydrocephalus due to vascular factors has characteristic white matter (WM) T2/FLAIR hyperintensities, and hydrocephalus due to impaired cerebrospinal fluid absorption will have disproportionately enlarged subarachnoid hydrocephalus (DESH) with ventriculomegaly, high-tight cortical sulci (red circle), and sulcal trapping (green circle)

Causes of and contributors to normal pressure hydrocephalus

There is clear evidence that hydrocephalus can be secondary to subarachnoid haemorrhage, acute and chronic meningitis, head injury, and neurosurgical intervention. Causes of primary or *idiopathic* HS are less well understood, but growing evidence suggests that this clinical syndrome is becoming less idiopathic as our understanding of contributory factors increases (Fig. 3) [51].

Congenital factors in adult hydrocephalus

An estimated 10–20% of patients with adult-onset hydrocephalus have a large head size [52, 53]. In 1996, Oi et al. described childhood onset hydrocephalus that became symptomatic in adulthood and coined the term 'long-standing overt ventriculomegaly in adults' (LOVA) [54]. They later identified aqueductal stenosis in all subjects from a cohort of 26 individuals with LOVA [55]. Third ventriculostomy is the treatment of choice in these cases although some may not respond, in which case shunting may be considered [56]. A recent study found that c.2/3 of individuals with symptomatic LOVA had aqueductal stenosis and responded favourably to third ventriculostomy and/or shunting [57]. This suggests that some individuals with congenital hydrocephalus without aqueductal stenosis have had a large head all their lives, but only decompensate later in life, leading to HS. Our recent work showed that individuals with congenital hydrocephalus experienced gait improvements after shunting [58].

Aqueductal stenosis can be difficult to detect in some cases. Advances in magnetic resonance imaging with heavily weighted T2 sequences such as Fast Imaging Employing Steady State Acquisition C (FIESTA-C) or constructive interference in steady state (CISS) allow for greater sensitivity to detect aqueductal stenosis or webbing. This type of imaging should be used in all suspected HS cases, but especially for patients with increased head circumference, triventriculomegaly sparing the fourth ventricle, and when the aqueduct is poorly visualised.

Vascular risk factors and HS

Increasing evidence supports an association between vascular pathology and HS. The INPH-CRasH study prospectively

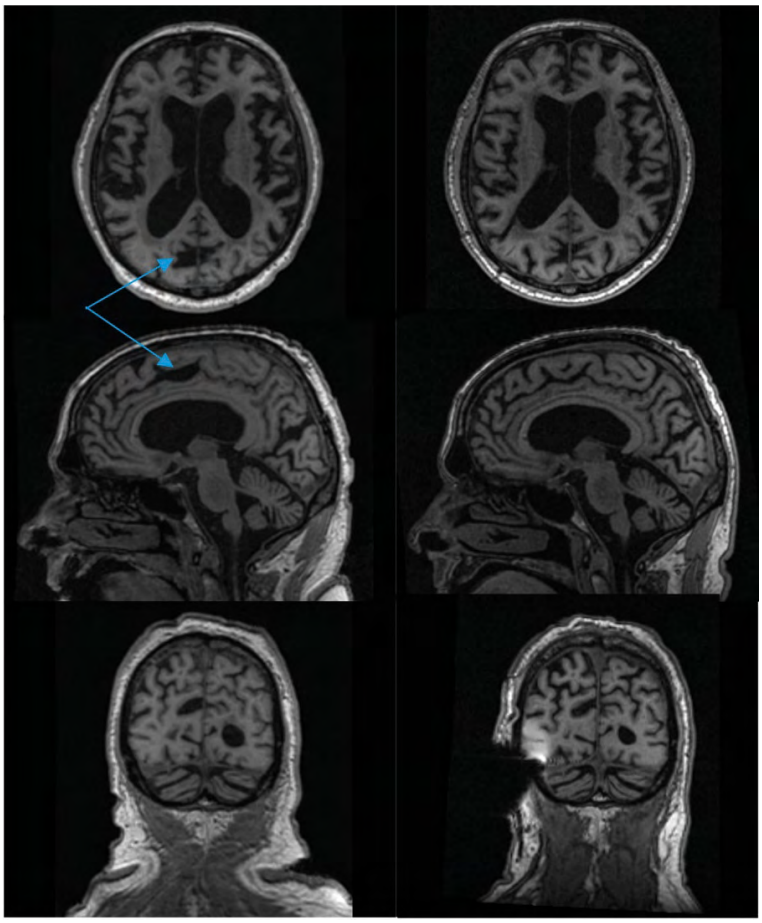


Figure 3. Post-shunt imaging changes. Magnetic resonance imaging of a patient with disproportionately enlarged subarachnoid hydrocephalus (DESH) who underwent ventriculoperitoneal shunting. *Left* images were acquired three days prior to shunting and demonstrate ventriculomegaly and sulcal trapping (blue arrows). *Right* images were acquired 33 months after shunting, and show shunt, decreased ventricular size, and reduced size of extraventricular cerebrospinal fluid pockets

assessed vascular risk factors in 176 HS patients compared to controls, and found that the population-attributable risk of vascular factors to HS was 24% [59]. Multivariable logistic regression analysis of this cohort of HS patients showed that hyperlipidemia, diabetes, obesity, and psychosocial factors were independently associated with HS. Moreover, hypertension, physical inactivity, cerebrovascular disease, and peripheral vascular disease were more frequent in HS. Pyykkö et al. assessed a cohort of 500 individuals with possible HS, among whom 283 were diagnosed with shunt responsive HS [60]. Comparing those with HS to other causes of dementia (Alzheimer's Disease, vascular cognitive impairment, non-specified) they found that diabetes mellitus type 2 and hypertension were more prevalent in the HS group. A Swedish study found that individuals with moderate to severe white matter lesions were at 5.2-times greater odds of having probable HS, while white matter lesions, diabetes mellitus, and hypertension increased the odds of having hydrocephalic ventriculomegaly on neuroimaging [61].

Animal studies have been particularly helpful in understanding mechanisms behind the contribution of vascular risk factors to the development of hydrocephalus. Ritter et al. showed that spontaneously hypertensive rats developed ventriculomegaly by four weeks of age and ventricular size increased by up to 270% [62]. Interestingly, pharmacological lowering of blood pressure in these rats did not alter ventricular size, suggesting that hypertension was not the sole cause of hydrocephalus [63]. A study of sheep induced hydrocephalus within one hour by increasing the amplitude of intraventricular cerebrospinal fluid (CSF) oscillations related to arterial pulsations (i.e. increasing pulse pressure) without altering the mean CSF pressure [64]. In a dog model of ventriculotomy-induced hydrocephalus, ligating the choroid plexus of one lateral ventricle while maintaining a patent interventricular foramen eliminated the pulse wave and prevented the development of hydrocephalus in that ventricle [65].

Human data also supports the role of hypertension in the development of hydrocephalus. One study of patients

with acute subarachnoid haemorrhage showed that hydrocephalus was more likely to develop among patients who had a history of hypertension or had hypertension at the time of admission or at any time during their hospitalisation [66]. The Atherosclerosis Risk in Communities (ARIC) study found that of the 1,112 study participants, those with increased systolic blood pressure or increased pulse pressure at baseline were at greater odds of having ventriculomegaly 10 years later [67]. The SPRINT study is a randomised study in which half had systolic blood pressure lowered to 140mmHg systolic and the other half to 120mmHg. A sub-study called SPRINT-MIND included 755 participants who had MRI scans [68]. In SPRINT-MIND, CSF volume and white matter lesion volume increased significantly by pulse pressure quartile and the study reported that pulse pressure was associated with white matter lesion volume change, and this mediated cognitive decline. This supports the notion of pulse pressure correlating with increased ventricle volume and white matter damage, which in turns mediates cognitive decline.

Patients whose hydrocephalus is primarily related to vascular factors may respond to shunting. A randomised double blind prospective study of shunting looked at 14 people with NPH due to vascular factors based on normal CSF absorption testing, ventriculomegaly, and white matter changes consistent with vascular disease [32]. Among these patients, 10 had hypertension, one had diabetes mellitus, and two had other cardiovascular disorders. Those randomised to immediate shunting had improved on measures of gait and cognition three months later. Other participants underwent shunt placement, but the valve was not opened until three months after surgery. These patients also improved on gait and cognitive measures, but only after the valve had been opened.

CSF absorption in HS

Impaired CSF absorption is another cause of hydrocephalus and is most notably observed in the setting of arachnoiditis. Inflammation of arachnoid granulations, the primary CSF drainage conduit, impedes absorption leading to acute high-pressure hydrocephalus. It has been proposed that insidious absorption impairment might cause hydrocephalus without an increase in pressure. Resorption capacity of CSF can be measured as conductance to outflow of CSF (C_{OUT}) [69]. Børgesen et al. showed that patients with HS and lower C_{OUT} values tended to experience the most sustained improvements with shunting, whereas those with higher C_{OUT} values tended not to respond to shunting [30]. Resistance to CSF outflow (R_{OUT}) is the inverse of C_{OUT} and is increased in individuals with HS. A Dutch study of 101 patients with HS who underwent shunting found that higher R_{CSF} correlated with a higher likelihood of shunt responsiveness [31]. Those whose R_{OUT} was 18 mmHg/mL/min were 3.5 times more likely to respond to shunting; however, some individuals with lower R_{OUT} (10–12 mmHg/mL/min) also improved, suggesting that impaired CSF absorption was not the only cause of their HS. R_{OUT} is a well-established prognostic factor for shunt responsiveness [70–73]. A study investigating this relationship obtained leptomeningeal biopsies during shunt surgeries of 25 patients with HS [70]. Nearly half of the participants had meningeal fibrosis; however, the presence of fibrosis did not correlate with R_{OUT}. This also suggests that other mechanisms may be, at least partly, responsible for these altered CSF flow dynamics.

Genetics of HS

New information about genetic factors of HS has led to an increased understanding of the mechanisms that contribute to this disease. A Finnish study of 375 cases of HS reported that nearly 5% had a family member who was also shunted for HS, and 11% had relatives with at least two clinical features of HS [74]. There were also eight multiplex families within this study. New insights into the genetics of HS have enhanced our understanding of how perturbations in CSF flow dynamics may lead to hydrocephalus. A recent study identified two heterozygous predicted loss-of-function variants within the *CWH43* gene in 15% of 53 unrelated patients with HS [75]. The authors validated the clinical effects of these gene variants by demonstrating that *CWH43* knock-out mice developed hydrocephalus and impaired gait/balance. These mice also had reduced ependymal ciliary populations and decreased locomotion of glycosylphosphatidylinositol-anchored proteins on the apical surfaces of choroid plexus and ependymal cells. We identified several different *CWH43* coding variants in 16% (15/94) of patients with HS [58]. These patients tended to have a larger head circumference, less frequent disproportionately enlarged subarachnoid hydrocephalus (DESH) and sulcal trapping, less white matter disease, and responded to shunting.

Other genes have also been implicated in HS. A Japanese study of an HS multiplex family identified a gene called *CFAP43*, which encoded for a cilia and flagella associated protein [76]. They generated a knock-out mouse model that had abnormal ciliary morphology and developed hydrocephalus. Copy number loss within intron 2 of the *SFMBT1* gene was initially seen in 4/8 patients with ventriculomegaly and features of HS on MRI compared to 0/10 controls [77]. The investigators localised the SFMBT1 protein to arterial walls, ependymal cells, and the choroid plexus epithelium. A separate study using polymerase chain reaction analyses identified this copy number loss *SFMBT1* in 26% of patients with shunt responsive HS compared to 4.2% of healthy individuals and 6.3% of patients with Parkinson's Disease [78]. A large European study of more than 1,400 individuals (944 with HS) found the same *SFMBT1* copy number variant in 10% of Finnish and 21% of Norwegian patients with HS, compared to only 5.4% of Finnish controls [79]. Kageyama et al. assessed 10 patients from five families with panventriculomegaly defined by a wide foramen of Magendie and large cisterna magna [80]. All three

patients from a single family carried a copy number variant in the *DNAH14* gene, which encodes a dynein heavy chain protein associated with motile cilia function. These patients had no evidence of a pressure gradient between the third ventricle and interpeduncular/prepontine cistern (absence of downward bulging of the third ventricle) but did have cognitive impairment that improved after endoscopic third ventriculostomy, lumboperitoneal shunting, or VPS.

Management of HS

Permanent CSF diversion is the treatment for HS, and it is most commonly accomplished with VPS in the United States, although ventriculoatrial and lumboperitoneal shunting can certainly be considered as an equivalent first line treatment and are commonly used outside the United States. A review of these approaches found no difference, so patient comorbidities (e.g. obesity or heart failure) and surgeon experience with shunt method should drive the selection of one method over the other [81]. The SINPHONI (Study of Idiopathic Normal Pressure Hydrocephalus for Neurological Improvement) trial reported that 80/100 patients improved by at ≥ 1 level on the Modified Rankin Scale at any evaluation point within one year of shunting [42]. Multiple reviews have shown that using programmable valves lowers the rate of shunt revisions and the occurrence of postoperative subdural haematomas due to overdrainage [81, 82]. Shunt outcomes data from 1,846 patients in a Swedish registry demonstrated that 90% of those with fixed valves required surgery for post-shunting subdural collections, compared to 30% of those with adjustable valves [83]. This rate can be further decreased by starting patients at a higher initial valve setting and slowly lowering it over several months [81]. Our group showed that more overdrainage-related complications occur when the initial valve opening pressure is set well below the lumbar puncture CSF opening pressure, and a follow-up study showed that setting the valve initial pressure close to the lumbar puncture opening pressure resulted in less overdrainage [84, 85]. Antigravitational valves appear to reduce the risk of overdrainage, as demonstrated by a randomised double-blind study that reported overdrainage in 7% compared to 43% with programmable value alone [86]. Freimann et al. also showed that antisiphon/antigravity components further decrease the risk of overdrainage throughout a mean follow-up duration of nearly three years [87].

The method of catheter placement into the peritoneum for ventriculoperitoneal shunts may have implications for failure rates. One study of 120 shunted patients found zero distal shunt failures among patients who underwent laparoscopically assisted shunt placement, compared to 5/60 with mini laparotomy [88]. Ventricular catheter placement using neuronavigation assistance also improves the accuracy of shunt placement and surgical outcomes. A randomised prospective study of primarily patients with HS or haemorrhagic hydrocephalus found greater accuracy of shunt position in those whose catheter was placed using a Mobile Health Assisted Device compared to standard free hand placement [89]. Yamada et al. improved the accuracy of free hand catheter placement by implementing a preoperative simulation of a parieto-occipital approach [90]. This is especially relevant given the increased challenge of a parieto-occipital approach for targeting a lateral ventricle. Infection rate is also a concern and was reported to be 6% with standard catheters in the BASICS randomised trial [91]. This trial demonstrated that using antibiotic-impregnated catheters significantly reduced the rate of shunt revision due to infection, to 2%. A recent review and meta-analysis of 19 clinical trials showed that antibiotic-impregnated catheters halved shunt-related infection rates [92].

The complication rate and prognosis of shunting for HS continue to improve [93]. Most recently, a large meta-analysis of 2,461 patients found post-shunt improvements in 74% of patients at three months, 79% at 12 months, and 72% at three years [81]. Complication rates included 9% for subdural haematomas, 2% for haemorrhagic or ischaemic events, 2% for infections, 2% for seizures, a 16% revision rate, and a 1.5% mortality rate.

Conclusions

This review makes the case that patients with adult-onset hydrocephalus without an obvious secondary cause should not be referred to as having idiopathic normal pressure hydrocephalus because fewer and fewer patients are idiopathic and many have higher CSF pressure, the latter often because BMI correlates with CSF pressure and a large number of adults are now overweight.

We suggest that this entity instead be called Hakim syndrome (HS) as an acknowledgement of the surgeon who first brought it to the attention of his colleagues. Epidemiology suggests that HS is more common than was once thought.

The cardinal clinical features of HS (gait impairment, cognitive decline, and urinary dysfunction) have many causes, especially in elderly individuals, thus posing a significant challenge to an accurate diagnosis. It is prudent to first evaluate the cause(s) of a patient's gait abnormality. If HS is a major component of the gait impairment determined by a thorough history, examination, and special testing including spine imaging, brain imaging, and temporary CSF diversion, then the patient is a good candidate for surgery. New advances in shunt technology and surgical techniques have decreased the surgical risks.

Growing evidence suggests that congenital factors, genetic variants, vascular disease, and abnormal CSF absorption all play important roles in HS. As those managing HS become more familiar with the details of this syndrome, patients will benefit from a shorter time before an accurate diagnosis, and more appropriate treatment.

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LEADING TOPIC

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Headache associated with intracranial hypotension: diagnostic challenges and difficulties in everyday neurological practice

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ABSTRACT

Low pressure of cerebrospinal fluid (CSF) is a rare cause of headache, except when the patient undergoes a lumbar puncture. Headache associated with a low CSF pressure i.e. intracranial hypotension causes diagnostic difficulties. Headaches related to spontaneous intracranial hypotension (SIH) pose a significant diagnostic challenge in everyday neurological practice. Patients with headaches due to SIH are usually diagnosed only after a long delay. Diagnostic problems may result in unnecessary invasive diagnostic procedures, or even neurosurgical operations. Diagnosing headaches attributed to SIH requires the consideration of several clinical scenarios, and the disease's features causing primary or secondary disturbances. In this review, we discuss the differential diagnosis of SIH-related headaches with reference to accumulated knowledge, including meta-analyses, guidelines, casuistry, and the applicable criteria of the International Classification of Headache Disorders. In addition, we discuss head and spine magnetic resonance imaging abnormalities, which may indicate intracranial hypotension.

Keywords: intracranial hypotension, spontaneous intracranial hypotension, orthostatic headache

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Introduction

The definition of intracranial hypotension (ICH) is a cerebrospinal fluid (CSF) pressure of less than 60 mm H_2O causing various clinical symptoms, including headache. However, in over 50% of cases, pressures are above 60 cm H_2O [1]. This applies to lumbar puncture opening pressure in the lateral decubitus position. It is possible that rather than low CSF pressure, it is in fact low CSF volume that is the primary cause of the symptoms of ICH.

Therefore, the term 'CSF hypovolemia' has also been used to describe this syndrome [2].

The symptoms of ICH are orthostatic headache, usually accompanied by nausea or vomiting, neck pain or neck stiffness, tinnitus, hearing disturbances, and visual symptoms including photophobia [3].

The most common reason for ICH is a CSF leak, either traumatic or iatrogenic. Otherwise, ICH can be a spontaneous condition. Spontaneous intracranial hypotension (SIH) is challenging to diagnose because of the variability of clinical symptoms and feasibly subtle imaging findings. SIH can be easily overlooked, and thus patients may await a correct diagnosis for many years.

Diagnostic criteria and clinical picture of headache resulting from low cerebrospinal fluid pressure

According to the 3rd edition of the International Classification of Headache Disorders, a headache resulting from ICH is classified as a secondary headache attributed to a non-vascular intracranial disorder caused by low CSF pressure [4]. Intracranial hypotension headaches are categorised

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Table 1. Diagnostic criteria of headache resulting from intracranial hypotension according to the International Classification of Headache Disorders [4]

Headache attributed to low CSF pressure:
A. Headache fulfilling criterion C
B. Either or both of:
a) Low CSF pressure (< 60 mm CSF)
b) Evidence of CSF leakage on imaging
C. Headache has developed in temporal relation to low CSF pressure or CSF leakage or led to its discovery
D. Not better accounted for by another ICHD-3 diagnosis.
Postdural puncture headache:
A. Headache fulfilling criteria for headache attributed to low CSF pressure, and criterion C below
B. Dural puncture has been performed
C. Headache has developed within five days of dural puncture
D. Not better accounted for by another ICHD-3 diagnosis.
CSF fistula headache:
A. Headache fulfilling criteria for headache attributed to low CSF pressure, and criterion C below
B. A procedure has been performed, or trauma has occurred, known sometimes to cause persistent CSF leakage (CSF fistula)
C. Headache has developed in temporal relation to procedure or trauma
D. Not better accounted for by another ICHD-3 diagnosis.
Headache attributed to spontaneous intracranial hypotension:
A. Headache fulfilling criteria for headache attributed to low CSF pressure, and criterion C below
B. Absence of a procedure or trauma known to be able to cause CSF leakage
C. Headache has developed in temporal relation to occurrence of low CSF pressure or CSF leakage or has led to its discovery
D. Not better accounted for by another ICHD-3 diagnosis.

CSF — cerebrospinal fluid; ICHD-3 — International Classification of Headache Disorders 3rd edition

as either a postdural puncture headache (PDPH), a CSF fistula headache, or a SIH-related headache. Table 1 sets out the diagnostic criteria for headaches related to ICH [4].

The hallmark of a headache attributed to ICH is frequently orthostatic, usually but not always related to changing position from supine to standing. It has been postulated that a decrease in CSF volume and the downward displacement of the brain cause traction on pain-sensitive structures [4]. The other current theory indicates that venous dilatation causes the symptoms (which we discuss later).

Symptoms can occur immediately after standing up, and resolve quickly after resuming a supine position, or may show delayed response to postural change, worsening after minutes or hours of being upright, and improving after minutes or hours of being horizontal [4].

In most cases, the onset of headache is gradual, reaching maximal intensity in a period ranging from several minutes to several hours. The severity of headache varies from mild and non-bothersome to very severe, resembling a sub-arachnoid haemorrhage [3]. It may be extremely painful and debilitating [5].

The orthostatic type of headache and posture-related component of this symptom may become less evident over time, leading to frequently delayed diagnosis and misdiagnosis [3].

Post-dural puncture headache

PDPH is the best-known type of headache caused by ICH. Previously, it was referred to as 'post-lumbar puncture headache' or 'post-puncture syndrome'. It is estimated that PDPH may affect up to 40% of patients who undergo a diagnostic or therapeutic lumbar puncture (LP) [6, 7]. The time correlation between the LP and the occurrence of orthostatic headache usually helps to establish the diagnosis, although there are interesting case reports of PDPH with extended latencies [8, 9]. Risk factors for PDPH include female gender, age 30-50, a previous history of this type of headache, and an orientation of the needle bevel perpendicular to the long axis of the spinal column during the LP [4]. The use of an atraumatic needle enables fewer complications after lumbar puncture [10].

Typically, PDPH occurs early, i.e. during the first attempts to tilt after LP, but it can also manifest after a delay. The current diagnostic criteria assume five days from dural puncture [3]. Emphasising this issue is especially important in the era of constant reductions in the length of hospitalisations after diagnostic or therapeutic LP.

The essential elements to effectively prevent PDPH include using atraumatic puncture needles and injecting the needle at an oblique angle to the spinal axis [7]. According to the study by Cognat et al. [6], other prophylactic methods such as hydration and bed rest are ineffective and might even contribute to a more severe course of PDPH. Optimal PDPH management has been precisely detailed in the recent multidisciplinary guidelines [11].

Cerebrospinal fluid fistula headache

Headaches caused by CSF leakage can cause enormous diagnostic difficulties. When discussing this type of headache, it is worth considering two clinical situations: a) a headache in a patient after a medical procedure; and b) a headache as a part of the complex symptoms in a patient after injury or trauma.These are the fistulas caused by rupture of meninges, as distinct from CSF venous fistula.

Headache caused by CSF leakage after a medical procedure is usually described in patients operated on due to spinal column diseases (i.e. disc herniation, spinal canal stenosis caused by herniated disc, and/or degenerative changes) [12]. This type of headache is often not recognised early enough for several reasons, e.g. the short duration of the patient's stay in the surgical ward, the treatment used in the postoperative period including parenteral hydration and analgesics, and even the marginalising of patient complaints and omitting this diagnosis in order to limit the number of adverse events in a clinical centre. All these factors may contribute to an

underestimation of the incidence of CSF fistula headache. If there is no spontaneous healing during the convalescence period, a patient with such a headache is usually referred to a neurologist. The longer the time between the procedure and the onset of symptoms, the more difficult it is to connect these facts and to establish the correct diagnosis and treatment.

Diagnosing headache due to CSF fistula is particularly difficult when a headache is a component of the post-traumatic symptoms due to brain/spinal injury. Symptoms of the disease can present up to several months after such an injury. This headache may not have a typical orthostatic nature. In addition, due to treatment that includes a bed regimen and analgesic treatment, symptoms may not appear at first. The symptoms of low CSF pressure may occur only during rehabilitation while standing, and then may be interpreted as symptoms of autonomic dysfunction and dysautonomia resulting from the prolonged supine position of a bedridden patient [13]. LP should be performed and the CSF pressure should be measured to verify the diagnosis [4]. This classification does not meet with the current recommendations. Most headache specialists rather deny the use of LP to diagnose ICH. In the most specialised clinical centres, there is a possibility of assessing the opening CSF pressure during neuroimaging (CT myelogram or DSM imaging) that allows the localisation of a CSF leak. In this clinically severe situation, a LP may be perceived as bizarre in a patient who has experienced injury or multiple injuries. Therefore, understanding the possible abnormalities in non-invasive imaging tests that can be performed in this group of patients will be extremely helpful in raising a suspicion of low CSF pressure. Findings in imaging studies that indicate ICH will be discussed in the next part of this article.

Headache attributed to spontaneous intracranial hypotension

The real diagnostic challenge among headaches attributed to ICH is the headache during SIH. The incidence of SIH is estimated at 3.7-5/100,000/year in the general population [14, 15]. Middle-aged people (30-50) are most often affected, although the disease can occur even in the first or the ninth decades of life. Women are affected more often than men [3, 14]. The literature highlights two critical issues of SIH. The first is a long delay from the onset of symptoms to the diagnosis, which may last several years. A second important aspect is the variety of the clinical picture of SIH-related headaches. The differentiation concerns the nature and location of the headache, changes such as pain over time, and a large diversity of symptoms accompanying the headache. All of these factors may contribute to confusion about this type of headache, with others more common in the population i.e. primary and secondary headaches.

The most common cause of SIH is a spontaneous CSF leakage through a tear or a defect in the dura of the spinal cord, leakage through a meningeal diverticulum, or a CSF-vein fistula [16]. The differentiator between a headache attributable to SIH and a CSF fistula headache is the absence (in the case of SIH) of a procedure or trauma known to be able to cause CSF leakage. Various conditions can lead to spontaneous leakage of CSF, e.g. congenital absence or focal weakness of dura around the nerve root sheaths, congenital connective tissue disorders causing structural abnormalities, osteophyte protrusions, or spinal disc herniation.

The symptoms of SIH are thought to be the result of pulling the meninges (dura mater), stretching of the brain, compression, and stretching of the structures of the posterior fossa (especially the dura mater, cranial nerves, and the opening of vestibular canaliculus) [17]. The SIH headache phenotype is discussed later.

Differential diagnosis of intracranial hypotension

Clinical symptoms that may occur during SIH are set out in Table 2 [3, 16, 17]. To emphasise the broad clinical picture and the diagnostic pathway of SIH, we have decided to present below two clinical situations that neurologists will meet in everyday clinical practice.

Diagnosis of headache due to spontaneous intracranial hypotension in a neurological emergency room: sudden-onset headache

In this section, we analyse a scenario when a patient with SIH is referred for urgent neurological evaluation with a sudden-onset headache. Misdiagnoses described in the literature are related to two main clinical scenarios. In the first, the headache is accompanied by symptoms indicating meningeal syndrome (which is defined as a group of symptoms caused by damage of meningitis for any possible reason). The second clinical picture is mainly marked by symptoms suggesting cerebrovascular diseases (e.g. transient ischaemic attack, TIA).

Scenario 1: Headache due to spontaneous intracranial hypotension with meningeal-like symptoms

Headache attributed to SIH can present with a sudden onset headache. Patients can indicate the exact time of onset. This type of headache's severity can sometimes be comparable to that of a primary thunderclap headache. Many symptoms can accompany headaches attributed to SIH, some of which are consistent with the symptoms of meningeal syndrome. These symptoms include, but are not limited to, nausea and vomiting, visual and hearing disturbances (including sensitivity to light and sound), disturbances of consciousness, neck pain, and stiffness. In such cases, SIH-related headaches should be differentiated from those in subarachnoid haemorrhage and those attributable to meningitis [18].

The exclusion of a subarachnoid haemorrhage is obligatory in the differential diagnosis of sudden onset headache, which has occurred for the first time in the patient's life. Most

Table 2. Symptoms other than headache of spontaneous intracranial hypotension [3, 16, 17]

CNS structures	Symptoms
CN II (and/or visual pathway)	Photophobia, transient visual obscurations, visual blurring, visual field defects
CN III, IV, VI	Diplopia: abducens nerve, oculomotor nerve, or trochlear nerve palsy
CN V	Facial pain or facial numbness
CN VII	Facial weakness/palsy, facial/hemifacial spasms, dysgeusia
CN VIII	Tinnitus, auditory disturbance ('underwater feeling', muffled heating, aural fullness), phonophobia, vertigo, dizziness; hypoacusis, unilateral hearing loss, acute hearing loss, hyperacusis
Posterior fossa	Nausea, vomiting
General brain dysfunction	Cognitive deficits/symptoms (cognitive impairment, behavioural changes, slow thinking)
	Unconsciousness, coma
	Seizures, status epilepticus
Basal ganglia and/or cerebellar dysfunction	Parkinsonism, tremor, chorea, ataxia
Hypothalamus, hypophysis	Hyperprolactinemia, galactorrhea
Brainstem	Bulbar palsy
Brain vessels	Posterior reversible encephalopathy syndrome (PRES)
	Reversible cerebral vaso-constriction syndrome (RCVS)
	Dural sinus and/or vein thrombosis
Meninges	Meningismus, posterior neck pain, neck stiffness
	Complex symptoms of leptomeningeal hemosiderosis (sensorineural hearing loss, ataxia, dementia)
Spinal cord	Cervical myelopathy, tetraplegia, progressive paraparesis due to secondary spinal cord herniation
Nerve roots	Radicular arm pain, arm numbness, interscapular pain, back pain

CN II — optic nerve; CN III — oculomotor nerve; CN IV — trochlear nerve; CN VI — abducens nerve; CN V — trigeminal nerve; CN VII — facial nerve; CN VIII — vestibulocochlear nerve

often, the first diagnostic test performed in the A&E is a head computed tomography (CT) scan, which is widely available and sensitive in detecting the presence of intracranial haemorrhage. However, a head CT scan may not detect signs of subarachnoid haemorrhage, or sometimes these symptoms can be missed due to their small extent. According to a systematic review and meta-analysis by Carpenter et al., the sensitivity of head CT is 94% in the first few hours. In such cases, the following diagnostic tests should be performed: LP and CSF assessment. The LP may provoke complications (including headaches), but they are irrelevant when we consider the possibility of overlooking a life-threatening condition, which is what SAH is. Some difficulties may arise in differentiating between headaches in the course of SIH and headaches in the course of subarachnoid haemorrhage. Firstly, a head CT scan, especially one without contrast, may not show any changes suggestive of SIH.

The proper neuroimaging examination to diagnose SIH is the head magnetic resonance imaging (MRI) with contrast [19]. Secondly, the performed LP and CSF examination may be non-diagnostic of SIH or can give a misleading picture.

It should be noted that the diagnosis of all headaches attributed to ICH includes a criterion of CSF pressure of less than 60 cm H_2O. Fulfillment of this criterion confirms the diagnosis of ICH, but the converse is not true, i.e. CSF pressure equal to or greater than 60 cm H_2O does not exclude an ICH headache. According to the previously cited meta-analysis by D'Anton et al., CSF pressure in SIH patients was normal in 32% of cases, but in 3% of cases was elevated [3]. The assessment of CSF can also be misleading. In patients with SIH, the technical aspects of LP may be difficult, which promotes CSF bleeding [18]. Cases of xanthochromic CSF during SIH have also been reported. The consequences of misdiagnosis may include further invasive diagnostic procedures for vascular pathology exclusion [17, 18].

In an emergency setting, headache caused by SIH should also be differentiated from headache attributed to intracranial infection. Differentiating between these two types of headache should not be a challenge. Therefore, one should consider the explanations behind the diagnostic errors described in the literature. Given the aetiology of meningitis, the most likely misdiagnosis is viral/aseptic meningitis. Meningitis can proceed without a strong expression of inflammatory symptoms and can be milder than neuroinfections of bacterial and fungal aetiology [20, 21]. In addition, attention should be drawn to the unreliable nature of elevated body temperature (fever or low-grade fever) as a symptom differentiating between these two diseases. A significant increase in body temperature is not a permanent symptom of neuroinfection. Furthermore, a patient with severe headaches will most likely take or be given painkillers and anti-inflammatory medications before going to Emergency Room. Hussein et al. [22] observed an increase in body temperature in SIH, which could be explained by inadequate activation of the thermoregulatory centre in the diencephalon as a consequence of the stresses resulting from stretching the brain along its long axis, compression by

swollen veins, or activation of the thermoregulatory centre by cytokines as a result of damage to the blood-brain barrier. Finally, a CSF analysis result can settle the argument regarding diagnosing and treating neuroinfections alone. CSF in patients with SIH may show lymphocytic pleocytosis, which may exceed 200 cells/mm^3. Elevated protein concentrations and decreased glucose concentrations have also been described in CSF taken from patients with SIH [17, 23].

Scenario 2: Headache due to spontaneous intracranial hypotension with transient ischaemic attack-like symptoms

Due to the disease's varied symptomatology and possible sudden onset, SIH-related headaches may also be misdiagnosed as headaches during TIA or even stroke [24]. Symptoms of SIH that may direct the diagnosis towards cerebrovascular diseases include dizziness, balance disorders, numbness or paresthesia of the face or limbs, vision and hearing disorders, taste disorders, and abducens nerve palsy [25, 26]. From a practical point of view, the most helpful tool in verifying the diagnosis will be a head MRI (with contrast). This examination also makes it possible to decide on the diagnosis i.e. TIA or ischaemic stroke [27].

Previously, this diagnosis was established based on the time criterion, i.e. if the symptoms of vascular brain dysfunction persisted for more than 24 hours, then stroke was diagnosed, and if it subsided within 24 hours, then TIA was diagnosed. In the presence of ischaemic focus in the brain, an ischaemic stroke is diagnosed, even if the symptoms of its damage have subsided within the first 24 hours of the disease. Contrast-enhanced head MRI can reveal abnormalities indicative of SIH and establish the diagnosis at this stage.

At this point, we must underline that brain venous thrombosis (i.e. cerebral venous stroke or sinus thrombosis) occurs more often in patients with SIH. The diagnosis of venous infarction itself is a diagnostic challenge. This is the least common type of stroke, usually with multifactorial aetiology and an often confusing clinical picture. It may manifest as a new daily persistent headache [28, 29].

Diagnosis of headache attributed to spontaneous intracranial hypotension in a neurology outpatient clinic: chronic headache

Due to the previously described diagnostic difficulties associated with SIH, the patient is rarely correctly diagnosed at the onset of the disease, even when the disease has an abrupt onset and is associated with orthostatic headache. Orthostatic headache occurs in most (c.80%) of patients, but in the remaining c.20% of cases it can take a different form, including pain independent of body position. In addition, even if the headache was initially orthostatic, it may lose this feature over time, persist, or even intensify, after assuming the supine position [16].

In the literature on headache due to SIH, the most common false diagnoses are tension-type headache, migraine, cervical headache, cervical radiculopathy, headache attributed to Chiari malformation type I, headache attributed to somatisation disorder, and cough headache. Suspicion of SIH requires differentiation from postural orthostatic tachycardia syndrome (POTS) and orthostatic hypotension.

Misdiagnosis of headaches attributed to SIH as either tension-type headaches or migraines can be explained by the high prevalence of these primary headaches in the general population. According to the Global Burden of Disease study published in 2022, it appears that the most common primary headaches in the population are tension-type headaches (26% of the population) and migraines (14% of the population) [30]. Therefore, these are the most frequently diagnosed headaches in everyday neurological practice [31].

The most important issue is to carefully collect the medical history from the beginning of the disease, even if this extends over several years. Headache due to SIH is usually chronic from the onset, whereas tension-type headaches and migraines evolve from episodic to chronic forms during the course of the disease. Another feature that may lead to misdiagnosis is the possible location of the headache attributed to SIH, which usually involves the occipital area, often with coat hanger distribution pain or the entire head. However, it can also be located in the temporal area or cover the top of the head. Limiting neuroimaging to head CT or MRI without contrast may favour diagnosing a primary headache, e.g. tension-type headache [3, 32]. In cases of concomitant visual disturbances, photosensitivity, nausea, or vomiting, migraine may be misdiagnosed. Patients with SIH-related headaches often experience reduced activity during the day because the symptoms tend to worsen in the second half of the day. This feature can be wrongly interpreted as typical migraine headaches that worsen with physical exertion [3, 32].

In particular, headaches attributed to SIH may be misdiagnosed as vestibular migraine. This mistake is facilitated by the frequent occurrence of balance disorders or symptoms of dizziness, which affects about half of patients with SIH [33].

Headache during SIH should be considered in the differential diagnosis of cervicogenic headache, neck pain, cervical radiculopathy, and cervical syndrome. Due to their common characteristics, these diseases will be discussed together.

The cervical part of the spine is the second location of discopathic and degenerative changes in the general population [34, 35]. This diagnosis is usually considered first in a patient with neck pain radiating to the back of the head. The typical characteristics of the headache, accompanied by stiffness in the neck and limitation of movement, may, therefore, be confusingly similar to the chronic pain associated with SIH. In addition, during SIH, numbness and paresthesia of the limbs may occur, which suggests the diagnosis of radicular syndrome. However, patients who experience dizziness and balance disorders may be misdiagnosed with cervical syndrome [3, 16, 17].

Incorrect results of imaging tests of the cervical spine, showing discopathy and/or degenerative changes, may contribute to persistent misdiagnosis of the symptoms of spinal disease.

At this point, it should be noted that an MRI of the cervical spine may reveal the abnormalities discussed below, indicating SIH.

The differentiation of headache attributed to SIH from headache due to Chiari type I malformation deserves separate discussion. In this case, a false diagnosis may result in an unnecessary suboccipital craniotomy. Both conditions share common symptoms: headache, dizziness, balance disorders, sensory disturbances, and cranial neuropathies [32]. The differentiating feature is the duration of the pain. In the case of Chiari type I malformation, the pain episodes are brief and, as emphasised in the diagnostic criteria, last up to five minutes, whereas headache during SIH lasts for hours or is a chronic pain. In both cases, the headache can be aggravated by coughing, Valsalva manoeuvre, or anything that increases intrabdominal pressure. Pain typically localises in the occipital location in both conditions.

One of the radiological signs described in SIH is the displacement of the cerebellar tonsils into the foramen magnum. It is strongly recommended to seek SIH features in neuroimaging to avoid misdiagnosing Chiari type I malformation [36]. CSF leakage should be excluded in all patients with headaches and features of this malformation in head MRI.

A possible reason for SIH-related headaches is heritable connective tissue disorders, e.g. Marfan syndrome and Ehlers-Danlos syndrome. Abnormalities of collagen, fibrillin, or elastin can cause dural weakness, which eventually plays a role in causing spontaneous low CSF pressure due to cryptic CSF leaks [37–39]. Dural diverticulum and perineural cysts are generally common and theoretically might be prone to rupture during a sudden sneeze, sports activity, fall, or benign trauma. Nevertheless, which dural cysts are more prone to rupture in healthy patients and people with connective tissue diseases is unclear. The presence of dural cysts and heritable connective tissue disorders does not necessarily increase the likelihood of a diagnosis of SIH if no active leakage is identified on imaging [40]. In rare cases, a CSF venous fistula can develop between the subarachnoid space and the adjacent spinal epidural veins. There is direct drainage of CSF from subarachnoid space into spinal epidural veins [41].

SIH-related headaches often worsen during coughing; therefore, a primary cough headache should also be included in the differential diagnosis [3, 42]. This type of headache has a different characteristic in that it starts shortly after coughing, and usually peaks within seconds. Unlike SIH-related headache, it should subside within two hours [4]. A feature that may lead to misdiagnosis is the location of the primary cough headache, which, as in SIH, usually affects the occipital area.

Due to the broad spectrum of accompanying symptoms of headache attributed to SIH, there is a risk of false diagnosis of headache attributed to somatisation disorders. Patients with headaches attributed to somatisation disorders (as well as in SIH) can experience nausea, vomiting, coordination and balance disturbances, diplopia, seizures, and sometimes even disturbances of consciousness. Headache can be constant or intermittent with fluctuations of other symptoms. To establish the correct diagnosis, it is vital to have a reliable approach and verification in additional tests of the patient's complaints. It is worth remembering that somatisation disorder is always a diagnosis of exclusion of somatic diseases, and should be established as the last possible option based on the psychiatric consultation [41].

In the SIH diagnostic and therapeutic consensus published in 2023, POTS and orthostatic hypotension were included in the differential diagnosis of this disease [19]. In both conditions, an orthostatic headache may occur. Accompanying symptoms may include dizziness, balance, vision, and consciousness disorders. Early initial verification of the diagnosis of both conditions is possible. However, caution should be taken when performing diagnostic tests due to the possibility of symptoms intensification during the orthostatic test, including loss of consciousness [43].

Abnormalities in head and spine magnetic resonance imaging associated with intracranial hypotension

The most important and widely available tests that can bring the clinician closer to a correct diagnosis are head MRI with contrast and spine MRI. The 2023 guidelines for the diagnosis of SIH define the protocols according to which head and spine MRI should be performed [19]. However, there are no unequivocal criteria for assessing abnormalities in MR neuroimaging in patients with SIH.

The results of studies on this issue differ in the frequency of individual signs in the studied groups of patients. Therefore, at least one MRI finding that may indicate SIH should increase diagnostic consideration and encourage the search for other findings, but cannot of itself result in a diagnosis of SIH.

Abnormalities in head magnetic resonance imaging in patients with spontaneous intracranial hypotension

Contrast-enhanced head MRI is the most important examination for every patient with symptoms (the so-called brain sagging and signs of venous engorgement) that may indicate SIH because of CSF leakage. The second of these pathomechanisms can be explained by referring to the Monro-Kellie doctrine. According to this, the sum of the volumes of the three components filling the skull (the brain tissue, the CSF, and the blood) is a constant value. As a result of the reduction in CSF volume, blood volume increases.

The symptoms most reported on head MRI include diffuse dural enhancement, the presence of epidural fluid collections, dilatation of the intracranial venous structures, and 'sagging' of the brain and pituitary engorgement [3, 16, 44, 45].

We suggest adopting the rule of assessing the MRI results from the top to the bottom of the head. It is important to distinguish between different types of sections and MRI sequences.

During such an assessment of the head MRI, attention should be paid to:

- The presence of subdural fluid collection, hygromas, or subdural haematomas [3, 16]. SIH can also lead to epidural haematomas (up to 25% in patients aged under 60), including recurrent ones [46].
- Diffuse contrast enhancement of the dura mater. This is the most frequently reported abnormality in head MRI during SIH [3, 16, 44, 45]. Particular attention should be paid to the current strong trend of limiting contrast-enhanced examinations (to reduce the incidence of contrast-induced nephropathy, gadolinium deposition, and toxic effects on the brain) [47, 48]. This tendency is sometimes unnecessary and can affect the sensitivity of the radiological examination.
- Enlargement of the dural venous sinuses [3, 16, 44, 45]. The symptoms are particularly visible when assessing the shape of the sagittal sinus in the coronal sections along its course on the skull vault. Typically, the lumen of the sinus should have a triangular cross-section, while in SIH the edges of the sinus created by the dura are bulging towards the cranial cavity.
- Presence of superficial siderosis, resulting from bleeding of overflowing and drawn tiny veins [45]. Superficial siderosis (SS) of the CNS is caused by repeated slow haemorrhage into the subarachnoid space with resultant hemosiderin deposition in the subpial layers of the brain and spinal cord [49]. The most common aetiology of SS is dural pathology: cerebral amyloid angiopathy, CNS tumours, arteriovenous malformations, head or spinal trauma, and craniospinal surgery [50]. Infratentorial SS has been recognised in 3.6% of patients with SIH due to CSF leaks, and the reasons were ventral CSF leak (10.4%), dural ectasia (3.9%), CSF-venous fistula (2.6%), and simple meningeal diverticula (0.9%) [51].
- Signs of brain sagging are most easily noticed in sagittal sections [3, 16, 44, 45].

Decreased dimensions of the CSF subarachnoid cisterns resulting from the vacuum effect from spinal CSF leakage are most easily noticed on sagittal sections. The effacement of the prepontine cistern has also been described in SIH. The sagittal sections also may show an opened pontomesencephalic angle. Furthermore, MRI reveals midbrain descent, kinking of the midbrain and pons toward the clivus, and the descent of the cerebellar tonsils to the foramen magnum.

The signs listed above do not include all the abnormalities in SIH patients described in the literature. Table 3 sets out the symptoms and parameters assessed by head MRI in patients with SIH. Some of them require measurement. Nevertheless, a neurological awareness of the radiological evaluation of a head MRI is beneficial in this troubleshooting diagnostic process. On referral for a head MRI in a patient with suspected SIH, a neurologist should ask the radiologist to take or extend the measurements to specific ones.

As mentioned above, there is no generally accepted scale for assessing changes in head MRI in patients with SIH. The current diagnostic criteria also do not specify radiological abnormalities during the diagnosis. However, the so-called Bern score is worthy of attention in diagnosing SIH [47]. This index requires an assessment of six findings in a head MRI. Three of them are referred to as 'major criteria'. These are the engorgement of venous sinuses, pachymeningeal enhancement, and effacement of the suprasellar cistern of 4 mm or less. The occurrence of each of the abovementioned abnormalities results in a score of 2 points. Signs assigned to 'minor criteria' are the presence of subdural fluid collection, effacement of theprepontine cistern by 5.0 mm or less, and a mamillopontine distance of 6.5 mm or less. One point is scored for meeting each minor criterion. The points make up a total, wherein the maximum score is 9 points. In this scale, the risk of SIH is defined as low if the total is up to 2 points, medium if it is 3-4, and high if it is 5 or more [52].

When discussing the importance of head MRI in diagnosing SIH, it should be noted that this examination may not show any abnormalities in up to 20% of patients with SIH [3]. Therefore, a head MRI that does not show any changes typical for SIH does not exclude such a diagnosis.

Abnormalities in magnetic resonance imaging of spinal canal in patients with spontaneous intracranial hypotension

MRI of the spinal canal with heavily weighted, fat-saturated sequences should be performed in each case of suspected SIH [19]. The most common abnormalities reported in patients with SIH are epidural fluid collections that usually extend over five segments of the spine. These reservoirs are called 'spinal longitudinal extradural collections/fluid (contrast)' (SLEC) and are more likely to be detected on axial images. The chance of SLEC occurring depends on the location and cause of the CSF leak. SLEC occurs when the dura mater ruptures on the dural sac's ventral surface or the spinal nerves' root sheath proximal to the intervertebral foramen leaks. SLEC is unlikely to occur in patients with CSF leakage of the spinal nerve root sheath located distally to the intervertebral foramen or through the CSF-vein fistula [53].

The C1-C2 symptom is the other important feature of SIH. In the sagittal sections in a T2-weighted sequence with attenuation of the fat signal, a reservoir with the CSF signal may be observed between the spinous processes of the C1 and C2 vertebrae. This symptom is called 'false localising C1--C2 symptom'. This image may rarely correspond to the location of the CSF leak [54], but usually does not.

According to the Monro-Kellie doctrine, the filling and engorgement of the venous structures increase to maintain pressure within the spinal canal in a CSF leak. This mechanism is responsible for the dilation of the epidural veins and the thickening of the epidural ventral venous plexus. Dural vasodilatation and engorgement may result in dural contrast enhancement. Such reinforcement is usually of a uniform and circular nature [47, 48,

Table 3. Head magnetic resonance imaging findings in intracranial hypotension/ spontaneous intracranial hypotension [4, 12, 13]

No measurement required:
– Subdural fluid collection, hygromas, haematomas, subdural haematomas
– Diffuse gadolinium pachymeningeal enhancement, hyperintense pachymeninges (FLAIR)
– Venous sinus enlargement
– Superficial siderosis
– Brain sagging: midbrain descent, kinking of midbrain and pons toward clivus, reduced distance from optic chiasm to pituitary gland, effacement of perichiasmatic and prepontine cisterns, descent of cerebral aqueduct, effacement of subarachnoid space, tonsillar descent
– Distended inferior intercavernous sinus
– Pituitary gland enlargement, posterior lobe pituitary haematomas
Measurement required:
Size measurement in mm:
– Effacement of suprasellar cistern of 4.0 mm or less
– Effacement of prepontine cistern of 5.0 mm or less
– Mamillopontine distance of 6.5 mm or less
– Tonsillar descent
– Midbrain descent*
– Pituitary height*
– Difference of pituitary height to age-adjusted and sex-adjusted reference*
– Tonsillar descent
Size measurement in mm^2:
– Area cavum veli interpositi*
– Angle measurements:
– Venous-hinge, pontomesencephalic
Other assessments:
– Superior surface of pituitary (concave, flat, convex)

*parameters rarely assessed, normal values are not yet established

53-55]. The pathology responsible for CSF leakage is most often located in the thoracic region (c.50% of dural tears in the upper thoracic spine) [53], then in the cervicothoracic junction, next in the cervical region, and finally in the lumbar region. To visualise the exact location and determine the nature of the lesion, it is necessary to perform more advanced tests, which according to the current guidelines include CT myelography, digital subtraction myelography, and ultrafast CT myelography [19]. Usually, performing advanced diagnostic procedures requires directing the patient to the specialistic centres.

Discussion of these subsequent tests ordered by neurosurgeons, neuroradiologists, or neurologists is beyond the scope of this article. Interested physicians are referred to the extensive literature available describing all the abovementioned imaging methods.

Summary

Headaches associated with ICH, especially in the case of SIH, are a frequent diagnostic challenge for neurologists.

A wide range of symptoms and similarities to other neurological diseases often lead patients to struggle with this problem for many years without improving after inadequate treatment. This article has presented several tips and possible clinical scenarios indicating the need of considering SIH as the cause of headaches in patients diagnosed in the neurological emergency department and outpatient neurological clinics.

To sum up, the diagnosis in such cases should be verified based on the medical history, in particular, the onset of the disease, the occurrence of any headache depending on the body position (especially if the headache is accompanied by varied neurological symptoms that also worsen when upright and improve when horizontal), an unsatisfactory effect of, or even complete resistance to, the applied treatment, and verification of the assessment of head and spine via a head MRI with contrast and a full spine MRI, as well as searching for easily overlooked or not typically described symptoms in these examinations that may suggest SIH.

A separate part of this paper has described abnormalities in the MRI of the head and spine that indicate SIH. These tests are widely available to neurologists and should be performed and interpreted appropriately. We hope that such a presentation of this problem will allow neurologists to improve their knowledge and more easily establish the proper diagnosis.

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LEADING TOPIC

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Spontaneous rhinorrhea and idiopathic intracranial hypertension: a complex and challenging association

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ABSTRACT

Introduction. Spontaneous CSF leak is a known complication of idiopathic intracranial hypertension (IIH). Patients with CSF rhinorrhea present a unique challenge within the IIH population, as the occurrence of a leak can mask the typical IIH symptoms and signs, complicating the diagnosis. Treatment of leaks in this population can also be challenging, with the risk of rhinorrhea recurrence if intracranial hypertension is not adequately treated.

Objective. The aim of this narrative review was to examine current literature on the association between spontaneous CSF rhinorrhea leaks and IIH, focusing on key clinical features, diagnostic approaches, management strategies, and outcomes.

Material and methods. A literature search was executed using the PubMed and Scopus databases. The search was confined to articles published between January 1985 and August 2023; extracted data was then analysed to form the foundation of the narrative review.

Results. This search yielded 26 articles, comprising 943 patients. Average age was 46.8 ± 6.5 years, and average body mass index was 35.8 ± 4.8. Most of the patients were female (74.33%). Presenting symptoms were rhinorrhea, headaches and meningitis. The most common imaging findings were empty sella and encephalocele. The standard treatment approach was endoscopic endonasal approach for correction of CSF rhinorrhea leak, and shunt placement was also performed in 128 (13%) patients. Recurrences were observed in 10% of cases.

Conclusions. The complex relationship between spontaneous CSF leaks and IIH is a challenge that benefits from multidisciplinary evaluation and management for successful treatment. Treatments such as endoscopic repair, acetazolamide, and VP/LP shunts reduce complications and recurrence. Personalised plans addressing elevated intracranial pressure are crucial for successful outcomes.

Keywords: cerebrospinal fluid rhinorrhea, spontaneous rhinorrhea, pseudotumour cerebri, neurosurgery shunt

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Introduction

Nontraumatic cerebrospinal fluid (CSF) rhinorrhea, also known as spontaneous CSF rhinorrhea (SCSFR), occurs without an apparent cause and is often associated with increased intracranial pressure, congenital anomalies, or idiopathic factors [1, 2]. While most CSF rhinorrhea leaks are attributable to traumatic causes such as head injuries or surgical procedures, a small percentage, up to 5%, are associated with other factors such as hydrocephalus, structural anomalies, cerebral venous thrombosis, or

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unknown causes [1, 2]. Primary spontaneous CSF leaks represent a unique subset of this condition, characterised by specific features including its target demographic and a high recurrence rate, of 2.9-46% after repair, compared to other types of CSF leak [3, 4].

Although not all patients with SCSFR have idiopathic intracranial hypertension (IIH), the connection between them was first proposed in 1994 by Clark et al., who identified female gender and obesity as significant risk factors due to their potential to increase intraabdominal pressure, thereby impairing venous return and elevating intracranial pressure (ICP) [6]. Subsequent research has suggested a link between chronic elevated ICP and secondary skull base bony erosion leading to leakage [1, 3, 7]. Recognising and understanding this relationship is crucial for improving treatment outcomes. However, patients with CSF rhinorrhea leaks present a unique challenge within the IIH population. The leak can act as a 'pressure release valve' potentially masking typical IIH symptoms and signs, and even reducing lumbar puncture opening pressure [1, 3, 8]. This can complicate diagnosis under the modified Dandy's criteria, which include papilloedema, absence of structural findings (hydrocephalus, masses and lesions) in neuroimaging, normal CSF composition, elevated ICP (≥ 25 cmH2O), and MRI stigmata of intracranial hypertension such as empty sella and venous sinus stenosis [9].

The aim of this review was to examine the most recent literature on the association between SCSFR leaks and IIH, focusing on key clinical features, diagnostic approaches, management strategies, and outcomes.

Material and methods

A literature search was executed on 9 August, 2023 to identify relevant articles on spontaneous CSF leak and IIH using the PubMed and Scopus databases. The search strategy incorporated the terms: 'idiopathic intracranial hypertension' OR 'pseudotumour cerebri' AND 'CSF leak'. The search was confined to articles published between January 1985 and August 2023, resulting in a total of 118 manuscripts after the removal of duplicates.

The selection of pertinent studies for inclusion in the systematic review was conducted through a two-stage screening process. Initially, titles and abstracts were independently reviewed by two authors to ascertain their relevance to the research topic. The inclusion criteria at this stage were articles discussing spontaneous CSF leak in the context of IIH and reporting on patients with rhinorrhea as a primary symptom. This initial screening resulted in the selection of 48 full-text articles for further evaluation. Articles that did not meet the inclusion criteria, such as those focusing on spinal leaks, articles not related to spontaneous CSF leak, articles exclusively discussing otorrhea as the presenting sign, and articles not directly relating CSF rhinorrhea leak to IIH (secondary intracranial hypertension), were excluded from further consideration.

As the second stage of screening, the selected full-text articles were meticulously reviewed by two of the authors to assess their eligibility for inclusion in the review. Any disagreements in the selection process were resolved through discussion and consensus among the authors. After reviewing the exclusion criteria, we removed three articles primarily focusing on spinal CSF leaks, four articles that did not pertain to spontaneous CSF leaks, one article exclusively discussing otorrhea without relevance to rhinorrhea, two articles discussing SCSFR but not related to IIH, and 10 articles that there were not criteria for IIH. Consequently, 26 articles [1–6, 10–13, 15, 17, 21–31, 34–36] were included in our review.

Data from the selected articles was extracted and organised into themes, including clinical presentation and reports of rhinorrhea in IIH, diagnostic approaches, treatment modalities, and outcomes. The extracted data was then synthesised and analysed to form the foundation of the narrative review.

Results

Patient characteristics

This review included 943 patients with suspected or definitive IIH and spontaneous CSF leaks. The cohort had a mean age of 46.8 ± 6.5 years and a mean body mass index (BMI) of 35.8 ± 4.8. In terms of gender, only one article didn't distinguished the patients [35]. Overall, most of the patients were female (74.33%), while only 23.97% were male, 929 in total. The data on age, BMI, and gender distribution was obtained from 26 [1–6, 10-13, 15, 17, 21–31, 34-36], 14 [1–3, 5, 10–12, 17, 28–31, 34, 36], and 25 [1–6, 10–13, 15, 17, 21–31, 34, 36] studies, respectively. The mean follow-up period was 22.5 months, based on data from 16 [1, 2, 4, 5, 10–12, 15, 22–24, 26–28, 30, 36] studies. Table 1 sets out the demographic characteristics of the study population. The papers included used either Dandy's criteria or modified Dandy's criteria to label the patients as either 'definitive' or 'suggestive' cases of IIH. This review identified 99 definitive cases [1, 5, 6, 10, 13, 17, 21–23, 25–27, 29–31, 36] of IIH and 782 suggestive ones [2–5, 11, 12, 15, 24, 28, 34, 35].

Clinical presentation

Our review of 26 articles revealed a wide range of clinical features in patients presenting with IIH and spontaneous CSF leak, from classical characteristics associated with IIH such as headache, visual changes, pulsatile tinnitus, and papilloedema, to symptoms directly resulting from a skull base defect, such as rhinorrhea, sinusitis and meningitis, as well as hormonal dysfunction such as elevated prolactin levels, irregular menstrual cycles, and infertility. Headache was the most common symptom among patients included in the review, reported in 19 of the included papers [1–5, 11–13, 17, 21–29, 36], and it was also the most prevalent symptom at presentation, reported in 192 subjects. Meningitis occurred in 110 patients. Moreover,

Table 1. Demographics of IIH patients with spontaneous CSF leak extracted from narrative review

Number of studied patients	943
Mean age	46.8 ± 6.5 years
Mean BMI	35.8 ± 4.8
Gender	
Female	701 (74.33%)
Male	226 (23.97%)
Mean follow-up	22.5 months
Diagnosis of IIH (%)	
Suggestive	782 (82.9%)
Definitive	99 (10.5%)

Table 2. Symptoms at presentation of spontaneous CSF leak and IIH patients

Spontaneous CSF leak (rhinorrhea)	943 (915)
Symptom at presentation	
Headaches (%)	192 (20.36%)
Meningitis (%)	110 (11.66%)
Other (%)	89 (9.43%)
Mean duration of symptoms	11.4 months

89 patients had other diverse symptoms. The average duration of symptoms was 11.4 months. While we presume that all the patients in this study had rhinorrhea as the primary sign, it was explicitly reported in only 915 out of the 943 patients (Tab. 2).

Imaging findings

The radiological data from the studies analysed showed a range of findings related to spontaneous CSF leak and IIH [1, 3–6, 11, 15, 17, 22–31, 34–36]. These imaging findings revealed conditions such as empty sella, optic nerve sheath and Meckel's cave widening, sinus stenosis, bone erosion, meningocele, encephalocele, arachnoid herniation at the olfactory cleft, defects on nasal cavity, sinus stenosis, enlarged ventricles, and others. Meningo/encephalocele was found in 338 cases, while partial/empty sella was reported in 399 cases (Tab. 3). The review also showed different abnormalities in the skull anatomy, such as defects in the anterior fossa, cribriform plate, ethmoid sinus, sphenoid sinus, frontal sinus, and skull base. The most common sites of origin of CSF leaks were the ethmoid and sphenoid sinuses, comprising 446 cases [1–3, 5, 6, 10–13, 15, 17, 21–31, 36]. Other important sites were the anterior fossa, cribriform plate, superior nasal cavity, olfactory cleft, tegmen tympani, skull base, and middle ear. Additionally, some studies indicated high opening pressure in lumbar puncture, with the mean value being 25.52 ± 6.3 cmH2O [1, 3, 5, 6, 10, 11, 13, 17, 21, 22, 26–31, 34, 36], showing the importance of high pressure in relation to CSF leak and its complications.

Table 3. Anatomical and radiological features of patients with spontaneous CSF leak and IIH

Spontaneous CSF leak location (%)	
Cribriform plate	155 (16.4%)
Ethmoid sinus	161 (17%)
Sphenoid sinus	285 (30.2%)
Other	87 (9.2%)
Imaging findings (%)	
Meningo/encephalocele	338 (35.8%)
Partial/empty sella	399 (42.3%)
Optic nerve sheath widening/tortuosity	88 (9.3%)
Flattening of posterior globe	47 (4.9%)
Transverse venous sinus stenosis	25 (2.6%)
Widened Meckel's cave	34 (3.6%)
Others	4 (0.4%)

Management, recurrence and complications

The management of spontaneous CSF leak and IIH in patients was heterogenous among the studies. Obesity was a common factor among patients, and weight loss interventions were often recommended [1–3, 5, 10–13, 15]. Endoscopic endonasal surgery for skull base reconstruction and leak repair was the selected approach to fix skull base defects. Fascia lata graft placement, vascularised nasoseptal flaps, and dura substitutes have been used for the repair of such defects, and the selection of the technique and the tissues for repair vary according to the site, size, previous procedures, and BMI [11, 15]. Leaks of small size and low volume usually can be repaired with the use of dura substitute and/or mucosa graft, while those of larger size and high volume and patients with recurrent leaks, especially those with high BMI and increased intracranial pressure, usually benefit from reconstruction based on vascularised flaps. The most commonly applied vascularised option for reconstruction is the nasoseptal flap, but other options such as lateral wall flap, temporoparietal fascia flap, and pericranial flap are also useful in selected cases.

Insertion of shunting is an important tool in the management of patients with IIH and spontaneous CSF leaks. The decrease in ICP (intracranial pressure) promoted by the presence of a shunt, either ventriculoperitoneal (VPS) or lumboperitoneal (LPS), has been well described as an adjunct in the repair of recurrent spontaneous CSF leaks in this population. In our current review, VPS/LPS placement was performed in 128 (13.57%) patients [3–6, 10, 12, 17, 21–23, 26, 28–31, 34, 36], to manage high intracranial pressure, while acetazolamide was used as an alternative treatment option in 170 [1, 3, 6, 10–12, 17, 21, 25, 28, 29, 31, 34–36] patients. Additionally, several invasive procedures were performed to address the underlying causes of IIH and associated CSF leak, such as perioperative lumbar drains or

Table 4. Treatment of spontaneous CSF leak, management of higher ICP, and surgical complications of spontaneous CSF leak in IIH patients

Treatment — CSF leak	
Patients undergoing surgical repair	792
Remission	713 (90%)
Recurrence	79 (9.97%)
Mean time of recurrence	20.5 ± 13 months
Raised ICP management	
Shunt placement	128 (13.57%)
Acetazolamide	170 (18%)
Long-term surgical complications	
Shunt malfunction/misplacement	14 (1.76%)
Meningitis	5 (0.63%)
Seizures	2 (0.25%)
Other	2 (0.25%)

external ventricular drains, dural venous sinus stent (for those with identified dural stenosis), and lumboperitoneal shunt placement [3, 5, 6, 10–13].

Of a total of 792 patients who underwent surgical repair, 713 were successful within the first surgery and 79 had a recurrence. The average time of recurrence was 20.5 ± 13 months [1, 4, 6, 11, 12, 15, 31], indicating the need for long-term follow-up and effective management strategies (Tab. 4). Long-term surgical complications associated with spontaneous CSF leak and IIH occurred in 23 patients, such as seizures, meningitis, and shunt malfunction/misplacement in a few patients, mainly due to the recurrence of previous symptoms. Some other surgical complications related to surgery were also reported, such as intraparenchymal haematoma, secondary respiratory acidosis, lacrimal dysfunction due to injury of the lacrimal drainage system, injury to the optic nerve, orbital haematoma, and bleeding from the anterior ethmoidal artery [5, 6, 10, 12, 15, 17, 22, 23, 25, 26, 36].

Discussion

Patient characteristics

Spontaneous CSF leak is a known complication of IIH, but its pathogenesis is still not fully understood. Several hypotheses have been put forward to account for how increased CSF pressure could lead to defects in the skull base, dura mater, arachnoid mater, or arachnoid villi [2–5]. However, these factors alone cannot explain why some patients develop a spontaneous CSF leak but others do not. Badia et al. [2] reported nine cases of high ICP and rhinorrhea, six females and three males, with an average age of 50 and an average BMI of 40. They proposed that obesity, especially visceral obesity, could predispose to a spontaneous CSF leak by increasing intra-abdominal pressure, impairing venous drainage, and exacerbating ICP fluctuations. They recommended weight reduction as a preventive measure [2]. Holzmann et al. [14] conducted a comparative study of 61 patients with spontaneous CSF leak of various origins, classified into five groups. They found that the only significant difference among the groups was BMI, which was much higher in the spontaneous CSF leak group, thereby corroborating the role of obesity as a risk factor for leak.

Clinical presentation

The diagnosis of IIH remains a complex task for clinicians, despite the existence of well-defined diagnostic criteria and a characteristic patient profile (i.e. female and obese). As most patients in our review had presumed or suspected IIH, not all of them fully fitted the criteria for IIH. Hong et al. [3] analysed 716 patients with a spontaneous CSF leak who were suspected of having IIH. They found that their mean age was older than that of newly diagnosed IIH patients, suggesting a slow progression of IIH in these cases, with the leak potentially serving as a 'pressure release valve' that alleviated the symptoms of elevated ICP and postponed the diagnosis. Similarly, other researchers have reported that the leak obscures the main manifestations of IIH such as headaches, papilloedema and even CSF opening pressure, leading to a delayed diagnosis, failure to meet the criteria, and the assumption that most patients with spontaneous CSF leak have underlying IIH and only developed rhinorrhea later. In a study by Bidot et al. [5], only 20% of 36 patients fulfilled the Dandy's criteria, while the rest had presumed or suggested IIH.

Ophthalmological evaluations serve as a crucial component in the diagnostic and follow up process, aiding in the comprehensive assessment of spontaneous CSF leak patients [8, 10, 22, 29]. Notably, the absence of papilloedema, a hallmark of traditional IIH, is frequently observed in spontaneous CSF leak patients. However, postoperative emergence of papilloedema following leak repair has been documented in certain cases, underlining the importance of thorough postoperative follow-up [42]. Proper postoperative management, including the administration of acetazolamide or shunting, is crucial in selected cases, reducing the risk of postoperative complications, and promoting favourable outcomes [20, 30, 34, 35].

Although lumbar puncture (LP) is routinely recommended for preoperative intracranial pressure assessment, the existence of the leak itself complicates the interpretation of preoperative ICP values, as it acts as a natural treatment for elevated ICP, hiding the typical symptoms of those with high ICP — headache or visual disturbance — often leading to underestimation [10]. Thus, careful monitoring of immediate and short-term postoperative ICP values is vital to evaluate the efficacy of the surgical intervention [40]. In a study by Aaron et al. [10], CSF opening pressure (CSF-OP) was measured in 16 patients who underwent surgical repair for spontaneous CSF leak. The mean CSF-OP before surgery was 27.4 cmH2O, which increased to 36 cmH2O at six hours after clamping and at 48 hours after repair, indicating a significant rise of CSF-OP following the

intervention. These patients were compared to a control group of 16 patients who had a previous diagnosis of IIH with papilloedema and no leak, and had a mean CSF-OP of 36.2 cmH2O.

The results suggest that both groups had the same underlying condition and that the spontaneous CSF leak acted as a 'treatment' for the high ICP symptoms such as papilloedema in the first group, as the CSF-OP increased to the level of the second group after the repair.

Imaging findings

The diagnosis and management of IIH and spontaneous CSF leak benefits from a multidisciplinary approach that employs a variety of diagnostic tools. Volumetric CT scans with thin cuts are crucial for accurate assessment of the bone anatomy and identification of the site of the leak, thereby facilitating precise surgical planning [4, 15, 21]. Furthermore, MRI plays a pivotal role in identifying the leak and associated intracranial pathologies, such as meningocele and encephalocele, providing a more comprehensive understanding of the condition [1–3, 5, 6, 10–32, 36, 37, 39–41]. Additionally, MR venography (MRV) is useful in evaluating the presence of venous sinus stenosis, guiding potential future management strategies [23]

The MRI features of IIH were recently investigated in a cohort of 117 patients by Rupa et al. [4]. The most prevalent finding was empty sella, observed in 62.4% of cases, followed by optic nerve sheath widening in 53%. Posterior globe flattening and widening Meckel's cave were less frequent, occurring in 27.1% and 23.1% of the patients, respectively. Only 12 patients had no MRI abnormalities, while 68 patients had at least one of the high specificity signs (i.e. empty sella, posterior globe flattening, or widened Meckel's cave). Notably, empty sella was present in all patients with these signs, and all patients with papilloedema (n = 11) had at least one MRI feature of IIH. These results suggest that the inclusion of MRI criteria in the Dandy's diagnostic framework could increase the accuracy and confidence of IIH diagnosis.

The role played by imaging studies in the diagnosis of spontaneous CSF leak associated with IIH is crucial, as they can reveal the location and nature of the leak, as well as signs of increased intracranial pressure, such as skull base erosion, arachnoid pits, enlarged foramen, and optic nerve sheath dilatation. Quatre et al. [15] reported a series of 65 patients with spontaneous CSF leak, of whom 15 (eight women and seven men), with a mean age of 50 and only three of them obese (BMI ≥ 30), had isolated rhinorrhea without any other symptom. MRI showed that eight of these patients had a dura defect, six had encephalo/meningocele, six had empty sella, and six had optic nerve sheath dilatation. These findings suggest that imaging studies can provide diagnostic clues even in patients who do not fit the typical profile or criteria for IIH.

Management, recurrence and complications

In terms of therapeutic interventions, conservative approaches including antibiotic therapy, weight management, and rest, have been widely discussed, although the efficacy of these measures remains the subject of debate [1–3, 5, 6, 10–12, 16, 17, 22, 23, 25, 26, 28, 29, 31, 34, 36]. Notably, weight loss of at least 10% has been suggested as a potential therapeutic target, and reports have highlighted the positive outcomes associated with certain bypass procedures in this context [1–3, 5, 10–15].

Endoscopic repair is a commonly advocated therapeutic approach considering the risks associated with persistent spontaneous CSF leak [19, 20, 32, 33]. Various repair techniques involving different types of grafts and flaps have been employed to address the leak; however, recurrence rates remain a concern [1, 4, 6, 11, 12, 14, 15, 32]. Failure to identify and treat elevated ICP has been identified as a significant factor contributing to higher recurrence rates associated with endoscopic repair in this specific patient population [1, 4, 6, 11, 12, 14, 15, 32]. The use of fluorescein for leak identification has been demonstrated to be useful and safe for successful endoscopic skull base repair [43]. Martinez et al. [11] reported that 35 patients who underwent surgical repair also received acetazolamide as an adjunct therapy for 6-8 months or until the symptoms of high ICP resolved. The recurrence rate was only 2.9%, indicating that acetazolamide may help regulate the ICP, lower the risk of papilloedema, and prevent recurrences. Spontaneous CSF leaks are known to have the highest recurrence rate among different leak aetiologies. Dallan et al. [12] described 18 patients with recurrent spontaneous CSF leak, defined as a new leak in a different site at least three months after the previous repair. Four patients required a ventriculoperitoneal shunt and one patient received acetazolamide for managing elevated ICP. That study suggested that interventions for elevated intracranial pressure increased the success rate of spontaneous CSF leak repair.

Conclusions

The complex relationship between spontaneous CSF leaks and IIH is a challenging issue that benefits from multidisciplinary evaluation and management for successful treatment. Obesity, especially visceral fat, plays a significant role in causing spontaneous CSF leaks by affecting intra-abdominal pressure, hindering venous drainage, and increasing intracranial pressure. This underlines the importance of weight management as a preventive measure. Moreover, endoscopic repair, and additional treatments such as acetazolamide and VP/LP shunts, have been shown to reduce postoperative complications and the recurrence of spontaneous CSF leaks. Managing elevated intracranial pressure is key to successful outcomes, highlighting the need for personalised treatment plans.

Spontaneous CSF leaks can mask IIH symptoms, making it difficult to meet diagnostic criteria. This review also underlines the importance of using multiple diagnostic methods, including CT scans and MRI, to locate the leak and identify related intracranial pathologies. These techniques, along

with careful monitoring of intracranial pressure before and after surgery, are vital for effective treatment and improved patient outcomes.

We conclude by emphasising the need for a comprehensive approach to manage the complex interaction between spontaneous CSF leaks and IIH. This includes timely diagnosis, appropriate intervention, and improved patient outcomes. Future research should focus on understanding the complex mechanisms underlying this relationship in order to improve diagnostic and therapeutic strategies.

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Genetics of Parkinson's Disease: state-of-the-art and role in clinical settings

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ABSTRACT

Introduction. Advances in sequencing technologies have enabled extensive genetic testing on an individual basis. Genome-wide association studies (GWAS) have provided insight into the pathophysiology of PD. Additionally, direct-to-consumer genetic testing has enabled the identification of genetic diseases and risk factors without genetic counselling. As genetics increasingly permeates clinical practice, this paper aims to summarise the most important information on genetics in PD for clinical practitioners.

State-of-the-art. *LRRK2* mutations may be found in c.1% of all PD patients with an indistinguishable phenotype from sporadic PD. *LRRK2*-PD is more prevalent in patients with a positive family history (5-6%) and among certain populations (e.g. up to 41% in North Africans and Ashkenazi Jews). Other familial forms include *PRKN* (patients with early onset, EOPD), *VPS35* (Western European ancestry), *PINK1* (EOPD), *DJ-1* (EOPD), and *SNCA*. *GBA* mutations are found in a large number of PD patients and are associated with faster progression and a poorer prognosis. GWAS have identified 90 genetic risk variants for developing PD and several genetic modifiers for the age at onset, disease progression, and response to treatment.

Clinical implications. Multigene panels using next-generation sequencing (NGS) are the first choice for genetic testing in clinical settings. Whole exome sequencing is increasingly being used, particularly as the second-tier testing in patients with negative results of multigene panels. NGS may not detect accurately copy number variants (CNV), meaning that additional analysis is warranted. In a case of a variant of unknown significance (VUS), we suggest firstly searching the up-to-date literature. Segregation studies and *in silico* predictions may shed more light on the character of the VUS; however, functional studies remain the gold standard. Several interventional clinical trials are active for carriers of *LRRK2* and/or *GBA* mutations.

Future directions. Application of artificial intelligence and machine learning will enable high-throughput analysis of large sets of multimodal data. We speculate that, in the future, the treatment landscape for PD will be similar to that in oncological conditions, in which the presence of certain gene mutations or gene overexpression determines the prognosis and treatment decision-making.

Keywords: hereditary, monogenic, familial, sequencing, GWAS

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Introduction

The clinical and research stance on the heritability of Parkinson's Disease (PD) has come full circle. It has long been acknowledged that PD is non-genetic; however, the mapping and discovery of the first genes in familial PD at the end of the 20th century proved the importance of genetic factors in PD [1, 2]. Over the past two decades, more than 100 genetic loci have been associated with PD and other forms of parkinsonism [3]. Recent advances in sequencing technologies and analyses have made it possible to conduct extensive genetic testing on an individual basis in clinically relevant timeframes [4]. However, the initial enthusiasm cooled when the emerging data revealed a low diagnostic yield of clinical genetic testing in PD, and so the extent of genetics relevance in PD remains an unsolved conundrum.

Although a positive family history in a first-degree relative increases the risk of developing PD two- to three-fold compared to controls, only 15% of patients have a positive family history, and even fewer, c.5–10%, have a familial form of the disease [5, 6].

Genome-wide association studies (GWAS), in which hundreds of thousands of genetic variants across many genomes are tested to check for potential phenotype associations, have raised fresh hopes in addressing the relevance of genetics in PD. GWAS have provided further insight into the risk factors of developing PD, its progression, and its response to treatment, although applying these findings in clinical practice remains challenging. In addition, commercial testing through direct-to-consumer genetic testing has enabled the identification of genetic diseases and risk factors without genetic counselling, and found many PD patients reporting to healthcare professionals to address issues raised by these tests.

As genetics increasingly permeates clinical practice, and as most patients will at some point approach their primary neurologist about their genetic status or advances in the field, we must learn genetics and become fluent in this new *lingua franca*.

Therefore, this paper aims to summarise the most important information on genetics in PD for clinical practitioners, and looks into the possible applications of genetic testing in managing PD patients in the near future.

State-of-the-art

Familial forms of PD (Tab. 1)

LRRK2

The most common genetic form of PD is related to mutations in *LRRK2*, which are inherited in an autosomal dominant fashion and display incomplete, age-dependent penetrance [3, 7, 8]. *LRRK2* mutations are found in 5–6% of familial, and 1% of sporadic, PD cases [3, 9]. As per the Human Gene Mutation Database Professional (HGMD, version 2023.2), to date almost all of the pathogenic mutations (97%) have been missense/nonsense variants [10]. Due to the founder effect, the prevalence of *LRRK2* mutations is even higher in certain populations, including North African Berber and Ashkenazi Jewish (p.G2019S mutation in up to 41% and 34% of familial and sporadic cases), as well as northern Spanish (p.R1441G), Italian and Belgian (p.R1441C) populations [9]. The phenotype is that of typical PD, with a late onset, slow progression, and good response to L-Dopa [3, 7, 9].

PRKN

Homozygous or compound heterozygous *PRKN* mutations are the second most common cause of genetic PD [3, 11]. They are most often found in early-onset PD (EOPD), accounting for up to 15%, and 50% with the onset aged 25-50 years [3, 12–14]. Most pathogenic mutations are exonic deletions, followed by missense/nonsense variants and exon duplications [10]. In certain populations, the prevalence of *PRKN*-PD may be higher; for instance, it accounts for 8% and 6% of familial and sporadic PD in Japan [15]. The phenotype is that of EOPD with slow progression, good response to L-Dopa, high frequency of bradykinesia, and rigidity.

VPS35

VPS35-PD is autosomal dominant familial PD with incomplete penetrance and c.150 cases reported worldwide, with an estimated prevalence of less than 1% of familial PD and 0.1% of sporadic PD cases [3, 16]. To date, pathogenicity has been confirmed only for the p.D620N mutation; however, three other missense/nonsense variants and one deletion have been suggested to be linked with PD [10]. The phenotype is that of typical PD, with slow progression, good response to L-Dopa, and a low risk of atypical features [3, 16].

PINK1

PINK1-PD is an autosomal-recessive with complete penetrance and an estimated prevalence of 0.1% of sporadic and less than 1% of familial PD [3, 17]. It is more common in younger patients, accounting for up to 5% of EOPD worldwide [3]. Most pathogenic mutations are missense/nonsense variants (70%), followed by structural variants [10]. The phenotype is EOPD with a benign course and good response to L-Dopa, albeit with a higher frequency of dystonia and dysautonomia [3, 17].

DJ-1

DJ-1-PD is a very rare genetic form of PD, with autosomal recessive inheritance, complete penetrance, and an estimated prevalence of 0.02% of sporadic, less than 0.5% of familial PD, and up to 1% of EOPD cases [3]. Missense/nonsense variants are the most common (42%), followed by deletions (36%) [10]. The phenotype is that of EOPD, with slow progression and a good response to L-Dopa. However, compared to typical PD, there is a higher susceptibility for psychiatric manifestations, dystonia, and dysautonomia [3].

Table 1. Characteristics of most common familial forms of Parkinson's Disease

	LRRK2	PRKN	VPS35	PINK1	DJ-1	SNCA	VPS13C
Prevalence: sporadic PD	1%	0.3-1%	0.1%	0.1%	0.02%	0.01%	< 0.01%
Prevalence: familial PD	5–6%	2–3%	< 1%	< 1%	< 0.5%	< 0.5%	< 0. 1%
Inheritance	AD	AR	AD	AR	AR	AD	AR
Penetrance	Incomplete, age-dependent, 15–95%	Complete	Incomplete, age-dependent	Complete	Complete	Incomplete	N/A
Pathogenic mutations	Missense/non-sense variants	Structural and missense/non-sense variants	Asp620Asn	Missense/ nonsense and structural variants	Missense/ nonsense and structural variants	Structural and missense/non-sense variants	Missense/ nonsense and structural variants
Phenotype	Typical PD, with a late onset, slow progres-sion, and good response to L-Dopa	EOPD, benign course, good response to L-Dopa, high frequency of bradykinesia and rigidity, susceptibility to impulse control disorder	Typical PD, slow progression, good response to L-Dopa, and a low risk of atypical features	EOPD, benign course, good response to L-Dopa, higher frequency of dystonia and dysautonomia	EOPD, slow progression, good response to L-Dopa, susceptibility for psychiatric symptoms, dystonia, dysautonomia	Duplications: benign pheno-type with slow progression; Triplications: early onset, rapid progres-sion, atypical features. Missense variants (A53T): intermediate phenotype	EOPD, fast progression, good response to L-Dopa, susceptibility for early cog-nitive decline, psychiatric symptoms, dystonia, atypi-cal features
Protein function	Neuronal vesi-cular trafficking, mitochondrial functions, autophagy	Mitochondrial homeostasis and mitophagy	Recycling of transmembrane receptors	Mitochondrial homeostasis and mitophagy	Mitochondrial homeostasis and mitophagy	Synaptic plasti-city, neuronal homeostasis, mitochondrial activity	Mitochondrial homeostasis and mitophagy
Post mortem features	α-synuclein, tau-pathology, TDP-43	Rarely α-synuclein pathology	Negative for α-synuclein*	α-synuclein*	tau-pathology*	α-synuclein	α-synuclein

*limited data; AD — autosomal dominant; AR — autosomal recessive

SNCA

Pathogenic *SNCA* mutations may be found in up to 0.01% of sporadic PD cases and less than 0.5% of familial PD cases [3]. *SNCA*-PD is inherited in an autosomal-dominant fashion and displays incomplete penetrance [3]. Whole-gene multiplications are the most common variants (70%), followed by missense variants [10]. Penetrance, age at onset, and phenotype severity are associated with *SNCA* dosage, with a higher copy number having a worse disease course [18].

VPS13C, DNAJC6 and other genes

VPS13C-PD is a very rare autosomal recessive form of PD, reported to date in only 18 cases [18]. Missense/nonsense variants are the most common, followed by deletions. The phenotype is that of EOPD with a good response to L-Dopa, albeit with faster disease progression, earlier cognitive decline, and higher risk for atypical features compared to sporadic PD [18].

DNAJC6-PD is another rare form of autosomal recessive PD with the age at onset of before 21 years, frequently accompanied by developmental delay, seizures, dystonia, myoclonus, and varied responses to L-Dopa and other dopaminergic medications [19, 20]. Mutations in several other genes have been identified as being associated with PD, including *ARSA, CHCHD2, DNAJC13, EIF4G1, GIGYF2, HTRA2, LRP10, NUS1, SMPD1, RIC3, TMEM230*, and *UCHL1*, but as the data on them is limited and sometimes contradictory, they await further validation [21].

Intermediate forms of PD

GBA encodes a lysosomal enzyme β-glucocerebrosidase (GCase), and biallelic variants within the gene were classically associated with Gaucher's Disease [3, 7]. At present, *GBA* variants are mostly researched and clinically tested in the context of PD, in which they occur in 5-30% of all patients, making it the most common genetic risk factor [3, 7, 22]. As a relatively high proportion of *GBA* variant carriers develop PD, there is as yet no consensus on whether it is a risk factor or a monogenic form of PD. Overall, the cumulative risk for developing PD in *GBA* variant carriers is 5%; however, this increases with age

up to 10% and 30% by the ages of 60 and 80, respectively [3, 7, 23]. To date, at least 240 *GBA* variants have been linked to PD, of which the majority are missense/nonsense variants (83%) [10]. The missense variants p.N370S, p.E326K, p.T369M, and p. L444P, are the most common and constitute more than 80% of *GBA* variants in the PD population [3].

The *GBA* variants differ in the extent to which they impact upon the activity of GCase, with the p.L444P variant decreasing the activity by the most, and being associated with the highest risk of PD and the worst severity. In contrast, the variants p.E326K and p.T369M have the mildest impact on GCase activity and convey lower risk and milder severity of PD, while p.N370S is intermediate in terms of PD risk development and phenotype severity [22]. Recent research has demonstrated that impairment of GCase activity leads to aggregation and accumulation of α-synuclein, which in turn further inhibits the activity of GCase [24].

Overall, *GBA* variants in PD are associated with younger age at onset, faster cognitive and motor progression, and a higher burden of non-dopaminergic symptoms (i.e. freezing of gait, postural instability) [3, 7, 22].

Population genetics of PD

Over the last 15 years, several GWAS have been conducted in PD, partly explaining the risk of developing the disease and its heterogeneity [3, 21]. So far, 90 independent common genetic risk variants have been identified, accounting for 16–36% of heritable disease risk [25]. Common genetic variation has also impacted upon the age at onset, with attributed variability of 8–11% [26, 27]. A number of genetic variants have been associated with the rate of motor progression, susceptibility to L-Dopa-induced dyskinesia, and motor fluctuations [28–31]. Common genetic variations have also been associated with non-motor symptoms, including susceptibility to cognitive decline, REM sleep behaviour disorder, insomnia, daytime sleepiness, and impulse control disorder [28–30, 32, 33]. One study looked into genetic determinants of clinical PD subtypes, tremor-dominant vs. postural instability and gait difficulty, identifying several suggestive associations, but none reached genome-wide significance [34]. Common genetic variants have also been linked to different treatment outcomes, including therapy with subthalamic deep brain stimulation [35].

GWAS nominated several novel genes to be included in the pathophysiology of PD, providing new insights into the biological pathways involved in PD [3, 21]. Furthermore, many of the 'top hits' from the GWAS have been linked to genes previously identified in familial forms of PD, which shows that sporadic and familial forms of PD share pathophysiological pathways [3, 21].

However, GWAS are also burdened with several shortcomings. Most of the findings from initial studies have not been replicated subsequently due to different designs (particularly in terms of population structure), non-sufficient statistical power, inconsistencies in clinical measures, and the possible inclusion of patients with disorders other than PD [3, 21]. Additionally, as the results from previous studies indicated that different genetic loci impact upon the risk of developing PD and its heterogeneity, studying them together could reduce the research yield [3].

Many of the identified variants in the GWAS are mapped to non-coding regions of the DNA, and pinpointing the causal gene is challenging [36]. Interestingly, only 30% of the causal genes are the nearest gene to the GWAS-identified variant [36]. In recent years, it has become possible to predict more reliably the functional effects of the candidate variants and identify the target gene [36]. However, *in silico* models may not be accurate enough, and animal studies are still required to confirm the causal gene [36].

Most previous studies were conducted on PD patients of European ancestry [21]. Therefore, the currently developed algorithms for polygenic risk score estimation are of limited use to patients of other ancestries, and more research on ethnically diverse populations is needed to ascertain the significance of the previously identified variants in the pathogenesis of PD [21]. Despite identifying more than 100 genetic risk variants or phenotype modifiers, at present they can only be used to estimate the likelihood of developing, but not to discriminate whether the patient finally develops, the disease and the particular phenotype. Thus far, the heritability and clinical heterogeneity of PD may only partly be explained by the polygenic scores, while most underlying causes remain undetermined. It is also possible that shared environmental factors, which remain common confounders in GWASs, could have falsely inflated the heritability estimates and influenced the heterogeneity, spuriously reducing the significance of the identified variants [36].

Polish patients

The population of Polish patients with PD remains genetically understudied (see Table 2). The most common monogenic form of PD is *LRRK2*-PD, with a prevalence of up to 1% [37, 38]. *PRKN*-PD and *PINK1*-PD have been detected in up to 5% and in 1% of Polish patients with EOPD, respectively [39, 40] [40, 41]. *SNCA*-PD was found in 0.3% of Polish patients with sporadic PD, whereas *VPS35* and *DJ-1*-PD have not yet been reported [42]. To date, two studies have investigated *GBA* mutations in the Polish population, including only two (p.N370S, p.T369M) of the four most common GBA variants [43, 44].

Overall, genetic studies on Polish PD populations have yielded lower results than those conducted in other European populations. This is surprising given the long history of interaction between Poland and its neighbours and the influx of immigrants, mainly from Germany (13–16th centuries), Italy (14–16th centuries), the Netherlands (15–16th centuries), Scandinavia (from 15th century), and England and Scotland (16th century) [45]. For instance, a family with

Table 2. Familial forms of PD and *GBA* mutations reported in Polish population

	LRRK2	PRKN	VPS35	PINK1	DJ-1	SNCA	GBA
Prevalence	0–1% [37, 38]	0–4.7% in EOPD [39, 40]	Not reported [46]	0.7–0.9%* [40, 41]	Not reported [40, 47]	0.3% of sporadic PD [42],	4%–11.6% [43, 44]
Variants reported	p.G2019S [38], p.N1437H [48]	Structural variants [11, 40, 47, 49, 50], p.E79* [47], p.K211N [11, 40, 47, 50], p.R275W [40, 47], p.Q34Rfs*5 [40, 47, 50], p.Q44fsX48 [49], p.P437L [47], p.C446F [47, 50]	N/A	p.A168P [47], p.Lys186Asn [40], p.I368N [40, 47, 51], p.G411S [41, 47], p.Q456X [47, 52], p.Ser535Leu [40]	N/A	p.A18T [42], pA29S [42], Duplication [11]	T369M [43], N370S [43], p.N409S [44], p.L483P [44]

*heterozygous carriers; EOPD — early-onset Parkinson's Disease; PD — Parkinson's Disease

PD-*LRRK2* p.N1437H, a mutation previously only reported in Scandinavia, was recently identified in Poland [56]. Moreover, Ashkenazi Jewish and Polish populations have shared a common history for more than 1 thousand years. Thus, the prevalence of genetic forms of PD, particularly *LRRK2*, in the Polish population is probably underestimated. However, recent genetic studies indicated homogeneity of the Polish population, with different frequencies of pathogenic alleles compared to other European populations [53]. We cannot exclude the possibility that there are other genetic forms of PD specific to Polish populations that remain undiscovered. Therefore, more studies are needed to ascertain the genetics of the Polish PD population.

Common genetic variants and PD symptomatology

Several common genetic variations have been identified as impacting upon the progression of the disease, the burden of motor and non-motor symptoms (particularly dementia), and prognosis in general [3]. Apolipoprotein E4 (APOE4) allele and polymorphisms in several other genes have been associated with faster cognitive decline [3, 54]. Susceptibility to developing impulse control disorder has been linked to variants in *COMT, DRD1, DRD2, DRD3,* and *DDC* [3]. The age of the first symptoms has been related to *SNCA, TMEM175,* and *BST1* variants [3]. The rate of motor progression, predisposition to develop dyskinesia, and fluctuations have been associated with polymorphisms in *COMT, DRD3, LRRK2, GBA, OPRM1,* and several other genes [3]. Some variants have been linked to a different clinicaltrajectory following treatment with advanced therapies, e.g. *CRHR1, IP6K2*, and *PRSS3* polymorphisms have been associated with a higher burden of axial symptoms following deep brain stimulation (DBS) [35]. Most of these variants individually have a low impact on the disease symptomatology, but combined they can be used to calculate polygenic risk scores and identify patients more prone to certain manifestations of the disease or to adverse effects of the therapy. For instance, carriers of APOE4 and GBA variants are more likely to develop cognitive decline post-DBS [55, 56].

Clinical implications: genetic testing in clinical settings

Genetic testing in clinical settings may include targeted, multigene, whole exome sequencing (WES), or whole genome sequencing (WGS) [4, 57]. Targeted analysis, in which a single gene or a few variants within it are tested, has currently limited utility due to other diagnostic methods providing more comprehensive genetic information. However, in light of the low cost per sample, it is still useful in highly selected patients suspected of particular genetic variants, e.g. in PD patients with a strong positive family history of a monogenic variant. Multigene panels, sequencing several genes associated with PD using next-generation sequencing (NGS), currently present the optimal benefit-to-cost ratio and are the first choice for genetic testing in clinical settings [4, 57]. In a recent survey of available multigene panels for PD from the United States (n = 7) and Europe (n = 4), the authors noted significant differences in terms of the number of included genes, which ranged from 5 to 62 [4]. However, all of them included the most important familial PD genes, i.e. *SNCA, PRKN, PINK1, DJ-1,* and *LRRK2*, whereas the inclusion of *VPS35* and *GBA* varied [4]. WES enables comprehensive testing of the whole protein coding genome using NGS and is being increasingly used in routine clinical practice, particularly as the second-tier testing in patients with negative results of multigene panels. Analysis of WES or WGS can still be targeted to a single variant, gene, or multigene panel but it potentially enables repeated analysis in future when novel pathogenic variants are identified, or extension to evaluate parts of the exome/genome that were not included in the original report. Of note, as multigene panels and WES use NGS, they may not detect copy number variants (CNV) (e.g. deletions, duplication, repeat expansions) [4, 57, 58]. Therefore, additional analysis of CNV is warranted, and it is

not always stated by the laboratory whether such an analysis was performed, which could result in false negative results in carriers of familial PD forms due to structural variants, e.g. *PRKN* or *SNCA* [4].

Many patients have been detected as carrying variants of uncertain significance (VUS), which are genetic variations for which the association with disease risk is unclear [59]. As the databases with genetic variants and the medical literature are continually broadening, we suggest first searching the literature and checking the current status of the VUS [59]. Segregation studies (requiring clinical and sample testing of other family members) and *in silico* predictions may shed more light on the character of the VUS. However, functional studies in cellular and animal models remain the gold standard to determine the pathogenicity, or lack thereof [59].

Future directions

Genetic testing remains largely underemployed in clinical settings [60, 61]. Its high cost and perceived lack of impact on treatment decision-making are the main reasons for this [60, 61]. However, both these arguments are becoming relics of the past. The cost of gene sequencing has decreased dramatically over the last few years. The cost of whole genome sequencing fell from over $1 million in 2007 to less than $1,000 in 2019 [62]. Currently, it is quoted at c.$500, and it will most likely be under $100 in the near future [63]. Furthermore, several initiatives offer complimentary genetic testing and counselling for patients with PD, including PD GENEration by the Parkinson's Foundation [64] and Parkinson's Progression Markers Initiative by The Michael J. Fox Foundation [65]. A lack of medical 'actionability' is also no longer valid. Several interventional clinical trials dedicated to carriers of specific gene variants are already in progress (Tab. 3). They offer new types of potential treatment for selected patients, although, most likely, findings from these studies will also be translated to the sporadic form of PD.

We speculate that the future treatment landscape for PD will be similar to that in oncological conditions such as breast cancer, in which the presence of certain gene mutations or gene overexpression determines the prognosis and treatment decision-making [66, 67]. Additionally, the application of artificial intelligence and machine learning will enable high-throughput analysis of large sets of multimodal data,

Table 3. Active clinical trials for patients with Parkinson's Disease who are carriers of *LRRK2* or *GBA* mutations. Data collected from Clinicaltrials.gov as of 28 September, 2023

Genetic variant	Intervention	Clinical-Trials.gov ID	Administration route	Mechanism of action	Study phase	Status	Location
LRRK2	DNL151 (BIIB122)	NCT05348785	Oral	Inhibition of LRRK2	2	Active (recruiting)	Austria, Canada, China, France, Germany, Israel, Italy, Japan, Netherlands, Poland, Spain, United Kingdom, United States
LRRK2	DNL151 (BIIB122)	NCT05418673	Oral	Inhibition of LRRK2	3	Active (not recruiting)	France, Germany, Italy, Spain, United Kingdom, United States
LRRK2	Trehalose	NCT05355064	Oral	Enhancement of autophagy	4	Active (not recruiting)	Not provided
LRRK2	BIIB094	NCT03976349	Intrathecal injection	Antisense oligo-nucleotide	1	Active (recruiting)	Canada, Israel, Norway, Spain, United Kingdom, United States
GBA	Ambroxol	NCT05287503	Oral	Enhancement of glucocerebrosida-se activity	2	Active (not recruiting)	Italy
GBA	Ambroxol	NCT02914366	Oral	Enhancement of glucocerebrosida-se activity	2	Active (not recruiting)	Canada
GBA	BIA-28-6156	NCT05819359	Oral	Enhancement of glucocerebrosida-se activity	2	Active (recruiting)	Canada, France, Germany, Italy, Netherlands, Poland, Portugal, Spain, Sweden, United Kingdom, United States
GBA	LY3884961	NCT04127578	Intra-cisterna magna	Gene therapy	1/2	Active (recruiting)	Israel, United States
GBA	Recombinant glucocerebro-sidase	NCT05565443	Intracerebral (intra-venous injections, followed by BBB disruption with MRgFUS)	Enhancement of glucocerebrosida-se activity	1/2	Active (not recruiting)	Not provided

BBB — blood-brain barrier; MRgFUS — magnetic resonance-guided focused ultrasound

including demographics, clinical, genomics (whole genome), transcriptomics, proteomics, and others [68].

Conclusions

Genetic testing remains largely underused in clinical settings. However, in light of the rapidly decreasing cost of genetic testing, and the emergence of the first potential therapies dedicated to carriers of specific gene mutations associated with PD, it is due time to reconsider attitudes toward the role of genetics in clinical settings. Clinicians should not be discouraged by VUSs, because with the growing amount of genetic data from PD patients, their significance will ultimately be resolved.

Finally, and hopefully, the widespread application of genetic testing will provide more insight into the pathophysiology of the disease, identify new potential therapeutic targets, and pave the way toward curative therapy in the future.

Article information

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RESEARCH PAPER

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LEADING TOPIC

Leading Topic Editor: Olga P. Fermo, MD, Department of Neurology, Mayo Clinic, Jacksonville, Florida, United States

Neuronal pentraxin 2 correlates with neurodegeneration but not cognition in idiopathic normal pressure hydrocephalus (iNPH)

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ABSTRACT

Aim of study. Neuronal pentraxin-2 (NPTX2) is a synaptic protein responsible for modulating plasticity at excitatory synapses. While the role of NPTX2 as a novel synaptic biomarker in cognitive disorders has been elucidated recently, its role in idiopathic normal pressure hydrocephalus (iNPH) is not yet understood.

Clinical rationale for study. To determine if NPTX2 predicts cognition in patients with iNPH, and whether it could serve as a predictive marker for shunt outcomes.

Materials and methods. 354 iNPH patients underwent cerebrospinal fluid drainage (CSF) as part of the tap test or extended lumbar drainage. Demographic and clinical measures including age, Evans Index (EI), Montreal Cognitive Assessment (MoCA) score, Functional Activities Questionnaire (FAQ) score, and baseline and post-shunt surgery Timed Up and Go (TUG) test scores were ascertained. CSF NPTX2 concentrations were measured using an ELISA. CSF β-amyloid 1–40 (Aβ1–40), β-amyloid 1–42 (Aβ1–42), and phosphorylated tau-181 (pTau-181) were measured by chemiluminescent assays. Spearman's correlation was used to determine the correlation between CSF NPTX2 concentrations and age, EI, MoCA and FAQ, TUG, Aβ1–40/Aβ1–42 ratio, and pTau-181 concentrations. Logistic regression was used to determine if CSF NPTX2 values were a predictor of short-term improvement post-CSF drainage or long-term improvement post-shunt surgery.

Results. There were 225 males and 129 females with a mean age of 77.7 years (± 7.06). Average CSF NPTX2 level in all iNPH patients was 559.97 pg/mL (± 432.87). CSF NPTX2 level in those selected for shunt surgery was 505.61 pg/mL (± 322.38). NPTX2 showed modest correlations with pTau-181 ($r = 0.44$, $p < 0.001$) with a trend for Aβ42/Aβ40 ratio ($r = –0.1$, $p = 0.053$). NPTX2 concentrations did not correlate with age ($r = –0.012$, $p = 0.83$) or MoCA score ($r = 0.001$, $p = 0.87$), but correlated negatively with FAQ ($r = –0.15$, $p = 0.019$).

Conclusions. While CSF NPTX2 values correlate with neurodegeneration, they do not correlate with cognitive or functional measures in iNPH. CSF NPTX2 cannot serve as a predictor of either short-term or long-term improvement after CSF drainage.

Clinical implications. These results suggest that synaptic degeneration is not a core feature of iNPH pathophysiology.

Keywords: neuronal pentraxin 2, normal pressure hydrocephalus, cerebro spinal fluid, biomarkers

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Introduction

Neuronal pentraxin 2 (NPTX2) is a member of the long pentraxin subfamily, a group of evolutionarily conserved proteins that play a role in regulating various processes in the brain and periphery [1]. NPTX2 has been implicated in glutamatergic signalling, which is involved in synaptic transmission and plasticity [1]. Disruptions in glutamatergic signalling have been recognised in various neurological disorders, including mild cognitive impairment (MCI) and Alzheimer's Disease (AD) [2]. Furthermore, NPTX2 plays a role in the formation and maturation of excitatory synapses [1]. In cerebrospinal fluid (CSF), reduced levels of NPTX2 have been observed in AD [3], genetic frontotemporal dementia [4], and dementia with Lewy bodies [5], leading to its promising potential use as a biomarker in these disorders.

Idiopathic normal pressure hydrocephalus (iNPH) is a neurological disorder that typically manifests with a triad of symptoms consisting of gait disturbance, cognitive dysfunction, and urinary incontinence [6]. Surgical insertion of a shunt, a common form of treatment in iNPH, is associated with a high rate of adverse events including risk of infection, shunt malfunction and subsequent revision surgery, and subdural haematomas and hygromas [7, 8]. Determining better biomarkers for predicting shunt responsiveness could potentially result in having to subject fewer patients to the risk of shunt surgery. In the context of cognitive dysfunction in iNPH, disruptions in synaptic function and loss of neurons have been reported [9], but the potential mechanisms remain to be elucidated.

In the present study, we aimed to determine if NPTX2 could function as a marker of cognitive dysfunction in iNPH. Secondarily, we evaluated whether CSF NPTX2 concentrations can serve as a predictor of short-term improvement after CSF drainage or long-term improvement after shunt surgery in a large iNPH cohort.

Clinical rationale for study

Identifying relevant proteins that contribute to the cognitive decline seen in iNPH may help both in identifying and in treating this condition, as well as in understanding the underlying mechanisms. NPTX2 is a proven biomarker of synaptic integrity, although it is not known whether it can serve as a marker for the cognitive dysfunction seen in iNPH. Cognitive impairment in iNPH has been hypothesised to be due to subcortical dysfunction due to poor bloodflow to these regions [10], impaired axonal signalling [11], and potentially to the impaired clearance of waste products due to glymphatic dysfunction [12].

Determining the correlation between CSF NPTX2 concentration and cognition, other CSF biomarkers, and gait function, in addition to determining whether NPTX2 concentrations could serve as a predictor of short-term improvement after CSF drainage or long-term improvement after shunt surgery, would further help in understanding the mechanisms of cognitive impairment in NPH, and potentially serve as a predictive biomarker after shunt surgery.

Materials and methods

Research subjects

CSF was collected from 354 probable iNPH patients who had been referred to the Johns Hopkins Centre for CSF Disorders and who underwent an outpatient tap test (TT) procedure where 40 mLs of CSF was removed or a three-day external lumbar drainage (ELD) where 300 mLs of CSF was removed. All participants referred for a TT or an ELD had to meet the criteria of presenting with some degree of gait impairment and cognitive impairment, in addition to the presence of ventriculomegaly determined through neuroimaging. Patients provided written informed consent for biospecimen banking for research under a Johns Hopkins IRB-approved protocol (IRB Application Number: NA_00029413).

Gait, cognitive, and MRI assessments

All patients who underwent a TT or an ELD participated in a full battery of gait testing, both before and after CSF drainage. The Timed Up-and-Go (TUG) test was used to assess gait speed and dynamic balance. The results of the pre-procedure and post-procedure gait testing were compared and used to determine gait improvement post-CSF drainage. An improvement of 30% or greater on the TUG test was used to define responders to CSF drainage, and subsequently used to select patients for shunt surgery. Baseline cognitive function was assessed using the Montreal Cognitive Assessment (MoCA). Ability to conduct activities of daily living (ADLs) was assessed using the Functional Activities Questionnaire (FAQ). All patients also underwent a structural MRI scan of the brain to determine the presence of ventriculomegaly, defined by an Evans Index (EI) greater than 0.3.

CSF sample processing protocol

CSF was collected directly in 10 mL polypropylene tubes (Sarstedt: 62.610.018) during the TT and ELD procedures. CSF was transported at room temperature until centrifugation at 2,000 g for 15 minutes at 5°C ± 3°C. CSF was transferred from original tubes to sterile 50 mL tubes (Sarstedt: 62.547.100) and centrifuged again at the same settings as the previous spin. Samples were then separated into 500 µL aliquots in low-binding polypropylene cryovials (Sarstedt: 101093-760) within one hour of collection and stored at −80°C until thawed for biomarker analysis.

Laboratory assays

CSF Aβ1–42, Aβ1–40, and pTau-181 concentrations were measured using LUMIPULSE G1200 chemiluminescent ELISA (Fujirebio, Malvern, PA, USA) directly from the cryovials without sample transfer. An internal CSF control was run on each day

Table 1. Patient baseline characteristics compared by cohort (non-shunted and shunted patients)

Characteristics	Non-shunted patients (n = 245)	Shunted patients (n = 109)
Age, years mean (± SD)	77.9 (± 7.4)	77.2 (± 6.4)
Male sex, n (%)	153 (62.4%)	72 (65.5%)
Race, n (%)		
Caucasian	225 (91.8%)	105 (96.3%)
African American	15 (6.12%)	2 (1.81%)
Other	5 (2.04%)	2 (1.81%)
Living status, deceased, n (%)	13 (5.30%)	5 (4.58%)
MRI Evans Index (0-1), mean (± SD)	0.36 (± 0.05)	0.38 (± 0.04)***
Baseline MoCA score, mean (± SD)	21.4 (± 5.56)	21.2 (± 5.73)
FAQ score, mean (± SD)	10.85 (± 9.02)	9.68 (± 8.37)
Baseline TUG score, mean (± SD)	20.06 (± 25.22)	29.70 (± 36.59)*
Post-shunt TUG score, mean (± SD)		17.69 (± 19.56)**
NPTX2 concentration, mean (± SD)	584.16 (± 472.41)	505.61 (± 322.38)
pTau-181 concentration, mean (± SD)	35.91 (± 27.25)	29.78 (± 20.34)*
Aβ40 concentration, mean (± SD)	7,761.34 (± 3,158.35)	6,994.87 (± 2,964.27)*
Aβ42 concentration, mean (± SD)	865.69 (± 385.77)	816.48 (± 366.64)
Aβ42/Aβ40 ratio, mean (± SD)	0.110 (± 0.03)	0.119 (± 0.03)**
NFL concentration, mean (± SD)	2,156.40 (± 1,679.10)	2,062.12 (± 1,832.94)
Aqueductal stenosis, n (%)	10 (4%)	5 (4.5%)
DESH, n (%)	71 (29%)	57 (52%)***
Cerebral atrophy, n (%)	46 (19%)	20(18%)
White matter disease, n (%)	137 (56%)	57 (52%)
Lacunar stroke, n (%)	25 (11%)	14 (13%)
Large vessel stroke, n (%)	10 (4%)	5 (4.5%)

Patients who were unable to complete the TUG were assigned a baseline TUG score of 300. Shunted patients who were unable to complete the TUG were assigned a post-shunt TUG score of 300. Additionally, 15 patients were not available for post-shunt surgery gait testing, so measures were not collected from these patients and they were also excluded. 97 patients who did not complete the FAQ were assigned a score of 999. Aβ40 — β -amyloid 40; Aβ42 — β -amyloid 42; DESH — disproportionately enlarged subarachnoid space hydrocephalus; FAQ — Functional Activities Questionnaire; MoCA — Montreal Cognitive Assessment; NPTX2 — neuronal pentraxin 2; pTau-181 — phosphorylated tau 181; TUG — Timed Up-and-Go; *p < 0.05, **p < 0.01, ***p < 0.001

that samples were analysed. NPTX2 concentration was measured by an in-house ELISA assay as previously described [13]

Statistical analysis

CSF NPTX2 concentrations were compared against baseline characteristics including age, MoCA score, FAQ score, baseline TUG score, post-shunt TUG score, Evans Index, Aβ1–42/1–40 ratio, and pTau-181 concentration. Spearman correlations were used to determine the correlation between CSF NPTX2 and the measures listed above. P-values of less than or equal to 0.05 were considered statistically significant. To determine if NPTX2 concentrations were a predictor of short-term improvement, defined as one hour after TT or ELD, or long-term improvement defined as two years median post-shunt surgery, simple univariate logistic regression models were used. Ten-fold cross-validation was used to evaluate the logistic regression models, and the means of the area under the receiver operating curve (AUC) values were calculated and plotted to compare model performance. The cross-validated AUC R package was used to compute 95% CIs for the cross-validated AUC estimates.

Results

The demographic characteristics of the patients included in this cohort are set out in Table 1. A total of 354 patients were included in this study, with a mean age of 77.7 years (± 7.06) and the majority were male (n = 225). Of these 354 patients, 109 were selected for shunt surgery and were followed for a median duration of 12 months. The MRI Evans Index was higher in the shunted group vs. the non-shunted group (0.038 ± 0.04 vs. 0.036 ± 0.05, p < 0.001, Tab. 1). A higher proportion of patients selected for shunt surgery had features

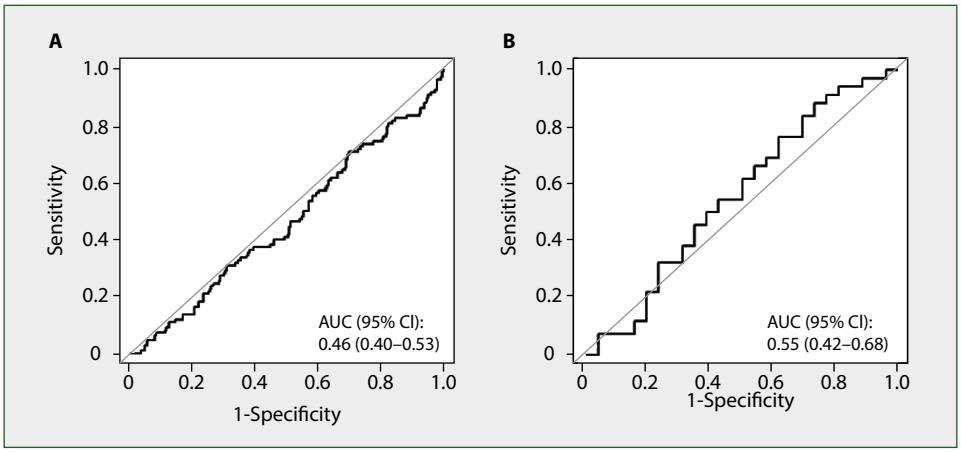

Figure 1. A. ROC for prediction of response to TT by CSF NPTX2 concentration; **B.** ROC for prediction of response to shunt by CSF NPTX2 concentration

of DESH (disproportionately enlarged subarachnoid space hydrocephalus) (52% vs. 29%, p < 0.001, Table 1). The groups did not differ in terms of white matter disease, cerebral atrophy, lacunar or large vessel strokes or aqueductal stenosis. CSF NPTX2 concentrations did not differ between the two groups. CSF ptau181, CSF Aβ40 concentrations were lower, while the Aβ42/Aβ40 ratio was higher, in the shunted group (Tab. 1).

A univariate logistic regression model indicated that CSF NPTX2 concentrations were not significantly correlated with short-term improvement, defined as a 30% or greater improvement on completion of the TUG test, after TT or ELD (OR 0.80, 95% CI 0.60–1.03, p-value = 0.109) (Fig. 1). The univariate logistic regression model also indicated that CSF NPTX2 concentrations were not significantly associated with long-term improvement following shunt surgery (OR 1.08, 95% CI 0.61–2.00, p-value = 0.797) (Fig. 1).

A significant positive correlation was found between CSF NPTX2 and CSF pTau-181 concentrations (R = 0.43, p-value = < 2.2×10^{-16}) (Fig. 2). In addition, significant though weak negative correlations were found between CSF NPTX2 and baseline TUG performance (r = –0.16, p = 0.0025) (Fig. 2) and between CSF NPTX2 and FAQ scores (r = -0.15, p = 0.019) (Suppl. Fig. 3), with a similar trend with Aβ42/Aβ40 ratio (r = –0.1, p= 0.053) (Fig. 2). There were no significant correlations found between CSF NPTX2 concentrations and age (r = 0.008, p = 0.88) (Suppl. Fig. 4), EI (r = –0.068, p = 0.20) (Suppl. Fig. 5), baseline MoCA score (r = –0.023, p = 0.67) (Fig. 2), or post-shunt surgery TUG performance (r = –0.14, p = 0.17) (Suppl. Fig. 6).

Discussion

While cognitive dysfunction is a prominent symptom of iNPH, the underlying biology is still not fully understood. There have been several potential mechanisms proposed to explain this decline in iNPH. A study investigating the altered glymphatic system in iNPH suggested impaired waste clearance may contribute to cognitive dysfunction [14]. Another study found that proteins involved in synaptic signalling were statistically lower in iNPH, and suggested dysregulated sphingolipids that are involved in cell signalling and membrane structure could contribute to the cognitive dysfunction seen in iNPH [15]. In a post mortem study conducted by Leinonen et al. on presumed iNPH patients, it was found that vascular pathology could explain cognitive dysfunction, although specific markers of synaptic loss were not investigated [16].

Our study aimed to determine if there is a link between NPTX2, a synaptic protein shown to be affected in other neurodegenerative disorders, and cognitive decline in iNPH.

The MoCA test is a widely used and well-validated method of evaluating cognitive function and change in clinical settings as well as in NPH [17]. However, studies have explored the presence of neurological co-morbidities, particularly AD, in iNPH patients [18]. The presence of AD pathology may contribute to the cognitive impairment observed in iNPH patients. Our study showed no significant correlation between CSF NPTX2 concentration and baseline MoCA score. The FAQ provides a standardised assessment of instrumental ADL. Impairment of ADLs is a significant concern in iNPH patients due to the combination of gait and cognitive impairment. Falls, and the fear of falling, are common in the iNPH population and can further impact upon their ability to perform ADL [19].

We observed a significant, though weak, negative correlation between NPTX2 and FAQ scores.

There have been many studies that have examined CSF biomarkers in iNPH, most notably the established AD CSF biomarkers including Aβ1–42, Aβ1–40, pTau-181 and NFL

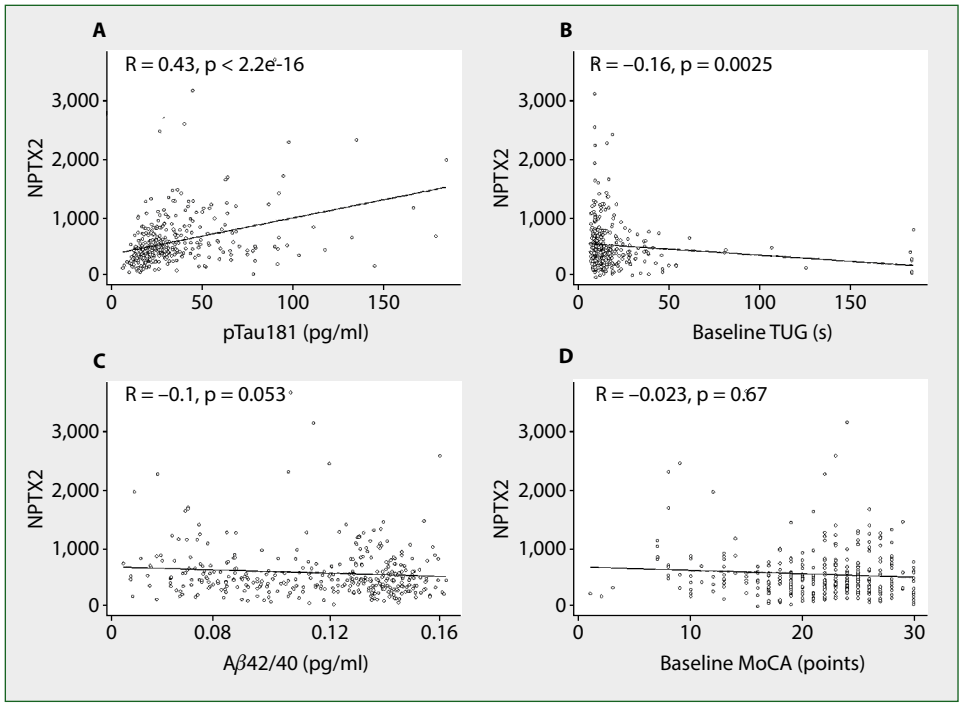

Figure 2. A. Correlation between CSF NPTX2 concentration and CSF pTau-181 concentration; **B.** Correlation between CSF NPTX2 concentration and baseline TUG score; **C.** Correlation between CSF NPTX2 concentration and CSF Aβ42/Aβ40 ratio; **D.** Correlation between CSF NPTX2 concentration and baseline MoCA score

[20,21]. Studies have focused on the measurement of CSF pTau-181 concentration primarily as a potential biomarker for differentiating NPH from other neurodegenerative diseases, including AD [22]. In the context of AD, there is an accumulation of hyperphosphorylated tau proteins, leading to increased CSF pTau-181 concentration [23]. However, the relevance of CSF pTau-181 concentration specifically in iNPH is still being investigated. Some studies have suggested that CSF pTau-181 concentration may be lower in iNPH patients compared to AD patients [23]. Our study demonstrated a significant positive correlation between CSF NPTX2 values and CSF pTau-181 values. This replicates the observation made in an earlier study, where increased CSF NPTX2 levels correlated with increased CSF pTau-181 levels to a similar extent [24].

Aβs are physiological peptides that are present in normal, healthy brains and are thought to be cleared from the interstitial space of the brain across the blood-brain barrier through CSF [25]. Disruptions to the clearance of Aβ proteins can cause the accumulation and deposition of Aβ proteins, creating Aβ plaques [26]. Alterations in Aβ clearance pathways, such as the glymphatic system, have been implicated in the pathophysiology of iNPH [27]. Since iNPH causes a reduction in CSF outflow absorption, Aβ deposition and subsequent neurodegeneration may occur [26]. Since Aβ1–40 and Aβ1–42 are core CSF biomarkers of neurodegeneration, these proteins have been extensively reported in iNPH biomarker studies. Aβ1–40 and Aβ1–42 differ in just two amino acids. However, they vary in metabolism, physiological function, toxicity, and aggregation mechanisms [28].

One review study showed that Aβ1–42 had a prognostic value for iNPH, whereas Aβ1–40 was not found to be a significant predictor [21]. However, the use of CSF AD biomarkers can be misleading when applied in the context of iNPH, as these proteins may have decreased movement from the interstitial compartment of the brain or the presence of dilution effects, where the excess CSF in iNPH dilutes the physiological components of CSF [23]. In AD, there is a characteristic imbalance in the production and clearance of Aβ peptides, leading to a decreased Aβ42/Aβ40 ratio [22]. This ratio is a well-accepted biomarker for AD, as it reflects the aggregation and deposition of Aβ1-42 as amyloid plaques [29].

In our study, we found a weak negative correlation between CSF NPTX2 values and Aβ42/Aβ40 ratio. In the iNPH subjects in our study, it appears that NPTX2 levels do not reflect neurodegeneration seen in other neurodegenerative disorders where lower levels are pathological. This could potentially be due to impaired clearance of NPTX2 from the interstitial and CSF compartments. However, there was no correlation between EI, a surrogate marker for ventriculomegaly and levels of NPTX2. Further studies including more accurate measures of ventricular volume are needed to evaluate this hypothesis.

Age in iNPH has been suggested to be a potential risk factor, as the prevalence of iNPH increases substantially with age [30]. Age-related changes in the brain, such as increased

vascular pathology, may contribute to the development and progression of iNPH [31]. Overall, age plays a role in the manifestation and treatment response of iNPH, highlighting the need for age-specific considerations in the management of this condition. Our study demonstrated that CSF NPTX2 concentrations had no significant correlation with age in our cohort.

The TUG test is a widely used assessment tool for evaluating gait and balance, particularly in the elderly population [32]. It is a fast and easy-to-administer test that has been validated for screening the risk of falls among elderly individuals [32]. The TUG test measures the time it takes for an individual to stand up from a chair, walk a set distance, turn around, and sit back down [33]. This has been shown to be reliable, cost-effective, safe, and time-efficient for evaluating overall functional mobility [33]. Additionally, a systematic review examined the diagnostic utility of simple tests, including an improvement in the total time to complete the TUG test post-CSF drainage in adults with iNPH [34]. The review also highlighted the diagnostic value of the improvement in TUG test completion time in identifying potential responders to shunt surgery.

Our study aimed to discern if NPTX2 concentrations correlated with performance on the TUG test at baseline and post-shunt surgery. We saw a significant, though weak, negative correlation between CSF NPTX2 values and baseline performance on the TUG. However, there was no significant correlation between CSP NPTX2 values and post-shunt TUG test performance evaluated at a median of two years post-shunt insertion.

The strengths of our study include a large cohort size, a long duration of follow-up, and the use of multiple biomarkers that reflect pathologies common in ageing. However, there are significant limitations to our study. Firstly, the study was limited to a single tertiary care centre and the patient referral pattern may not reflect the types of iNPH patient seen at other centres. Secondly, we did not evaluate other well-established markers of synaptic degeneration including SNAP25, neurogranin and GAP-43. Lastly, we do not have cognitive outcomes on patients who underwent shunt surgery because MoCA testing is not standard practice after shunting unless patients have cognitive symptoms.

Overall, our findings from this study reinforce the published literature demonstrating correlations of NPTX2 concentrations with pTau-181 concentrations, although NPTX2 does not correlate with cognition in iNPH unlike other neurodegenerative disorders such as AD and FTD.

Clinical implications and future directions

The identification of CSF biomarkers for iNPH would allow clinicians to differentiate iNPH from other neurological diseases, although it is difficult to determine which biomarkers are relevant to the iNPH population. Furthermore, the selection of patients for shunt surgery as a treatment of iNPH must be evaluated by both short-term improvement and a more sustained long-term improvement after shunt placement.

NPTX2 did not demonstrate strong promise as a diagnostic biomarker in the iNPH population, and was not a predictive biomarker of short-term improvement after CSF drainage through TT or ELD procedures.

NPTX2 also did not predict long-term improvement post-shunt surgery. The lack of synaptic injury in iNPH also reinforces the paradigm that iNPH is a subcortical process and could explain the reversibility of cognitive impairment given the preservation of synaptic structure.

The potential role played by synaptic degeneration in aetiological subtypes, especially compensated congenital hydrocephalus manifesting in mid-life or late-life with iNPH like symptoms, requires further study.

Article information

Data availability statement: *Original contributions presented in the study are included in both the article and as Supplementary Materials. Any further inquiries may be directed to the Corresponding Author, Dr. Abhay Moghekar.*

Ethics statement: *Patients provided written informed consent for biospecimen banking for research under a Johns Hopkins IRB-approved protocol (IRB Application Number: NA_00029413).*

Authors' contributions: *MP compiled data for analysis and wrote manuscript; YZ performed data analysis; M-FX performed assays on collected samples; PW developed assays and contributed to data analysis; AM developed study design, oversaw study, contributed to data analysis, and contributed to writing of manuscript.*

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Conflicts of interest: *None.*

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LEADING TOPIC

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Recurrence of cerebrospinal fluid-venous fistulas at different spinal levels following transvenous embolisation or blood/fibrin glue patching

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ABSTRACT

Aim of the study. This study presents cases of recurrent cerebrospinal fluid-venous fistulas (CVFs) de novo at a different spinal level following successful treatment of initial CVFs. The aim was to highlight this rarely described phenomenon and report the clinical and imaging features after initial treatment, providing insights into the dynamics of recurrent CVFs.

Clinical rationale for the study. Understanding the course of CVFs post-treatment is crucial for optimising patient management, especially when symptoms persist or recur.

Material and methods. We performed a retrospective chart review of all patients with recurrent CVFs at a different level after treatment of their initial CVF at our institution. Clinical and imaging records were reviewed and summarised, including Bern score features on brain magnetic resonance imaging (MRI) before and after treatment.

Results. Four patients with five recurrent CVFs were identified. Recurrent or persistent symptoms encouraged subsequent brain MRI scans, which revealed different outcomes: i.e. persistence, or improvement, or complete resolution of abnormal findings. Initial positive responses included improvement of the pachymeningeal enhancement and venous sinus distension. These improvements were reversed when recurrent symptoms arose, which was also correlated with changes in the Bern score.

Conclusions and clinical implications. Recognising the factors of CVF recurrence is crucial for comprehensive management. This study underlines the significance of repeated evaluation of persistent or recurring symptoms of CSF leak after treatment for CVFs.

Keywords: cerebrospinal fluid-venous fistula, spontaneous intracranial hypotension, Bern score, recurrence, myelography, embolisation, patch

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Introduction

Cerebrospinal fluid-venous fistulas (CVF), also known as type III cerebrospinal fluid (CSF) leaks, are spontaneous abnormal connections that form between the spinal subarachnoid space and a paraspinal vein. This results in unregulated CSF volume loss and spontaneous intracranial hypotension (SIH). The diagnosis of SIH is often established via an MRI of the brain showing diffuse smooth pachymeningeal enhancement and brainstem sagging secondary to insufficient CSF volume [1–3]. Bern SIH score is a radiological scoring system that predicts the probability of identifying a spinal CSF leak source associated with SIH based on six findings on brain MRI including pachymeningeal enhancement, effaced suprasellar

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cistern, venous sinus distension, decreased mamillopontine distance, effaced prepontine cistern, and the presence of subdural fluid collections [4] (Tab. 1). Identification and localisation of CVFs requires advanced myelographic techniques including lateral decubitus dynamic computerised tomography myelography (CTM) or digital subtraction myelography (DSM) [2, 3]. CVFs can be treated via surgical ligation, fibrin glue/blood patching, or, the most recently devised method, transvenous embolisation.

De novo recurrence of CVF at a new level after treatment has been recently described after surgery [5], but it has not been well described following transvenous embolisation or fibrin patching. Furthermore, only a few cases of recurrent CVF have been described. The purpose of our study is to report four cases of recurrent CVF at new levels after successfully treated initial CVF, highlighting clinical and imaging features after treatment and prior to the discovery of a new CVF.

Clinical rationale for the study

Recurrent CVFs pose a rarely discussed clinical challenge. Understanding the dynamics and clinical and imaging features of this phenomenon will guide more effective diagnostic and management strategies, and ensure optimal patient care.

Material and methods

Institutional Review Board (IRB) approval for this study was obtained. A retrospective chart review of all patients with CVFs at our institution was performed. The charts of patients who had recurrent CVF at a different level after treatment for their initial CVF were reviewed to collect the clinical and imaging features (Tab. 2). The successful treatment of their initial fistulas was proved by the absence of the initial CVF upon repeat myelography.

Table 1. Bern SIH score

Feature	Point(s)	Scoring	
Engorgement of venous sinuses	2	≤ 2	Low
Pachymeningeal enhancement	2		
Suprasellar cistern ≤ 4 mm	2	3–4	Intermediate
Subdural fluid collections	1		
Prepontine cistern ≤ 5 mm	1	≥ 5	High
Mamillopontine distance ≤ 6.5 mm	1		

Table 2. Characteristics of initial and recurrent CSF-venous fistula

Age/ /sex	Initial CVF level and side	Treatment	Symptoms improved post--treatment?	Time to symptom recurrence	Follow-up brain imaging findings	Recurrent evel
Current study						
68M	R T5	Embo	Partial	4 w	1 m: partially improved (initial Bern 5 to 3 at follow-up) 3 m: subtle worsening dural enhancement, improved from baseline (Bern 3)	R T7
60F	L T9	Embo	Yes	15 m	3 to 15 m: progressive resolution of dural enhancement and brain sagging (initial Bern 8, then 4 at 3 months, 2 at 12 and 15 months) 19 m: worsening dural enhancement, brain sagging, venous distension (Bern 8)	L T6
78M	R T6	Fibrin Patch	No	10 d	1 m: unchanged (initial Bern 4 and unchanged at follow-up)	R T9
50F	R T7	Embo	Yes	4 m	1 m: partially improved (initial Bern 8, improved to 5)	R T12
					7 m: worsened, still improved from baseline (Bern 6)	
	R T12	Embo	No	Immediately	1 m: partially improved (Bern 5) 7 m: similar to previous (Bern 5)	R T8
Malinzak et al. 2021 [5]						
60F	R T6	Surgery	Yes	3 m	3 m: unchanged	R T5 (6 m)
67M	L T10	Surgery	Yes	5 m	2 m: partially improved 5 m: worsened, subdurals	L T9 (24 m)
56F	L T11	Surgery	Yes	4 m	15 m: partially improved	L T8 (13 m)
51F	L T7	Surgery	Yes	1.5 m	2 m: unchanged	L T10 (10 m)

d — days; F — female; m — months; M — male; R — right; L — left; T — thoracic; w — weeks

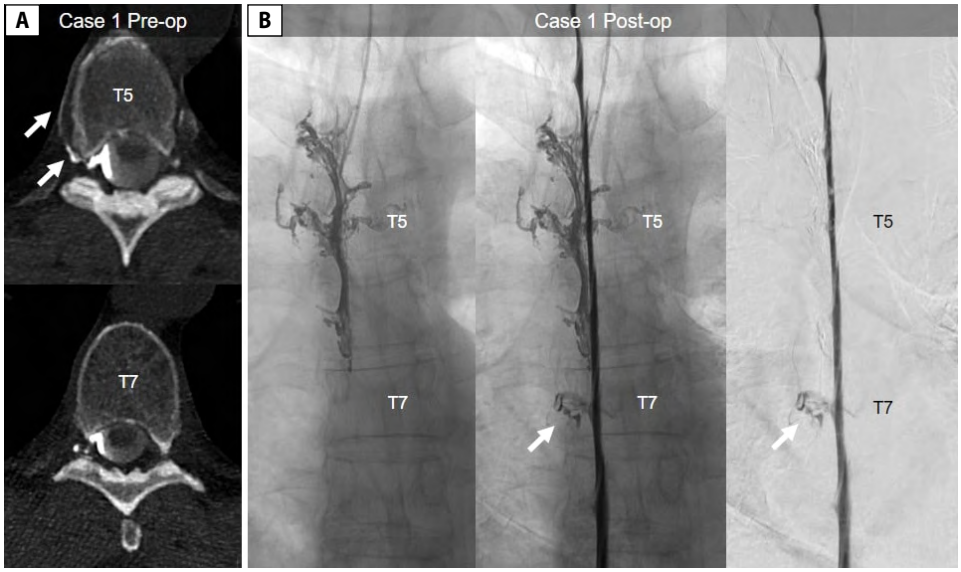

Figure 1. Patient 1. **A.** Pre-embolisation of T5 CVF: right lateral decubitus CTM showing CVF at right T5 (arrow) with no evidence of CVF at right T7 level. **B.** Post-embolisation of T5 CVF: lateral decubitus DSM showing new CVF at right T7 level (arrows) with no evidence of residual leak at embolised right T5 level

Results

A total of 42 patients with CVFs were identified at our institution. After the first treatment, either with fibrin glue/blood patching or transvenous embolisation, 10 patients had residual or recurrent symptoms.

Four of these 10 patients had new CVF at a new level confirmed on myelography, and the details of these four are presented in this research paper.

Five patients had suspected or confirmed residual CVF at the initial level, and one patient had further work-up pending.

Patient 1

A 68-year-old male presented with a 1.5-year history of progressive neck pain, frontal headache, tinnitus, imbalance and photosensitivity that are Valsalva-induced and exacerbated when in an upright position or coughing. Brain MRI showed thick smooth pachymeningeal enhancement, venous distension, and effaced prepontine cistern (Bern score 5). Right lateral decubitus CTM identified a CVF at the right T5 level, treated with transvenous embolisation (Fig. 1). The symptoms improved slightly over four weeks, but gradually returned. Brain MRI four weeks after treatment showed improved but persistent thin pachymeningeal enhancement, improved venous distension, and persistent prepontine cistern effacement (Bern score 3). There was concern for persistent CVF surrounding the embolisation cast, and a transforaminal fibrin glue patch was performed at T5 three months post-embolisation. This however did not improve the symptoms. Repeat brain MRI at five months showed subtly worsened pachymeningeal enhancement without venous distension (Bern score 3); there was a slight increase in pituitary size although the suprasellar cistern remained > 4 mm in height. At eight months post-treatment, lateral decubitus DSM showed new CVF at the right T7 level without residual leak at the previously embolised level at right T5. Additional embolisation of the right T7 CVF resulted in partial improvement of symptoms. A brain MRI four months after the last treatment showed slight improvement in pachymeningeal enhancement and decreased size of the pituitary gland (Bern score 3).

Patient 2

A 60-year-old female presented for evaluation of a 5-year history of orthostatic headaches exacerbated by Valsalva, laughing, and coughing. Brain MRI showed brainstem sagging, pachymeningeal enhancement, venous sinus distension, decreased mamillopontine distance, effaced prepontine cistern, and effaced suprasellar cistern (Bern score 8). Lateral decubitus dynamic CTM showed clear CVF at left T9 level (Fig. 2). Transvenous embolisation resulted in a complete resolution of symptoms. Brain MRI after three months revealed resolution of the pachymeningeal enhancement and venous distension (Bern score 4). At 15 months following the procedure, she experienced recurrence of new daily headaches akin to the ones prior to treatment. A repeat brain MRI at 15 months did not show clear new worsening of SIH features compared to an MRI brain at 1 year post-procedure (Bern score 2). The patient's symptoms however further worsened and follow-up brain MRI 19 months after procedure showed worsening SIH features including recurrent pachymeningeal enhancement, brain sagging, and venous distention (Bern score 8). A lateral

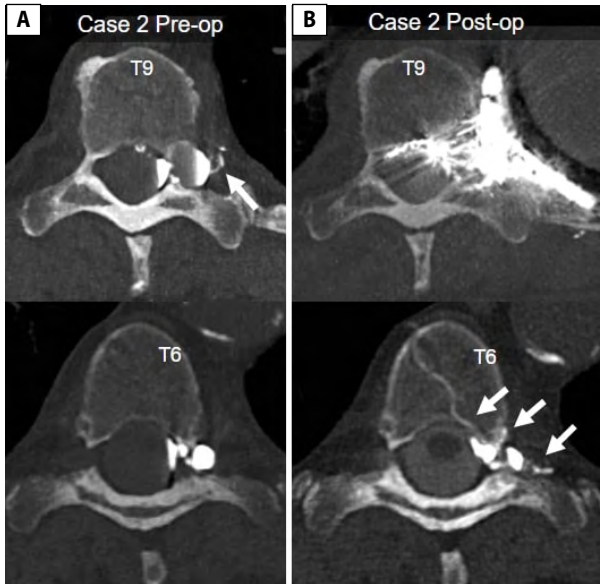

Figure 2. Patient 2. **A.** Pre-embolisation of left T9 CVF: Lateral decubitus dynamic CTM showing left T9 CVF (arrow) with no evidence of CVF at T6 level. **B.** Post-embolisation of left T9 CVF: lateral decubitus dynamic CTM showing new CVF at left T6 level with a connection to basivertebral vein (arrows). Embolisation cast at left T9 also noticed

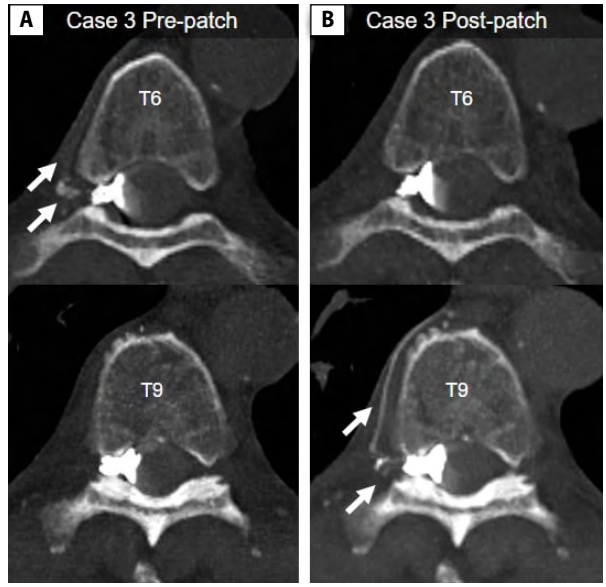

Figure 3. Patient 3. **A.** Pre-patching of right T6 CVF: lateral decubitus dynamic CTM showing CVF at right T6 level before treatment (arrows). **B.** Post-patching of right T6 CVF: lateral decubitus dynamic CTM showing a new CVF at right T9 level (arrows), with no evidence of previously treated CVF at T6 level

decubitus dynamic CTM clearly identified a new CVF at left T6 level with no residual leaking at the previously embolised level at left T9 (Fig. 2). Embolisation of this new CVF was performed, and the patient reported significant improvement of her leak-related headaches, which was sustained at 3-month follow-up. MRI brain at 3-months post-second treatment showed marked improvement with only mild residual reduced mamillopontine and prepontine distances (Bern score 2).

Patient 3

A 78-year-old male presented with new persistent daily bitemporal headaches, most prominent when turning his head briskly from side to side. Brain MRI was significant for diffuse, smooth pachymeningeal thickening/enhancement and right venous sinus distension (Bern score 4). Multiple blood patches yielded only a transient response, and MRI findings were unchanged from the previous exam (Bern score 4). A conventional myelogram performed at another hospital demonstrated potential leak sites at ventral T10-11, and left T3-4. Targeted fibrin glue/blood patching resulted in resolution of the headache, and a follow-up brain MRI showed decreased pachymeningeal thickening (Bern score 4). About three years later, the patient started experiencing similar symptoms. Brain MRI showed worsened, mild, and diffuse dural thickening/enhancement and right venous sinus distension (Bern score 4). Right lateral decubitus dynamic CTM at our institution showed a new right T6 CVF (Figure 3). Two sequential targeted CT-guided epidural blood and fibrin glue patches were performed at right T6. Each however yielded only a transient benefit for 2–3 weeks.

Repeat brain MRI 1.5 months after the second patch showed persistent dural thickening/enhancement and venous distension (Bern score 4). Repeat right lateral decubitus dynamic CTM showed a new CVF arising from the right T9 level (Fig. 3). Notably, the previous right T6 CVF was no longer visualised, indicating successful treatment. The patient responded well to CT-guided right T9 transforaminal epidural fibrin glue patch for only one month. Brain MRI one month post-treatment showed stable smooth dural thickening/enhancement in the supratentorial region with no interval change from the previous study (Bern score 4). According to patient preference, additional fibrin patching has been scheduled.

Patient 4

A 50-year-old female presented with a 3-year history of progressive pressure-like orthostatic headaches associated with neck pain, nausea, vomiting, blurred vision, dizziness, disorientation, muffled hearing, tinnitus and imbalance. Brain MRI showed typical stigmata of SIH: i.e. severe brain sagging, pachymeningeal enhancement/thickening, venous sinus distension, effaced suprasellar cistern, decreased mamillopontine distance, and effaced prepontine cistern (Bern score 8). Lateral decubitus CTM showed CVF at the right T7 level (Fig. 4) which was treated with venous embolisation.This resulted in complete resolution of CSF leak-induced symptoms. Brain MRI showed improvement of pachymeningeal thickening and normal mamillopontine distance (Bern score 5). After four months, she started having orthostatic headaches again, associated with nausea and vomiting. Brain MRI showed

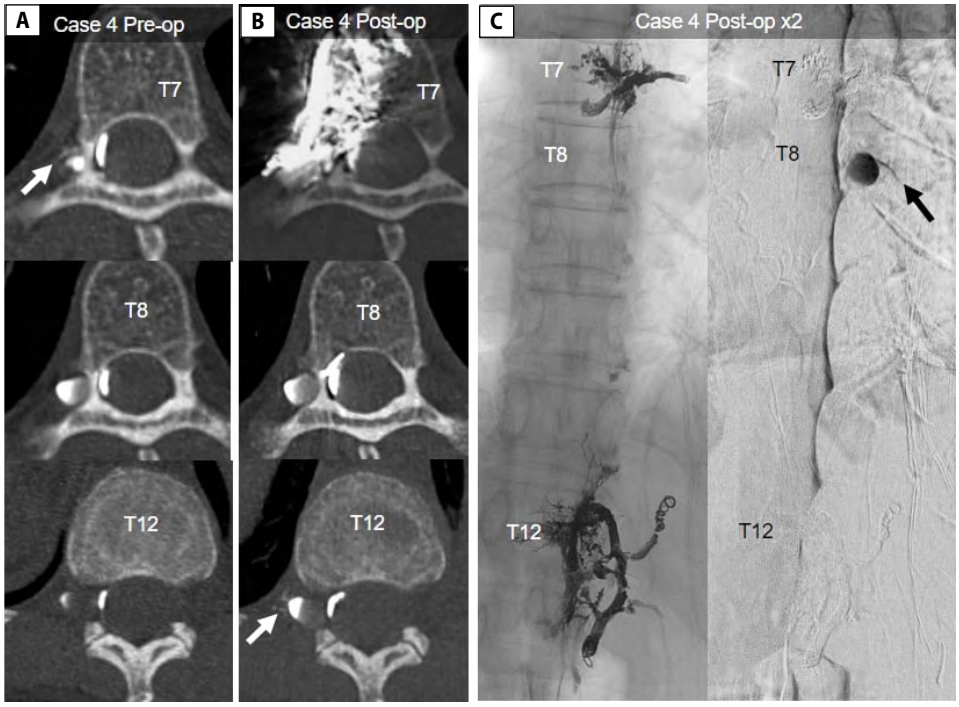

Figure 4. Patient 4. **A.** Pre-embolisation of right T7 CVF: lateral decubitus dynamic CTM showing CVF at right T7 level before treatment (arrow) with no evidence of CVF at right T8 or right T12. **B.** Post-embolisation of right T7 CVF: lateral decubitus dynamic CTM showing a new CVF at right T12 level (arrow). Embolisation cast at right T7 is also noticed. **C.** Post-embolisation of right T7 and T12 CVFs: lateral decubitus DSM showing new CVF at right T8 level (arrow) with embolisation casts seen at right T7 and right T12 levels

recurrence of a reduced mamillopontine distance compared to the previous scan (Bern score 6). Lateral decubitus CTM visualised clear CVF arising at the right T12 level with no residual leaking at the previously embolised level at right T7 (Fig. 4). Embolisation of the new CVF did not result in alleviation of her symptoms, follow-up brain MRI showed normal mamillopontine distance with persistent venous distenion (Bern score 5). A trial of CT-guided right T7 and T12 fibrin glue patch was performed, to which her symptoms responded well, but for only a couple of weeks. Subsequent brain MRI showed persistent venous sinus distension again (Bern score 5). Another lateral decubitus DSM clearly visualised CVF arising at right T8 level (Fig. 4), for which she underwent a CT-guided right T8 fibrin glue/blood patch. No leaking was seen on the previously embolised levels of right T7 and right T12. The symptoms improved for only one week. Six days after the patch, pituitary engorgement and venous distension on brain MRI were persistent with only subtle improvements (Bern score 5).

Discussion

We present four patients with recurrent CSF-venous fistulas, at separate levels from the initially treated fistula, after the effective treatment of the initial fistula by transvenous embolisation or fibrin glue/blood patching. Treatment success of the initial fistula was proven by the absence of the initial CVF upon repeated lateral decubitus myelography. These patients experienced either persistent or recurrent symptoms either shortly after treatment or months or even years afterwards, which prompted a repeat brain MRI followed by myelography. On the initial post-treatment MRI scans, the previously observed abnormal findings were unchanged or improved. We observed that the signs which first responded to treatment were pachymeningeal enhancement/thickening, venous sinus distension, and low mamillopontine distance. Importantly, these signs were also noted to deteriorate or reappear on MRI scans when patients began to manifest recurrent symptoms. In two of the patients, the Bern score exhibited an improvement after successful treatment, followed by a deterioration upon the exacerbation or recurrence of symptoms. This observation could open the doors towards investigating the reliability of the Bern score in identifying recurrent CSF leaks, specifically those related to recurrent CVF, and in guiding subsequent diagnostic steps such as repeat myelography.

In other words, a re-increase in Bern score after initial treatment, or a persistently high Bern score, may prompt consideration for repeat myelography evaluating for the possibility of a new CVF.

Malinzak et al. first documented a series of four cases involving the emergence of new CVFs after the surgical ligation of initial fistulas (Tab. 2). Their findings were similar to ours. The new CVFs were detected at distinct levels from the original ones.

Brain MRI demonstrated either a deterioration or lack of change of abnormal findings when symptom recurrence was reported by the patients. Additionally, during the transient resolution of symptoms following surgical ligation, resolution of pachymeningeal enhancement was documented in two of their patients. They suggested the presence of multilevel fistulous connections between CSF and veins in particular types of CVFs. As a result, the ligation of one connection could potentially prompt other connections to compensate for drainage [5]. Another hypothesis is the plausibility of baseline intracranial hypertension originating from underlying disorders such as Chiari malformation or obstructive sleep apnoea (OSA). This, in turn, might potentiate the development of decompressive CSF leaks. Herein, whenever a leak site is subjected to embolisation, ligation, or patching, a new site of leakage may arise in compensation.

These insights underline the importance of evaluating patients with recurrent leaks for conditions like underlying OSA and other disorders that could potentially increase intracranial pressure.

Clinical implications/future directions

This study demonstrates that new CVFs may underlie patients' reports of persistent or recurrent CSF leak symptoms after initial CVF treatment, particularly when their brain MRI scans show persistent or worsening abnormalities. Repeat myelography may be required in some patients, despite the successful treatment of initial CVFs.

Article information

Data availability statement: *The authors state that original contributions presented in the study are included in the article (and as Supplementary Material, if applicable) and that further inquiries can be directed to the corresponding author.*

Ethics statement: *IRB approval was obtained. Mayo Clinic Institutional Reviewer, IRB#: 21-005449.*

Authors' contributions: *RZ: design of study, data collection, data interpretation and analysis, drafting, revision and approval of final manuscript; OPF: design of study, data collection, data interpretation and analysis, drafting, revision and approval of final manuscript; TJH: design of study, data collection, data interpretation and analysis, drafting, revision and approval of final manuscript.*

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RESEARCH PAPER

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Clinical significance and prognostic value of serum autoantibody tests in multiple sclerosis

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ABSTRACT

Introduction. It is known that multiple sclerosis (MS) often coexists with other autoimmune diseases. Hence, autoantibody (auto-Ab) tests may prove useful in the differential diagnosis of MS. The objectives of this study were to: (a) investigate the prevalence of auto-Ab positivity at the beginning of the MS diagnostic process; (b) assess whether Auto-Ab+ and Auto-Ab- patients differ in baseline clinical, laboratory, and radiological parameters; and (c) investigate the prognostic value during a two-year follow-up period.

Material and methods. This retrospective study consisted of 450 patients aged between 18 and 55 years. All patients underwent a wide range of auto-Ab tests, anti-nuclear antibody (ANA) tests in particular. The expanded disability status scale (EDSS) scores of the patients were recorded at the time of diagnosis and at the end of a two-year follow-up period.

Results. The mean age of the 212 patients, 148 (69.8%) female and 64 (30.2%) male, included in the study sample was 37 ± 10.83 years. The rate of relapsing cases was 84% (178). Oligoclonal band (OCB) was positive in 142 (86.6%) of the 164 tested cases. At least one of the auto-Ab tests was positive in 51 (24.1%) of the cases. ANA test was positive in 21 (9.9%) cases. There was no significant difference between patients with at least one positive auto-Ab test and without any positive auto-Ab test and between ANA-positive and ANA-negative patients in terms of age, gender, clinical features of MS, presence of brain stem lesion, presence of spinal lesion, OCB positivity, level of clinical improvement after the first pulse steroid treatment, family history, presence of comorbidity, presence of autoimmune disease, or EDSS scores recorded at the end of the two-year follow-up period ($p > 0.05$).

Conclusions. Our study findings revealed that Auto-Ab positivity was more common in MS patients than in the general population. However, given their limited contribution to the diagnosis and differential diagnosis of MS with no effect on the prognostic process, auto-Ab tests should be requested only in the event of accompanying autoimmune disease symptoms, and in cases where the diagnosis of MS may be suspected.

Key words: multiple sclerosis, antinuclear autoantibodies, antineutrophil autoantibodies, autoimmunity

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Introduction

The diagnosis of multiple sclerosis (MS) requires not only the demonstration of central nervous system (CNS) demyelinating lesions that spread in space and time, but also the active exclusion of alternative diagnoses [1]. As a rule, an MS diagnosis can be made only if there is "no better explanation" for the clinical condition of the patient. However, the absence of a diagnostic test that can easily distinguish MS from other diseases renders the diagnosis of MS a significant challenge [2]. A number of uncommon inflammatory and non-inflammatory diseases should be considered in the differential diagnosis of MS [2–4].

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Some conditions, e.g. compressive myelopathy, stroke etc, can be easily excluded in the differential diagnosis of MS, whereas others, e.g. neuromyelitis optica spectrum disorder (NMOSD), neurosarcoidosis, Susac syndrome, etc. featuring abnormalities in magnetic resonance imaging (MRI) may strongly indicate an alternative diagnosis, and hence require autoantibody (auto-Ab) tests [3, 5]. It is known that MS predisposes to other autoimmune diseases, possibly due to the increased humoral autoimmune response associated with MS. In this context, biomarkers used in the diagnoses of autoimmune diseases known to accompany MS may be used in the differential diagnosis of MS [6–8].

The use of comprehensive laboratory tests, e.g. anti-nuclear, antiphospholipid, antithyroid and aquaporin antibody tests, has only contributed a little to the differential diagnosis of MS [9, 10]. Anti-nuclear antibody (ANA) is one of the most frequently used autoimmune markers in the differential diagnosis of MS. The rate of MS patients with ANA positivity reported in the literature ranges between 3.6% and 63.5% [7]. Although the clinical significance of the prevalence of ANA positivity in MS patients situation is not yet clear, some studies have stated that ANA positivity is associated with disease activity, while others have reported that ANA positivity will not have a clinical significance unless there are systemic symptoms indicating an underlying connective tissue disorder [11, 12]. Different studies have reported the prevalence of anticardiolipin antibody (aCL) in MS patients of between 4.8% and 44%, and did not find any significant difference between MS patients and healthy controls in this regard. Thus, it has been concluded that aCL was not associated with any clinical features of MS patients or symptoms suggestive of primary antiphospholipid syndrome [13]. The prevalence of anti-Sjögren's syndrome type A (anti-SSA) and type B (anti-SSB) antibodies in MS patients reported in the literature varies between 0–13.3% and 0–1.7%, respectively [14, 15]. The relationship between Auto-Ab positivity and MS disease remains unclear and the positivity for most auto-antibodies is not necessarily specific to a particular autoimmune disease, yet may indicate an increased risk for disease development [16].

In light of the foregoing, the primary objective of this study was to evaluate the benefit of including auto-Ab tests in the initial evaluation of patients with suspected MS who do not have the primary clinical signs indicating other autoimmune diseases. In this context, the secondary objectives of this study were to (a) investigate the prevalence of auto-Ab positivity in the beginning of the MS diagnostic process, (b) assess whether Auto-Ab+ and Auto-Ab- patients differ in baseline clinical, laboratory, and radiological parameters of demyelinating disease, and (c) investigate the relationship between Auto-Ab positivity and disease prognosis during a two-year follow-up period.

Material and methods

The population of this retrospective study consisted of 480 Turkish patients aged between 18 and 55 years who were diagnosed with MS according to the McDonald 2017 criteria [1] and followed up in Sakarya University Education and Research Hospital's MS outpatient clinic. Patient data was obtained from their medical records dated between 2018 and 2022. The patients who underwent immunological tests [ANA, extractable nuclear antigen (ENA) profile (SSA, SSB), antineutrophil cytoplasmic antibodies (ANCA), aCL antibodies, anti-thyroid peroxidase antibodies (anti-TPO), anti-thyroglobulin antibodies (Anti-TG), angiotensin-converting enzyme (ACE), lupus anticoagulant (LA), anti-dense fine speckled-70 antibodies (DFS-70), anti-mitochondrial antibodies (AMA), and rheumatoid factor (RF)] within the scope of the initial diagnostic process prior to the immunomodulator and/or steroid therapy were included in the study. On the other hand, patients who had received corticosteroid or immunomodulatory treatment in the previous three months and patients with missing laboratory tests were excluded from the study. Eventually, the study sample consisted of 212 patients.

The study protocol was approved by the Sakarya University Ethics Committee. Patients' demographic characteristics, family histories, and MS subtype, disease severity, disease duration, oligoclonal band positivity, the presence of brainstem and spinal lesions, response to pulse steroid therapy, and concomitant rheumatological disease data, as well as information on other accompanying diseases, were recorded. All patients were interviewed by a neurologist at three- to six-month intervals in terms of accompanying rheumatological symptoms (including specific questions about arthritis, oral or genital ulcers, alopecia, sicca syndrome, Raynaud's disease, photosensitivity, recurrent abortion and other symptoms that would suggest the presence of other autoimmune diseases) and family history. Laboratory tests were not repeated as there were no associated rheumatological symptoms. The Expanded Disability Status Scale (EDSS) was used to determine the severity of the disease [17]. The EDSS scores of the patients were recorded at the time of diagnosis and at the end of the two-year follow-up period.

All laboratory tests were performed under the same laboratory conditions, using standard methods recommended by the manufacturer. Blood samples were taken in the seated position after 12–14 hours of fasting. Routine biochemical tests were performed by using a Beckman Automatic Analyser at the University of Sakarya Faculty of Medicine's Laboratory of Biochemistry. All samples were evaluated by the STA Analyser (Diagnostica Stago) for aPTT (with STA-CK Prest Kit) and PT (with STA Neoplastin CI Plus Kit). The measurement methods and kit information used in autoantibody tests are given in Table 1. Given its high sensitivity in rheumatic diseases, an ANA titre above 1:100 dilution was accepted as the positive cut-off point.

In MRI examinations, T1 weighted-imaging (WI), T2 weighted-imaging T2-WI and fluid attenuated inversion recovery (FLAIR) sequences were analysed with a 1.5 Tesla MRI device (GE Healthcare, Chicago, IL, US). The MRI

Table 1. Auto-antibody assay methods

Auto-Ab tests	Methods	Kit name, company name, country
ANA	IIF	HEp 20-10, Euroimmun, Germany
Serum ACE	Automated kinetic assay	Commercial kits (SENTINEL, Italy) Autoanalyzer (Beckman Coulter, AU5800, CA, USA)
aCL antibodies	ELISA	Orgentec Diagnostika GmbH, Mainz, Germany
Anti-thyroglobulin	IIF	Euroimmun, Lubeck, Germany
Anti-TPO	IIF	Euroimmun, Lubeck, Germany
ANCA	IIF	Euroimmun, Lubeck, Germany
LA	DRVVT	Staclot Lupus Anticoagulant Kit (Diagnostica Stago)
DFS-70	IIF	Euroimmun, Lubeck, Germany
Anti-SSB	IIF	Euroimmun, Lubeck, Germany
Anti-ENA	IIF	Anti-ENA Profile Plus IgG, Euroimmun, Lubeck, Germany
AMA	IIF	Euroimmun, Lubeck, Germany

ACE — angiotensin-converting enzyme; aCL — anticardiolipin; AMA — anti-mitochondrial antibodies; ANA — anti-nuclear antibody; ANCA — antineutrophil cytoplasmic antibodies; Anti SSB — anti–Sjögren's-syndrome-related antigen B; Anti-TPO — anti-thyroid peroxidase antibodies; Auto-Ab — autoantibody; DFS-70 — anti-dense fine speckled-70 antibodies; DRVVT — dilute Russell viper venom time; ELISA — enzyme-linked immunosorbent assay; ENA — extractable nuclear antigen; IIF — indirect immune fluorescent; LA — lupus anticoagulant; MS — multiple sclerosis

examinations of all patients were evaluated for the presence and distribution of demyelinating lesions in the beginning, and at the end of the six, 12 and 24-month follow-up periods. Radiological findings were interpreted by the same neuroradiologist.

Statistical analysis

Statistical analyses of the collected data were carried out using the SPSS 23.0 (Statistical Product and Service Solutions for Windows, Version 23.0, IBM Corp., Armonk, NY, US) software package. Descriptive statistical methods, i.e. mean and standard deviation, frequency (n), percentage (%) values, were used to express the data. Pearson's chi-squared test was used to compare the categorical data. Kolmogorov-Smirnov test was used to analyse the normal distribution characteristics of the quantitative data. Levene's test was used to evaluate the homogeneity of the data determined to conform to the normal distribution. Student's t-test was used to compare two independent groups featuring homogeneous data. The probability (p) statistics of < 0.05 were deemed to indicate statistical significance.

Results

The study sample consisted of 212 MS patients, 64 (30.2%) male and 148 (69.8%) female. The mean age of the sample was 37 ± 10.83 years. There was no significant difference between the gender-based groups in terms of age ($p > 0.05$). Of the 212 MS patients, 178 (84%) had relapsing-remitting MS (RMS), 27 (12.7%) had secondary progressive MS (SPMS), and seven (3.3%) had primary progressive MS (PPMS). Oligoclonal band (OCB) was not studied in 48 (22.6%) cases. Of the 164 tested cases, 142 (86.6%) were OCB positive and 22 (13.4%) were OCB negative.

The analysis of the MRI data revealed that 114 (53.8%) patients had brainstem lesions and 172 (81.1%) had spinal lesions. Twenty (9.4%) patients had a family history of MS. Of the 200 patients who received pulse steroid therapy, 96 (48%) and 98 (49%) patients had partial and complete clinical improvement, respectively. Six patients did not respond to steroid treatment, and so plasmapheresis was applied in these patients. The most common comorbidity was neuropathic pain which was observed in 17 (8%) patients, followed by restless leg syndrome in 16 (7.5%) patients, depression in 15 (7.1%) patients, thyroid dysfunction and anxiety disorder in nine (4.2%) patients each, epilepsy in five (2.4%) patients, psoriasis in three (1.4%) patients, Behçet's disease in two (0.9%) patients, and diabetes and malignancy in one (0.5%) patient each. There was no significant difference between those with and without at least one comorbidity in mean EDSS scores recorded at the end of the two-year follow-up period (1.23 ± 1.14 vs. 1.17 ± 1.04, respectively; $p = 0.825$).

The number of patients with at least one positive auto-Ab test was 51 (24.1%). Of these patients, 21 (9.9%) had a positive ANA test result. The results of other auto-Ab tests are given in Table 2. There was no significant difference between the patients with at least one positive auto-Ab test and without any positive auto-Ab test in terms of age, gender, clinical features of MS, presence of brainstem lesion, presence of spinal lesion, OCB positivity, level of clinical improvement after the first pulse steroid treatment, family history, presence of comorbidity, presence of autoimmune disease, or EDSS scores recorded at the end of the two-year follow-up period ($p > 0.05$) (Tab. 3). There was also no significant difference between the patients with and without ANA positivity in age, gender, clinical features of MS, presence of brainstem or spinal lesion, OCB positivity, level of clinical improvement after the first pulse

Table 2. Distribution of MS patients by auto-antibody test positivity

Auto-Ab tests	Auto-Ab positive patients (n, %)	Auto-Ab negative patients (n, %)
ANA	21 (9.9%)	191 (90.1%)
Serum ACE	6 (2.8%)	206 (97.2%)
aCL antibodies	1 (0.5%)	211 (99.5%)
Anti-thyroglobulin	13 (6.1%)	199 (93.9%)
Anti-TPO	14 (6.6%)	198 (93.4%)
ANCA	2 (0.9%)	210 (99.1%)
LA	1 (0.5%)	211 (99.5%)
DFS-70	6 (2.8%)	206 (97.2%)
Anti-SSB	1 (0.5%)	211 (99.5%)
Anti-ENA	4 (1.9%)	208 (98.1%)
AMA	1 (0.5%)	211 (99.5%)

ACE — angiotensin-converting enzyme; aCL — anticardiolipin; AMA — anti-mitochondrial antibodies; ANA — anti-nuclear antibody; ANCA — antineutrophil cytoplasmic antibodies; Anti-SSB — anti–Sjögren's-syndrome-related antigen B; Anti-TPO — anti-thyroid peroxidase antibodies; Auto-Ab — autoantibody; DFS-70 — anti-dense fine speckled-70 antibodies; ENA — extractable nuclear antigen; LA — lupus anticoagulant; MS — multiple sclerosis

steroid treatment, family history, presence of comorbidity, presence of autoimmune disease, or EDSS scores recorded at the end of the two-year follow-up period ($p > 0.05$).

Discussion

Nearly a quarter of the MS cases had positivity in at least one of the auto-Ab tests, the most common being ANA positivity. There was no significant difference between the patients with at least one positive auto-Ab test and without any positive auto-Ab test and between patients with and without ANA positivity in any clinical, radiological and 2-year prognostic parameters.

Evaluation of autoantibodies in MS patients is a comprehensive research area subject to ongoing research featuring the complexity underlying the immunological pathways of autoantibodies against CNS structures and serum autoantibodies of other autoimmune diseases [5, 18].

Definitive diagnosis is very important in the context of MS considering the related therapeutic consequences. MS drugs, e.g. monoclonal antibodies, can induce secondary autoimmune processes. Despite the conflicting data in the literature, many studies have shown that autoantibody positivity is higher in MS patients than in the general population [5–7, 11, 12]. Collard et al. [12] determined that MS patients had higher serum ANA levels than the general population, and that 22% of MS patients had elevated serum ANA levels. They attributed ANA positivity to systemic immune dysregulation related to exacerbations in MS and other diseases. Similarly, Spadaro et al. reported significantly higher serum levels of various autoantibodies in MS patients than in the general population (66.6–13.3%). They also reported higher rates of autoantibodies in the progressive phase and during acute exacerbations, indicating the occurrence of a more widespread immune dysregulation in the progressive phase and acute exacerbation periods of the disease. Autoantibody positivity has been shown to be lower in early-onset MS patients than in late-onset MS patients, suggesting a more benign course in early-onset patients [19].

Another study reported a higher frequency of ANA positivity, which was associated with shorter disease duration and lower disability, in MS patients. The effect of ANA on the course of MS remains unclear. However, lower EDSS scores may imply a protective humoral response that prevents neuronal damage resulting in shorter disease durations [7, 20]. Higher rates of antiphospholipid antibody positivity have been reported in MS patients than in the general population. However, no relationship has been found between antiphospholipid antibody positivity and disease severity [13, 21].

In line with the literature data, a higher prevalence of auto-Ab positivity, ANA positivity in particular, was detected in MS patients included in our study than in the normal population. However, there was no significant difference between the patients with at least one positive auto-Ab test in the clinical features of MS, radiological findings, OCB positivity, family history, presence of comorbidity, concomitant autoimmune diseases or 2-year prognosis parameters. No additional autoimmune disease developed in any patient during the follow-up period.

These findings suggest that routine autoantibody testing is not necessary during the initial diagnostic process in all MS patients. Therefore, it would be a more cost-effective approach to subject only those MS patients with atypical clinical-radiological findings to autoantibody tests.

In a study by Dal-Bianco et al. featuring comprehensive analyses similar to this study, ANA, perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), cytoplasmic ANCA (c-ANCA), antiphospholipid antibodies, anti-double stranded deoxyribonucleic acid (anti-dsDNA), extractable nuclear antigens (ENA) and rheumatoid factor (RF) were studied in patients with a definite diagnosis of MS. Consequently, it was found that 18.8% of the MS patients had at least one autoantibody positivity. However, only one patient had an autoantibody-related autoimmune disease. In line with the findings of our study, the authors concluded that autoantibody positivity was not associated with disease activity and thus that the results of the autoantibody tests did not have any effect on the diagnosis of any patient with suspected MS, and that routine application of large autoantibody panel was not cost-effective [22].

In a long-term follow-up study conducted with clinically isolated syndrome type MS patients, there was no significant correlation between ANA positivity and clinical, laboratory and radiological parameters, and also no significant difference between MS patients and the general population in the rate of patients with antibody positivity who developed autoimmune diseases. Thus, they concluded that autoantibody studies are not useful in the absence of clinical findings [11]. In another

Table 3. Distribution of demographic, clinical, radiological and 2-year prognosis data by patients with at least one auto-Ab test positivity and without auto-Ab test

		At least one auto-Ab positivity		p-value
		Present (n = 51) (n, %)	Absent (n = 161)	
Clinical type of MS	PMS	1 (2%)	6 (3.7%)	0.379*
	RMS	46 (90.2%)	132 (82%)	
	SPMS	4 (7.8%)	23 (14.3%)	
Brainstem lesion	+	27 (52.9%)	87 (54%)	0.891*
	–	24 (47.1%)	74 (46%)	
Spinal lesion	+	39 (76.5%)	133 (82.6%)	0.329*
	–	12 (23.5%)	28 (17.4%)	
OCB[1]	Positive	36 (83.7%)	106 (87.6%)	0.571*
	Negative	7 (16.3%)	15 (12.4%)	
Level of clinical improvement after first pulse steroid treatment[2]	Partial	24 (47.1%)	72 (48.3%)	0.876*
	Complete	27 (52.9%)	77 (51.7%)	
Familial MS	+	4 (7.8%)	16 (9.9%)	0.656*
	–	47 (92.2%)	145 (90.1%)	
Comorbidity	+	7 (13.7%)	14 (8.7%)	0.295*
	–	44 (86.1%)	147 (91.3%)	
Gender	Male	17 (33.3%)	47 (29.2%)	0.575*
	Female	34 (66.6%)	114 (70.8%)	
Concomitant autoimmune disease[3]	+	6 (11.8%)	10 (6.2%)	0.191*
	–	45 (88.2%)	151 (93.8%)	

*chi-square test
[1]Patients in whom OCB was not studied were excluded from statistical analyses
[2]Patients who did not receive pulse steroid therapy were excluded from statistical analyses
[3]Patients with Behçet's disease, psoriasis, cancers, and thyroid diseases were included in statistical analyses
Auto-Ab — autoantibody; OCB — oligoclonal band; PPMS — primary progressive multiple sclerosis; RMS — relapsing-remitting multiple sclerosis; SPMS — secondary progressive multiple sclerosis

study conducted with clinically isolated syndrome type MS patients, none of the patients with at least one auto-Ab positivity developed an autoimmune disease during the follow-up period [23]. It has been speculated that ANA and antiphospholipid antibody positivity may be associated with ongoing increased B cell-mediated CNS damage [15]. Nevertheless, the prognosis of the MS patients included in this study did not differ under B and T cell mediated treatments during the follow-up period. In conclusion, the relationship between Auto-Ab positivity and MS disease remains unclear.

The primary limitations of our study are its retrospective design and relatively small sample size. The two-year follow-up period featured may be deemed insufficient in terms of arriving at a conclusion regarding autoimmune disease development or disease prognosis, and thus considered a limitation. The absence of grouping in terms of active attack and remission periods was another limitation. Then again, none of the patients received any immunotherapy during the testing period. The absence of recurrent auto-Ab testing may be deemed another limitation of the study as it renders difficult to comment as to whether the result of the respective auto-Ab test was due to a persistent or to a transient response. The strengths of our study include featuring a rigorous analysis, large autoantibody panels, and correlation analyses with respect to the clinical, demographic, radiological and prognostic data.

Conclusion

In conclusion, our study findings have revealed that Auto-Ab positivity is more common in MS patients than in the general population. However, given their limited contribution to the diagnosis and differential diagnosis of MS with no effect on the prognostic process, auto-Ab tests should be requested only in the event of accompanying autoimmune disease symptoms and in cases where the diagnosis of MS may be suspected.

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Ethical approval: *Approval was obtained from the Ethics Committee of Sakarya University. The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants included in the study. The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.*

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Translation and cross-cultural adaptation of Polish version of Neuropathic Pain Questionnaire (NPQ-PL) and its comparisons with different questionnaires

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ABSTRACT

Aim of the study. The aim of this study was to assess the validity and reliability of the Polish version of the Neuropathic Pain Questionnaire (NPQ-PL), and to compare it to other diagnostic tools.

Clinical rationale for the study. Neuropathic pain is a burdensome condition, of which the exact prevalence is difficult to estimate. During initial screening, pain questionnaires are helpful in alerting clinicians about the need for further evaluation.

Material and methods. The NPQ-PL has been developed following the guidelines for translation and cultural adaptation. A total of 140 patients with chronic pain (ChP), 90 with neuropathic pain (NP), and 50 with nociceptive pain (NoP), were enrolled into this study.

Results. The study group consisted of 60.71% women and 39.29% men; the mean age of patients (standard deviation, SD) was 53.22 years (15.81), and the average NPQ-PL score (SD) was 0.49 (1.27). Statistically significant relationships were found between higher age distribution and greater pain intensity in the NP group compared to the NoP group. There were also significant differences in pain levels between people of different ages, with the predominance in the elderly. Cronbach's alpha coefficient of the whole questionnaire was 0.85 and the intraclass correlation coefficient (ICC) for test-retest reliability was 0.635. Using receiver-operating characteristic (ROC) curve analysis, the area under the curve (AUC) was 0.97 and the best cut-off value was 0.002, which resulted in the highest sensitivity (93.3%) and specificity (96.0%).

Conclusions and clinical implications. The NPQ-PL is a valid tool for discriminating between neuropathic and nociceptive pain. It can be used by physicians of various disciplines when assessing patients with ChP of various origins.

Keywords: ageing, cross-cultural adaptation, neuropathic pain, neuropathic pain questionnaire, nociceptive pain

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Introduction

Neuropathic pain (NP) syndrome rates are fairly high, with an estimated prevalence of 7–10% of the general population [1, 2]. Pain that persists beyond the normal healing time, and usually lasts or recurs for more than 3–6 months, is considered chronic and affects 20% of people worldwide. Chronic NP is classified as one of chronic pain subtypes [3, 4]. Studies have shown a worse prognosis with a higher degree of impairment for patients with NP compared to individuals with nociceptive pain (NoP) [5–7]. Nonetheless, the burden of chronic pain (ChP) should be considered by clinicians, together with

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somatic and mental disorders as well as professional status [8, 9], and family and social environment [10].

Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as: 'pain caused by a lesion or disease of the somatosensory nervous system'. NP cannot be considered as a single disease because it can be caused by multiple mechanisms or have different aetiologies [11]. NP may be clinically characterised by a combination of negative and positive symptoms, and manifests as a constellation of different signs that are determined by different mechanisms. Positive symptoms include abnormal painful sensations (gain-of-function), while negative phenomena usually embrace neurological sensory deficits (loss-of-function) in the painful area and other deficits which are determined by the location of the lesion [12–15].

Clinical rationale for the study

Along with a suggestive patient history, pain questionnaires are useful tools in initial screening to alert clinicians to the need for further evaluation [16, 17]. In a large-scale study conducted in 15 European countries and Israel, the percentage of the total European population using a pain scale was 9%. Poland had one of the lowest rates, at 5% [18].

The objectives of this study were to validate i.e. translate and adapt the Polish version of the Neuropathic Pain Questionnaire (NPQ), as well as to compare this questionnaire to other diagnostic tools. Additionally, we wished to highlight the importance of translation and validation of different scales into other languages, which would be essential in objective assessment in future population studies, as well as in clinical and research settings [19, 20].

Material and methods

A single-centre prospective observational study was designed, accepted and approved by the Ethics Committee of the Medical University of Lublin, Poland (KE-0254/147/2020).

Patients

Eligible patients were identified at referral and asked to participate in the study. All participants received verbal information regarding the study procedures, and provided their written informed consent prior to participation. Further, in order to be enrolled, patients had to meet the following inclusion criteria: (1) age over 18 years; (2) men or women with ChP for ≥ 3 months; and (3) ability to speak and read Polish. Patients were excluded if they had cognitive or communication impairments that precluded administration of the questionnaire, or a history of severe psychiatric disease. Individuals with unidentifiable nerve injury, or pain syndromes associated with diffused pain were also excluded. When patients were doubtful about filling out the survey, the main physician or an assistant explained the content of the questionnaire and/or clarified the type of pain.

Instrument

The original version of the NPQ [21] consists of 12 items selected out of 32 items representing various aspects of pain quality. In this self-report assessment, patients' response to questions pertaining to symptom quality, exacerbating factors, and affective impact is measured. For these descriptors, subjects numerically rate their usual pain on a scale of 0 (no pain) to 100 (the worst pain imaginable) for each item. The obtained results are multiplied by the coefficient of the discriminant function, and then summed up using a given constant value [22]. A result equal to or greater than 0 indicates NP, while scores below 0 denote non-NP [21]. This questionnaire was originally developed in the United States, and provides a sensitivity of 66.6% and a specificity of 74.4%. The authors state that this instrument can be used in initial screening of NP patients, as well as for monitoring their treatment and treatment results [21]. The NPQ has been translated and validated for languages such as Swedish [23], Chinese [24], Turkish [25] and Persian [26], and has achieved quite good measurement properties and a Cronbach's Alpha Coefficient greater than 0.80. In order to conduct a test-retest reliability evaluation, a subgroup of 50 patients (31 with NP and 19 with NoP) completed the NPQ-PL questionnaire for a second time 14–21 days after their enrollment.

Other instruments used in analysis

The self-completed Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) has been developed to identify pain of predominantly neuropathic origin based on the patient's current signs and symptoms. This tool arises from the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire, and unlike the original version does not require sensory testing. The sensitivity and specificity of S-LANSS for the cut-off point of 12 or more were 74% and 76%, respectively [27], while for the Polish version, measured for a cut-off of ≥ 11 points, they were 62% and 77% [28].

The Numerical Rating Scale (NRS) has been used since the 1950s. This tool has sufficient discriminatory power to characterise pain intensity in patients with ChP (non-malignant) [29]. Compared to the Visual Analogue Scale (VAS), the NRS features higher compliance and greater ease of use [30]. To assess the subjective severity of pain during the interview, the authors used an 11-scored NRS, where 0 corresponded to 'no pain' and 10 corresponded to 'the worst pain imaginable'. Participants were asked about their average pain experienced.

The Hamilton Rating Scale for Depression (HRSD) is a 17-variable tool intended to assess a patient's depression symptoms over the past week. In psychotherapeutic and psychiatric research, this scale is considered the gold standard [31, 32]. The HRSD produces the following scores: no depression (0–7); mild depression (8–16); moderate depression (17–23); and severe depression (≥ 24) [33]. For our trial, patients were

assessed once by a single evaluator. The use of this scale was aimed at estimating the impact of neuropathic or nociceptive pain on the appearance of depressive symptoms.

Translation

Permission to translate the NPQ into Polish was granted by Dr Miroslav Bačkonja, who created the original version of this tool. The Polish version of this questionnaire was firstly developed through translation and back-translation. In the first phase, linguistic adaptation was made in order to develop an NPQ-PL. The cross-cultural adaptation was based on the guidelines proposed by Beaton et al. [34]. The procedure involved two forward translations of the original version of the NPQ, performed by independent bilingual translators from different backgrounds, whose mother tongue is the target language. The next step was synthesis of the unified versions of the questionnaire. Then backward translation was made by two professional translators, both philologists unaware of the original versions of the questionnaire. The obtained versions were evaluated and compared to the original tool. Next, the prefinal versions, preserving the original meaning, were tested by patients who filled out a questionnaire and highlighted unclear sentences. All findings were re-evaluated, and the final version, approved and accepted by the scientists involved in the study, is included in this paper. Finally, the definitive Polish version was validated in a clinical setting.

Study design

For the purposes of this study, 140 patients with ChP were invited to complete some questionnaires. Each patient was interviewed and medically examined to assess their type of pain (i.e. neuropathic or non-neuropathic) as well as to collect socio-demographic characteristics. The diagnosis of neuropathic or nociceptive pain was evaluated according to the IASP guidelines. The study was conducted between January 2021 and December 2022 in a single centre, the Independent Clinical Hospital No. 4 in Lublin, affiliated to the Medical University of Lublin, Poland. The NPQ-PL was compared to the Polish version of self-completed S-LANSS, NRS, and HDRS. All obtained results were compared in order to find correlations between the scales.

Statistical calculations

A database was developed using Statistica software (version 13.3, StatSoft, Lublin, Poland). Frequencies and descriptive statistics were examined for each variable. Statistical comparisons were performed between the neuropathic and nociceptive subgroups concerning demographic characteristics and the results of particular questionnaires. The Chi-squared test (χ^2) was used to compare the relationships between variables expressed in the qualitative scale. Statistical differences between nondependent groups were calculated using the nonparametric Mann–Whitney U test.

The Cronbach's alpha (α) coefficient was calculated for this 12-item questionnaire, as well as after removing each of the items. The higher the value obtained, the better the internal consistency of the tool. Good and very good strength of agreement is seen for values of 0.61 to 0.80 and above 0.80, respectively [35]. The Spearman's correlation coefficient (R) [36] was used to calculate the correlations between different scales used and to assess the associations between variables. To determine test–retest reliability, the intraclass correlation coefficient (ICC) with corresponding 95% confidence intervals (CI) between first and second total scores for NPQ was calculated. An ICC value of ≥ 0.75 was considered good, while a value of 0.5-0.75 was considered moderate [37].

The predictive validity was estimated using receiver operator characteristic (ROC) curves. The area under the curve (AUC), known as a measure of the diagnostic power of the test, and its 95% CI for the ROC curve, were calculated. A result exceeding 0.81 is considered as good, and > 0.91 as very good. Also, to maximise the sum of sensitivity and specificity for all the possible values of the cut-off point, the Youden index was calculated [38]. Data expressed on a qualitative scale was presented as the number or mean and standard deviation (SD), percentage of a sample. A value of $p < 0.05$ was set for statistical significance.

Independently from the missing data, if the entire NPQ questionnaire was completed, patients were included in the analysis. Incomplete or unclear data from other questionnaires used was omitted from statistical analysis.

Results

The final version of the NPQ-PL is presented as Supplementary Material. Following the universal guidelines for translation and cultural adaptation, the authors collected quantitative data from the validation process and tried to reach the maximum equivalence between the original and Polish documents.

Clinical and demographical characteristics

A total of 140 patients, 90 with NP and 50 with NoP, were enrolled into this study. Clinical and demographic variables concerning the whole group of patients are set out in Table 1 and Supplamentary Table 1, while Figure 1 sets out detailed data of the NP group. The study group included 60.71% women (n = 85) and 39.29% men (n = 55). The mean age (SD) of patients was 53.22 (15.81). Taking into account division by gender, the age of the patients (SD) was 52.42 (16.44) for women and 54.45 (14.85) for men. There was no significant difference between the sex distribution of the two groups, Pearson's $\chi^2 = 0.35$, $p > 0.05$.

The division of the study group according to the age of the participants was as follows: age 21–40 — 26.43% (NoP 19 and NP 18 subjects), age 41–60 — 36.43% (NoP 19 and NP

Table 1. Clinical and demographic characteristics of total group

		N	%	Mean (SD)
Gender	Male	55	39.29	
	Female	85	60.71	
Group characteristics	NP	90	64.29	
	NoP	50	35.71	
Age	Total	140		53.22 (15.81)
	NP	90		55.82 (15.26)
	NoP	50		48.54 (15.87)
NPQ	Total	140		0.49 (1.27)
	NP	90		1.22 (0.91)
	NoP	50		–0.84 (0.55)
S-LANSS	Total	140		11.30 (7.16)
	NP	90		14.90 (5.45)
	NoP	50		4.82 (4.96)
NRS	Total	140		6.49 (2.27)
	NP	90		7.20 (1.82)
	NoP	50		5.20 (2.43)
HDRS	Total	140		9.14 (7.89)
	NP	90		10.37 (8.04)
	NoP	50		6.92 (7.15)

HDRS — Hamilton Depression Rating Scale; NoP — nociceptive pain group; NP — neuropathic pain group; NPQ — Neuropathic Pain Questionnaire; NRS — Numerical Rating Scale; S-LANSS — self-completed Leeds Assessment of Neuropathic Symptoms and Signs; SD — standard deviation

	Central pain	CIDP	Metabolic neuropathy	Malignant neuropathy	Trigeminal neuralgia	Postherpetic neuralgia	Painful polyneuropathy	Painful radiculopathy	
								Low back pain	Cevical pain
Group size (n)	15	9	17	9	4	3	8	20	5
Age (±SD) [years]	51.93 (12.24)	58.22 (13.26)	60.29 (17.57)	68.56 (8.31)	56.75 (7.89)	53.33 (14.84)	55.13 (13.79)	50.50 (15.84)	48.20 (22.52)
Gender (F/M)	8/7	4/5	12/5	5/4	3/1	2/1	4/4	11/9	4/1
Symptoms duration (±SD) [months]	37.53 (42.97)	49.11 (26.61)	78.35 (92.28)	21.44 (37.46)	24.50 (28.20)	12.33 (10.21)	36.86 (57.73)	53.00 (86.36)	8.00 (4.06)

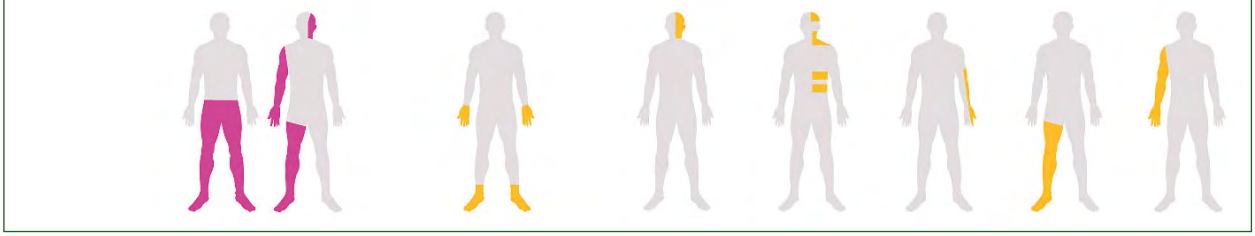

Figure 1. Detailed data on NP group. CIDP — chronic inflammatory demyelinating polyneuropathy; F — female; M — male; SD — standard deviation

32 subjects), and age 61+ — 37.14% (NoP 12 and NP 40 subjects). A significant relationship was found between the age distribution of the NP and NoP groups, $\chi 2 = 7.61$, $p < 0.05$. This may be related to the higher age of patients with NP. Also, using Yates's $\chi 2$ test, a significant difference was found in the occurrence of NP according to the NPQ-PL between the NP and NoP groups, $\chi^2 = 104.52$, $p < 0.001$.

Cronbach's α coefficient, test-retest reliability, and ROC/reliability and validity

The NPQ-PL showed very good reliability, with a value of the Cronbach's α coefficient of 0.85. As a result of the division into NP and NoP, the Cronbach's α coefficients were 0.74 and 0.73, respectively. Cronbach's α coefficient was also calculated after removing individual items from

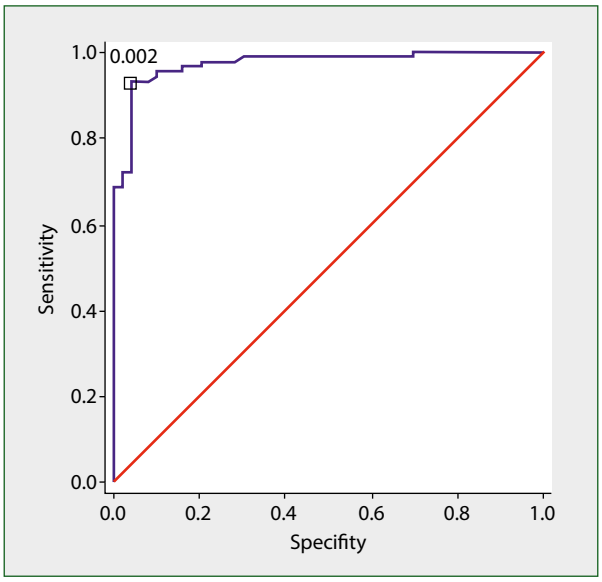

Figure 2. Polish version of Neuropathic Pain Questionnaire receiver operating characteristic curve

NPQ-PL comparisons with different questionnaires/construct validity

NPQ-PL and S-LANSS

In the NP group, there was no significant difference between the assessment of NP using the S-LANSS questionnaire and the assessment of NPQ-PL. For this data, the results are very consistent, Yate's $\chi^2 = 1.00$, $p > 0.05$. Similarly to the results for NPQ-PL ($p < 0.001$), according to the S-LANSS questionnaire, a significant difference in the occurrence of NP was found between the NP and NoP groups, $\chi^2 = 50.89$, $p < 0.001$.

NRS

There was no significant difference in the intensity of pain between women and men, $\chi^2 = 0.18$, $p > 0.05$. However, there were significant differences in pain levels between people of different ages, $\chi^2 = 11.83$, $p < 0.05$. This means that greater intensity of pain is more common in older patients (Suppl. Tab. 3) and/or that the pain sensation or intensity may increase with age. Also, the NP group reported significantly greater pain intensity compared to the NoP group; data are shown in Supplementary Table 4, $\chi^2 = 23.37$, $p < 0.001$.

Table 2. Correlations between NPQ-PL and S-LANSS, NRS and HDRS

	R		
	S-LANSS	NRS	HDRS
NPQ-PL NP group	0.39*	0.20	0.09
NPQ-PL NoP group	0.26	0.44*	–0.01

HDRS — Hamilton Depression Rating Scale; NoP — nociceptive pain; NP — neuropathic pain; NPQ-PL — Polish version of Neuropathic Pain Questionnaire; NRS — Numerical Rating Scale; R — Spearman's rank correlation coefficient (* $p < 0.001$); S-LANSS — self-completed Leeds Assessment of Neuropathic Symptoms and Signs

the scale. In the case of the NP group, the exclusion of item numbers 4 (numbness), 7 (squeezing pain), and 8 (freezing pain) increased the reliability of Cronbach's α by 0.75, 0.75, and 0.76, respectively.

Reproducibility of the results was assessed using ICC, which ranges from 0 to 1. The closer the score is to 1, the more reliable the scale. The ICC value for the NPQ-PL was 0.635, which equates to moderate reliability. The NPQ-PL demonstrated outstanding diagnostic ability, with an AUC of 0.97. The ROC curve analysis identified a score of 0.002 as the best discriminating cut-off value betweetn NP and NoP (Fig. 2). This consistently resulted in the highest sensitivity (93.3%) and specificity (96.0%) of this translated version of the 12-item questionnaire.

Psychometric properties of NPQ-PL

The average NPQ-PL score (SD) was 0.49 (1.27) (Tab. 1), dividing the group into NP and NoP, the results being 1.22 (0.91) and –0.84 (0.55), respectively. Noteworthy is the slightly higher result of women compared to men (Suppl. Tab. 1). Mean scores (SD) for each response, divided into NP, NoP and the entire group, are presented in Supplementary Table 2.

Correlations between NPQ-PL and different scales used in study

The Spearman correlation coefficient (R) was calculated separately for the NP and NoP groups. The NP scores were reasonably correlated with the S-LANSS ($R = 0.39$, $p < 0.001$) but poorly correlated with NRS and HDRS ($R = 0.20$ and $R = 0.09$, respectively). The NoP scores revealed a statistically significant, fairly positive, correlation with the NRS ($R = 0.44$, $p < 0.001$; Tab. 2).

Discussion

Obtaining the most accurate assessment of the prevalence of NP, despite the continual development of research and increasing awareness, still requires a great deal of effort. The best current estimates come from studies using validated questionnaires [1, 39]. However, these instruments only detect pain at the level of 'possible NP' [16, 40]. Some authors have claimed that, regardless of the validation of the tools in the conditions of a pain clinic, their predictive value remains unknown and may overestimate the results for the general population [5]. Nevertheless, due to their ease of use and simplicity, their use in everyday clinical practice as a screening tool [41] is undeniably advantageous.

This study has demonstrated the good reliability and validity of the Polish version of the NPQ in distinguishing between neuropathic and nociceptive types of ChP. Our analysis also showed high sensitivity and specificity of the questionnaire, as well as good internal consistency of the test measured by Cronbach's α of 0.85. This result is comparable to the results revealed by previous versions of language adaptations [24–26]. Reproducibility of the questionnaire by using the ICC value has been calculated in Persian [26] and Turkish [25] versions, and demonstrated good test-retest reliability (ICC value of ≥ 0.75). This result may be related to the earlier retest time (the test was repeated after three days in both cases) compared to our study.

In the original version of the questionnaire, the authors reported that the sensitivity and specificity of NPQ were 66.6% and 74.4%, respectively [21]. We obtained results of 93.3% and 96.0%, respectively, which is higher than that reported in previous studies [23, 24, 26]. Despite the availability of questionnaire formats for self-completion by the patient, we decided to conduct an interview completion of the questionnaires, taking into account only patients with ChP. We suppose that this contributed to the high accuracy of our obtained results. A similar phenomenon was observed in the validation of the S-LANSS [27], in which the authors compared unaided completion to interviewed completion of the questionnaire. We did not compare self- and assisted formats in our patients, with the expectation that the self-completion format would be used in epidemiological studies. Additionally, features shared by NPQ and S-LANSS questionnaires, therefore symptoms such as prickling, tingling, hot or burning sensations, or pain evoked by a light touch [42], may account for the consistency between these tools.

On the other hand, patients with mixed pain syndromes were also included in our study, which may have influenced the results. Mixed pain is a condition which is still poorly defined and clinically manifests as a combination of the different types of pain, such as neuropathic, nociceptive and nociplastic, which act simultaneously, concurrently and/or overlap [43, 44]. The diagnosis of mixed pain is based on a detailed history-taking, physical examination, and clinical evaluation, rather than fulfilling diagnostic criteria. Therefore, this diagnosis still seems demanding. Nevertheless, it is allowed to use validated screening instruments to detect the presence of NP component [44]. Many studies have excluded patients with mixed pain conditions from their analysis, and research that has included these patients has not had consistent results regarding changes in specificity and/or sensitivity, thereby limiting the generalisability of the results [45].

The results of our study showed a positive Spearman's correlation between the NP group and the S-LANSS, as well as between the NoP group and the NRS ($p < 0.001$), although there is little data available on correlation of the NPQ with other questionnaires. Yurdakul et al. [25], using the Pearson correlation test (r), correlated the total NPQ score with the NRS and LANSS, obtaining a moderate correlation with the NRS ($r = 0.43$, $p < 0.001$), and a high correlation with the LANSS ($r = 0.64$, $p < 0.001$). Regarding the latter, there are many common verbal descriptions in both questionnaires, which may be responsible for the high level of correlation. Another Turkish study investigated the relationship between LANSS, S-LANSS, VAS and NPQ [46]. Statistically significant concordances ($p < 0.01$) were found on S-LANSS total scores and all NPQ items, except for items 3, 4 and 7 ($p > 0.05$). Perhaps this fact coincides with the very good validity and reliability of the questionnaire; the sensitivity and specificity of the scale were 98% and 97% respectively.

The statistically significant positive correlation between the NRS and NoP groups may indicate a better interdependence between the NRS questionnaire and NoP. Nonetheless, most patients with NoP experienced moderate pain (NRS 4–7), while the NP group declared significantly higher pain intensity (Suppl. Tab. 4). Reports on this proposal are controversial, since some studies have confirmed these findings and others have not [47, 48]. Older patients not only suffered from NP more often, but also had greater pain intensity. An assessment of the prevalence of NP in the elderly is difficult, and often in fact impossible, due to the impairment of cognitive functions or communication difficulties of patients [49]. Consistent with our results, demographic data on the older age of patients with NP compared to NoP was also obtained by Dworkin et al. [50], who also reported different pain symptoms in both groups. Sharp and dull pain was noted in NoP patients, while pain quality was rated as hot, cold, itchy or tender in NP patients. Perhaps these differences may explain positive correlations between NoP and the NRS.

Some researchers have reported that the elderly tolerate acute pain better than persistent pain, which may be due to lower pain perception and/or an augmented pain threshold. In ChP, weaker outcome may be associated with poorer emotional pain processing, independent of a decrease in the pain sensitivity [51]. An important role may also be played by age-related changes in the functioning of endogenous mechanisms of pain inhibition [52, 53]. Both an elevated pain threshold and impaired inhibitory mechanisms contribute to later activation and insensitivity in the elderly. Nevertheless, over time, appraisal processes (such as compensatory mechanisms or reduced functional connectivity) and dysfunction of pain modulation processes may escalate and result in increased pain perception [52].

In our study, NP was also associated with depression. As shown in the tables, patients with NP had a higher rate of depression than patients with NoP. In addition, women's scores were slightly higher than men's. However, these differences are not significant. It is worth mentioning that in the NP group, of 53 women surveyed, only 25 (47%) did not have symptoms of depression, while 23 (43%) suffered from moderate, severe, or very severe depression. The same data applied to 38% of men and 42.5% of patients over 61 years of age. This confirms

previous data on the co-occurrence of depression and ChP [54] and its higher incidence in females [55]. By limiting the data on comorbidity to the group of elderly patients, they indicate that up to 13% of individuals comorbid high depressive symptom and chronic activity-limiting pain [56]. On the other hand, the comorbidity rate of NP and depression has been estimated at circa 30% [57]. This remains an important issue to consider and treat for any patient with NP or ChP, because pain increases the severity and frequency of depression symptoms [58], and this effect appears to be bidirectional [59].

Our results should be interpreted with some caution due to the limitations of our study. The inclusion of patients with mixed pain conditions may affect the psychometric properties and conclusions of the research. Also, the fact that we included only patients with ChP might limit the usefulness of the questionnaire. It is also undeniable that screening tools cannot be used as the diagnostic gold standard, which leads to a limitation of their use.

Clinical implications/future directions

To the best of our knowledge, our study is the first cross-cultural adaptation of NPQ for the Polish population. We have demonstrated that our translated version of NPQ is reliable and valid for use, has very good psychometric properties, and good internal consistency.

We believe that this tool will be of benefit to physicians of various specialisms when assessing patients with diverse types of pain, as well as in research settings.

The next step would be to use the self-completion format in epidemiological studies or to compare the use of the questionnaire in acute NP patients to that in chronic NP patients. Also, a multicentre epidemiological survey on the prevalence of NP and depression in ageing populations could provide valuable information.

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External quality monitoring facilitates improvement in already well-performing stroke units: insights from RES-Q Poland

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ABSTRACT

Introduction. The Registry of Stroke Care Quality (RES-Q) is used in Poland for quality monitoring by numerous hospitals participating in the Angels Initiative. Our aim was to assess the degree of improvement in highly stroke-oriented centres that report cases to the RES-Q each year.

Material and methods. This retrospective analysis included Polish stroke units that from January 2017 to December 2020 contributed to the RES-Q at least 25 patients annually.

Results. Seventeen out of 180 Polish stroke units reported patients each year (2017, n = 1,691; 2018, n = 2,986; 2019, n = 3,750; 2020, n = 3,975). The percentage of ischaemic stroke patients treated with alteplase remained stable (26%, 29%, 30% and 28%, respectively). The door-to-needle time progressively decreased, from a median 49 minutes to 32 minutes. The percentage of patients treated ≤ 60 minutes and ≤ 45 minutes significantly increased (from 68% to 86% and from 43% to 70%, respectively), with no change observed between 2019 and 2020. Despite a general improvement in dysphagia screening (81%, 91%, 98% and 99%), screening performed within the first 24h from admission became less frequent (78%, 76%, 69% and 65%). In-hospital mortality significantly increased (11%, 11%, 13% and 15%), while the proportion of patients discharged home remained stable.

Conclusions. Quality-oriented projects facilitate the improvement of stroke care, even in centres demonstrating good baseline performance. Polish stroke units that consistently reported cases to the RES-Q demonstrated improvement in terms of door-to--needle time and dysphagia screening. However, there is still a need to shorten the time to dysphagia screening, and carefully monitor stroke unit mortality following the COVID-19 pandemic.

Keywords: acute stroke, quality monitoring, stroke care management, outcome, registry, Poland

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Introduction

Stroke is a leading cause of death and disability worldwide [1]. In Poland, the annual number of acute ischaemic stroke admissions ranges from 70,000 to 74,000 [2]. Ischaemic strokes constitute over 80% of all stroke cases, making them potentially eligible for highly effective reperfusion therapies [3–5]. The efficacy of intravenous thrombolysis and mechanical thrombectomy is very time-sensitive [3–5]. Achieving the shortest possible door-to-needle and door-to-groin times requires optimisation of logistics not only from neurologists but also from the ambulance service, Accident & Emergency Department personnel, and radiologists [3–8]. An example from Czechia proves that the national recombinant tissue plasminogen activator (rtPA) rate can exceed 20% of all ischaemic strokes, with a median door-to-needle time of 20 minutes [6].

Stroke care extends beyond the hyperacute phase and encompasses a well-functioning stroke unit, access to rehabilitation, and long-term outpatient care. Therefore, optimising and coordinating the entire chain of care is essential from a public health perspective. This poses a major challenge for each national healthcare system, which has been properly addressed in the Stroke Action Plan for Europe (SAP-E) 2018–2030 [9]. This approach aligns with the objectives of the Angels Initiative, an international stroke improvement programme endorsed by the European Stroke Organisation (ESO) and the Cerebrovascular Section of the Polish Neurological Society (CSPNS) [10].

Both the ESO and the CSPNS strongly support the implementation of registries, considering them to be a powerful tool (i) to confirm that the evidence from randomised controlled trials is transferable to routine services, (ii) to address questions that could never be tested in a randomised setting, and (iii) to measure actual stroke care quality [9].

The core features of a stroke registry, such as having a clear purpose, limiting the number of items to the necessary minimum, and a long lifespan, were defined over 50 years ago and continue to be relevant today [11]. The key performance measures for modern national stroke care quality programmes were agreed upon in 2014 [12]. These measures formed the foundation for the development of the international Registry of Stroke Care Quality (RES-Q) [13]. The RES-Q has gained increasing global recognition as a free-to-use tool for identifying gaps in hospital processes and facilitating their subsequent optimisation [14–19]. For reasons of feasibility, the RES-Q in its original version consciously refrained from capturing detailed information about clinical outcomes, especially the long-term functional outcomes. In Poland, the registry was introduced in 2017 through the collaborative efforts of the CSPNS and the Angels Initiative [14].

Clinical rationale for the study

To maximise the likelihood of delivering the best healthcare services, it is necessary to ensure: (i) feedback and transparency; (ii) intervention sustainability; (iii) adherence to clinical practice guidelines; (iv) productive partnerships; and (v) a whole-team approach. These strategies work together synergistically and rely on reliable evidence obtained from non-opportunistic registries [21].

Within the Polish healthcare system, it is obligatory to report every acute stroke case directly to the electronic registry run by the National Health Fund (NHF) immediately after discharge from the stroke unit. However, the registry's data completeness is below the optimal level, accounting for c.70% of all eligible cases in 2020–2021 [2]. Nonetheless, the registry still serves as a valuable tool for NHF analysts to identify gaps in stroke care quality, assess overall performance, and provide assistance to policymakers [2].

In addition to being a valuable resource for research purposes, the national stroke registry holds the potential to enhance local stroke care quality [20]. However, in order to facilitate improvement in an individual hospital or at the regional level, the registry must provide convenient access to up-to-date and processed information to all relevant stakeholders, including individual hospitals, PNS, and Regional Consultants in Neurology [21, 22]. The RES-Q fulfills these requirements by offering features such as the ability to monitor one's own performance through user-friendly graphical presentation, and to benchmark against national averages. It is important to note that there is considerable overlap between the data collected in the RES-Q and the data that has been required for the NHF registry since 2020.

Previous analyses of the Polish RES-Q data showed that the registry is likely to exhibit a bias towards well-performing centres, and therefore cannot be considered fully representative of the general population. Nonetheless, it remains a valuable source of information for individual hospitals in their pursuit of quality improvement programmes [14].

The aim of our study was to indirectly investigate the usefulness of the RES-Q in supporting quality improvement programmes in stroke-oriented and well performing Polish hospitals, by assessing the overall degree of improvement captured in the RES-Q data from 2017 to 2020.

Material and methods

This retrospective analysis included all stroke patients reported to the RES-Q registry by Polish stroke units from January 2017 to December 2020, provided that a stroke unit contributed at least 25 patients each year. The methodology of the RES-Q has been described in detail elsewhere [23]. Briefly, the RES-Q is an open-access registry capturing major performance measures of a single stroke unit that voluntarily reports series of cases with acute stroke or transient ischaemic attack. Over the years, the registry has evolved and currently includes items describing neurological and functional outcomes, both at discharge from the stroke unit and three months after stroke. However, this data was not collected throughout the whole studied period. Patients with the final diagnosis of a transient ischaemic attack were excluded from analysis so as to reduce heterogeneity.

The key metrics of interest were grouped into three domains. As the major measures of performance, we used (i) the proportion of patients receiving intravenous thrombolysis, or (ii) any acute reperfusion therapy, (iii) door-to-needle time (DNT), and (iv) early dysphagia screening. As the major measures of proper secondary prevention, we used the proportions of stroke survivors who at discharge from the stroke unit received (i) antihypertensives, (ii) statins, (iii) oral anticoagulants in cases of atrial fibrillation, (iv) advice about smoking cessation in cases of being an active smoker, and (v) were recommended to see a stroke specialist for follow-up. The main safety measure was stroke unit mortality.

This study was conducted in accordance with the Declaration of Helsinki. Due to its observational character and the anonymisation of data, approval from the Ethics Committee and additional consents were not required.

Data supporting the findings is available from the corresponding author upon reasonable request.

Statistical analysis

Categorical variables are reported as the number of valid observations, and proportions are calculated with exclusion of unknown values from the denominator. Continuous variables are presented as a median with an interquartile range (1st quartile to 3rd quartile, Q1–Q3) due to the non-normal distribution.

Comparisons were made initially using the overall chi-square test or Kruskal-Wallis test to identify the presence of intergroup differences in the whole study population. Only if the overall tests were significant, pairwise comparisons between particular years were attempted. For that purpose, the chi-square test, or the two-tailed exact Fisher's test, or the Mann-Whitney U test was used, as appropriate. As the annual samples from individual centres could be small and biased by patient selection, we limited intra-centre and inter-center comparisons.

All tests were two-sided, and $P < 0.05$ was considered statistically significant. Calculations were carried out using STATISTICA 13.3 software package (TIBCO Software Inc., Palo Alto, CA, USA).

Results

Seventeen of 180 Polish stroke units reported patients each year (2017, n = 1,691; 2018, n = 2,986; 2019, n = 3,750; 2020, n = 3,975) (Suppl. Tab. 1). Overall, there were no significant changes in patient age (median 72 to 73 years) or in the proportion of ischaemic strokes (89% to 91%) (Table 1). Despite significant fluctuations, the occurrence of atrial fibrillation (AF) did not change between 2017 and 2020 (Table 1). Fluctuations were also observed in the proportions of patients with diagnosed AF prescribed with oral anticoagulants at discharge (77%, 83%, 79%, and 74%). The prescription rates for statins and the use of antihypertensives were very high throughout the whole study period (Table 1). The proportion of active smokers significantly decreased (from 28–30% to 20–21%) alongside an increase in providing advice about smoking cessation for stroke survivors (from 72–79% to 89–85%) (Table 1).

Table 1. Overall changes in patient characteristics and stroke care quality indicators 2017 to 2020

	2017 (n = 1,691)	2018 (n = 2,986)	2019 (n = 3,750)	2020 (n = 3,975)	Overall P	17 v. 18	17 v. 19	17 v. 20	18 v. 19	18 v. 20	19 v. 20
Demographics											
Male sex, n (%)	815/1,691 (48.2)	1,531/2,986 (51.3)	1,921/3,750 (51.2)	1,887/3,975 (47.5)	**0.001**			+		+	+
Age (years), median (Q1; Q3)	72 (63; 82)	72 (64; 82)	73 (64; 82)	73 (65; 82)	**0.101**						
Active smokers, n/N (%)	474/1,692 (28.0)	906/2,986 (30.3)	784/3,747 (20.9)	778/3,975 (19.6)	**< 0.001**		+	+	+	+	
Current stroke											
Ischaemic stroke, n/N (%)	1,527/1,691 (90.3)	2,717/2,986 (91.0)	3,351/3,750 (89.4)	3,582/3,975 (90.1)	0.169						
Brain CT within 60 minutes of admission, n/N (%)	1,478/1,676 (88.2)	2,733/2,963 (92.2)	3,470/3,644 (95.2)	3,675/3,834 (95.9)	**< 0.001**	+	+	+	+	+	
NIHSS at admission, median (Q1; Q3)	7 (4; 13)	7 (4; 13)	7 (4; 14)	8 (4; 15)	**< 0.001**		+	+	+		
Reperfusion therapy for ischaemic stroke, n/N (%)	406/1,527 (26.6)	794/2,717 (29.2)	1,104/3,351 (33.0)	1,245/3,582 (34.8)	**< 0.001**		+	+	+	+	
Intravenous thrombolysis for ischaemic stroke, n/N (%)	399/1,527 (26.1)	785/2,717 (28.9)	1,002/3,351 (29.9)	1,014/3,582 (28.3)	0.055		+				
Mechanical thrombectomy, n/N (%)	10/1,527 (0.7)	31/2,717 (1.1)	150/3,351 (4.5)	317/3,582 (8.8)	**< 0.001**		+	+	+	+	+
Door-to-needle time (min), median (Q1; Q3)	49 (35; 74)	40 (25; 60)	34 (20; 50)	32 (20; 50)	**< 0.001**	+	+	+	+		
Door-to-needle time ≤60 min, n/N (%)	263/387 (68.0)	594/773 (76.8)	875/996 (87.9)	868/1,013 (85.7)	**< 0.001**	+	+	+	+	+	
Door-to-needle time ≤45 min, n/N (%)	168/387 (43.4)	445/773 (57.6)	715 (71.8)	710/1,013 (70.1)	**< 0.001**	+	+	+	+	+	
Dysphagia screening at any time, n/N (%)	1,354/1,676 (80.8)	2,696/2,952 (91.3)	3,615/3,689 (98.0)	3,897/3,920 (99.4)	**< 0.001**	+		+	+	+	+
Dysphagia screening within first 24 hours, n/N (%)	1,324/1,691 (78.3)	2,268/2,986 (76.0)	2,569/3,750 (68.5)	2,573/3,975 (64.7)	**< 0.001**		+	+	+	+	+
Stroke unit stay (days), median (Q1; Q3)	10 (8; 14)	9 (8; 12)	9 (8; 13)	9 (8; 12)	**< 0.001**	+	+	+			
Secondary prevention											
Atrial fibrillation, n/N (%)	472/1,532 (30.8)	837/2,788 (30.0)	1,039/3,609 (28.8)	1,270/3,975 (32.0)	**0.026**						+
Anticoagulant for atrial fibrillation at discharge in survivors, n/N (%)	266/346 (76.9)	551/661 (83.4)	679/862 (78.8)	756/1,020 (74.1)	**< 0.001**	+			+	+	+
Antihypertensive at discharge in survivors, n/N (%)	1,324/1,496 (88.5)	2,263/2,561 (88.4)	2,852/3,188 (89.5)	2,971/3,214 (92.4)	**< 0.001**			+		+	+
Statin at discharge, n/N (%)	1,328/1,401 (94.8)	2,396/2,455 (97.6)	2,806/2,933 (95.7)	2,911/3,037 (95.9)	**< 0.001**	+			+	+	
Advice about smoking cessation for surviving smokers, n/N (%)	291/407 (71.5)	650/819 (79.4)	605/676 (89.5)	594/697 (85.2)	**< 0.001**	+	+	+	+	+	+
Recommended follow-up by a stroke specialist in survivors, n/N (%)					**< 0.001**				+	+	+
– visit advised and scheduled	NA	49/628 (7.8)	510/1,943 (26.3)	444/3,372 (13.2)							
– visit advised only	NA	20/628 (3.2)	527/1,943 (27.1)	2,487/3,372 (73.8)							
Stroke outcome											
Stroke unit death, %	191/1,691 (11.3)	329/2,986 (11.0)	491/3,750 (13.1)	603/3,975 (15.2)	**< 0.001**			+	+	+	+
Discharge destination in survivors					**< 0.001**		+	+	+	+	+
– patient's home	991/1,500 (66.1)	1,721/2,657 (64.8)	2,253/3,259 (69.1)	2,308/3,372 (68.5)							
– other ward in same hospital	311/1,500 (20.7)	608/2,657 (22.9)	604/3,259 (18.5)	431/3,372 (12.8)							
– another hospital	74/1,500 (4.9)	134/2,657 (5.0)	203/3,259 (6.2)	446/3,372 (13.2)							

CT — computed tomography; NIHSS — National Institutes of Health Stroke Scale + indicates significant differences in year-to-year pairwise comparisons

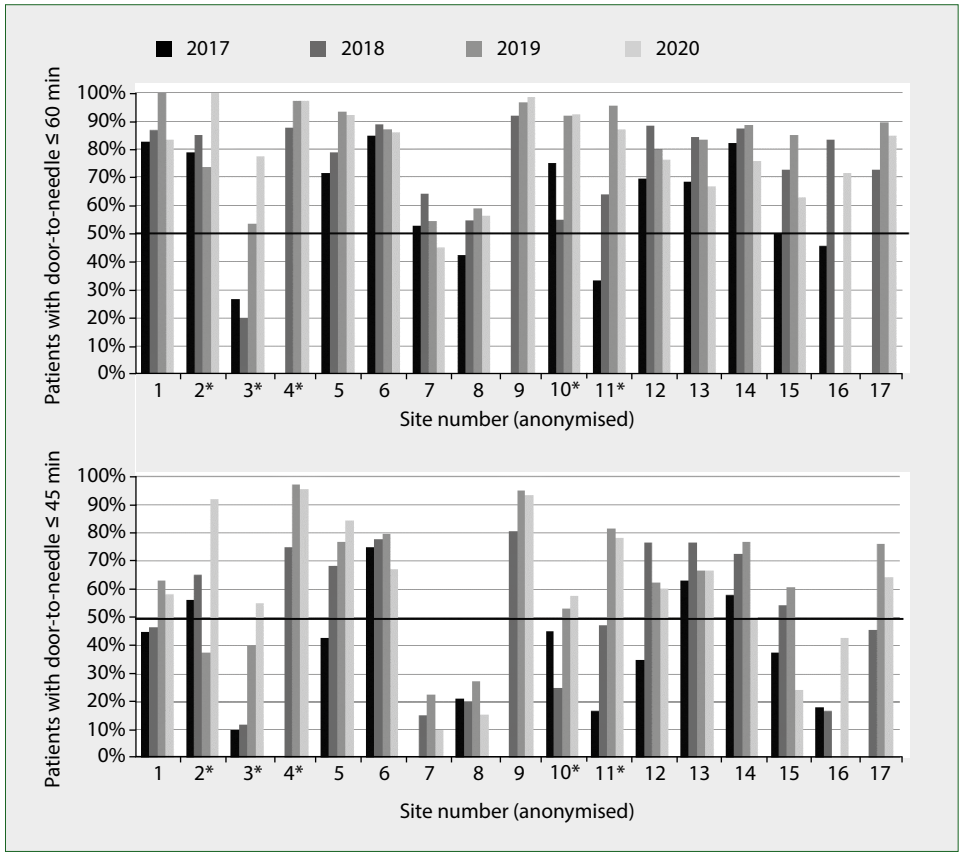

Figure 1. Changes in door-to-needle time in individual hospitals from 2017 to 2020
*overall p value within one site < 0.05
Site numbers are not related to the order of co-authors

The thrombolysis rate remained stable (ranging from 26% to 30%), but with marked hospital-to-hospital variability (Table 1, Suppl. Tab. 1). However, the overall use of reperfusion therapy became more frequent (from 27% to 35%), especially in the case of mechanical thrombectomy (from 0.7% to 9%). There was also a gradual and significant improvement in DNT (from a median of 49 min to 32 min) (Table 1). Significantly more patients received rtPA with door-to-needle time of ≤ 60 minutes and ≤ 45 minutes (from 68% to 86% and from 43% to 70%, respectively), with a marked variability between hospitals, but no overall decrease between 2019 and 2020 (Table 1, Figure 1).

There was a significant increase in the proportion of patients undergoing formal screening for dysphagia at the stroke unit (from 81% to 99%), again with a marked hospital-to-hospital variability (Table 1, Figure 2). However, the proportion of patients screened for dysphagia within 24 hours of admission actually decreased (from 78% to 65%) (Table 1). The year-on-year changes in dysphagia screening and the hospital-to-hospital variability are shown in Figure 2.

The median length of stroke unit stay decreased from 10 to nine days. However, stroke unit mortality became higher (from 11% in 2017–2018 to 15% in 2020), which can also be observed at the level of individual hospitals (Table 1, Suppl. Tab. 1). The structure of discharge destination in survivors also changed, while the proportion of patients discharged home showed only minor fluctuations (66%, 65%, 69% and 69%). Follow-up visits in the neurological outpatient clinic were advised significantly more often (NA, 3%, 27% and 74%). However, no such trend was observed for those visits that were actually scheduled (NA, 8%, 26% and 13%) (Table 1).

Discussion

As previously mentioned, the Polish RES-Q data tends to overrepresent high-performing hospitals [14]. This observation is indirectly confirmed by the thrombolysis and mechanical thrombectomy rates that are clearly superior to the national average reported by the NHF (approximately 13% and < 1% in 2017; 15% and < 1% in 2018; 17% and 2% in 2019; 16% and 3.5% in 2020) [2, 24].

In our study, the observed overall increase in the availability of reperfusion therapies was from 27% in 2017 to 35% in 2020. According to the NHF, the Polish national average rose over the same time from 13% to 19% [2]. It is worth emphasising that this improvement was not driven

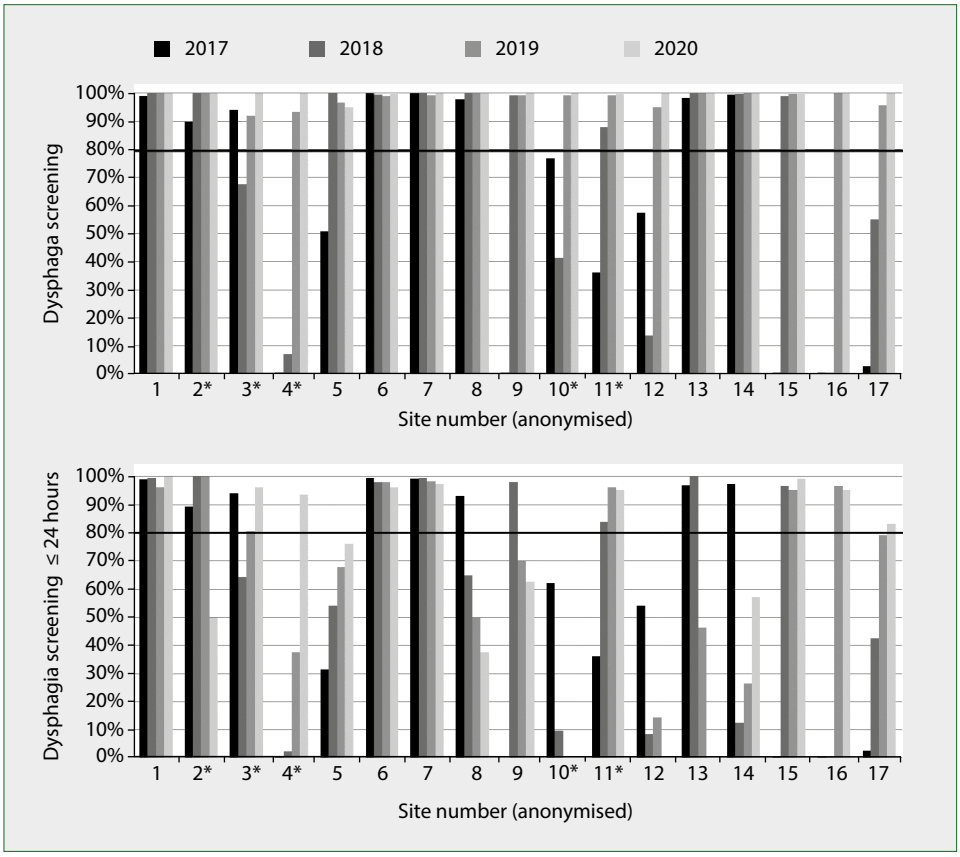

Figure 2. Changes in dysphagia screening in individual hospitals from 2017 to 2020
*overall p value within one site < 0.05
Site numbers are not related to the order of co-authors

by the increased use of intravenous thrombolysis. Several overlapping factors may explain this phenomenon. Firstly, the well-performing stroke centres may have encountered a 'near-ceiling' effect regarding the use of rtPA, meaning that they had already reached a saturation point in terms of rtPA usage. Secondly, the organisational challenges imposed by the COVID-19 pandemic may have impacted upon the administration of rtPA. And lastly, the introduction of the National Pilot Programme for Thrombectomy played a significant role in promoting the wider availability of mechanical thrombectomy [7, 25].

An analysis of the Polish RES-Q registry data made in 2018 identified the key areas requiring improvement, namely dysphagia screening, door-to-needle time, and the availability of carotid endarterectomy or stenting [14]. As a consequence, the proper diagnosis and management of dysphagia was prioritised by the Angels-Poland Initiative. The Initiative, with the collaboration of PNS, attempted to implement routine dysphagia screening into clinical practice.

Our findings confirm that significant progress has been achieved, even in the skewed population of well-performing stroke units. Dysphagia screening has become an established part of everyday clinical routine in this subset of Polish stroke units.

Furthermore, the RES-Q registry captured an important gap in terms of not performing the dysphagia screening within the first 24 hours from admission. This finding should tailor further interventions to ensure that screening takes place prior to the patient's first meal. This is crucial for minimising the risk of aspiration and pneumonia which can affect about 15% of stroke unit patients [25].

It is essential to prioritise and promote the establishment of comprehensive post-stroke outpatient services to ensure that stroke survivors receive appropriate follow-up care and interventions aimed at preventing recurrent events. The initiation of secondary stroke prevention measures in the analysed stroke units has shown satisfactory results since 2017. However, the availability of post-stroke outpatient care remains suboptimal and probably needs major systematic changes. By actively encouraging and facilitating the development of this particular service, the NHF can contribute significantly to improving the overall continuum of care for stroke patients.

The high-performing hospitals regularly reporting cases to the RES-Q seemed to have a shorter duration of stroke-unit stay than the national average in 2017, and were able to reduce it even further to nine days. Across 2013 to 2018,

the mean length of stroke unit stay in Poland was 13.0 days, showing a high region-to-region variability (from 10 to 18 days) [27].

National data on post-stroke mortality has revealed two major patterns. Firstly, the mortality rates are clearly lower in stroke units than in other wards (6% *vs.* 13%). Secondly, there is considerable interregional variability in standardised stroke unit mortality (ranging from 3% to 9%) and 90-day mortality (ranging from 12% to 19%) [2]. The significant increase in overall mortality in analysed hospitals observed in 2019 and 2020 raises a red flag. This increase may be partly attributable to the COVID-19 pandemic [26–30]. However, an increase in average post-stroke mortality in Poland started in 2020, not in 2019 [2]. It is possible that the implementation of thrombectomy has also skewed the population of patients treated in comprehensive stroke units towards a higher proportion of severe cases. Special attention is needed to ensure that this finding is not indicative of a systematic trend, but rather represents a temporary fluctuation.

Study limitations

Our analysis is based on declarative data of samples of consecutive patients reported to the registry from multiple centres on a voluntary basis. As a result, there was a high variability observed in the annual numbers of contributed cases, both among different hospitals and across different years.

It was also not possible to determine how many patients, and for what reasons, were not reported to the registry, nor to ascertain the causes of missing values in particular variables. For instance, site no. 2 in 2019 evidently reported almost exclusively cases treated with rtPA, rather than all consecutive patients within a predefined timeframe. This selection bias may affect statistical analyses on a year-to-year basis in individual hospitals or comparisons between hospitals. Therefore, we graphically present data about DNT and dysphagia screening (Figures 1 and 2), refraining from comparisons between hospitals. This source of bias has also been reported in RES-Q-based analyses of stroke care in Greece and Estonia [17, 18]. It is vital to recognise that the performance metrics used in high quality registries like the RES-Q are formulated based on expert consensus and scholarly agreement [12, 31]. While these metrics function as surrogate markers presumed to have a major impact on clinical outcomes, they do not serve as direct substitutes for clinical endpoints.

Despite the aforementioned limitations, the overall sample size is sufficiently large to derive meaningful conclusions regarding changes in stroke performance within the subset of Polish stroke units that exhibit relatively high baseline performance. These findings hold significance for international benchmarking purposes, and can provide informative insights for policymakers, almost matching the requirements of the Achievable Benchmark of Care methodology [31].

Clinical implications/future directions

The overall performance of Polish stroke units that consistently reported series of cases to the RES-Q registry between 2017 and 2020 improved in several respects, particularly in terms of the availability of mechanical thrombectomy, the door-to-needle time, and dysphagia screening. There was no evident deleterious effect of the COVID-19 pandemic in 2020. However, it is still necessary to shorten the time to dysphagia screening, to reduce disparities in rtPA logistics across different hospitals, and to ensure effective outpatient follow-up care.

External quality-oriented projects have the potential to drive improvement, even in centres with already good baseline performance. However, it is crucial to encourage continuous data reporting and the use of collected data for the purpose of planning interventions to improve performance at local and national levels. This would encompass the ESO-EAST effort to show the real picture of stroke care quality by reporting complete series of cases for one month in Spring and one month in Autumn, each year.

To effectively achieve the goals outlined in the SAP-E, it would be optimal to make practical use of the data that is mandatorily reported to the NHF. This could involve feedback to individual hospitals through quarterly reports, or integrating the data with validated registries such as the RES-Q, enabling transparent and international benchmarking.

Article information

Data availability statement: *The data supporting the findings is available from the corresponding author upon reasonable request.*
Ethics statement: *This study was conducted in accordance with the Declaration of Helsinki. Due to its observational character and the anonymisation of data, approval from the Ethics Committee and additional consents were not required.*
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Clinical and radiological consequences of delayed therapy escalation in patients with relapsing-remitting multiple sclerosis

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ABSTRACT

Aim of the study. To evaluate the clinical and radiological consequences of delayed escalation of therapy in patients with relapsing-remitting multiple sclerosis (RRMS), in whom, despite finding platform therapy ineffective, high-efficacy drugs were introduced with a delay.

Material and methods. We performed a single-centre, observational study evaluating patients with RRMS for ineffectiveness of disease-modifying therapies (DMTs). Depending on the time of therapy escalation to high-efficacy drugs, the patients were divided into an early escalation or a late escalation group, both of which were then observed for 48 months. All patients underwent a neurological examination every six months and a brain magnetic resonance imaging (MRI) every 12 months. The primary endpoint was a change in the Expanded Disability Status Scale (EDSS) score during the observation period. The secondary endpoint was the time to 6-month confirmed disability progression (6mCDP). In addition, we analysed the annualised relapse rate and the cumulative number of new Gd+ and T2 lesions on brain MRI.

Results. 165 patients were qualified for the analysis. On treatment initiation, mean age was 38 years (± 10.9), and mean EDSS was 1.41 ± 0.38. After 48 months, there was a statistically insignificant decrease in the EDSS score in the early escalation group (–0.17 ± 0.35; $p > 0.05$), while in the late escalation group there was an increase in the EDSS score. The highest increase was noted in the group in which the escalation was performed with a delay of more than two years (1.2 ± 0.63; $p < 0.001$), and moreover 80% of patients in this group met the 6mCDP criteria.

The median time to 6mCDP was 4.6 years (LESC1) and 4.5 years (LESC2) in the late escalation groups. In the early escalation group, zero subjects met the 6mCDP criteria after 48 months of observation.

Conclusions. In everyday practice, the long-term outcomes in patients with RRMS and disease activity, despite DMT being used, are more favourable after early implementation of high-efficacy drugs. Delaying therapy escalation results in the accumulation of permanent disability in patients with RRMS.

Keywords: multiple sclerosis, therapy escalation, treatment failure, access to therapy, highly effective disease-modifying therapy

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Introduction

Multiple sclerosis (MS) is the most common autoimmune disorder of the central nervous system (CNS) among young adults. The disease is usually diagnosed between the ages of 20 and 40 and is one of the most common causes of disability in young people [1]. According to the data of the National Health Fund (NFZ) as at the end of 2021, MS was diagnosed in Poland in 54,887 people, a rate of 144 per 100,000 residents [2].

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Relapsing-remitting MS (RRMS) occurs in more than two in three MS patients [1, 3, 4]. In recent years, the treatment options for this type of disease have increased significantly due to the registration of many new disease-modifying therapies (DMT). Currently, the available therapies are commonly referred to as 'moderate efficacy DMT' (ME-DMT, platform therapy, including interferon-beta, glatiramer acetate, dimethyl fumarate, and teriflunomide) or 'high efficacy DMT' (HE-DMT, including alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, and newly approved ozanimod, ponesimod and ofatumumab) [5–7].

MS is incurable and no drug is fully effective. Therefore, the type and duration of therapy are crucial for inhibiting disease activity and irreversible brain damage, which translates into permanent disability. Thus far, MS treatment has been based on an escalation model, with HE-DMT following the failure of ME-DMT. This model has worked well in patients with low or moderate disease activity. Moreover, the high safety profile of platform drugs is worth underlining.

However, in patients with high clinical and magnetic resonance imaging (MRI) activity from the onset of the disease, and with unfavourable prognostic factors, such treatment does not bring the expected benefit.

Therefore, the current paradigm of MS therapy is that highly active drugs should be started as early as possible [5]. Pathophysiological studies indicate that inflammatory processes predominate in the early stages of the disease [8]. Therefore, the use of drugs with high anti-inflammatory activity in this period makes it possible to properly interrupt the immunopathological cascade, and may reduce, or even stop, the progression of the disease more effectively.

This concept has been confirmed in randomised clinical trials and recently in studies based on data from national and international registries [9–11]. Early use of high efficacy therapy has been shown to reduce disease activity and significantly delay disability progression. It also defers disease conversion to secondary progressive MS [9, 12].

The treatment model in MS changes based on new pathophysiological and clinical data, but also depends to a large extent on administrative and reimbursement regulations in the particular country. In Poland, until November 2022, based on the recommendations of the Ministry of Health, a typical escalation model of RRMS treatment was in force. This model included strictly defined clinical and radiological rules for the use of HE-DMT which significantly limited or withheld the use of highly active drugs.

To assess the consequences of delaying or not implementing escalation therapy in a group of patients with RRMS, we conducted a study evaluating patients treated with DMT according to the drug programme financed by Poland's National Health Fund (NFZ, Narodowy Fundusz Zdrowia).

The aim of our study was to analyse the clinical and radiological consequences of delayed treatment escalation in patients who, despite the ineffectiveness of the current therapy, were started on high efficacy drugs after a delay. Our analysis was based on data from one centre, thus enabling a uniform assessment of patients.

Material and methods

Study design

Data from 1,008 patients with MS treated in a specialist MS centre were analysed; 537 patients with RRMS diagnosed according to the 2010 McDonald criteria and treated with DMT platforms between January 2013 and June 2022 were identified. Then, 165 patients were included in the study group according to our inclusion criteria, which were: (1) RRMS; (2) age ≥ 18 years; (3) a minimum of 12 months of treatment with IFN beta, glatiramer acetate, dimethyl fumarate or teriflunomide; (4) a confirmed lack of clinical and/or radiological treatment efficacy in any period of therapy; and (5) the ability to analyse data for 48 months after determining treatment inefficacy. Patients who had a break in treatment (e.g. withdrawal from treatment, pregnancy), or who had been previously treated in clinical trials, or those in whom clinical data was insufficient or the observation period too short, were excluded. Demographic information (age, sex) and clinical data (date of first symptoms, date of diagnosis, number of relapses in the 12 months prior to treatment initiation, date of treatment initiation) were collected. Neurological status on treatment initiation was assessed according to the Expanded Disability Status Scale (EDSS). Then, after determining the date of complete or partial therapy failure, the possible escalation of treatment was assessed. Complete failure was diagnosed if, during the 12-month period of DMT, there were two or more moderate relapses, or one severe relapse after six months of DMT, along with new lesions found on brain MRI — (> 1 change in Gd+ or > 2 changes in T2). In the drug programme financed by the NFZ, meeting such criteria made it possible to change the therapy and use a high-efficacy drug. Partial failure was diagnosed if, within 12 months of DMT, the patient had clinical and/or radiological disease activity that did not meet the criteria for complete treatment ineffectiveness. These were patients with clinical failure — they experienced only relapses, and radiological failure — they had only new T2 or Gd+ lesions on brain MRI or with clinical and radiological failure, but less than required for a complete failure. According to the criteria of the drug programme in force at that time, these conditions did not allow the use of HE-DMT. Data from any treatment period during which complete or partial treatment failure occurred was considered as reference data.

On this basis, two groups of subjects were distinguished: group A, and group B. Group A comprised patients with complete ineffectiveness of treatment. In this group, a switch to a high-efficacy drug was made immediately after treatment failure (EESC, early escalation group). Group B comprised patients with partial treatment failure. This group was divided into three subgroups: B1 — patients with only a relapse

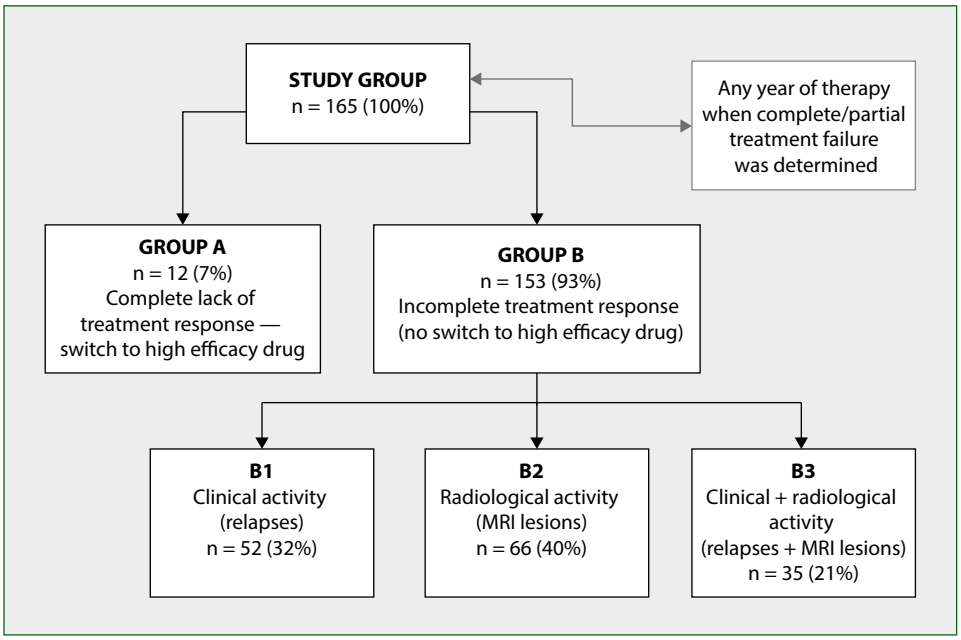

Figure 1. Flowchart of patient selection procedure. MRI — magnetic resonance imaging

during the observation period; B2 — patients with only new brain MRI lesions during the observation period; and B3 — patients with both a relapse and brain lesions in MRI during the observation period. These patients were either switched to a high-efficacy drug at a later time (LESC, late escalation group) or did not receive such therapy (NESC, no escalation group) (Fig. 1).

All patients were observed for 48 months after treatment failure. Every six months, the EDSS score was evaluated, and every 12 months the number of relapses and the new Gd+ and/or T2 lesions on brain MRI were assessed. The final review of the clinical data and the final EDSS evaluation were performed by the same investigator. Brain MRI and their evaluation were performed according to the same protocol and in the same MRI centre.

At the end of the observation stage, study endpoints were assessed. The primary endpoint was a change in EDSS score in relation to the reference score (ΔEDSS = EDSS score after 48 months – reference EDSS score). The secondary outcome was the time to a confirmed disability progression (6mCDP) defined as an increase in EDSS score confirmed on two consecutive visits at least six months apart. The required increase was defined as: ≥ 1.5 in patients with a baseline EDSS score of 0.0–0.5, ≥ 1 point in patients with a baseline EDSS score between 1.0–5.0, and ≥ 0.5 points in patients with a baseline EDSS score at least ≥ 5.5. EDSS increase had to occur in the absence of a relapse.

We defined our outcome date as the date of the confirmation of EDSS worsening. In addition, the annualised relapse rate (ARR) and the cumulative number of new Gd+ and/or T2 lesions on brain MRI compared to the reference data were assessed during the observation period in each group. Written consent to participate in the study was obtained from all patients. This study was approved by the Bioethics Committee at the University of Rzeszów (Resolution No. 3/01/2020).

Statistical analysis

Depending on the type and properties of the variable, the median test, the Mann–Whitney U test and the Kruskal–Wallis H test were used for intergroup comparisons. In addition, Cox regression analysis was used to assess progression within the groups. Linear regression analysis was used to assess the impact of individual variables on the change in EDSS over 48 months of observation. Models were adjusted for gender, age at treatment, year of DMT initiation, and year of escalation of therapy.

ARR (so-called crude ARR) in individual groups and a comparison of ARR between groups (estimating the so-called RR — relapse rate ratio) were calculated using the criteria defined by Akaishi et al. in 2022 [13].

Results

Complete or partial treatment failure according to the accepted definitions was found in 165 (31%) patients with RRMS treated with DMT. Failure occurred after a mean of 15.83 months (SD = 10.29), median 11 months (range 6–64). In this group, 12 (7%) patients met the criteria for complete failure and were switched to high efficacy drugs very quickly (Group A, EESC). The remaining 153 (93%) patients had signs of partial treatment failure in the form of clinical and/or radiological activity, but did not meet the required criteria for inclusion in HE-DMT (group B) (Fig. 1). There were no differences between groups A and B regarding sex, age, EDSS score

Table 1. Demographic and clinical characteristics of study group

Parameter	Entire group (n = 165)	Group A (complete ineffectiveness) (n = 12)	Group B (partial ineffectiveness (n = 153)	P A/B
Age at treatment initiation, mean (SD)	31.03 (10.72)	27.89 (10.71)	30.1 (10.5)	U Test
Median (range)	31 (14–62)	22 (17–47)	31 (14–62)	U = 632; p = 0.34
Sex – n (%)				Chi-square test:
Female	102 (62%)	8 (67%)	95 (62%)	$\chi^2(1) = 0.8$;
Male	63 (38%)	4 (33%)	58 (38%)	p = 0.78
EDSS on treatment initiation, mean (SD)	1.41 (0.68)	1.39 (0.35)	1.41 (0.69)	U Test
Median (range)	1.5 (0–3.5)	1 (1–2.5)	1.5 (0–3.5)	U = 547; p = 0.87
Time from first symptoms to treatment (months), mean (SD)	28.9 (32.1)	33.6 (31.7)	26.4 (32.9)	U Test
Median (range)	14 (1–120)	24.5 (1–120)	9.5 (1–120)	U = 779.5; p = 0.019
Number of relapses within 12 months prior to treatment, mean (SD)	1.28 (0.77)	1.44 (0.53)	1.27 (0.78)	Median test:
Median (range)	1 (0–3)	1 (1–2)	0 (0–3)	$\chi^2(1) = 0.28$;
ARR (95% CI)	1.28 (1.09–1.5)	1.44 (0.77–2.47)	1.27 (1.08–1.49)	p = 0.53 RR (95% CI) = 1.13 (0.51–2.05) p = 0.8
Time (months) from treatment initiation to ineffectiveness, mean (SD)	15.83 ± 10.29	12.67 ± 3.81	16.5 ± 10.56	U Test
Median (range)	11 (6–64)	11 (6–20)	11 (6–64)	U = 628.5; p = 0.36
EDSS on determining treatment ineffectiveness, mean (SD)	1.57 (0.75)	2.11 ± 1.14	1.53 ± 0.7	U Test
Median (range)	1.5 (0–5)	1.5 (1.5–5)	1.5 (0–4)	U = 313; p = 0.032

ARR — annualised relapse rate; CI — confidence intervals;EDSS — Expanded Disability Status Scale; RR — risk ratio;SD — standard deviation

at the start of therapy, or the number of relapses during the 12 months prior to treatment. However, patients from group A had a significantly later start of treatment, and significantly higher EDSS score in the period of therapy ineffectiveness. Demographic and clinical data of individual groups are set out in Table 1.

During the observation period, 28 (17%) patients in group B had treatment escalation at a later stage (LESC, late escalation group). Fifteen (9%) patients were switched to HE-DMT within the first two years after determining treatment ineffectiveness (LESC1), and 13 (8%) more than two years afterwards (LESC2). There was no therapy escalation for 125 (82%) patients, but 15 of these patients were treated with another moderately effective drug.

53% of late escalation patients with partial ineffectiveness were recruited from the group where clinical and MRI activity occurred simultaneously. The subjects who did not undergo therapy changes constituted a group presenting only MRI activity.

The relationships between the type of partial treatment ineffectiveness and the change of therapy are set out in Figure 2.

EDSS change

Baseline mean EDSS score before starting DMT was comparable in all groups. In the EESC group it was 1.39 (SD 0.35), LESC1 — 1.36 (SD 0.81), LESC2 — 1.5 (SD 0.62), and in the NESC group 1.42 (SD 0.72) (test H $\chi^{(2)} = 0.41$ p = 0.93). The EDSS score at the moment of determining treatment ineffectiveness was in the EESC group 2.11 (SD 1.14), LESC1 — 1.68 (SD 0.64), LESC2 — 1.55 (SD 0.76) and was in the NESC group 1.55 (SD 0.76) (test H $\chi^{(2)} = 4.84$ p = 0.18). After the observation period, the mean EDSS in groups changed, and statistically significant differences were found between the EESC and LESC2 groups. (U test = 70.5, p = 0.032). Comparing the value of the EDSS change in relation to the reference values, it was found that in the EESC group the neurological status of the patients was stable, and the EDSS in this group fell insignificantly. In the remaining groups, the neurological condition deteriorated, and the EDSS score increased. The largest increase in EDSS score was noted in the LESC2 group, and the smallest in the no escalation group (Tab. 2, Fig. 3). The assessment of the change in EDSS score between groups (using Bonferroni correction for multiple testing) showed statistically

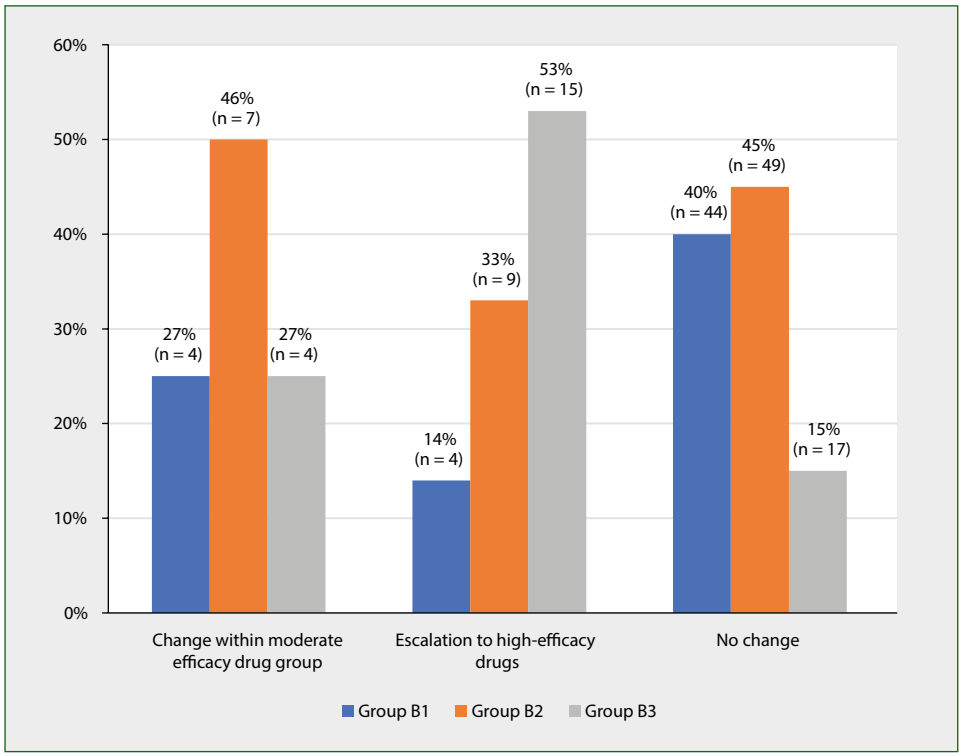

Figure 2. Change in treatment within 48 ± 3 months depending on type of partial ineffectiveness

Table 2. Comparison of EDSS score and number of GD+ and T2 lesions in groups after 48 ± 3 months of observation

	EESC group (n = 12)	LESC1 group (n = 15)	LESC2 group (n = 13)	NESC group (n = 110)	
EDSS after 48 months	M = 1.94; SD = 0.85 Md = 1.5; range 1.5–4	M = 2. 23; SD = 0.75 Md = 2; range 1–3.5	M = 2.75; SD = 1.14 Md = 2.5; range 1.5–5.5	M = 2.12; SD = 0.98 Md = 2; range 1–6	Test H: $\chi^2(2) = 5.96$; p = 0.11
ΔEDSS	M = –0.17; SD = 0.35 Md = 0; range 1–0	M = 0.73; SD = 0.72 Md = 0.5; range 0–2.5	M = 1.2; SD = 0.63 Md = 1; range 0.5–2.5	M = 0.62; SD = 0.56 Md = 0.5; range 0–2.5	Test H: $\chi^2(2) = 24.32$; p < 0.001
No. of Gd+ lesions	M = 1.11; SD = 2.98 Md = 0; range (0–9)	M = 8.73; SD = 11.06 Md = 2; range (0–30)	M = 9; SD = 8.83 Md = 6; range (0–25)	M = 0.81; SD = 2.93 Md = 0; range (0–24)	Test median $\chi^2(2) = 28.31$; p < 0.001
No. of T2 lesions	M = 2.11; SD = 3.65 Md = 0; range (0–9)	M = 9.64; SD = 7.49 Md = 9; range (2–25)	M = 10.4; SD = 8.64 Md = 8; range (2–30)	M = 1.67; SD = 3.13 Md = 0; range (0–18)	Test median $\chi^2(2) = 31.64$; p < 0.001

EDSS — Expanded Disability Status Scale; M — mean; Md — median; SD — standard deviation; EESC — early escalation group; LESC1 — late escalation group 1; LESC2 — late escalation group 2; NESC — no escalation group

significant differences between the EESC and LESC2 groups ($p < 0.001$), between LESC1 and NESC ($p = 0.001$), and between LESC2 and NESC ($p = 0.002$). There were no significant differences between the LESC1 and LESC2 groups.

Time to confirmed 6-month disability progression (6mCDP)

In the EESC group, none of the subjects met the 6mCDP criteria after the observation period. The highest percentage

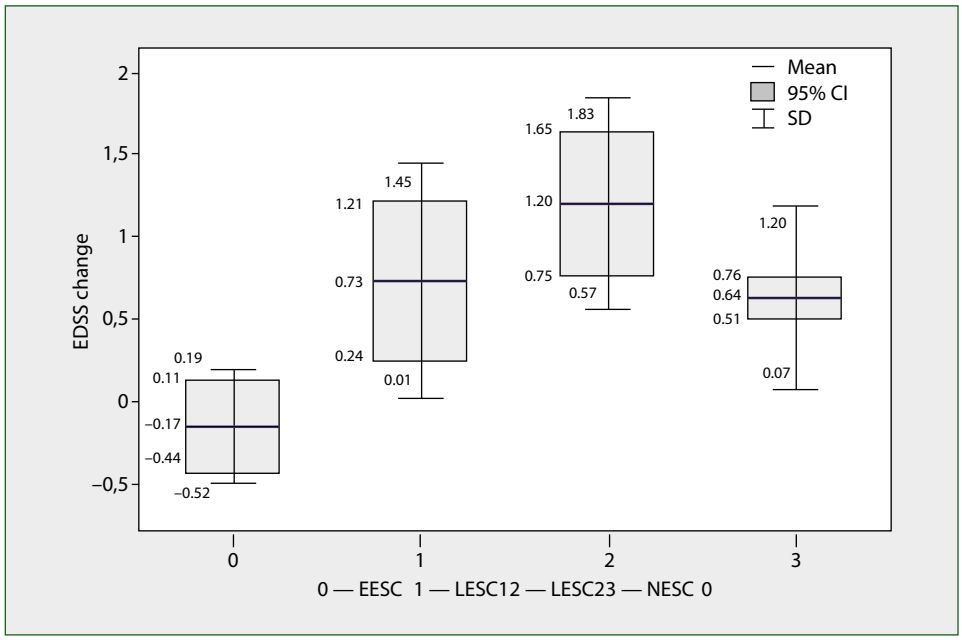

Figure 3. EDSS score change in groups after an observation period. CI — confidence intervals; EESC — early escalation group; LESC1— late escalation group 1; LESC2 — late escalation group 2; NESC — no escalation group; SD — standard deviation

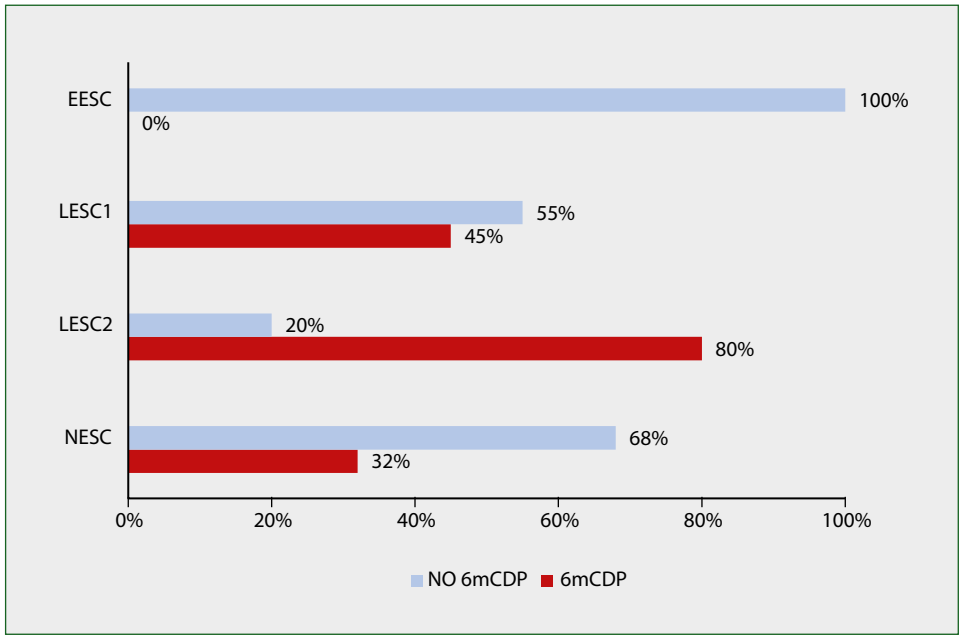

Figure 4. Percentage of patients meeting 6mCDP criteria after 48 ± 3 months of observation depending on escalation of therapy

(80%) of patients meeting the 6mCDP criteria was found in the LESC2 group (Fig. 4). In order to assess the risk of long-term accumulation of disability in the LESC1 and LESC2 groups and in the NESC group, Cox regression analysis was performed. The type of group was included in the baseline model, and the following variables were included in the adjusted model: gender, age at treatment initiation, year of treatment initiation, and time of treatment escalation during four years of observation. The median time to onset of 6mCDP in the LESC1 group was 55.5 months, (95% CI, 24–57), in the LESC2 group it was 54 months, (95% CI, 43–57), and in the NESC group it was 57 months, (95% CI, 55–57). The differences between the groups were statistically significant (log-rank test, p = 0.039). The primary model

Table 3. Cox regression model statistics

	HR (95% CI)	p-value
Baseline model		
LESC2	1.05 (0.38–2.9)	0.92
Group without change	0.463 (0.1–1.066)	0.07
Adjusted model		
LESC2	0.9 (0.323–2.511)	0.84
No escalation group	0.38 (0.16–0.9)	0.022
Age at treatment initiation	1.036 (1.003–1.069)	0.033

Note — reference group LESC1; other variables which were not included in table were not related to 6mCDP risk. CI — confidence intervals; HR — hazard ratio; LESC2 — late escalation group 2

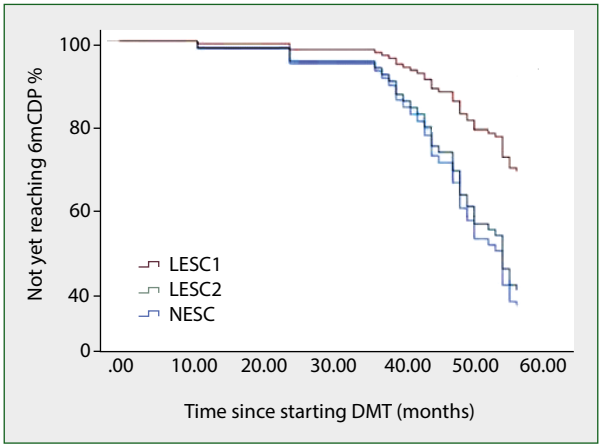

Figure 5. Time to 6mCDP depending on treatment strategy

(Cox regression analysis) showed no differences for 6mCDP risk in the compared groups. In the adjusted model, the risk of 6mCDP was lower in the NESC group (hazard ratio 0.38, 95% CI 0.16–0.9; p = 0.027). The risk was related to age at treatment initiation and was higher with older patient age (hazard ratio 1.036, 95% CI 1.003–1.069; p = 0.033). Statistical analysis for the baseline and adjusted models is set out in Table 3. The risk of reaching 6mCDP in the distinguished groups is set out in Figure 5.

Assessment of disease activity

In all study groups, a decrease in ARR was observed after DMT started, compared to the value before treatment. The largest reduction in ARR was in the EESC group (100%). In the LESC1 group, there was a decrease in ARR by 59%, and in the LESC2 group by 67%, compared to the baseline value.

The EESC group had no relapses during the observation period, while in the LESC groups ARR was 0.61 (0.45–0.8; 95% CI) and in the NESC group ARR was 0.17 (0.13–0.22; 95% CI). Comparison of the ARR values revealed significant differences between the LESC groups and the NESC group: relapse rate ratio 3.59 (95% CI, 0.252–0.609); p < 0. 001. There were no differences in ARR between the LESC1 and LESC2 groups.

A comparison of the cumulative number of GD+ and new T2 lesions in groups from the entire observation period is set out in Table 2. Statistically significant differences were found when comparing the number of Gd+ lesions in the EESC group to the LESC2 group (median test $\chi^2(1) = 9.019$; p = 0.005). The highest mean number of Gd+ and T2 lesions were recorded in the LESC2 group. A comparison between the LESC groups using Bonferroni correction for multiple testing showed that there was no significant difference between the LESC1 and LESC2 groups in either T2 (p = 1) or Gd+ (p = 0.86) lesions. However, statistically significant differences occurred when comparing Gd+ and new T2 lesions in the LESC groups with the NESC (p < 0.001). The lowest number of Gd+ and new T2 lesions was found in the NESC group.

Discussion

To date, RRMS therapy has comprised mostly the escalation model, in which a drug of moderate efficacy is initially selected, and then in the case of continued disease activity despite the treatment, this therapy is escalated to one of high efficacy drugs. To achieve optimal therapeutic results, early detection and prompt response to the effectiveness of the moderately effective DMT is necessary.

For administrative restrictions, Polish patients with RRMS have had limited access to high-efficacy drugs. Consequently, escalation therapy has not been implemented despite the fact that the ongoing treatment proved to be ineffective, and many patients were kept on previously selected treatment. In our study, we compared the clinical status and brain MRI results depending on the time of therapy escalation in 165 patients with RRMS treated with platform therapy, in whom clinical and/or radiological evidence of treatment ineffectiveness was observed.

Due to the applicable reimbursement criteria, only 7% of the respondents were able to use high efficacy drugs immediately after the therapy had been found to be ineffective. The others continued platform therapy or received delayed high efficacy treatment. This confirms our previous research demonstrating that therapy escalation was rarely used (in 9% of patients), and that the most common reason for changing treatment was the prevalence of side effects [14]. In addition, the data is consistent with the results obtained by Brola et al., who assessed access to high efficacy therapy in Poland in a multi-centre study [4]. During the observation period of 48 months, another 17% of patients met the criteria for escalation to high efficacy DMT, showing the obstacles in using active treatment due to administrative reasons, which are consistent with the data of National Health Fund, which shows that in 2014–2022 in Poland 6–9% of patients received high efficacy drugs [15]. In contrast, Patti et al. and Papp et al. documented an escalating rate of 53–60% after treatment with dimethyl fumarate and teriflunomide, and in a group of

German patients 43.5% received a subsequent high efficacy DMT as a second line therapy [16–18].

Our research has shown that in patients who, despite the use of platforms DMTs, show clinical activity of the disease, the lack of early escalation of therapy leads to worsening of the neurological condition and permanent disability. Comparison of long-term treatment effects in the EESC group with the effects in the late escalation groups (LESC1 and LESC2) showed stabilisation of the neurological status and reduction of the EDSS score in patients with early escalation, while the highest increase in the EDSS score was found in the LESC2 group. When assessing the increase in the EDSS score, the difference between the groups was clear, especially when comparing the EESC group to the LESC2 group, where the escalation was made more than two years after determining ineffectiveness.

This allows us to conclude that delaying the escalation of treatment in these patients resulted in worsening of their neurological status. Similar results were obtained when evaluating permanent disability. Subjects who escalated early (immediately when therapy was found to be ineffective) showed significantly less disability progression compared to patients who escalated later. In the EESC group, none of the subjects met the 6mCDP criteria at the end of the observation. The highest progression of disability was noted in patients who were treated with high-efficacy drugs more than two years after determining ineffectiveness. After 48 months, 45% of patients in the LESC1 group and 80% of patients in the LESC2 group met the 6mCDP criteria.

In the available literature, we found papers that assessed the clinical condition of patients after delaying the escalation of therapy [9, 10]. Our results are consistent with recently published observations in groups of patients from multi-centre studies, although the concept behind these studies is completely different [9, 11, 20]. The above studies compared patients starting MS treatment with high-efficacy drugs to those who escalated therapy after having determined the ineffectiveness of previous treatment.

In our study, all patients started treatment with drugs of moderate efficacy, and the escalation options in our group were limited.

Despite different groups, the clinical consequences are the same: in patients with active disease, the late use of highly active drugs leads to a worsening of the neurological condition.

In all groups, there was a decrease in ARR after the introduction of DMT, with the largest noted in the early escalation group. In the groups where the high-efficacy treatment was applied later, the reduction in ARR was not as significant. Our results are consistent with those of Harding et al. [9], who showed that an early start of high efficacy therapy lowers relapse frequency.

Many studies have evaluated T2 brain lesion counts and volumes after disease onset versus disability progression. A recent review and meta-analysis confirmed that lesion counts and volumes could be associated with disability progression [21]. Our study concentrated on the change in the cumulative number of Gd+ and T2 lesions depending on the time of therapy escalation. It is worth emphasising that during 48 months of observation in patients without treatment escalation, and with late escalation, the cumulative number of Gd+ or T2 changes increased significantly. The largest increase in MRI lesions was found in the LESC2 group. New, clinically silent lesions on MRI are 5–10 times more frequently observed than reported clinical relapses, and MRI disease activity has also been reported as a valid surrogate marker for clinical activity in relapsing MS [22]. Moreover, scoring systems combining MRI and clinical markers have been shown to predict long-term treatment non-response. Furthermore, a 1-year MRI lesion activity occurring with relapses justified the treatment outcome of EDSS worsening [23, 24].

In our study, we found a significant increase in the number of lesions, both Gd+ and T2, in the group of patients with late escalation, i.e. in patients who were constantly active despite treatment. In this group, we also found an increase in disability, which is consistent with the results of previous studies [20]. 67% of patients starting DMT did not switch therapy during the entire observation period. There was no significant increase in EDSS or brain MRI lesions in this group, and the median time to 6mCDP was 4.8 years. The only variable associated with the risk of 6mCDP in this group was patient age at the time of initiation of the first DMT. Ageing of the immune system and a worse response to DMT in patients aged over 40 is well-established [25]. A meta-analysis of randomised, blinded, DMT clinical trials showed that higher efficacy treatments exert their benefit over lower efficacy treatments, although this is observed only during the early stages of MS [26]. The relationship was not confirmed in a recent meta-analysis of clinical trials. Zhang et al. reported that DMTs for RRMS show efficacy in treating disease activity irrespective of age [27]. Furthermore, data on the importance of relapses and number of MRI lesions for predicting changes in EDSS and increasing disability are inconclusive.

An important parameter contributing to disability progression in MS, that was not taken into consideration, is brain atrophy. Brain volume loss happens independently from disease activity and cannot be prevented by early DMT implementation [28]. A previous work showed that the presence of an isolated relapse without changes in EDSS score during the first two years of treatment did not significantly impact upon an increased risk of developing marked long-term disability over a median five years [29]. But other, more recent, studies have revealed that clinical activity, defined as an EDSS score change or relapses during the first years of IFN-β treatment, had a very negative effect on the long-term prognosis [30, 31], and the same with the MRI scan. In patients treated with fingolimod, isolated MRI activity during the first year of treatment did not show a significant risk of future disease activity [32]. However, during the first year of IFN-β treatment, the

presence of substantial MRI activity increased the ability to predict treatment failure. The study concluded that substantial MRI activity during the first year of treatment with IFN-β, particularly if it is in combination with clinical relapses, indicates a significant risk of treatment failure and EDSS worsening over the short term [33]. Clinical and MRI activity in isolation may be not sufficient to determine treatment response, whereas the combination of these measures using composite scores appears preferable [34].

In our study, the patients who remained on treatment were mostly those with partial clinical or radiological failure. They were also more likely to have lower disease activity, which allowed them to maintain a good response to first-line treatment.

The limitations of our study concerned its retrospective and observational nature and the small size of the group, which are the results of it being a single-centre study. In addition, patients were included in DMT at different time periods from the onset of symptoms, which may affect disease activity and treatment response. However, in contrast to multicentre studies, EDSS was assessed by a single investigator, which significantly reduces the variability of results. This is important because EDSS is a scale characterised by high inter-rater variability and fluctuation. In addition to assessing parameters such as EDSS and ARR, the cumulative increase in the number of demyelinating lesions in brain MRI was also evaluated.

Permanent disability in the course of MS depends on many factors, including the consequences of relapses, the effects of the inflammatory and neurodegenerative process, and the effects of the treatment applied. It is likely that there is an 'early window' of therapeutic opportunity where disease modification is possible, bringing about long-term benefits. After some time a threshold is crossed, above which accumulated immune damage leads to permanent and progressive neurological disability [9].

In light of this data, we suggest it is justified to use rapid escalation of therapy in patients with suboptimal response to treatment, as a delay may result in increasing disability.

Changes in the NFZ therapeutic programme also make it much easier these days to start HE-DMT earlier in Poland, e.g. applying monoclonal antibodies in treatment-naive patients.

Article information

Data availability statement: *The original contribution presented in the study is included in the article; further inquiries may be directed to the corresponding author.*

Ethics statement: *The study protocol was approved by the local Bioethics Committee and the participants involved in the study gave their consent.*

Author contributions: *Malgorzata Popiel — collection of materials, calculations, conclusions; Halina Bartosik-Psujek — substantive supervision at each stage of the work.*

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Supplementary material: *Not applicable.*

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RESEARCH PAPER

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Small vessel disease in primary familial brain calcification with novel truncating PDGFB variants

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ABSTRACT

Introduction. Primary familial brain calcification (PFBC) is a neurodegenerative disease characterised by bilateral calcification in the brain, especially in the basal ganglia, leading to neurological and neuropsychiatric manifestations. White matter hyperintensities (WMH) have been described in patients with PFBC and pathogenic variants in the gene for platelet-derived growth factor beta polypeptide (PDGFB), suggesting a manifest cerebrovascular process. We present below the cases of two PFBC families with *PDGFB* variants and stroke or transient ischaemic attack (TIA) episodes. We examine the possible correlation between PFBC and vascular events as stroke/TIA, and evaluate whether signs for vascular disease in this condition are systemic or limited to the cerebral vessels.

Material and methods. Two Swedish families with novel truncating PDGFB variants, p.Gln140* and p.Arg191*, are described clinically and radiologically. Subcutaneous capillary vessels in affected and unaffected family members were examined by light and electron microscopy.

Results. All mutation carriers showed WMH and bilateral brain calcifications. The clinical presentations differed, with movement disorder symptoms dominating in family A, and psychiatric symptoms in family B. However, affected members of both families had stroke, TIA, and/or asymptomatic intracerebral ischaemic lesions. Only one of the patients had classical vascular risk factors. Skin microvasculature was normal.

Conclusions. Patients with these *PDGFB* variants develop microvascular changes in the brain, but not the skin. *PDGFB*-related small vessel disease can manifest radiologically as cerebral haemorrhage or ischaemia, and may explain TIA or stroke in patients without other vascular risk factors.

Keywords: stroke, TIA, idiopathic basal ganglia calcification-5, Mendelian inheritance in man number 615483, cerebral small vessel disease, microbleeds, genetic diseases

(*Neurol Neurochir Pol 2024; 58 (1): 94–105*)

Introduction

Pathogenic variants in the *PDGFB* gene, encoding for platelet-derived growth factor B, are one of several known causes of primary familial brain calcification (PFBC), also known as Fahr's disease/syndrome or idiopathic basal ganglia calcification. PFBC is characterised by abnormal peri-microvascular calcium deposition in the brain [1–4]. The typical

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radiological findings are bilateral calcifications in the basal ganglia, and sometimes also in the thalamus, cerebellum, subcortical white matter, or other brain regions, in computed tomography (CT) images [4]. Currently, pathogenic variants in *SLC20A2, PDGFRB, PDGFB, XPR1, MYORG, JAM2,* and *CMPK2* are known to be genetic causes of PFBC [5]. White matter hyperintensities, presumably of vascular origin, have previously been described in PFBC patients with *SLC20A2* [6], *PDGFRB* [7] and *PDGFB* [8–10] variants, and have been explained by the impairment of pericyte recruitment during angiogenesis leading to vascular dysfunction [8, 11]. One previous study has reported alterations in the architecture of extracerebral blood vessels of one patient with PFBC and a pathogenic *PDGFB* variant [8].

A limited number of patients with PFBC have been reported to have ischaemic or haemorrhagic stroke, transient ischaemic attacks (TIA), and/or intracerebral aneurysms [12–18]. However, these are not considered typical or common clinical events in PFBC. The typical manifestations of PFBC are usually progressive symptoms such as parkinsonism, cerebellar symptoms, cognitive impairment, seizures, migraine, and psychiatric disorders [19].

Clinical rationale for the study

Our study aimed to investigate the clinical significance of white matter changes seen in patients with PFBC caused by *PDGFB* variants and to describe two families with novel truncating *PDGFB* variants.

Material and methods

Patient group and clinical data

Two unrelated index patients (one from family A and one from family B) with clinically manifest PFBC caused by probably pathogenic variants in the *PDGFB* gene, were identified at the Department of Neurology, Skane University Hospital in Lund, Sweden. Additional aetiologies for secondary intracranial calcification, including conditions such as hypercalcaemia and hyperparathyroidism, were excluded. The patients, as well as their symptomatic and asymptomatic family members, were invited to participate in this study. Five affected and two unaffected family members were examined using CT and brain magnetic resonance imaging (MRI), laboratory tests, skin biopsies and genetic analysis (Fig. 1). Clinical records and radiological examinations from two deceased family members were reviewed. We followed family A for eight years and family B for four years. We documented: a) known disease manifestations of PFBC; b) the presence or absence of classical vascular risk factors (i.e. diabetes mellitus, hypertension, heart disease, smoking, hyperlipidemia); c) TIA/stroke episodes; d) other radiological signs of cerebrovascular disease i.e. ischaemic lesions or intracerebral bleeding; and e) any relevant comorbidities or treatments. The occurrence of stereotypies in the index patient (individual III:1) of family A has previously been described [20].

Genetic analyses

Blood samples of the index patients and their available family members were collected and sent to commercial diagnostic laboratories (BGI in Denmark, Centogene in Germany, and BluePrint Genetics in Finland) for genetic testing. Whole exome (WES) or whole genome sequencing (WGS, Illumina) was performed for the index patients, followed by targeted investigation of all known genes related to PFBC.

This revealed two novel variants in the *PDGFB* gene (NM_002608.4): c.418C>T, p.(Gln140*) in family A and c.571C>T p.(Arg191*) in family B. These variants are predicted to introduce a translation termination (stop) codon at amino acid residues 140 respectively 191 and are absent in gnomAD v2.1 (https://gnomad.broadinstitute.org/). Other truncating *PDGFB* variants had previously been described as causes of PFBC [9, 21–25], and for this reason both novel variants have been classified as likely to be pathogenic according to the American College of Medical Genetics [26]. The sequenced data was also filtered by using a stroke gene panel for all genes reported to potentially cause monogenic stroke, including stroke related to cerebral small vessel disease [27, 28]. Sanger sequencing was used to examine affected and unaffected relatives.

Pathology

In order to detect possible extracerebral involvement, skin biopsies of 3 mm diameter were obtained from the upper arm of three variant carriers and of one non-carrier from family A. The vascular and microvascular structure of the skin was investigated. From each person, 7–8 sections of skin containing subcutaneous capillary vessels were stained by haematoxylin and eosin and examined using light microscopy and electron microscopy by a pathologist (E.E). The images were reviewed by a dermatologist with specific expertise in interpreting electron microscopy images of the skin (I.B.).

Neuroradiology

Available brain CT scans and MRI data of affected and unaffected family members were analysed in order to assess the presence of basal ganglia calcifications, white matter hyperintensities, and other vascular alterations including ischaemic lesions, cerebral haemorrhages, and aneurysms. Mutation carriers without available brain images underwent a CT scan and a brain MRI. All radiological images were collectively reviewed in collaboration with a neuroradiologist (J.W.). The calcium deposition load on CT scans was quantified using the Total Calcification Score [29] to better compare CT scans of different subjects at different ages.

Review of published cases

We have systematically reviewed all published cases of PFBC caused by pathogenic variants in the *PDGFB* gene (idiopathic basal ganglia calcification-5, Mendelian inheritance in man number 615483). A PubMed literature search

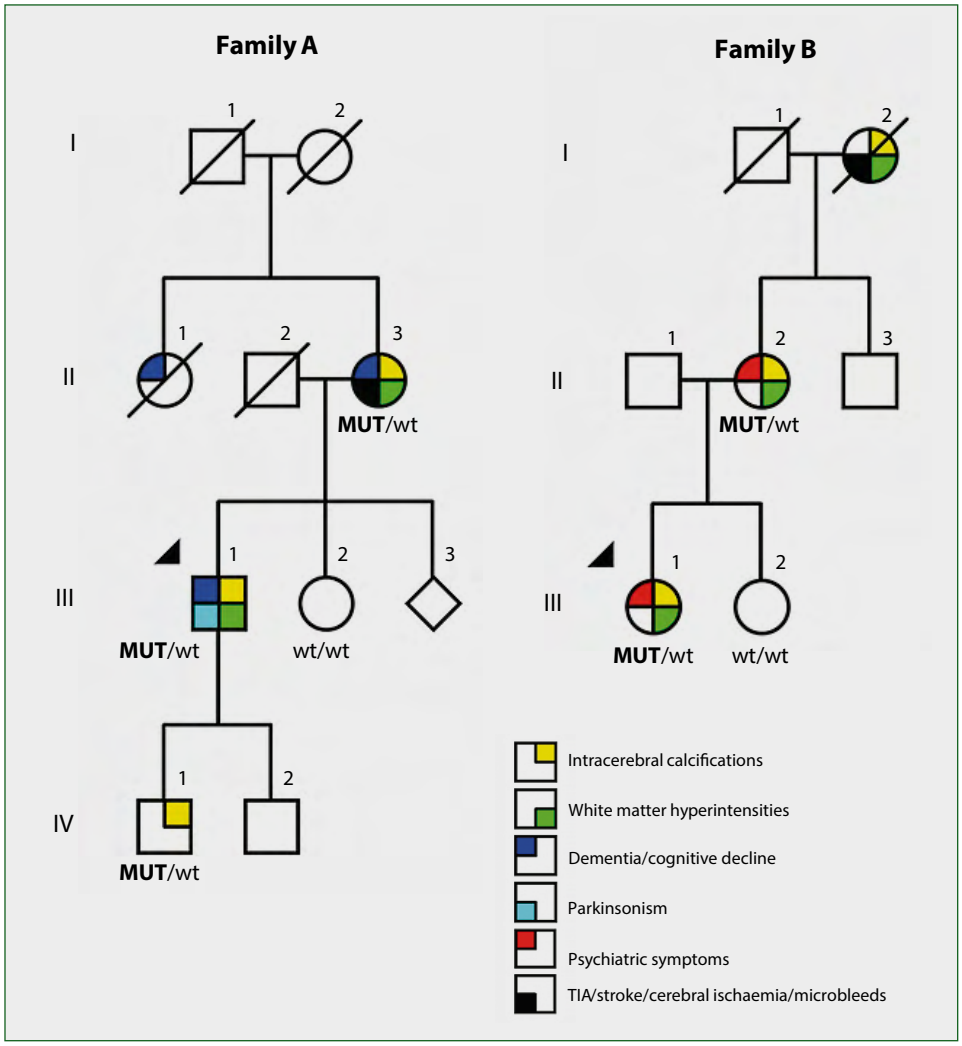

Figure 1. Family pedigrees. Standard symbols are used in pedigree drawings. Round symbols denote females and squares males. MUT — mutation carrier; WT — wild type

was performed for relevant articles, using the following search terms: idiopathic basal ganglia calcification; Fahr's Disease; *PDGFB* mutations; and white matter hyperintensities. Information on the presence and anatomical location of the brain calcifications, the presence of white matter hyperintensities, and the reported clinical manifestations, was extracted.

Results

Clinical findings

Family A: Four family members were examined clinically, and clinical records were reviewed from a fifth (Fig. 1).

The index patient (III:1) experienced challenges in initiating gait and changing direction at the age of 64 years, which demonstrated improvement upon the administration of levodopa treatment (200 mg daily). Mild cervical dystonia was noted on neurological examination. Two years later, he developed troublesome motor and vocal stereotypies [20] which partly improved with a small dose of clonazepam. Cognitive testing revealed memory problems and mild cognitive decline when he reached the age of 66. During the eight-year follow up he did not develop any stroke or TIA.

His son (IV:1), when examined at age 45, did not report any clinical complaints; however, a subtle postural tremor was identified during neurological clinical examination conducted as part of our study. He remained clinically unaffected eight years later, despite carrying the same variant in the *PDGFB* gene as his father.

The index patient's mother (II:3), also carrier of the same *PDGFB* variant, had an episode of sudden weakness in the right half of her face and her right arm, and head drop, at age 57. When examined by a neurologist two hours after onset, these symptoms had improved but mild weakness was documented in her right upper extremity. Over subsequent years, she reported that she had experienced repeated episodes, each lasting for a few minutes, of sensory disturbances or

process, or of malignancies that could otherwise account for her late-onset seizures. Additionally, she had experienced a single ischaemic stroke episode characterised by expressive aphasia. Her clinical neurological examination was otherwise normal. No previous psychiatric symptoms, movement disorders or other neurological deficits were described by her relatives, or mentioned in her medical records.

Family member III: 2 does not carry the genetic variant, and has remained asymptomatic including at the most recent contact.

Neuroradiology

In both families, the *PDGFB* variants co-segregated with the presence of bilateral calcifications in the basal ganglia and with cerebellar white matter hyperintensities of vascular appearance in all the identified mutation carriers (Fig. 1, Tab. 1). The total calcification score calculated for the affected individuals in families A and B is shown in Supplementary Data 1.

Family A: The index patient (III:1) showed extensive calcifications in his basal ganglia, thalamus, and cerebellum on CT, as well as subcortical and cerebellar WMH on MRI. His mother (II:3) and son (VI:1) had similar CT findings, with bilateral calcification at the same locations; MRIs showed WMH which were more prominent in patient II:3 at age 87 and subtle in patient VI:1 at age 45 and 51 (Fig. 2). Examination of patient II:3 with conventional angiography at age 57 revealed a vessel wall irregularity. This was interpreted as an arteriosclerotic plaque in the posterior wall of the right carotid bifurcation that was described as 'minimal'. There were no signs of large vessel disease in the left carotid artery. Renewed examination with conventional angiography at age 61 again showed signs of a mild, non-stenosing plaque in the (right) brachiocephalic artery and now revealed signs of a 'discrete' plaque proximally in the left common carotid artery; there were atherosclerotic vessel wall alterations bilaterally in the carotid siphons that were graded as 'lesser' on the left side and as 'mild to moderate' on the right side.

Family B: CT scans of the index patient (III:1) at age 17 and 23 showed very discrete calcifications in the basal ganglia that became more visible at age 29. The initial MRI scans, at age 16 and 26, showed very subtle white matter hyperintensities bilaterally in the frontal lobe; these became more prominent and visible on MRI at age 27. Her three consecutive CT angiographies revealed no evidence of atherosclerosis or aneurysms. Her mother's (II:2) CTs showed extended bilateral calcifications at the age of 36, and progression of these calcifications 14 years later. Her brain MRIs at age 53 showed bilateral white matter hyperintensities mainly in the frontal lobes, as well as older ischaemic lesions.

Table 1. Summary of genetic, clinical and radiological findings

Family	ID	Age	Sex	Genotype	Symptoms and signs	Classical vascular risk factors (HTN/S/HD/DM/HC)	Calcifications	White matter hyperintensities (MRI)	Ischaemic/haemorrhagic brain lesions	Transient ischaemic attack/stroke
A	II:3	87	F	c.418C > T p.(Gln140*)	Moderate cognitive decline. Recurrent episodes of right-sided weakness and paresthesias (TIAs). Permanent right central facial palsy (stroke)[§]	N/Y/N/N/Y	Pallidum, putamen, cerebellum	Yes, Fazekas III	N/N	Y/Y[§]
A	III:1	68	M	c.418C > T p.(Gln140*)	Gait disturbance, blepharospasm, cervical dystonia, vocal tics	N/N/N/N/N	Pallidum, putamen, caudate, thalamus, cerebellum	Yes, Fazekas III	N/N	N/N
A	IV:1	46	M	c.418C > T p.(Gln140*)	None	N/N/N/N/N	Pallidum, putamen, cerebellum	Yes, Fazekas I	N/N	N/N
B	I:2	78	F	c.571C > T p.(Arg191*)	Seizures, expressive aphasia (stroke)	N/N/N/N/N	Pallidum, putamen, parietal and occipital cortex	Yes, Fazekas III	Y/Y	N/Y
B	II:2	56	F	c.571C > T p.(Arg191*)	Depression, anxiety, bipolar disorder, psychosis	N/N/N/N/N	Pallidum	Yes, Fazekas I	Y/N	N/N
B	III:1	29	F	c.571C > T p.(Arg191*)	Depression, anxiety, bipolar personality disorder, vertigo, headaches, aphasia with limb weakness, involuntary muscle jerks, vocal tics	N/N/N/N/N		Yes, Fazekas I	N/N	N/N

DM — diabetes mellitus; F — female; HD — heart disease; HC — hypercholesterolaemia; HTN — hypertension; ICH — intracerebral haemorrhage; M — male; MRI — magnetic resonance imaging; N — no; S — smoking; Y — yes. [§]This individual had recurring episodes with unilateral weakness that included her facial musculature and sensory symptoms, but on examination had a persistent central facial palsy on same side; *truncating variant

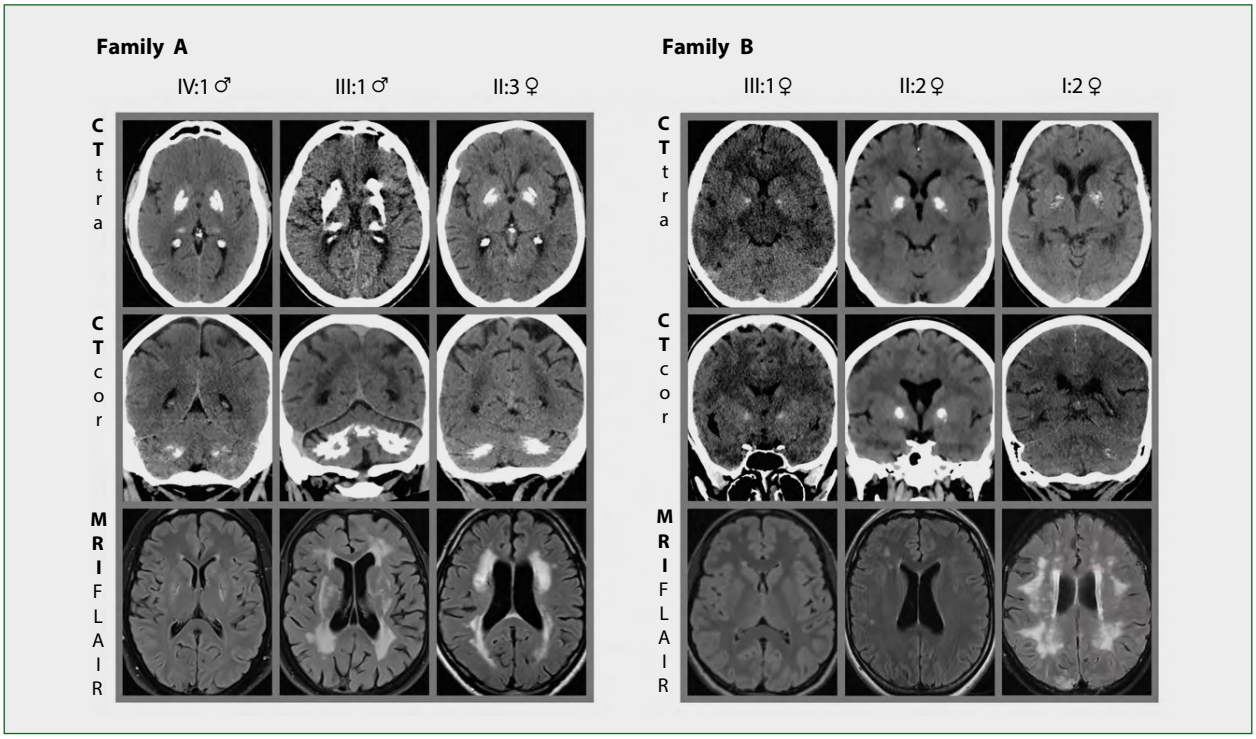

Figure 2. Radiological examinations of families A and B. Computed tomography (CT) scans from affected individuals in family A show bilateral calcifications in basal ganglia and cerebellum, while in family B they are present in basal ganglia of all three affected individuals; only discrete calcifications in the cerebellum are noted. Magnetic resonance imaging (MRI) shows white matter hyperintensities in all six mutation carriers. Both calcifications and small vessel disease are more prominent in older individuals

transient weakness in her right arm and hand. Some of these episodes were accompanied by dizziness and/or a subjective feeling of imbalance. A diagnosis of recurrent TIAs was made at the time, but when examined within our study at age 86, she had discrete right central facial palsy that had become permanent, compatible with a clinical diagnosis of stroke. Cardiac investigations including electrocardiography and trans-thoracic echocardiography, as well as assessments of the large artery with Duplex ultrasound of the cervical vessels and conventional angiography of cervical and intracranial vessels, yielded normal results except for atherosclerosis on the right subclavian and left vertebral arteries, with less than a 40% diameter reduction. She refused to participate in cognitive testing, but reports from family members suggested moderate cognitive decline.

Other than the individual II:3 who was a smoker and had hypercholesterolaemia, none of the other investigated persons in these two families had classical vascular risk factors (Tab.1).

A fourth member (III:2) was examined clinically and tested genetically, without any abnormal findings.

Family B: Three family members were examined clinically, and clinical records of a fourth were reviewed (Fig. 1).

The index patient (III:1) presented with depression, anxiety and anorexia from the age of 14. She had been diagnosed with bipolar and borderline personality disorder. Her previous medical history included asthma, inflammatory bowel syndrome, and chronic urinary retention demanding periodic catheterisation. From the age of 24, she suffered from chronic vertigo and migraine. She had recurrent episodes of transient aphasia and limb weakness leading to emergency admissions. Investigations conducted by the treating neurologists failed to yield a definitive diagnosis either of a vascular event (TIA) or of seizures/epilepsy. Additionally, she manifested nonspecific involuntary myoclonic jerks in the shoulder and neck regions, accompanied by vocal tics. Clinical examination revealed diplopia, with mild balance disturbance as well as myoclonus in her hands when stretching them forward. Her muscle jerks demonstrated improvement upon the administration of clonazepam 0.5 mg/d. In recent years, she had had intermittent episodes of generalised myoclonus that had been repeatedly considered to be non-epileptic in nature by neurologists, and where her postictal EEGs were repeatedly normal.

Her mother (II:2) had had a history of depression and anxiety since her early 20s, and had been diagnosed with bipolar disorder at age 36. Clinical examination at 52 years revealed normal neurological findings. She had not had a TIA or a stroke, and had no classical vascular risk factors.

The grandmother of the index patient (I:2) was deceased at the time of the study. Her medical records reported focal and secondary generalised seizures at age 72. There was no documented history of trauma, or of signs of a systemic or localised cerebral inflammatory or infectious metabolic

Unfortunately, no previous MRI scans were accessible for comparative analysis. The grandmother's (I:2) CT scan at age 72 showed bilateral calcifications in the cerebellum and globus pallidus, more pronounced compared to the younger members of her family, but less intense than all affected individuals in family A. Images are provided in Figure 2 and Supplementary Data 2. Furthermore, she exhibited cortical calcifications of c.1 mm diameter in the left parietal region and bilaterally in the occipital lobes. Her MRI scan at the same age showed hundreds of supratentorial micro-bleedings compatible with probable cerebral amyloid angiopathy according to the Boston 2.0 2022 criteria [30] (Supplementary Data 2 and 3). Extensive WMH were observed in the periventricular, supra- and infratentorial regions. A CT scan performed > 3 hours after the onset of expressive aphasia showed several acute microbleeds and patchy hypodensities fronto-parietally in the left hemisphere located subcortically, and in a few areas reaching to the cortex (Supplementary Data 3). CT angiography revealed no large vessel abnormalities.

Genetics

Genetic testing of clinically and radiologically unaffected family members from both families revealed the absence of these probably pathogenic variants, while all individuals carrying these variants presented with PFBC (Fig. 1). Thus, carrier status was associated with the presence of PFBC and clinical symptoms in an autosomal dominant manner, although with incomplete penetrance concerning clinical symptoms, but manifesting full penetrance in the context of brain calcifications observed via CT scans. No rare pathogenic variants in stroke genes were identified.

Pathology

Skin biopsies from the upper arms of the three mutation carriers (II:3, III:2, IV:1) and one healthy member (III:2) of family A were obtained and analysed with both light and electron microscopy. This showed a normal number and appearance of the pericytes as well as the basement membrane material of the venular and arteriolar vessels. There was no evidence of calcium in or around the vessels, and the elastic fibres appeared normal. There was no difference between the vessels of the affected members carrying the gene variant from those of the unaffected member not carrying the variant (Supplementary Data 4).

Review of published cases

We reviewed a total of 16 articles describing previous publications on patients with *PDGFB*-related PFBC. Thirty different pathogenic *PDGFB* variants have been reported. Reports on 15 variants have included brain MRI findings, and nine of these 15 reports showed hyperintensities in the white matter. Stroke or TIA was not reported. The results are set out in Table 2. The published electron microscopy images, reported as showing disturbed microvessel architecture [8] were reviewed, but we considered them to show normal findings.

Discussion

In this research paper, we describe two families with PFBC caused by novel truncating mutations in the *PDGFB* gene. All variant carriers had intracerebral calcifications in CT scans and had signs of white matter disease in MRI examinations. White matter disease has previously been reported in the majority of patients with *PDGFB*-related PFBC [8–10, 23, 24, 31] (Tab. 2). In this study, we additionally found that two of the six affected family members (family A, II:3 at age 57, and family B, I:2 at age 78) had stroke and/or TIA, one of these also had abundant cerebral microbleeds, and a third individual (family B, II:2) had ischaemic lesions on MRI that had remained clinically silent.

In the three patients who underwent angiography, clinically relevant large vessel disease was excluded, but vascular imaging was not available for the remaining individuals. Among these three individuals, two did not have any classical vascular risk factors. One of these three individuals (family A II:3) was a smoker, and had hypercholesterolaemia along with moderate radiological evidence of atherosclerotic changes in extracranial vessels not relevant for her symptomatology, and her TIA episodes consistently manifested clinically as lacunary syndromes, suggesting small vessel disease. All the cerebrovascular events in these three individuals were probably secondary to cerebrovascular small vessel disease. The possible exception is family B I:2 who had an episode of expressive aphasia and CT showing acute microbleeds and patchy subcortical and cortical hypodensities. This might be caused by large-vessel disease, but we interpreted the clinical and radiological results as being more compatible with the effect of multiple microbleeds in the same area, also indicating small vessel disease.

Our data suggests that *PDGFB* variants may increase the risk for stroke, TIA, silent brain infarcts and cerebral microbleeds, caused by cerebral small vessel disease.

White matter hyperintensities of putatively vascular origin are a well-established marker of cerebral small vessel disease [32], and have in PFBC patients been explained by the inactivation of the *PDGFB* gene [9]. PDGFB, a growth factor for mesenchymal cells, plays a crucial role in the recruitment of pericytes during angiogenesis [11], and once inactivated can cause vascular dysfunction. Studies in mouse models carrying hypomorphic *PDGFB* alleles, and in patient-derived induced pluripotent cells, showed that loss of endothelial PDGFB correlated with the presence of fewer pericytes around cerebral small vessels, and with blood-brain barrier deficiency [23, 24].

It has previously been suggested that the neurological abnormalities in patients with PFBC are caused by a slow and progressive inflammatory process in the white matter, rather than by the calcifications, which are thought to occur later in the disease [33]. In our study, one patient (family B, III:1) was longitudinally followed-up with repeated imaging, including three MRT investigations over a span of 12 years. These scans illustrated mild progression of WMH. A second variant carrier

Table 2. Previously published cases of idiopathic basal ganglia calcification-5, with *PDGFB* variants

Variant	Familial/ /sporadic	Number of families	Number of cases, sex	Clinical characteristics	Calcifications (CT)	White matter hyperintensities (MRI)	Extracerebral involvement	Reference
c.3G > A p.(Met1Ile) missense	Familial	1	3F	Cramping, headaches, neck twitches, dyslexia, short term memory problems, migraines, muscle tightening	Basal ganglia	–	–	[23]
c.3G > C p.(Met1Ile)	Familial	1	3F, 2M	Seizures (pat IV-2), migraine (all 5)	Pallidum, pulvinar, dentate	Yes, in all 5 patients	Pat III-5: capillary basal membrane abnormalities with microangiopathy	[8]
c.26T > G p.(Leu9Arg) missense	Familial	1	2M, 2F	Migraines with aura, postural tremor, depression, speech and concentration difficulties, hyperactivity disorder	Basal ganglia, white matter, thalamus, cerebellum	–	–	[23]
c.33_34delCT p.(Cys12Leufs*20) nonsense	Sporadic		1M	Dizziness, mild cognitive impairment, mild bradykinesia	Pallidum, caudate, pulvinar, dentate, subcortical and periventricular regions	No	–	[24]
c.64-3C > G intronic splicing	Familial	1	3	Not available	Yes	–	–	[34]
c.160 + 2TA intronic splicing	Familial	1	1M	Depression, anxiety, mild cognitive impairment, cerebellar ataxia	Pallidum, caudate, pulvinar, dentate	–	–	[24]
c.220G > T p.(Glu74*) nonsense	Sporadic	–	1F	Dizziness	Basal ganglia, cerebellum	–	–	[41]
c.232C > T p.(Arg78Cys) missense	Familial	3	1F, 2M	Jerky movements, stiffening of limbs, anxiety	Pallidum, caudate, thalamus, subcortical white matter	–	–	[42]
c.283G > A p.(Ala95Thr) missense	Sporadic	–	1	–	–	–	–	[34]
c.328C > G p.(Leu110Val) missense	Sporadic	–	1	–	–	–	–	[34]
c.329T > C p.Leu110Pro missense	Sporadic	–	1M	Paroxysmal dystonia, migraine with aura	'Non-specific findings'	–	–	[43]

↓

Table 2 cont. Previously published cases of idiopathic basal ganglia calcification-5, with *PDGFB* variants

Variant	Familial/ /spora-dic	Number of families	Number of cases, sex	Clinical characteristics	Calcifications (CT)	White matter hyperintens-ities (MRI)	Extracerebral involvement	Reference
c.342_343insG p.Asn115Glnfs*52 nonsense	Sporadic	–	1F	Dementia (diagnosis of Alzheimer's Disease), impaired postural reflexes, frontal lobe impairment,	Pallidum, pulvinar, caudate, dentate	Yes	–	[24]
c.356T > C p.(Leu119Pro) missense	Familial	1	3M	severe motor and language impairment, migraine	Basal ganglia, subcortical white matter, cerebral white matter	–	–	[23]
c.356T > C p.(Leu119Pro) missense	Sporadic	–	1	–	–	–	–	[34]
c.365C > T p.(Pro122Leu) missense	Familial	1	4F	Psychosis, depression, jerky ocular pursuit, chorea, midline ataxia, unsteady gait, complex motor tic, dystonic posturing of feet	Pallidum, dentate	Yes (one patient IV.4)	–	[31]
c.394G > C p.(Gly132Arg) missense	Sporadic	–	1	Asymptomatic	Pallidum, putamen, dentate nuclei	–	–	[25]
c.425G > A p.(Arg142His) missense	Sporadic	–	1	Cognitive, mood, movement disorder	Pallidum, putamen, dentate nuclei, caudate nuclei, thalamus	No		[25]
c.433C > T p.(Gln145*) nonsense	Familial	1	3M, 3F	Chorea, orobuccal dyskinesia, psychiatric symptoms, gait problems, parkinsonism, dysexecutive syndrome, tremor. 1 asymptomatic	Basal ganglia, thalamus, cerebellum, cerebral white matter, subcortical white matter	–	–	[23]
c.439C > T p.(Gln147*) nonsense	Sporadic (de novo)	1	1F	Asymptomatic	Pallidum, putamen, caudate	Yes (very discrete)	–	[9]
c.439C > T p.(Gln147*) nonsense	Sporadic	–	1	–	–		–	[34]
c.445C > T p.(Arg149*) nonsense	NA	2	4M	Depression, dysexecutive syndrome with memory impairment, anxiety, depression, akinetic-rigid syndrome, tremor	Basal ganglia	Yes	–	[23, 25]

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Table 2 cont. Previously published cases of idiopathic basal ganglia calcification-5, with *PDGFB* variants

Variant	Familial/ /sporadic	Number of families	Number of cases, sex	Clinical characteristics	Calcifications (CT)	White matter hyperintensities (MRI)	Extracerebral involvement	Reference
c.446 + 1G > A intronic splicing, skipping of exon4, inducing frameshift	Familial	1	2F	Migraine, depression	Pallidum, putamen, thalamus, dentate nuclei, cortex	Yes	–	[25]
c.456 + 1G > A intronic splicing	Sporadic	–	1F	Headaches, nausea, slowness in writing	Basal ganglia, thalamus, cerebellum	No	–	[4]
c.457 – 1G > T intronic splicing	Familial	1	2F, 1M	Headache, behavioural changes (refusal to attend school)	'Spotty' lesions in pallidum, caudate, thalamus, dentate nuclei	Yes	–	[24]
c.602 – 1G > T intronic splicing	Sporadic	2	1F	Depression	Pallidum, putamen, caudate, dentate	–	Myasthenia gravis	[44]
c.610C > A p.(Pro204Thr) missense	Familial	–	1M	Asymptomatic	Yes	–	–	[41]
c.724T > C p.(Ter242GlnExt*89) stop loss	Sporadic	–	1	Seizure, migraine, depression, cognitive impairment	Pallidum, putamen, caudate, dentate	No	–	[25]
c.726G > C p.(242TyrExt*89) stop loss	Familial	2	6M, 3F	Dyskinesia, pyramidal signs, tics, alcohol abuse, aneurysm in medial cerebral artery	Basal ganglia, cerebellum, cerebral white matter	Yes	–	[23, 25]
Exon 2–5 deletion	Sporadic	–	1F	Memory impairment, bipolar disorder, gait disorder, subtle static cerebellar syndrome	Pallidum, putamen, cerebellum	Yes	–	[9]
22q13.1 deletion including entire *PDGFB* gene	Familial	1	1M	Blepharospasm, headache, paroxysmal dystonia	Basal ganglia and dentate nuclei	No	–	[21]

CT — computed tomography; F — female; M — male; MRI — magnetic resonance imaging

did not show radiological progression of WMH between the ages of 45 and 51. Regarding the brain calcifications, moderate progress was observed in parallel with clinical progression (Supplementary Data 2), consistent with previous observations by others [19, 34–36].

We were unable to establish a reliable correlation between the symptomatology and radiologically detected vascular changes, nor could we determine the importance of vascular process in disease progression.

Apart from the presence of WMH, postmortem neuropathological investigations of individuals with PFBC have revealed pronounced vascular changes in the brain, including calcium deposits and degeneration of brain capillaries and arterioles [2, 17, 18, 37, 38]. These findings have also confirmed the presence of a degenerative small vessel disease. Whether this vascular process is limited to the brain, or is rather part of a systemic vascular disease, remains unclear. Studies performed on mouse models with partly or completely inactivated *PDGFB* have reported the involvement of extracerebral microvessels in the retina and renal glomeruli [11]. A previous study of skin biopsies from one patient with a *PDGFB* variant causing PFBC reported thickening of the basement membrane and membrane fragmentations in the vessels, which was interpreted as signs of extracerebral microangiopathy [8].

However, skin biopsies obtained from our three symptomatic and one asymptomatic individuals showed no abnormality in the basal lamina, nor did they indicate differences in the number or appearance of pericytes per vessel (Supplementary Data 4). An expert review of the published images [8] could not confirm any abnormality. In our patients with *PDGFB* pathogenic variants, we found no evidence for extracerebral vascular involvement. We have not been able to investigate further neuropathological evidence regarding the possible presence of systemic vascular disorder from any other organ or system apart from the skin.

Our results are difficult to generalise, as we were studying the occurrence of stroke and TIA, two very common conditions in the general population, in only two unrelated families with rare *PDGFB* variants. However, previous publications have reported cases of individuals with PFBC who have presented with ischaemic or haemorrhagic stroke, TIA, and/or intracerebral aneurysms [12–18].

While there have been several previous case reports on patients with WMH acting as warning signs of underlying cerebral vascular conditions and PFBC [11–16], the occurrence of basal ganglia calcifications has to date been considered an incidental finding in patients with cerebral vascular disease and stroke.

Our study adds to the existing literature three cases presenting with TIA, stroke, cerebral ischaemia and microbleeds putatively complicating a cerebral small vascular degenerative process in patients with bilateral brain calcifications.

Clinical implications/future directions

Our study highlights that *PDGFB*-related PFBC is a cerebral small vessel disease that may manifest with stroke and TIA, microbleeds and silent brain infarcts. The patients in this study had normal skin microvasculature, which does not suggest systemic vasculopathy as found in other genetic forms of cerebral small vessel disease, including CADASIL or COL4A1/COL4A2-related disorder [39, 40].

Article information

Availability of data and materials: *Original data presented in this study is included in the article and as Supplementary Material. Further inquiries may be directed to the corresponding author.*

Ethics approval and consent to participate: *This study was approved by the Regional Ethical Review Board in Lund, Sweden, and written informed consent was obtained from all participants.*

Authors' contributions: *M.Y.F.: major role in acquisition of clinical data, interpretation of data, drafting and revising manuscript for content; J.W.: interpretation of radiological investigations, review of manuscript; E.E.: obtained and interpreted pathological examination, review of manuscript; I.B.: interpretation of pathological examination, review of manuscript; A.P.: study concept and design, major role in acquisition of clinical and genetic data, interpretation of data, revising manuscript for content; A.I.: study concept and design, major role in acquisition of clinical and genetic data, interpretation of data, drafting and revising manuscript for content, obtaining funding.*

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Conflicts of interest: *None.*

Supplementary material: *Yes.*

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Changes in frontal aslant tract tractography in selected types of brain tumours

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ABSTRACT

Aim of the study. To present differences in frontal aslant tract (FAT) tractography among patients diagnosed with primary brain tumours and metastatic brain tumours.

Material and methods. The analysis included 38 patients diagnosed with a frontal brain tumour. A control group of 30 healthy patients was also considered. The FAT was delineated, taking into account ROI 1 — the superior frontal gyrus, and ROI 2 — SMA. Endpoints were determined on the pars opercularis and pars triangularis of the inferior frontal gyrus. FAT was delineated in four different ways for each patient.

Results. In the group of patients with a brain tumour, a lower volume of FAT and a reduced quantity of fibres were observed compared to the control group. Comparison of the examined parameters between patients with glioblastoma and metastasis revealed statistically significant differences for MD ($p < 0.001$) regardless of the selected projection.

Conclusions. The difference in MD (mean diffusivity) among patients with metastatic tumours may be related to an increased oedema zone.

Keywords: tractography, DTI, FAT, brain tumour

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Introduction

The frontal aslant tract (FAT) is a short fibre tract predominantly located in the left hemisphere, first described by Catani in 2012. It connects the superior frontal gyrus (SFG) with the inferior frontal gyrus (IFG) and supplementary motor area (SMA). Extensive analysis of the fibre course, fMRI findings, and direct cortical stimulation have demonstrated a significant role played by the FAT in speech processing [1].

The role of the FAT extends beyond mere connectivity, as it serves as a critical connection between motor planning, initiation, and language control. FAT is involved in various language functions, particularly speech production and language control. The pre-SMA, connected to the IFG through the FAT, plays a role in several aspects of language processing, such as articulatory planning and control. Conversely, the IFG plays a vital role in language production, speech fluency, and language control processes [2].

The FAT facilitates the transformation of linguistic intentions into motor plans, ensuring the seamless execution of speech production [3].

Despite the growing interest and an increase in publications on the FAT, there remains limited knowledge about this white matter bundle in clinical practice. FAT exhibits

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connections to the upper frontal lobe, lower frontal lobe, SMA, and pre-SMA. Damage to these white matter connections can have more significant clinical effects compared to damage to the cerebral cortex. This is because the consequences of cortical damage can be mitigated over time due to the high plasticity of the cortex [4].

Therefore, and due to the numerous functions performed by the FAT, there is a need to share knowledge about the anatomy of the SMA region and related white matter pathways. This subject should be particularly well understood, especially in the case of frontal lobe tumour surgery [5].

The aim of this study was to present the anatomical variability of the FAT, with a particular emphasis on demonstrating the length and volume of the pathway based on the chosen region of interest (ROI).

Material and methods

Patients treated for frontal lobe tumours at a single institution were retrospectively reviewed. A total of 38 adult patients (20 males, 18 females) who underwent resection surgery at the Neurosurgery and Neurology Department of Jan Biziel University Hospital in Bydgoszcz, Poland (blinded for peer review purposes) between 2020 and 2022 were included in the study. The mean age in the treated group was 56.93 ± 15.46 years. The mean standard volume of the tumour was 3.517cc ± 2.227cc.

The study focused on patients diagnosed with a brain tumour involving the frontal lobe. Among them, 17 patients had a tumour affecting the right frontal lobe, while 21 patients had a tumour affecting the left frontal lobe. All patients underwent surgical treatment.

MRI and DTI acquisition

In this study, MRI and DTI acquisition parameters similar to those previously developed by the authors in other publications were used. This is because all investigations in this study, as well as in the authors' previous publications, were conducted using the same MRI scanner, and tractography was generated using the same software (DSI studio). Therefore, the methodology section in the article has already been published.

All patients underwent imaging at 3.0 T using a Philips Ingenia scanner manufactured in 2015 and a 32-channel head coil. The head was scanned without any angulation, with an angle of 0° in all directions (AP, RL, FH).

A deterministic fibre tracking method was used with a DTI diffusion scheme and a total of 60 diffusion sampling directions. The in-plane resolution was 1.87514 mm, and the slice thickness was 2 mm. The angular threshold for fibre tracking was set at 60 degrees. Regions of interest were automatically defined based on an anatomical atlas loaded into the DSI Studio program (http://dsi-studio.labsolver.org) [6–8].

Statistical analysis

The statistical analysis was performed using Statistica 13 software. The Shapiro-Wilk test was used to assess the normal distribution of qualitative data. Parametric tests, such as Student's t-test for dependent and independent variables, and Pearson's rank correlation test, were employed if the data exhibited normal distribution.

For data that did not follow a normal distribution, non-parametric tests were used. The Mann-Whitney test was used for group comparisons, the Wilcoxon test for dependent variables, and the Spearman's rank correlation test for analysing correlations. A significance level of $p < 0.05$ was considered for all analyses.

DTI analysis

All analysis of images was provided using DSI Studio software (dsistudio.labsolver.org, BSD License.). The anisotropy threshold was determined automatically by the software. A total of 15,000 tracts were calculated. When reconstructing the FAT, we obtained tract statistics, including the number of tracks, the mean length, and the volume of the FAT [8].

Fibre tracking

We reconstructed the FAT based on ROIs: ROI 1 - gyrus frontalis superior (SFG) and ROI 2 - SMA. End points were based on pars opercularis of gyrus frontalis inferior (IFG-op) and pars triangularis of gyrus frontalis inferior (IFG-tri).

Start points were designated as: SFG and SMA. The end points were based on: gyrus frontalis inferior pars triangularis (IFG-tri) and gyrus frontalis inferior pars opercularis (IFG-op). By mixing and matching start and end points, we obtained FAT for analysis by four different types in each patient (Fig. 1).

Results

The FAT was reconstructed using four different algorithms for each patient in the study.

Among the 38 patients, 14 were diagnosed with primary tumours, specifically glioblastoma multiforme WHO IV (eight patients IDH-mutant, and six patients IDH wildtype), and five patients had astrocytoma anaplasticum WHO III. Additionally, 19 patients had metastatic tumours, including 10 with lung cancer metastasis, six with colorectal cancer, and three with melanoma.

Comparisons of fractional anisotropy (FA) and mean diffusivity (MD) in both groups are set out in Table 1.

In the study group, the number of fibres and volume of FAT were lower than in the control group, regardless of the chosen method for FAT plotting. Additionally, a significant statistical difference ($p < 0.05$) in the number of fibres was identified between patients in the control and study groups, in each of the selected projections. Regarding the volume of the tract, statistical significance was achieved in the SMA-IFG

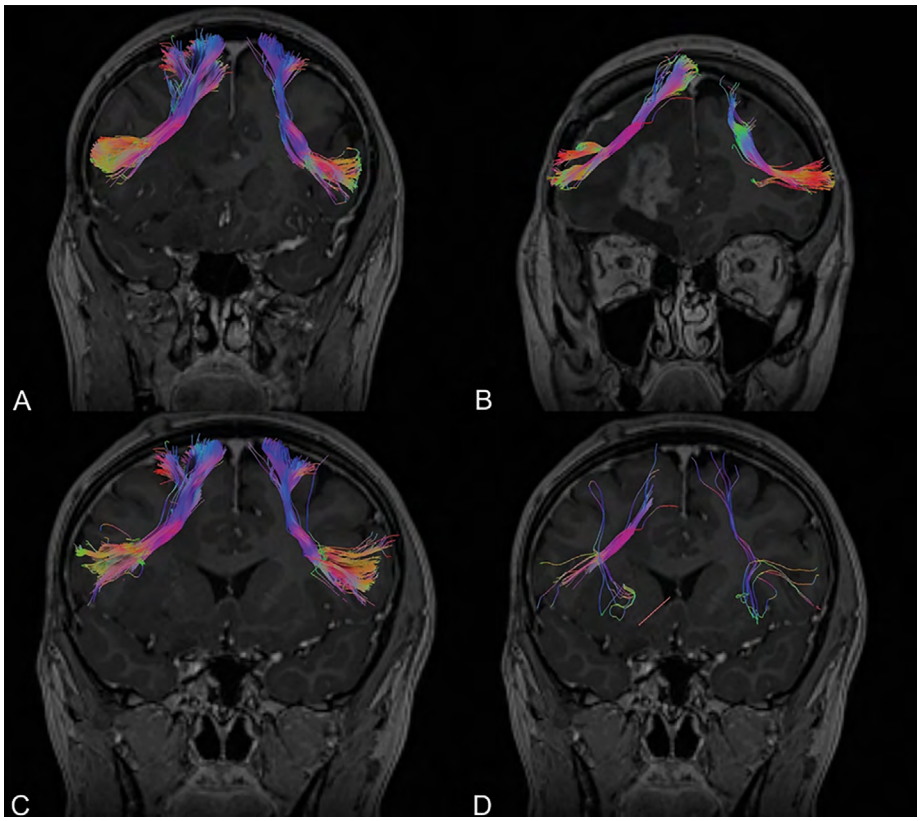

Figure 1. F rontal aslant tract (FAT); **A.** ROI 1 — gyrus frontalis superior with end point-pars opercularis of gyrus frontalis inferior (IPG-op), **B.** ROI 1 with end point-pars triangularis of gyrus frontalis inferior (IPG-tri), **C.** ROI 2 — SMA with IPG-op, **D.** ROI 2 with IPG-tri

Table 1. Comparison of FA and MD values in study and control groups depending on region of interest and endpoints

	MD study group			MD control group			p-value	FA study group			FA control group			p-value
		SD	Me		SD	Me			SD	Me		SD	Me	
SFG–IFGop	0.77	0.13	0.72	0.49	0.06	0.50	< 0.001	0.42	0.05	0.42	0.69	0.09	0.69	< 0.001
SFG–IFG tra	0.78	0.09	0.77	0.48	0.07	0.49	< 0.001	0.42	0.04	0.42	0.74	0.06	0.74	< 0.001
SMA–IFGop	0.75	0.09	0.72	0.48	0.07	0.49	< 0.001	0.44	0.05	0.46	0.76	0.07	0.78	< 0.001
SMA–IFG tra	0.77	0.06	0.79	0.47	0.08	0.49	< 0.001	0.46	0.06	0.46	0.76	0.07	0.79	< 0.001

MD — mean diffusivity; FA — fractional anisotropy; SD — standard deviation; Me — median; SFG — superior frontal gyrus; IFG — inferior frontal gyrus; SMA — supplementary motor area

tri projection ($p < 0.001$; 464.8 ± 92.5 *vs.* 632.3 ± 89.6; study group *vs.* control group), SMA-IFG op projection ($p < 0.001$; 2,738.3 ± 1,374.7 *vs.* 5,028.3 ± 1,238.1; study group *vs.* control group), and SFG-IFG op projection ($p < 0.001$; 40,806.7 ± 9,284.5 *vs.* 52,831.7 ± 2,399.0; study group *vs.* control group). However, in terms of fibre length, the threshold of statistical significance was reached only in the SMA-IFG projection ($p = 0.045$; 81.8 ± 6.4 *vs.* 86.5 ± 5.7; study group *vs.* control group).

Comparison of the examined parameters between patients with glioblastoma and metastasis revealed statistically significant differences for MD ($p < 0.001$) regardless of the selected projection. The specific values are set out in Table 2. However, no statistically significant differences were found for the remaining parameters in the projections used, except for the SMA-IFG op projection. In this projection, statistically significant differences were also identified in the number of fibres ($p = 0.028$; 179.6 ± 90.0 *vs.* 304.6 ± 106.5; glioblastoma *vs.*

Table 2. Comparison of FA and MD values depending on regions of interest and endpoints in group of patients with primary tumours and metastases

	MD GBM group			MD metastasis group			p-value	FA GBM group			FA metastasis group			p-value
		SD	Me		SD	Me			SD	Me		SD	Me	
SFG–IFGop	0.66	0.04	0.67	0.89	0.05	0.89	< 0.001	0.42	0.06	0.41	0.42	0.03	0.42	0.985
SFG–IFG tra	0.70	0.03	0.70	0.86	0.05	0.84	< 0.001	0.42	0.04	0.43	0.42	0.03	0.41	0.874
SMA–IFGop	0.68	0.04	0.69	0.84	0.04	0.82	< 0.001	0.44	0.06	0.43	0.45	0.03	0.46	0.862
SMA–IFG tra	0.72	0.04	0.71	0.82	0.03	0.82	< 0.001	0.46	0.08	0.45	0.46	0.03	0.46	0.875

MD — mean diffusivity; FA — fractional anisotropy; SD — standard deviation; Me — median; SFG — superior frontal gyrus; GBM — glioblastoma; IFG — inferior frontal gyrus; SMA — supplementary motor area

metastasis) and tract volume ($p = 0.032$; 2,040.8 ± 1,042.0 *vs.* 3,535.4 ± 1,323.9; glioblastoma *vs.* metastasis).

Based on analysis of the results obtained in the group of cancer patients, statistically significant differences ($p < 0.05$) were observed between the results recorded in the SFG-IFG op and SMA-IFG op ROIs for the parameters related to the number of fibres ($p < 0.001$; 1,548.5 ± 397.1 *vs.* 237.9 ± 114.3; SFG *vs.* SMA) and the tract volume ($p < 0.001$; 40,806.7 ± 9,284.5 *vs.* 2,738.3 ± 1,374.7; SFG *vs.* SMA). However, the parameters MD, FA, and fibre length did not reach the level of statistical significance. A strong positive correlation was identified for MD using Pearson's rank correlation test ($0.9 < R < 1.0$), and this reached statistical significance ($p < 0.001$).

In the same group, when analysing data obtained in the SFG-IFG tra *vs.* SMA-IFG tra ROIs, statistical significance ($p < 0.05$) was observed for the number of fibres ($p < 0.001$; 470.1 ± 106.8 *vs.* 24.8 ± 11.0; SFG *vs.* SMA) and the tract volume ($p = 0.001$; 6,288.5 ± 3,790.3 *vs.* 464.8 ± 92.5; SFG *vs.* SMA), as well as for fibre length ($p = 0.008$; 91.41 ± 3.92 *vs.* 87.18 ± 6.544; SFG *vs.* SMA) and FA ($p = 0.037$; 0.42 ± 0.004 *vs.* 0.46 ± 0.006; SFG *vs.* SMA). However, MD and fibre length analysis results in the above ROIs did not reach statistical significance. Additionally, two statistically significant ($p < 0.05$) positive correlations were identified for fibre length ($p = 0.022$) and MD ($p < 0.001$).

Discussion

In this study, we employed DTI diffusion tractography as a valuable non-invasive technique for mapping white matter fibres in patients with brain tumours [9, 10]. This method plays a critical role in surgical planning, allowing for a balance between radical tumour resection and the preservation of neuronal functions [11, 12]. However, DTI has limitations that can impact the quality of white matter fibre visualisation. Factors such as reduced fractional anisotropy (FA), mass effect, tumour infiltration, neoplastic vascular oedema, and destruction of white matter tracts can disrupt the spatial orientation of fibres and alter the direction of water diffusion, thereby affecting the effectiveness of the technique [13–16].

DTI has shown promise in the differential diagnosis of glioblastoma and metastatic tumours, but consistent data from independent studies is lacking [17]. Our results comparing glioblastoma and metastatic tumours demonstrated a statistically significant difference in the MD parameter across all four projections, with higher average diffusivity values observed in metastatic tumours [17].

These findings differ from the existing literature, highlighting the lack of consensus regarding DTI metrics when comparing glioblastoma and metastatic tumours [18–20]. Byrnes et al. [21] reported higher MD values in the glioblastoma area, with even higher values in the tissue surrounding the metastasis compared to the peri-glioblastoma region.

In our study, we did not find statistically significant differences in the FA parameter between patients with glioblastoma and metastases. Moreover, the values obtained were practically identical, regardless of the defined fibre assignment by continuous tracking (FAT) projections. This result may be attributable to the small sample size in our study. However, existing literature suggests higher FA values in glioblastoma compared to metastatic tumours [22–24]. The FA parameter reflects water diffusion direction for each voxel, determining the degree of anisotropy in the studied structure [25]. Several variables, such as fibre structural integrity, packing density, myelination degree, and fibre diameter, significantly influence this parameter [26–28]. Wang et al. [29] proposed that the increase in fractional anisotropy in glioblastoma might be related to the spatial orientation of the tumour-overproduced extracellular matrix infiltrating adjacent healthy tissue, suggesting a relationship between scalar values and cell orientation in the imaged voxel. These authors also reported significantly higher FA values in glioblastoma compared to metastatic tumours, and did not find statistically significant differences in the MD parameter between the two. However, there is a lack of consistency in the available literature regarding FA and MD parameters. For instance, Wang et al. [29] and Reiche et al. [30] reported lower fractional anisotropy in gliomas compared to brain metastases.

The heterogeneity of results obtained in subsequent studies may be attributed to differences in the choice of techniques for

defining the ROI, and the small size of patient groups. Various hypotheses have been proposed to explain the inconsistency of results. Reiche et al. [30] suggested that discrepancies arise from the inclusion of different tumour areas in the study. The solid part of the tumour, which corresponds to the enhanced area, contains fibres that have been damaged or displaced by tumour expansion. On the other hand, the non-enhanced area consists of both solid tumour tissue and remnants of white matter fibres, which can result in increased FA values [30–32]. On the other hand, Wang et al. [29] suggested that higher FA values result from increased cellularity in glioblastoma compared to metastasis, leading to a reduction in extracellular space volume and an increase in water diffusion directivity [31].

Higher FA values have also been associated with highly differentiated brain tumours, along with lower MD values compared to intracranial metastases, probably due to differences in tumour structure organisation [32]. However, even in this case, the data on DTI metrics for differentiating high-grade gliomas from metastases is inconsistent [33].

It is important to consider that developing tumours impact upon surrounding tissues, resulting in changes such as vascular oedema and fibre infiltration, sometimes leading to damage [14–16]. These changes are reflected in FA and MD values. Byrnes et al. [21] demonstrated significant differences in these parameters in the oedema area surrounding glioblastoma and metastases. MD was significantly higher, and FA was significantly reduced, in the oedema surrounding metastases compared to oedema around glioblastoma multiforme. Additionally, the glioblastoma area showed significantly higher MD. Based on these findings, the authors concluded that simultaneous determination of DTI metrics in both the tumour area and adjacent peritumoural tissue could serve as a reliable tool for differentiating glioblastoma from intracranial metastasis. Lu et al. [34] suggested that lower FA values in the tissue around glioblastoma are a consequence of the destructive effect of tumour-derived cells on white matter fibres.

Furthermore, it should be considered whether the histological type of intratumoural metastasis may influence DTI parameters in the surrounding tissue.

During our analysis, we observed a statistically significant difference in the MD parameter between metastatic tumours and primary lesions, consistently observed in each selected projection.

Another proposed explanation for the differences in FA and MD between primary tumours and metastases is the dissimilarity in the nature of oedema surrounding the lesions. Peritumoural oedema predominantly forms around metastatic tumours, leading to an increase in MD. In contrast, tumour infiltration oedema, characteristic of glioblastoma, results in lower MD values. Additionally, the FA value around the tumour does not show a significant difference for both types of lesions due to the overlapping effects of both types of oedema to varying degrees [35]. This theory partly explains our MD results for metastatic tumours.

Conclusions

The presence of a brain tumour affects the parameters of FAT tractography, leading to a reduction in the volume of the pathway and the number of fibres within the bundle. Furthermore, we observed differences in MD depending on the type of brain tumour. The difference in tractography parameters in the study group may be associated with the tumour infiltration into the FAT and the oedematous zone around the tumour.

Article information

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Ethics statement*: All patients signed informed consent to participate in the study. Consent for the study was issued by the local bioethics committee with the number KB 532.*

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Analysis of seroconversion following COVID-19 vaccination among multiple sclerosis patients treated with disease--modifying therapies in Poland

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ABSTRACT

Clinical rationale for the study. The rapid spread of SARS-CoV-2 throughout the world has highlighted the importance of vaccinations to control the pandemic and to protect people at risk for severe disease courses. Disease-modifying therapies (DMT) in multiple sclerosis (MS), whether immunomodulatory or immunosuppressive, may affect the immune response. Therefore, the question arose as to whether these vaccinations would be effective.

Aim of the study. We planned a study to assess the immune response to SARS-CoV-2 vaccines by type of therapy.

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Material and methods. Participants were recruited from 14 Polish MS centres. The data was obtained by neurologists using a questionnaire. We collected data on 353 MS patients (269 females, 84 males) who received complete primary SARS-CoV-2 vaccination. All persons with MS (PwMS) were treated with disease-modifying therapies.

Results. 305 out of 353 PwMS (86.4%) were positive for IgG Abs against SARS-CoV-2 S domain S1 Ag after vaccination. A strong immune response was noted in 129 PwMS (36.5%). The rate of seroconversion after SARS-CoV-2 vaccination in PwMS who received immunomodulatory DMTs (interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, natalizumab) was 91.5%, in PwMS receiving immune reconstruction therapy (alemtuzumab, cladribine) was 92%, and in immunosuppressive DMTs (fingolimod, ocrelizumab), the seroconversion rate was 59%.

Conclusions and clinical implications. Our study shows that, in PwMS receiving immunomodulatory therapy, the immune response to vaccination is generally excellent. Even in immunosuppressive patients, seroconversion is satisfactory.

Keywords: multiple sclerosis, disease-modifying therapies, vaccines, COVID-19, immune response, antibodies, immunosuppressive therapy

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Introduction

The COVID-19 pandemic has caused significant morbidity and mortality worldwide. Vaccination is the primary method for preventing and controlling the pandemic, but vaccination in autoimmune diseases, including multiple sclerosis, has posed a significant challenge. Although recommended by international MS societies and expert panels [1, 2], vaccinating against SARS-CoV-2 is associated with significant patient concerns about the safety of vaccines. In recent years, research has been carried out on, inter alia, vaccination against influenza or hepatitis. However, the COVID-19 pandemic made it imperative that patients with multiple sclerosis be immunised rapidly. At that time, there were many questions regarding the safety and effectiveness of vaccines, especially since a new type of vaccination — the mRNA vaccine — was being widely used. There is international consensus that mRNA vaccinations are safe in PwMS [1, 3, 4]. While COVID-19 infections themselves may be associated with an increased relapse risk, this has not been observed for vaccinations [5]. Unfortunately, some patients, especially those who had been ill for longer, were afraid of vaccinations. These concerns also arose from the level of acceptance of COVID-19 vaccination in society [6, 7]. Disease-modifying therapies in multiple sclerosis are often immunosuppressive and may therefore influence the immune response. The main question was whether all vaccines were equally effective and recommended for PwMS. Another question was the influence of other factors such as age, the severity of the autoimmune disease, and comorbidities. Therefore, we analysed immune response to SARS-CoV-2 vaccination in a cohort of Polish PwMS.

The Multiple Sclerosis and Neuroimmunology Section of the Polish Neurological Society reacted very quickly to the new situation in which doctors and PwMS found themselves at the outbreak of the pandemic. As soon as April 2020, there was a statement on the treatment of MS in the case of the risk of infection with the coronavirus causing COVID-19, and in February 2021, a statement on the vaccination of patients with MS was released [5]. It was also decided to collect data from PwMS on the safety of vaccination [2, 3, 9], as well as its effectiveness.

Material and methods

The Multiple Sclerosis and Neuroimmunology Section of the Polish Neurological Society published an announcement about the study at www.ptneuro.pl, and every MS centre in Poland was invited to participate. Eventually, participants were recruited from 14 Polish MS centres, and data was obtained by neurologists using a questionnaire. The same questionnaire was used at each MS centre. Patients were recruited to the study during standard visits to a particular MS centre. During these visits, blood samples were taken, including for antibody testing. PwMS diagnosed according to the 2010 and 2017 McDonald criteria who had received the anti-SARS-CoV-2 vaccines and who underwent serological testing for SARS-CoV-22 neutralising antibodies, i.e. anti-Spike protein (anti-S), at least one month following the completion of the vaccination cycle (two doses) were included.

All PwMS were treated with one of the DMTs available in Poland (interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, alemtuzumab, cladribine, natalizumab, or ocrelizumab). Disability was assessed using the Expanded Disability Status Scale (EDSS).

We collected patient demographics, data regarding specific features of multiple sclerosis, comorbidities, information about vaccination against SARS-CoV-2, the presence of leukopenia or lymphopenia, SARS-CoV-2 infection before vaccination, relapse and treatment with corticosteroids within the three months prior to vaccination, and anti-SARS-CoV-2 antibodies concentration.

We collected data until 15 January, 2022. By that time in Poland, most patients had received two doses of the SARS-CoV-2 vaccination; hence, data on the booster dose was not taken into account. The study was conducted retrospectively. The study was approved by the Bioethics Committee at the Medical University of Warsaw, Poland.

The presence and titre of SARS-Cov2-neutralising (anti-S) antibody response were measured. Anti-S antibody testing was performed in accredited medical laboratories with electrochemiluminescence immunoassay (ECLIA)-based methods (commercial kits Elecsys, Roche Diagnostics Ltd, Switzerland) or anti-SARS-CoV-2 QuantiVac ELISA IgG (Euroimmun); antibody titres were expressed in binding antibody units per mL (BAU/mL). Antibody titres below the lower detection cut-off, according to the manufacturer's instructions, were recorded as negative.

Categorical variables were characterised by frequency and percentage. The collected research material was developed with the use of basic descriptive statistics, presenting the values of mean and standard deviations and other parameters. A sample t-test was used to compare the differences between the groups that were independent with normal distribution. In the absence of such a distribution (Gaussian), the non-parametric Mann–Whitney U test was used. Pearson's chi-squared test of independence was used to compare the incidence. A significance level alpha = 0.05 was assumed. All calculations were performed using Statistica 13.0 software. First of all, we assessed whether the PwMS at least developed positive antibodies. Among these PwMS, we selected a group in whom the immune response was very strong (the maximum concentration of anti-SARS-CoV-2 antibodies specified by the manufacturer of the test). The presence or absence of an immune response and its strength was correlated with various variables such as age, sex, course of multiple sclerosis, neurological status (EDSS), type of vaccine used, comorbidities, any relapse treated with corticosteroids in the three months prior to vaccination, type of therapy, presence of leukopenia or lymphopenia, and previous history of COVID-19.

Results

We collected data on 353 PwMS (269 females, 84 males) who received the complete primary SARS-CoV-2 vaccination. The mean age of patients was 41.5 ± 10.4 years (range, 19–67; median, 41.0), the mean duration of the disease was 9.8 ± 6.8 years (range, 1–48; median, 9.0), and the mean EDSS, 3.2 ± 1.2 (range, 0–7.0; median, 3.0). The PwMS had different courses of the disease: relapsing–remitting — 291 people; secondary progressive — 46; and primary progressive — 16. Demographic and clinical data is set out in Table 1. The anti-SARS-CoV-2 antibody concentration was assessed a mean 3.2 ± 1.9 months (median, 3 months; range, 1–10) after the second dose of vaccination. In 80% of cases, antibodies were measured 1-5 months after the second dose of vaccination

According to the local regulations, patients received two doses of the Comirnaty (BioNTech/Pfizer), the Moderna, or the Vaxzevria (AstraZeneca) COVID-19 vaccine or one dose of the Johnson & Johnson's Janssen COVID-19 vaccine. Most PwMS (n = 243) were vaccinated with the Comirnaty vaccine (BioNTech/Pfizer), 64 received the COVID-19 AstraZeneca (Vaxzevria) vaccine, 36 PwMS received the Moderna COVID-19 vaccine, and eight received the Johnson & Johnson's Janssen COVID-19 vaccine. The system of administering COVID-19 vaccines in Poland was nationwide and the intervals between doses were strictly controlled. The interval between two doses of the Comirnaty and the Moderna vaccine was five weeks. For the COVID-19 AstraZeneca vaccine, it was 12 weeks. All PwMS received vaccination in this regime.

For ocrelizumab, which is given every six months, the interval between the last dose of the drug and the first dose of vaccination was on average 4.5 months (median, 4; range, 3–6).

Most PwMS (n = 216) had no comorbidities. Arterial hypertension, hyperlipidemia, and thyroid disease were reported in 137 persons. A history of COVID-19 infection confirmed by PCR was demonstrated in 116 PwMS.

Twenty-six PwMS had a relapse of MS in the three months prior to vaccination, of whom 22 were treated with intravenous methylprednisolone (1,000 mg/day for five days).

All the PwMS were treated with DMT (see Tab. 1). Seventy-four patients had lymphopenia: grade 1 (800–999/mm^3) or 2 (500–799/mm^3) — 70 persons; grade 3 (200–499mm^3) — four persons; and grade 4 (< 200 mm^3) — 0. PwMS with lymphopenia had been treated with the following drugs: interferon beta — 6; glatiramer acetate — 0; teriflunomide — 9; natalizumab — 0; fingolimod — 23; alemtuzumab — 0; ocrelizumab — 8; and cladribine — 3. Fifty-one patients had leukopenia: grade 1 (3.0–3.9 × 10^3/mm^3) — 43; and grade 2 (2.0–2.9 × 10^3/mm^3) — 8. PwMS with leukopenia had been treated with the following drugs: interferon beta — 5; glatiramer acetate — 0; teriflunomide — 8; natalizumab — 0; fingolimod — 11; alemtuzumab — 0; ocrelizumab — 3; and cladribine — 9.

In total, 305 out of 353 PwMS (86.4%) were positive for IgG Abs against SARS-CoV-2 S domain S1 Ag after vaccination. A strong immune response was noted in 129 PwMS (36.5%).

Seroconversion was not influenced by gender, age, duration of MS, course of multiple sclerosis, neurological status (EDSS), comorbidities, MS relapse treated with intravenous corticosteroids in the three months prior to vaccination, or type of vaccination. The correlation between a previous COVID-19 infection and the presence of antibodies after vaccination was not statistically significant (p = 0.089). The type of therapy and the presence of lymphopenia had a significant influence on the occurrence of anti-SARS-CoV-2 antibodies.

Forty-eight PwMS did not develop antibodies despite undergoing a complete vaccination course. Patients were treated with the following drugs: interferon beta — 4 (10.8% of patients); glatiramer acetate — 1 (6.2%); teriflunomide

Table 1. Demographics and clinical characteristics of patients with MS

	N	%	Mean	Median	SD
Study population	353	100%			
Female	269	76.2			
Male	84	23.8			
Age (years)			41.57	41.0	10.42
EDSS			3.19	3.0	1.27
Disease duration			9.87	9.0	6.8
MS relapses	26	7.4			
Treatment with intravenous corticosteroids	22	6.2			
Comorbidities	137	38.8			
Disease course					
RRMS	291	82.43			
SPMS	46	13.03			
PPMS	16	4.53			
DMTs					
Interferon beta	37	10.48			
Glatiramer acetate	16	4.53			
Dimethyl fumarate	115	32.57			
Teriflunomide	72	20.39			
Natalizumab	44	12.46			
Fingolimod	33	9.34			
Ocrelizumab	23	6.51			
Alemtuzumab	3	0.84			
Cladribine	9	2.54			
Confirmed COVID-19	116	32.86			
Lymphopenia before vaccination	74	20.96			
Grade 1 or 2	70	19.83			
Grade 3	4	1.13			
Grade 4	0	0			
Type of vaccination					
mRNA vaccine	279	79.03			
Vector-based vaccine	74	20.97			

DMTs — disease-modifying therapies; EDSS — expanded disability status scale; MS — multiple sclerosis; PPMS — primary progressive multiple sclerosis; RRMS — relapsing-remitting multiple sclerosis; SD — standard deviation; SPMS — secondary progressive multiple sclerosis

— 7 (9.7%); dimethyl fumarate — 12 (10.5%); fingolimod — 14 (42.4%); ocrelizumab — 9 (39.1%); and cladribine — 1 (11.1%). According to these figures, treatment with interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, alemtuzumab, or cladribine did not significantly affect the immune response against the SARS-CoV-2 virus. An interesting result was obtained in PwMS treated with natalizumab — 100% of persons had positive antibodies against SARS-CoV-2 ($p = 0.004$). A similar situation occurred in PwMS treated with alemtuzumab, but the number of persons was small ($n = 3$), and all patients had received the last course of the drug more than 18 months earlier. Treatment with fingolimod or ocrelizumab was associated with a decreased immune response (fingolimod $p < 0.0001$; ocrelizumab $p = 0.0002$).

The rate of seroconversion after SARS-CoV-2 vaccination in PwMS who received immunomodulatory DMTs (interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, natalizumab) was 91.5%, in PwMS receiving immune reconstruction therapy (alemtuzumab, cladribine) was 92%, and in immunosuppressive DMTs (fingolimod, ocrelizumab), the seroconversion rate was 59%.

The factors that influenced the development of a strong immune response after vaccination against COVID-19 (the maximum antibody concentration provided by the manufacturer of a given test) were also assessed. In this case, this was also not affected by gender, age, duration of MS, EDSS, comorbidities, form of multiple sclerosis, disease relapse treated with intravenous corticosteroids within the three months

Table 2. Characteristics of PwMS depending on immune response to COVID-19 vaccination

	IgG Abs against SARS-CoV-2		
	Negative n (%)	**Positive n (%)**	**Maximum concentration specified by manufacturer of test n (%)**
Study population	48 (13.6)	305 (86.4)	129 (36.5)
Female	39	230	102
Male	9	75	27
Age (years)	41.66	41.55	40.97
EDSS	3.15	3.46	3.15
Disease duration (years)	8.72	10.05	9.63
Disease course			
RRMS	36	255	108
SPMS	6	40	19
PPMS	6	10	2
DMTs			
Interferon beta	4 (10.8)	33 (89.2) p = 0.60	15 (40.5%) p = 0.59
Glatiramer acetate	1 (6.2)	15 (93.8) p = 0.38	8 (40.0%) p = 0.25
Dimethyl fumarate	12 (10.5)	102 (89.5) p = 0.24	37 (32.4) p = 0.28
Teriflunomide	7 (9.7)	65 (90.3) p = 0.28	37 (51.4) p = 0.003
Natalizumab	0	44 (100%) p = 0.004	18 (40.9) p = 0.52
Fingolimod	14 (42.4) p < 0.0001	19 (57.6)	4 (12.2)
Ocrelizumab	9 (39.1) p = 0.0002	14 (60.9)	3 (13.0)
Alemtuzumab	0	3 (100) p = 0.49	1 (33.3) p = 0.9
Cladribine	1 (11.1)	8 (88.9) p = 0.82	5 (55.5) p = 0.23
Lymphopenia before vaccination	18 (24.3) p = 0.002	56 (75.7)	22 (29.7)
Grade 1 or 2	16	54	22
Grade 3	2	2	0
Grade 4	0	0	0

DMTs — disease-modifying therapies; EDSS — expanded disability status scale; PPMS — primary progressive multiple sclerosis; PwMS — persons with MS; RRMS — relapsing-remitting multiple sclerosis; SPMS — secondary progressive multiple sclerosis

prior to vaccination, or the type of vaccination. Previous COVID-19 infection significantly influenced the generation of a strong immune response (p = 0.002). Leukopenia and lymphopenia did not have a significant effect on a strong immune response. Treatment with interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, alemtuzumab, or cladribine resulted in a strong immune response. In the case of a strong response, treatment with natalizumab did not influence its occurrence. Treatment with fingolimod and ocrelizumab significantly reduced the occurrence of a strong response to vaccination against SARS-CoV-2 (fingolimod p = 0.002; ocrelizumab p = 0.01). High levels of antibodies were obtained in patients treated with the following drugs: interferon beta—15 (40.5% of patients); glatiramer acetate — 8 (50.0%); teriflunomide — 37 (51.4%); dimethyl fumarate — 37 (32.4%); natalizumab — 18 (40.9%); fingolimod — 4 (12.2%); alemtuzumab — 1 (33.3%); ocrelizumab — 3 (13.0%); and cladribine — 5 (55.5%). The characteristics of PwMS depending on the immune response to COVID-19 vaccination are set out in Table 2.

Discussion

The rapid spread of SARS-CoV-2 throughout the world has highlighted the importance of vaccinations to control the pandemic and to protect people at risk for severe disease courses. Studies have provided data on factors influencing the effectiveness of COVID-19 vaccinations. Parameters such as age, disease duration, course of MS, and neurological status (EDSS) do not affect the effectiveness of SARS-CoV-2 vaccination. This is important information, because earlier studies [10] showed that the immune response to vaccination decreases with age. The explanation for this phenomenon is that most of our patients are young (median age — 41 years). Decreased responsiveness to vaccination has been demonstrated in older people (> 65 years) [10]. The young age of patients can also explain the lack of influence of the presence of comorbidities on seroconversion.

Recommendations on the use of high doses of corticosteroids and vaccinations are not uniform. Some experts recommend an interval between corticosteroid treatment and vaccination only in live vaccines [11, 12]. Others recommend delaying vaccination for 2–4 weeks when administering high doses of corticosteroids. [13]. In our study, disease relapse treated with intravenous methylprednisolone had no effect on the emergence of a vaccine response. Most likely, doctors followed the recommendations of the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society [8] to postpone the vaccination for 4–6 weeks after treatment with high doses of corticosteroids.

The rate of seroconversion after SARS-CoV-2 vaccination in PwMS who received DMTs was very high (86.4%). Among the PwMS being treated with immunomodulatory DMTs, the rate of seroconversion was excellent (91.5%). Other researchers have obtained similar results [14–16].

DMTs, such as interferon beta, glatiramer acetate, dimethyl fumarate, and teriflunomide, do not affect the efficacy of vaccination against SARS-CoV-2. Consequently, there is no need to reschedule treatment for MS, and PwMS receive the same protection against infection from vaccination as the rest of the population. For high-efficacy disease-modifying therapies, the formation of a humoral immune response to COVID-19 vaccination depends on the type of drug and, in many cases, on the time elapsed since the last dose of the drug. Natalizumab is an example of a high-efficacy disease-modifying therapy which makes possible a very good immune response to vaccination. In our study, 100% of pwMS treated with natalizumab had positive anti-SARS-CoV-2 antibodies. Other researchers have obtained similar results [17].

In PwMS treated with immunosuppressive DMTs, the rate of seroconversion after SARS-CoV-2 vaccination was 64.7%, but this was clearly drug dependent. In the case of alemtuzumab, 100% of PwMS achieved seroconversion, and 88.8% achieved seroconversion in the case of cladribine. However, conclusions must be limited due to the small size of these groups (three and nine patients, respectively). The most important fact in both cases was that the time between the last treatment course and vaccination was long (alemtuzumab — over 18 months; cladribine — over four months; most others over 12 months). Slightly worse results were obtained for fingolimod (57.6%) and ocrelizumab (60.9%), but still more than half of the patients seroconverted after two doses of the SARS-CoV-2 vaccine. These figures are much better than those presented in other works. Achiron et al. [18] reported seroconversion in only 22.7% of patients treated with ocrelizumab and 3.8% with fingolimod. Sormani et al. [19] achieved better results. The percentage of patients on fingolimod and ocrelizumab with antibody levels above the cut-off of positivity was 90.6% and 40.5% respectively among PwMS vaccinated with Comirnaty COVID-19 vaccine. Such differences can arise due to several reasons. The antibody testing in our study was performed, on average, three months after the second dose of vaccination, but in the case of an Israeli study, it was one month. PwMS treated with ocrelizumab were vaccinated at least three months after the last dose, usually after 4–5 months. Sormani et al. showed that the Moderna COVID-19 vaccine elicits 3.25-times higher antibody levels than the Comirnaty vaccine. We did not find such a relationship, which might be due to the small group of patients vaccinated with Moderna COVID-19 vaccine. Another important factor may be when the antibodies were tested. In our group, the tests were performed three months after vaccination, whereas in an Italian work this interval was one month. Many papers, as shown in the meta-analysis by Wu at al. [20], have described a reduced response to vaccination in the case of anti-CD20 or sphingosine-1-phosphate receptor modulators therapy, but the scale of this problem is also important. Our work shows that with good planning of therapy and treatment, most patients achieve post-vaccination immunity. The need to plan vaccination treatment cycles and administer booster doses of SARS-CoV-2 vaccinations has also been emphasised by other authors [21].

We still do not know what antibody level is sufficient to obtain protection against COVID-19, especially since the cellular response must also be taken into consideration. Therefore, it is important to know which PwMS treated with which preparations obtain a very high concentration of antibodies, and therefore have a better chance of avoiding infection. The best results were achieved in PwMS treated with cladribine (55.5%), teriflunomide (51.4%), glatiramer acetate (50.0%), natalizumab (40.9%), and interferon beta (40.5%). Up to 13% of PwMS treated with ocrelizumab and 12% treated with fingolimod developed a strong immune response. It is worth noting that none of these people had COVID-19 before vaccination.

A great advantage of our study is that it is a result of multicentre cooperation. We have collected data from large MS centers from all over Poland.

However, it also has its limitations. We could only determine the humoral response to vaccination, and we do not have

data on the cellular response, so the conclusions of our work can only be partial. Another limitation of our work concerns the COVID-19 vaccination system in Poland in the initial phase of the pandemic. In Poland, mainly the Comirnaty vaccine was available and the vast majority of PwMS were vaccinated with it. For this reason, differences between the effectiveness of different vaccines may have been obscured due to too few patients being vaccinated with other types of vaccine.

However, these limitations do not detract from the fact that this study shows the influence of various DMTs on the formation of the humoral response to vaccination.

Clinical implications

The COVID-19 pandemic is over, but the SARS-CoV-2 infection has stayed with us and can still be dangerous for some people. The annual influenza epidemics are a challenge. In the current demographic situation with a return to ease of travel, further pandemics can be expected. Data on the effect of multiple sclerosis treatment on seroconversion after vaccination is still very important.

Conclusions

The currently obtained data on the efficacy of vaccinations in patients with multiple sclerosis treated with DMT is very valuable. We now know that, in PwMS receiving interferon beta, glatiramer acetate, dimethyl fumarate, and teriflunomide and natalizumab, the immune response to vaccination is very good. In the case of reconstitution therapies, the immune response was also very good, but the groups of these patients in our study were very small. In PwMS treated with immunosuppressants (sphingosin-1 receptor modulators and anti-CD20 B-cell-depleting therapies), seroconversion was significantly reduced, although it still occurred in more than half of the patients. In the case of long-acting immunosuppressants, it is still important that the vaccination and therapy are well planned. Insufficient humoral immune response in some patients under immunosupressive therapies underlines the importance of fulfilling vaccinations, e.g. against hepatitis B, before such a therapy is started.

Article information

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Ethics statement: *The study was approved by the Bioethics Committee at the Medical University of Warsaw, Poland.*
Authors' contributions: *conceptualisation: A.P-P.; methodology: A.P-P., M.N., and J.S. (Janusz Sierdziński); software : J.S. (Janusz Sierdziński); validation: A.P-P. and J.S. (Janusz Sierdziński); formal analysis: A.P-P. and J.S.; investigation: A.P-P., A.K., H.B-P., K.R., M.A-S., A.G. and W.B.; resources: J.S. (Jakub Stawicki), B.L., M.P., A.P., A.J-W., J.C., K.K-B., N.N., K.W., E.J., P.P., E.K., A.L-B., A.W-H., A.S., M.P-O., B.K., A.K. (Aleksandra Karuga), and B.S.; data curation: A.P-P.; writing — original draft preparation: A.P-P.; writing — review and editing: A.P-P., M.M., W.B., J.C., A.K., M.A-S., K.R., and H.B-P.; supervision: B.Z.-P. All authors read and agreed to published version of manuscript.*
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RESEARCH PAPER

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Changes in cervical sagittal balance following anterior cervical discectomy with fusion

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ABSTRACT

Introduction. Change in the sagittal balance after anterior cervical discectomy with fusion (ACDF) is a phenomenon that has not yet been sufficiently studied. The aim of this study was to assess such changes.

Material and methods. 28 patients who underwent ACDF for cervical spondylosis were examined. The study was divided into three stages: preoperative, early postoperative, and late postoperative. Sagittal alignments were analysed based on X-ray AP and lateral images: angles C1-C7, C2-C7, C1-C2, C1-C4, C4-C7 and cervical sagittal vertical axis (cSVA).

Results. The cervical lordosis C2-C7 decreased by 13% in early monitoring, after which it increased by 60% in the late postoperative phase. Post hoc analysis showed that the measured values between early and late postoperative monitoring differed significantly. Cervical sagittal vertical axis (cSVA) increased by 23% in early control and then decreased by 18% in the late postoperative phase. Post hoc analysis showed that the measured values significantly differed between preoperative and early postoperative monitoring, and between early and late postoperative monitoring.

Conclusions. We have shown that the long-term effect of ACDF is correction of the sagittal balance of the cervical spine. Immediately after the procedure, a disturbance in the cervical spine curvature to the morphology of the entire spine is observed.

Keywords: postural balance, spine, spondylosis, cervical spine, anterior cervical discectomy with fusion, biomechanics

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Introduction

Recent years have seen important advances regarding the understanding of sagittal balance (SB) changes following surgical treatment of cervical spondylosis by anterior cervical discectomy with fusion (ACDF) [1–6].

A relationship between ACDF and an increase in the cervical lordosis angle, or a decrease in the kyphosis angle, has been proven [1–3, 5–10]. The same effect of ACDF on the angle of the fused segment has also been demonstrated [1–3, 5, 6, 8].

The summarised conclusions have allowed the hypothesis to be put forward that primary correction of the sagittal balance on the segments operated on positively correlates with an improvement of the position of the entire cervical spine [1, 6]. However, it is not clear whether the improvement in the global setting is related to the surgery itself. According to some authors, it occurs over time [1–3, 5, 6]. However, other results indicate a slight decrease in the described angles during the observation period [2, 3]. The decrease is more clearly expressed in the case of measurements of the curvature of the entire cervical spine as a fused segment [1, 2]. It has been proved that the cervical lordosis correction degree after ACDF may depend on the type of interbody implant used, but their final effect remains unclear [2, 3, 11]. The relationship between the use of the anterior plate and the correction of the sagittal balance is also debatable [1, 2]. However, it has been

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shown that the degree of cervical lordosis angle improvement positively correlates with the length of stabilisation [1, 2]. Other analyses have shown that more correction is achieved in patients with more advanced preoperative disorders of the sagittal balance [12, 13].

The cervical lordosis angle has a negative correlation with the cervical sagittal vertical axis (cSVA) [6] A 10% increase in cSVA after ACDF has been observed [6, 14]. A cadaver study showed that a postoperative increase in biomechanical loads on the levels adjacent to stabilisation increased with increasing cSVA [15]. As the sagittal imbalance of the cervical spine progresses, the biomechanical loads observed in the intervertebral discs are likely to increase.

Postoperative changes in cervical spine angles affect the effects of treatment. A relationship between lordosis correction and improved patient condition has been demonstrated [5, 16, 17]. In the case of cSVA, both pre- and postoperative values are an independent prognostic factor of treatment effectiveness. The majority of patients with cSVA > 40 mm achieve positive treatment effects only in terms of myelopathy symptoms [14]. An effect of ACDF on the global sagittal balance of the spine has also been observed. Decreased sagittal vertical axis (SVA), increased pelvic tilt (PT), and decreased sacral slope (SS) have been observed in patients with a large preoperative cervical lordosis angle [17].

The aim of this study was to make a comprehensive assessment of changes in the sagittal balance of the cervical spine after ACDF.

Material and methods

28 patients who underwent ACDF for cervical spondylosis at the Department of Neurosurgery and Paediatric Neurosurgery at the Pomeranian Medical University in Szczecin, Poland from March 2012 to June 2013 were examined. The retrospective case study protocol was approved by the Institutional Review Board. All subjects gave informed consent for treatment and additional tests. The PROCESS reporting guideline has been implemented.

The group consisted of 22 women and six men. Their average age was 51 years (range: 31–61, SD 7.69). All patients were operated on by the same surgeon, Prof. Leszek Sagan. PEEK parallel interbody cages and titanium lordotic anterior plates were used. The study was divided into three stages. The first (preoperative) took place on the day preceding the procedure in 28 patients included in the assessment, the second (early postoperative) along with routine postoperative monitoring between the 4th and 5th days after surgery in 27 patients, and the third (late postoperative) with routine outpatient follow-up of on average 38 months (range: 11–46, SD 7.83), in 24 patients. Descriptive statistics for the ages and the intervals between study stages are set out in Table 1. The diminishing number of patients included in each subsequent stage of the study was a result of difficulty in continuing regular follow-up visits. Missing data was supplemented by substituting the arithmetic mean of individual parameters.

Table 1. Descriptive statistics for age and time between preoperative and late postoperative stages

Feature	Mean	Min	Max	SD
Age [years]	51.29	31.0	61.0	7.69
Time [months]	37.71	11.0	46.0	7.83

Classic X-ray images taken in clinical practice were used for the analysis. AP and lateral images taken at each stage of the study were evaluated. All images were obtained using an AXIOM Aristis FX digital RTG camera (Siemens Healthcare). Patients were placed in Morvan's standard position for sagittal imaging. The patients assumed a natural, upright posture, standing barefoot, with their feet slightly apart, with straight knees, with their upper limbs hanging down freely [18]. The posture was not modified by raising their hands on the photo projection supports.

The sagittal balance of the cervical spine was defined as the angle of curvature C1-C7. The segment C1-C7 was divided into upper parts C1-C2, C1-C4, and lower parts C2-C7, C4-C7. The widely recognised Cobb angle method was used to measure curvatures [19–23]. This method involves running four straight lines. Depending on the analysed parts, horizontal lines run between the anterior and posterior C1 nodules, parallel to the lower endplate of C2, C4 or C7. Then vertical straight lines are drawn perpendicular to the appropriate horizontal ones, and the angle formed by their intersection determines the value of the curvature. Lordosis is defined as positive angles, and kyphosis as negative.

The cervical sagittal vertical axis was determined by measuring the horizontal distance between the C2 plumb line (C2PL), i.e. the vertical straight line passing through the centre of the C2 body, and the upper-posterior corner of the C7 body [6, 14–16].

The drawing of lines and the calculation of angles were made using the Surgimap program (Nemaris, Inc.) distributed with a freeware licence. The algorithms included in this program allow the precise and repeatable determination of spinal osteometric parameters [24, 25].

Descriptive statistics were used in the statistical analysis, wherein mean, standard deviation, minimum, and maximum values were calculated. The arithmetic average method was used to fill in the missing data. Assumptions regarding the normality of the distribution of quantitative variables were checked using the Shapiro–Wilk test. The differences between the values of the collected features before and after the operation were calculated using Friedman's ANOVA and post hoc tests. Correlations were established using the Pearson linear correlation coefficient. The results were considered significant at $p < 0.05$. Calculations were carried out using Statistica 12 (StatSoft).

Table 2. Descriptive statistics of sagittal balance parameters and p-values for Friedman's ANOVA test, examining differences in cervical lordosis angles between individual stages of study

Feature	Mean	Min	Max	SD	P-value
SB C2-C7 preop. [°]	11.62	–11.0	34.0	12.73	**p = 0.014**
SB C2-C7 postop. 1 [°]	10.12	–12.0	24.0	6.76	
SB C2-C7 postop. 2 [°]	16.25	3.0	31.0	7.84	
SB C1-C7 preop. [°]	38.46	15.0	67.0	12.85	p = 0.285
SB C1-C7 postop. 1 [°]	37.19	15.0	51.0	7.70	
SB C1-C7 postop. 2 [°]	41.79	12.0	63.0	12.90	
SB C1-C2 preop. [°]	26.12	15.0	36.0	6.02	p = 0.433
SB C1-C2 postop. 1 [°]	27.12	15.0	41.0	5.81	
SB C1-C2 postop. 2 [°]	26.92	14.0	37.0	6.08	
SB C1-C4 preop. [°]	29.73	13,0	47.0	9.28	p = 0.953
SB C1-C4 postop. 1 [°]	26.96	–9.0	40.0	10.46	
SB C1-C4 postop. 2 [°]	28.46	–13.0	50.0	12.37	
SB C4-C7 preop. [°]	8.23	–13.0	35.0	10.69	p = 0.272
SB C4-C7 postop. 1 [°]	8.73	–2.0	19.0	5.81	
SB C4-C7 postop. 2 [°]	10.83	–2.0	35.0	8.29	
cSVA preop. [mm]	22.00	3.2	45.4	10.08	**p = 0.007**
cSVA postop. 1 [mm]	27.12	9.5	41.5	9.51	
cSVA postop. 2 [mm]	22.04	5.4	48.9	10.54	

SB — sagittal balance

Results

The average cervical lordosis angle C2-C7 was 11.6° (–11.0 to 34.0; SD 12.7) preoperatively, 10.1 ° (range: –12.0 to 24.0; SD 6.8) in early postoperative monitoring, and 16.3° (range: 3.0 to 31.0; SD 7.8) in late postoperative monitoring. C1-C7 values were 38.5° (range: 15.0 to 67.0; SD 12.8) in the 1st stage of the study, 37.2° (range: 15.0 to 51.0; SD 7.7) in the 2nd stage, and 41.8° (range: 12.0 to 63.0 ; SD 12.9) in the 3rd stage. C1-C2 were 26.1° (range: 15.0 to 36.0; SD 6.0) preoperatively, 27.1° (range: 15.0 to 41.0; SD 5.8) in early postoperative monitoring, and 26.9° (range: 14.0 to 37.0; SD 6.1) in late postoperative monitoring. C1-C4 were 29.7° (range: 13.0 to 47.0; SD 9.3) in the 1st stage, 26.9° (range: –9.0 to 40.0; SD 10.5) in the 2nd stage, and 28.5° (range: –13.0 to 50.0; SD 12.4) in the 3rd stage. C4-C7 were 8.2° (range: –13.0 to 35.0; SD 10.7) preoperatively, 8.7° (range: –2.0 to 19.0; SD 5.8) in early postoperative monitoring, and 10.8° (range: –2.0 to 35.0, SD 8.3) in late postoperative monitoring. The average cSVA values were 22.0 mm (range: 3.2 to 55.4; SD 10.1) in the 1st stage, 27.1 mm (range: 9.5 to 41.5; SD 9.5) in the 2nd stage, and 22.4 mm (5.4 to 48.9; SD 10.5) in the 3rd stage. Detailed values of the cervical lordosis angle of the studied sections and cSVA, as well as p-values for the differences before and after ACDF, are set out in Table 2. Figure 1 shows the correction of the sagittal balance of the cervical spine by increasing the lordosis angle.

A statistically significant difference was found in the cervical lordosis angle before and after ACDF in C2-C7 (p = 0.014). In relation to the preoperative stage, this angle decreased by 13% in early postoperative monitoring, and then increased by 60% in the late postoperative stage compared to the early monitoring (Fig. 2). Post hoc analysis showed statistically significant differences in the value of the cervical lordosis angle between early and late postoperative monitoring (Tab. 3). There was no statistically significant difference in cervical lordosis angles in other cervical spine sections after ACDF.

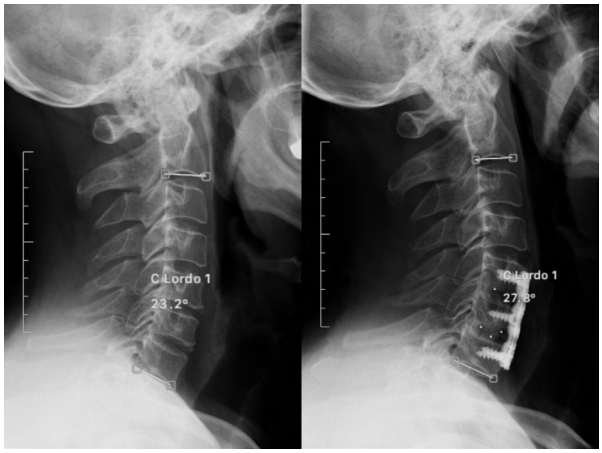

Figure 1. Lateral, pre- and late postoperative X-rays showing correction of sagittal balance of cervical spine by increasing lordosis angle

A statistically significant difference was found in the cSVA values before and after ACDF (p = 0.007). Compared to the preoperative stage, this parameter increased by 23% in early postoperative monitoring, and then decreased by 18% in the

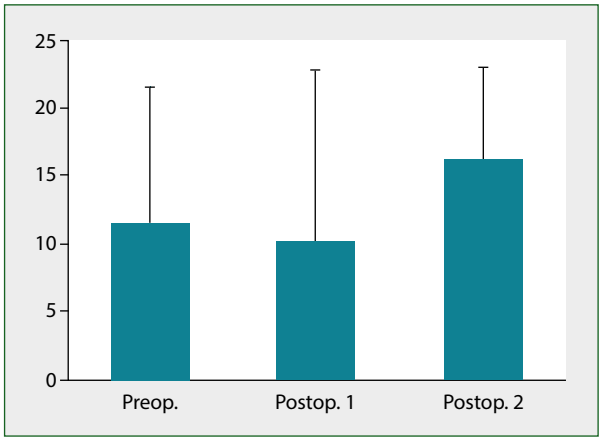

Figure 2. Distribution of C2-C7 lordosis angle values at three different time intervals. Postop. 1 means early postoperative monitoring, and postop. 2 means late postoperative monitoring. Square represents average value and limit represents maximum

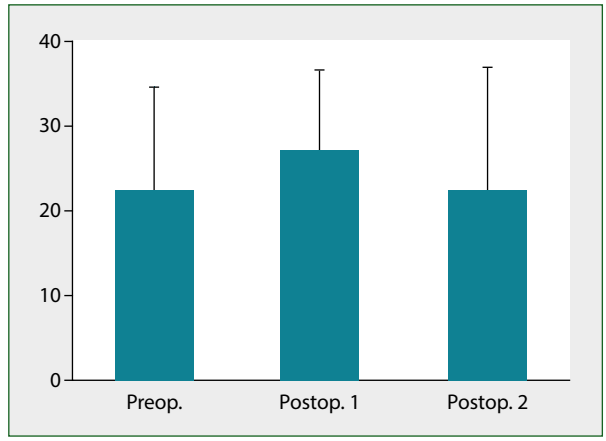

Figure 3. Distribution of cSVA values at three different time intervals. Postop. 1 means early postoperative monitoring, and postop. 2 means late postoperative monitoring. Square represents average value and limit represents maximum

Table 3. Freidman's ANOVA post hoc test results for lordosis angle C2-C7, showing differences in average rank values between individual pairs of variables

	SB C2-C7 preop.	SB C2-C7 postop. 1	SB C2-C7 postop. 2
SB C2-C7 preop.	—	0.25	0.59
SB C2-C7 postop. 1	0.25	—	**0.84**
SB C2-C7 postop. 2	0.59	**0.84**	—

SB — sagittal balance

Table 4. Freidman's ANOVA post hoc test results for cSVA, showing differences in mean rank values between individual pairs of variables

	cSVA preop.	cSVA postop. 1	cSVA postop. 2
cSVA preop.	—	**0.82**	0.00
cSVA postop. 1	**0.82**	—	**0.82**
cSVA postop. 2	0.00	**0.82**	—

Table 5. Pearson correlation coefficients between cSVA values measured at individual test stages

	cSVA preop.	cSVA postop. 1	cSVA postop. 2
cSVA preop.	1.00	**0.80**	**0.76**
cSVA postop. 1	**0.80**	1.00	**0.66**
cSVA postop. 2	**0.76**	**0.66**	0.00

late postoperative stage compared to the early monitoring (Fig. 3). Post hoc analysis showed that differences in cSVA measured in the preoperative phase and in the early postoperative monitoring were statistically significant. In addition, a significant difference in cSVA values occurred between the early and late postoperative stages (Tab. 4).

The cSVA values measured at each stage of the study were compared. Statistically significant, positive correlations were found between values obtained in the preoperative and early postoperative stages and the standard postoperative, as well as between early and standard postoperative stages (Tab. 5).

Discussion

The results obtained of C2-C7 lordosis angle variability before and after ACDF suggest that correction of the sagittal balance of the cervical spine is not associated with an intraoperative change in the morphology of spinal curvature potentially made by implantation of the stabilising system, and occurs within 38 months of observation.

In the literature, the cervical lordosis angle is given in the range of 20–40^{O}, with up to 30% of healthy, adult people characterised by cervical kyphosis [26–31]. Benzel et al.

[32] showed that reduction, typical for osteoarthritis, in the height of the intervertebral disc is more strongly expressed in its abdominal area. As a consequence, greater loads are transferred through its front part, which may be responsible for the gradual loss of the lordotic cervical spine orientation observed in osteoarthritis [32]. This observation explains why, in the studied population of patients, preoperative values of the cervical lordosis angle were lower than the potential norm. This was confirmed by the studies of Chen et al. [2] and Gillis et al. [6] assessing the sagittal balance of the cervical spine in patients with cervical spondylosis, in which values similar to our study were obtained. Jackson et al. [33] and Hardacker et al. [28] proved that 75–80% of the cervical lordosis angle is formed by C1-C2 segments, with only 15% falling on C4-C7. This, in turn, explains the limited possibilities of absolute correction of the cervical lordosis angle by ACDF as the method intended for the treatment of pathology in C3-C7 segments.

There is a proven relationship between ACDF and an increase in the cervical lordosis angle or a decrease in the kyphosis angle [1–3, 5–10]. The same effect of ACDF on the setting of the segment subjected to spondylodesis has been demonstrated [1–3, 5, 6, 8].

Combining these two observations proves that primary correction of the sagittal balance within the segments operated on positively correlates with improvement of the position of the entire cervical spine [1, 6].

In this study, we have shown that correction of the sagittal balance of the cervical spine is not associated with an intraoperative change in the morphology of the curvature of the spine, and occurs during further observation. This conclusion is consistent with the observations of other authors. Gillis et al. [6] showed that the cervical lordosis angle C2-C7 increases by 12% in six weeks after ACDF and by another 18% over the next 12 months. Tomé-Bermejo et al. [5] observed that the cervical lordosis angle C1-C7 decreased by 4% in the 48 hours following ACDF, after which it increased by 18% in eight weeks and by another 4% over the next 12 months.

On the other hand, Chen et al. [2] showed that the cervical lordosis angle C2–C7 increases more than twice immediately after ACDF, after which it decreased by 23% systematically over 42 months of follow-up. However, contrary to the two previously mentioned studies, no statistical significance was demonstrated by Chen et al. [2]. This demonstrated lack of increase in the cervical lordosis angle immediately after implantation of the stabilising system is related to the observations of Villavicencio et al. [11], who found no effect of the use of lordotic interbody cages on the postoperative segmental and section lordosis angle.

In the available literature, results confirm the doubts arising from this study with regard to the shape of the implants used in ACDF on the correction of sagittal balance.

The results obtained of cSVA variation before and after ACDF suggest that the change in cSVA is associated with intraoperative correction of the cervical spine position by implantation of the stabilising system. Its further changes are a consequence of processes occurring during 38 months of observation.

Due to the small number of studies assessing cSVA, no norms have been set for this parameter. Gillis et al. [6] showed little variation after ACDF. According to their observation, six weeks after ACDF, cSVA increased by 9%, after which it decreased by 5% for the next 12 months. Similarly to the present study, this parameter increased early following ACDF, after which it decreased in further observation. In turn, Roguski et al. [14] demonstrated an 11% increase in cSVA one year after ACDF, and observed that pre- and postoperative cSVA values are an independent prognostic factor in treatment effectiveness. Most patients with cSVA > 40 mm achieved positive treatment effects only in terms of myelopathy symptoms. Patwardhan et al. [15], in a cadaver study, proved that the postoperative increase in biomechanical loads of adjacent to stabilisation levels increases with increasing cSVA.

It should therefore be assumed that the postoperative increase in cSVA is a negative effect, indicating a disturbance in the ratio of cervical curvature to the morphology of the entire spine. Gillis et al. [6] showed that cSVA positively correlates with the Th1 slope (T1S). Knott et al. [34] described T1S as a substitute parameter describing the sagittal balance of the cervical spine. Confirmed by this study and data obtained by Gillis et al. [6], the gradual return of cSVA to the baseline values before ACDF corresponds to the increase in the cervical lordosis angle observed at the same time.

Analysis of the relationship between cSVA values measured at various stages of the study proves a dependence between the degree of postoperative cervical spine curvature disorders and the morphology of the entire spine on their preoperative shaping.

It seems reasonable to assume that after ACDF there is a change in the biomechanics of the cervical spine, which in time leads to positive correction of the sagittal balance. This issue requires further research, which should first focus on the impact of ongoing spondylodesis, sagittal balance variability, muscle tone, and an ongoing degenerative process.

Kim et al. [17] showed that ACDF affects the correction of sagittal vertical axis, pelvic tilt, and sacral slope.

Therefore, future studies on postoperative variability of the sagittal balance after ACDF cannot be limited to assessing the morphology of the cervical spine only, and for a full understanding of the processes should include observations of whole body posture.

Part of the X-ray images assessed in this study did not show the Th1 circle. Consequently, it was impossible to perform measurements determining the parameters of the cervical-thoracic joint (thoracic inlet angle, neck tilt, T1 slope). Their examination would allow clinicians to refer changes in the sagittal balance of the cervical spine to the position of the thoracic part.

Conclusions

A long-term result of anterior cervical discectomy with fusion is correction of the sagittal balance of the cervical spine. This is not dependent only on the surgery itself, but also occurs in the postoperative period by increasing the lordosis angle. Immediately after the procedure, a disturbance in the cervical curvature to the morphology of the entire spine is observed by increasing the cervical sagittal vertical axis. This effect depends on their preoperative formation, and returns during observation.

A larger, prospective, and preferably multicentre, study should be conducted to confirm these conclusions.

Article information

Data availability statement: *The data that supports the findings of this study is available from the corresponding author, upon reasonable request.*

Ethics statement: *The study protocol was approved by the Ethics Committee of Pomeranian Medical University.*

Authors' contributions: *BL — main contribution; LS — review and guidelines; KL — review; WP — guidelines.*

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SHORT COMMUNICATION

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KinesioTaping: impact on non-motor symptoms in cervical dystonia patients treated with botulinum toxin injection

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ABSTRACT

Aim of the study. To assess whether combined therapy with botulinum toxin injections (BoNT) and KinesioTaping could be helpful in managing non-motor symptoms (NMS) of cervical dystonia (CD).

Material and methods. Seventeen patients with CD were enrolled in this single-centre, prospective, evaluator-blinded, randomised, crossover trial. We compared three forms of treatment: BoNT treatment alone, or combined with KinesioTaping, or combined with ShamTaping. NMS were assessed using the 14-item self-reported questionnaire proposed by Klingelhoefer, the Hospital Anxiety and Depression Scale (HADS) and the Pittsburgh Sleep Quality Index (PSQI).

Results. There were no significant differences between the groups concerning mean results of HADS and PSQI scales, or mean total number of NMS after the procedures. The mean change from baseline HADS and PSQI scores, and total number of NMS after the procedure, also did not differ significantly between groups. ShamTaping combined with BoNT significantly increased the prevalence of pain.

Conclusions and clinical implications. Our study did not confirm the effectiveness of combined therapy of BoNT and KinesioTaping in the management of NMS in patients with CD. Due to a potential negative effect of improper taping on pain in CD, patients with CD should only experience KinesioTaping as an adjunctive therapy, and if it is performed by a trained, experienced physiotherapist.

Key words: cervical dystonia, non-motor symptoms, botulinum toxin injection, KinesioTaping

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Introduction

Cervical dystonia (CD) is the most prevalent form of adult-onset focal dystonia and is considered mostly a motor disorder [1]. Recently, attention has been drawn to the presence of non-motor symptoms (NMS) in the course of the disease.

Thirty-six percent of CD patients experience marked NMS such as sensory and perceptual abnormalities, psychiatric symptoms, pain, sleep impairment, or sexual dysfunction [2]. Pain is the most frequent NMS, reported by as many as 90% of CD patients [3], followed by disrupted sleep with a prevalence of 67.3%. Psychiatric symptoms, such as anxiety and depression, are also common, ranging from 21-65.5% and from 25-47.1% respectively [4]. Compared to motor symptoms, NMS are significantly linked to a poor quality of life [4]. Nevertheless, the relationship between motor symptoms and NMS is still being researched. It has been proposed that motor symptoms and NMS in CD could be explained by a common pathophysiological deficit. In primary CD, the core

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abnormality is centred in the cortico-striatal-thalamo-cortical circuits. Its non-motor consequences would be expected given that these circuits have been linked not only to motor, but also to sensory, cognitive, and reward processing [5].

Intramuscular botulinum toxin injections (BoNT) are the treatment of choice for motor symptoms in CD. However, BoNT treatment meets only limited patient satisfaction [6]. The therapeutic response becomes apparent within 1-2 weeks after the BoNT injection, with peak effects at approximately 4-6 weeks and a gradual decline thereafter [7, 8]. Thus, patients with CD treated with BoNT experience a 'rollercoaster' effect, as they receive treatment with waning effectiveness over time that then increases again following the subsequent injection [9]. It might be useful to combine BoNT with an adjunctive therapy for a beneficial synergy.

Only a few studies have investigated the effect of BoNT on NMSs in CD patients [10, 11]. Evidence for the effectiveness of rehabilitation strategies in CD patients is also scarce. Kinesiology taping involves a combination of tension applied along the tape and stretching of the target muscle. That, amongst others, results in a change of recruitment activity patterns of the muscles, and alleviates prolonged muscle contraction and even postural deviation [12].

To the best of our knowledge, the effect of KinesioTaping on NMSs in patients with focal dystonia has so far been analysed in only one study [13].Our current study is a continuation of our recently published research [14]. Our observations help to elucidate the possible role of combined BoNT-A plus KinesioTaping therapy in the management of NMS in patients with CD.

Material and methods

This was a single-centre, prospective, evaluator-blinded, randomised, crossover trial. The participants were recruited from the Movement Disorders outpatient clinic of the Department of Neurology of the University Hospital in Kraków, Poland between January 2019 and January 2021. The study included patients with CD previously treated with BoNT within Poland's National Health Fund (NHF) programme. Patients with segmental, multifocal, generalised dystonia and hemidystonia, with a history of invasive dystonia treatment (deep brain stimulation or neck surgeries), with contraindications for KinesioTaping (wounds, fresh scars, allergies to acrylic glue, tape intolerance), or who were still undergoing diagnostic evaluation for dystonia, were all excluded from the study. All patients provided written informed consent.

We obtained demographic characteristics and a medical history and performed a neurological examination during the initial visit. Participants were then randomly assigned 1:1:1 to one of three groups using a computer-generated random number:

- Group 1: BoNT + KinesioTaping
- Group 2: BoNT + ShamTaping
- Group 3: BoNT + no taping

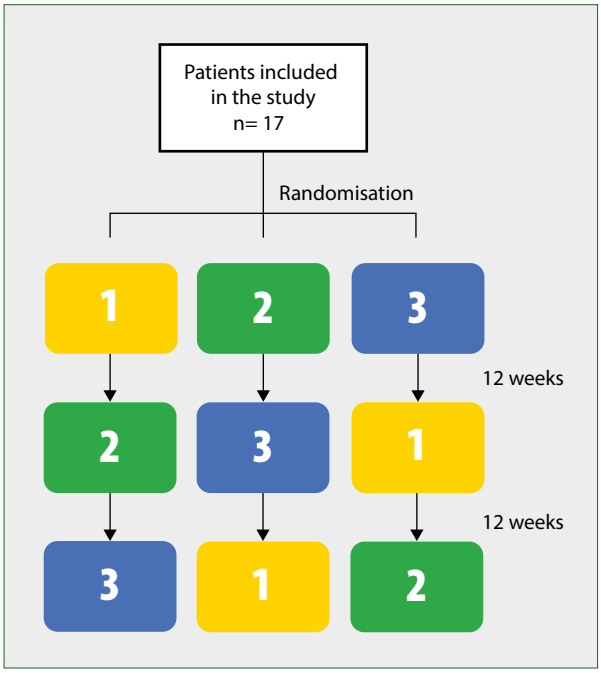

Figure 1. Study design. Group 1 = botulinum toxin injections (BoNT) + KinesioTaping; Group 2 = BoNT + ShamTaping; Group 3 = BoNT

Every 12 weeks, the participants were switched to another treatment group, so as to apply all treatment options to all patients over the course of 36 weeks (Fig. 1). The KinesioTaping and ShamTaping and no taping arms were included to assess the possible placebo effect of the taping.

BoNT injections were received by patients at the beginning of the 12-week cycle. The injection pattern was individual and based on the patient's cervical dystonia subtype according to the collum-caput (*Col-Cap*) concept [15]. In each cycle, patients received the same dose and same brand of BoNT in the same localisation. The injections were ultrasound-guided. BoNT preparations were used, depending on the individual tolerance and availability at the hospital: onabotulinumtoxin type A or abobotulinumtoxin type A.

In Groups 1 and 2, the BoNT injection was followed by KinesioTaping or ShamTaping respectively, which was performed after seven days and continued for four consecutive weeks, with tapes being changed once per week by an experienced physiotherapist informed about the patient's group allocation as described previously [14].

In Group 1, the tape was applied in the direction of fascial restriction. The physiotherapist slid a fascia over an individual muscle or group of synergistically acting muscles and assessed the presence of involuntary movements of the head and neck and the posture of cervical-thoracic (C-Th) spine and shoulder girdle, gluing the tape when an improvement was seen. Additionally, patients were taped using the analgesic (ligament) technique in the area of the C-Th spine or the shoulder

complex (depending on which was subjectively indicated as being more painful by the patient). Analgesic taping was executed with a single transverse application or double cross application (applying the central part of the tape with 75-100% tension and two ends without tension). If a patient did not report any pain, this application was omitted.

In Group 2, patients were taped in a non-therapeutic manner, which means applying the tape without tension and without stretching the muscles or moving the head and neck. The tape was applied in two vertical slices and one horizontal slice glued to the C-Th area of the spine. Patients were unable to feel the difference between KinesioTaping and ShamTaping during application.

Participants were assessed by a neurologist twice per cycle: firstly on the day of the BoNT injection, and secondly during the control visit six weeks later. The patient and the assessing neurologist were unaware of the group allocation. During the assessment visits, information on NMSs was gathered according to a 14-item self-report questionnaire [2]. The patients' mood and the presence of anxiety were assessed using the Hospital Anxiety and Depression Scale. The presence of sleep impairment was evaluated with the Pittsburgh Sleep Quality Index (PSQI). Disease severity was assessed using the Toronto Western Spasmodic Torticollis Rating scale (TWSTRS).

Data was gathered in a database and statistical analysis was performed using a PS Imago Pro 6.0 statistical package. Categorical data was presented as counts and percentages, and continuous data as mean and standard deviation. Chi-Square test was used to compare the prevalence of individual NMS after interventions. McNemar test was used to assess the influence of each intervention on the prevalence of individual NMS within the group. Continuous variables were compared using a nonparametric Kruskall-Wallis test (due to a limited sample size). Differences were considered statistically significant with the two-sided p-value of less than 0.05.

Ethical approval was granted by the institutional review board (opinion number 1072.6120.217.2018).

Results

The groups consisted of 17 patients aged 29–72 with a mean age of 53.5 (± 12.77) years. 13/17 (76.47%) were female. Age at dystonia onset varied from 23 to 58 years with a mean 40.47 (± 11.42) years. Disease duration was 4–47 years with a mean 13.18 (± 12.01) years. Three patients were diagnosed with concomitant depression, for which two were receiving pharmacotherapy and one was in remission. Each patient received a stable dose of BoNT, 14 of the patients were treated with onabotulinum type A (mean dose: 186.4 SD = 31.0 units), and the other three with abobotulinum type A (1,000 units). None was treated with physiotherapy or psychotherapy before or during the study.

Before interventions, 92.16% of patients declared that they experienced NMSs. The most common NMS was fatigue/lack of energy limiting everyday activity. The distribution of individual NMSs before and after intervention in each group is presented in Table 1. The analysis using McNemar test showed that, in Group 2, ShamTaping combined with BoNT significantly increased the prevalence of pain. The procedures in each group had no statistically significant effect on the prevalence of any other NMS. The prevalence of individual NMSs in the control assessment was compared between groups using a Chi-square test. No statistically significant differences were found.

The results of the Kruskall-Wallis test showed that the mean total number of NMSs after interventions and the mean change from baseline number of NMSs after interventions did not differ significantly between groups. There were also no statistically significant differences concerning the mean scores obtained with TWSTRS, PSQI, HADS-A, HADS-D and HADS-total scales after intervention or in the mean change from baseline score after intervention (see Table 2, supplementary material).

Discussion

In this study on NMS of KinesioTaping in patients with CD, we did not observe superior efficacy of taping as an adjunctive therapy to BoNT injection versus BoNT alone. We noticed significant worsening of pain reported by the group treated with BoNT and ShamTaping. Fatigue and lack of energy limiting everyday activity was the most common complaint, with a prevalence of 47.1%. This aligns with the literature, where the prevalence of this symptom ranges from 46% to 64% [16].

Pelosin et al. evaluated the effectiveness of KinesioTaping on NMSs in patients with focal dystonia not treated with BoNT [13]. Compared to ShamTaping, KinesioTaping decreased the subjective sensation of pain and modified the ability of sensory discrimination. CD patients treated with ShamTaping had higher results on the VAS-W scale (assessing the worst pain) after intervention than they did at baseline.

It has been proven that BoNT injection significantly reduces pain associated with CD [17] and other neurological conditions such as migraine [18]. KinesioTaping has been found to be effective in decreasing pain in musculoskeletal disorders [19].

The direct antinociceptive mechanism of BoNT in CD is unclear, although several hypotheses have been proposed. BoNT affects muscle spindles acting as proprioceptors. BoNT-induced relaxation of hypertonic muscles contributes to decompression of nerve fibres, thus decreasing afferent activity of spindles and reducing excitability of motoneurons [20]. Relief of local ischaemia, secondary to muscle relaxation, reduces lactate production, and diminishes traction-related and positional pain [20–22]. BoNT may also inhibit neurogenic inflammation and peripheral sensitisation by inhibiting the release of local neuropeptides involved in pain transmission

Table 1. Impact of treatment on non-motor symptoms in studied group

	Group 1 (BoNT + KinesioTaping)			Group 2 (BoNT + ShamTaping)			Group 3 (BoNT)		
	Before intervention	After intervention		Before intervention	After intervention		Before intervention	After intervention	
Lack of confidence, social withdrawal [n (%)]	8 (47.1%)	**7 (41.2%)**	p = 1.000	7 (41.2%)	**8 (47.1%)**	p = 1.000	8 (47.1%)	**5 (29.4%)**	p = 0.250
Problems with falling and/or staying asleep [n (%)]	7 (41.2%)	**6 (35.3%)**	p = 1.000	6 (35.3%)	**5 (29.4%)**	p = 1.000	7 (41.2%)	**7 (41.2%)**	p = 1.000
Insomnia [n (%)]	2 (11.8%)	**4 (23.5%)**	p = 0.500	3 (17.6%)	**5 (29.4%)**	p = 0.625	3 (17.6%)	**5 (29.4%)**	p = 0.625
Fatigue/lack of energy limiting everyday activity [n (%)]	11 (64.7%)	**8 (47.1%)**	p = 0.375	10 (58.8%)	**12 (70.6%)**	p = 0.500	10 (58.8%)	**10 (58.8%)**	p = 1.000
Problems with gait [n (%)]	3 (17.6%)	**4 (23.5%)**	p = 1.000	0 (0.0%)	**2 (11.8%)**	p = 0.500	4 (23.5%)	**2 (11.8%)**	p = 0.500
Problems with balance [n (%)]	6 (35.3%)	**6 (35.3%)**	p = 1.000	7 (41.2%)	**4 (23.5%)**	p = 0.250	6 (35.3%)	**8 (47.1%)**	p = 0.500
Vertigo/dizziness [n (%)]	6 (35.3%)	**4 (23.5%)**	p = 0.625	5 (29.4%)	**4 (23.5%)**	p = 1.000	7 (41.2%)	**7 (41.2%)**	p = 1.000
Pain (not caused by known comorbidities) [n (%)]	6 (35.3%)	**4 (23.5%)**	p = 0.625	3 (17.6%)	**10 (58.8%)**	p = 0.016	7 (41.2%)	**9 (52.9%)**	p = 0.625
Feeling tired after sleeping for whole night [n (%)]	6 (35.3%)	**6 (35.3%)**	p = 1.000	7 (41.2%)	**7 (41.2%)**	p = 0.727	7 (41.2%)	**5 (29.4%)**	p = 0.625
Anxiety [n (%)]	9 (52.9%)	**9 (52.9%)**	p = 1.000	11 (64.7%)	**11 (64.7%)**	p = 1.000	9 (52.9%)	**10 (58.8%)**	p = 1.000
Lowered mood, depression [n (%)]	2 (11.8%)	**4 (23.5%)**	p = 0.500	6 (35.3%)	**4 (23.5%)**	p = 0.500	5 (29.4%)	**5 (29.4%)**	p = 1.000
Paraesthesia [n (%)]	5 (29.4%)	**4 (23.5%)**	p = 1.000	7 (41.2%)	**9 (52.9%)**	p = 0.687	7 (41.2%)	**5 (29.4%)**	p = 0.625
Dysphagia [n (%)]	3 (17.6%)	**3 (17.6%)**	p = 1.000	3 (17.6%)	**6 (35.3%)**	p = 0.375	4 (23.5%)	**5 (29.4%)**	p = 1.000
Dysarthria [n (%)]	1 (5.9%)	**3 (17.6%)**	p = 0.625	3 (17.6%)	**3 (17.6%)**	p = 1.000	4 (23.5%)	**3 (17.6%)**	p = 1.000
Problems with vision [n (%)]	3 (17.6%)	**3 (17.6%)**	p = 0.625	3 (17.6%)	**3 (17.6%)**	p = 1.000	5 (29.4%)	**4 (23.5%)**	p = 1.000
Mood swings [n (%)]	6 (35.3%)	**5 (29.4%)**	p = 1.000	10 (58.8%)	**7 (41.2%)**	p = 0.375	7 (41.2%)	**6 (35.3%)**	p = 1.000
Any of above symptoms [n (%)]	15 (88.24%)	**16 (94.12%)**	p = 1.000	16 (94.12%)	**16 (94.12%)**	–	16 (94.12%)	**15 (88.24%)**	p = 1.000

Table 2. Mean results of HADS, PSQI, TWSTR and total number of NMS after procedures. Mean differences in results of HADS, PSQI, TWSTR and total number of NMS before and after procedures

	Group 1 (BoNT + KinesioTaping)	Group 2 (BoNT + ShamTaping)	Group 3 (BoNT)	Kruskall-Wallis test
Total number of NMS after intervention	4.71 (+/– 3.58)	5.88 (+/– 3.87)	5.65 (+/– 4.33)	p = 0.646
ΔNMS	–0.24 (+/– 2.7)	0.53 (+/– 2.07)	–0.24 (+/– 2.56)	p = 0.668
Total PSQI after intervention	6.12 (+/– 3.44)	6.18 (+/– 3.38)	5.76 (+/– 3.88)	p = 0.898
ΔPSQI	0.76 (+/– 3.17)	0.18 (+/– 2.74)	–0.35 (+/– 2.52)	p = 0.667
HADS-A after intervention	6.47 (+/– 3.99)	6.53 (+/– 3.63)	5.47 (+/– 4.16)	p = 0.608
HADS-D after intervention	5.06 (+/– 3.07)	5.35 (+/– 4.11)	5.29 (+/– 4.33)	p = 0.987
Total HADS after intervention	11.53 (+/– 6.19)	11.88 (+/– 6.97)	10.76 (+/– 7.54)	p = 0.746
ΔHADS-A	–1.12 (+/– 2.91)	–0.94 (+/– 1.82)	0.06 (+/– 1.78)	p = 0.296
ΔHADS-D	0.00 (+/– 1.23)	–0.12 (+/– 2.09)	0.65 (+/– 2.21)	p = 0.395
ΔTotal HADS	–1.12 (+/– 3.60)	–1.06 (+/– 2.68)	0.71 (+/– 3.44)	p = 0.162
Total TWSTRS after intervention	16.06 (+/– 9.01)	17.76 (+/– 9.40)	14.76 (+/– 8.31)	p = 0.733
ΔTotal TWSTRS	–15.39 (+/– 8.52)	–14.49 (+/– 7.12)	–14.09 (+/– 4.34)	p = 0.771

from sensory nerves (substance P, calcitonin gene-related peptide, glutamate, and transient receptor potential vanilloid) [23–24]. The evidence suggests that changes to the afferent input caused by BoNT may result in short-term and long-term plastic changes in the network associated with pain in CD, causing a therapeutic effect [21]. A recent study has shown that the antinociceptive BoNT effect may last longer than motor improvements [25].

The mechanism of KinesioTaping is not yet fully understood. Sensorimotor, proprioceptive feedback mechanisms, inhibitory and excitatory nociceptive stimuli, and mechanical restraint have all been suggested [26–28]. We hypothesise that incorrect tape application may activate other muscles, such as deep-seated cervical muscles with high densities of muscle spindles. In turn, change in muscle tone may cause excitability of motoneurons and additionally mechanoreceptors and nociceptors activation, thus modifying pain transmission.

Slawek et al. reported depression in 47.5% of CD patients that was improved after BoNT-A treatment [29]. Costanzo et al. reported significant improvements in psychiatric disturbances, pain, and disability, whereas sleep disorders remained unchanged one month after BoNT-A injection in CD patients. Our study did not confirm these results.

In both the aforementioned studies, NMS assessment was performed at baseline (a washout period meaning 16 weeks after the last BoNT-A injection) and one month, or in Costanzo's cohort, three months, after BoNT-A. It is known that BoNT-A's effects wear off at 16 weeks, but that they are still present to a lesser extent after 12 weeks [30]. In the current study, there was no such 'washout period' before the intervention, due to ethical concerns. Poland's National Health Fund Programme approves BoNT injection every 12 weeks in CD patients. Thus, we did not notice any significant change from baseline after the treatment in NMS assessment.

Sleep disturbances are usually persistent and can be due to varying confounding factors such as environmental factors, occupational factors, physiological changes, medical and psychiatric disorders. It is possible that the short-term prospective design of the study looking at them did not allow reliable results to be obtained [31].

This study has some limitations such as a small sample size. Accordingly, this research was designed to be evaluator-blinded, randomised and crossover to overcome the weakness of the small number of patients participating in the study. Its short-term prospective design did not allow us to observe BoNT-induced changes beyond its timeframe. As mentioned above, we did not pursue a 16-week washout period after the previous BoNT injection, and thus we cannot fully exclude BoNT's impact on the study's baseline assessment. Moreover, we used different types of BoNT depending on individual tolerances and medication availability at the hospital, which may have had an impact on the results [32, 33].

To conclude, our study showed that combined BoNT and KinesioTaping therapy was not effective in the management of NMS in patients with CD. It is worth underlining that incorrect KinesioTaping application can actually worsen pain in CD patients.

Clinical implications/future directions

Our results require confirmation in larger studies. Due to a potential negative effect of improper taping on pain in CD, patients with CD should only experience KinesioTaping as an adjunctive therapy and if it is performed by a trained, experienced physiotherapist.

Conflicts of interest: *Malgorzata Dec-Cwiek has received speaking fees from IPSEN Poland sp z o. o., AbbVie sp. z o. o.,*

and Merz Pharmaceuticals. Karolina Porebska has received speaking fees from IPSEN Poland sp z o. o. The other authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Numb chin syndrome — a seemingly innocent symptom that can indicate a serious disease

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Key words: NCS, numb chin syndrome

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To the Editors

Numb chin syndrome (NCS) is a sensory neuropathy of the mental nerve manifested by paresthesias and hypoaesthesia of half of the chin and lower lip. In c.10–15% of cases, the symptoms may be bilateral. NCS was first described by Charles Bell in 1830 in a patient with disseminated breast cancer who accidentally noticed hypoaesthesia to touch on one half of her lower lip. The mental nerve is one of the terminal branches of the inferior alveolar nerve, responsible for the sensory innervation of the half of the chin and lower lip [1].

NCS is a symptom often underestimated by patients, due to its negligible impact on daily functioning. The differential diagnosis of NCS is very wide — dental causes, which account for 63% of cases, must firstly be ruled out. After excluding dental causes, the patient should be referred for oncological screening. The disseminated neoplastic process accounts for c.22% of NCS cases [2].

A 68-year-old female patient was admitted to our neurology department due to numbness in the left half of her chin and lower lip of two days' duration and periodic shortness of breath. She was being chronically treated for rheumatoid arthritis and epilepsy. The neurological examination revealed decreased sensation and numbness in the left half of the chin and the left half of the lower lip, as well as pain on percussion of the thoracic spine. CT of the head showed leukoaraiosis. X-ray of the lungs revealed single atelectatic bands in the lower field of the left lung, but otherwise no inflammatory or focal changes were found. The diagnostics was extended by chest CT, which revealed a tumour in the left lung hilum, numerous enlarged mediastinal lymph nodes, and fluid in the left pleural cavity. In laboratory tests: ESR 62/h (n < 10/h), CRP 8.22 mg/dL (n < 0.5 mg/dL), CA-125 94 U/mL (n < 35 U/mL). An EBUS examination was performed with the collection of material for histopathological examination, in which small cell carcinoma cells were found. On the basis of the entire clinical picture and the results of additional tests, neuropathy of the left mental nerve was diagnosed in the course of a disseminated neoplastic process. The patient died within six months of diagnosis.

Malignant neoplasms metastasise to the mandible only in c.1% of cases. Of all cases of NCS caused by tumour cell dissemination, in c.47% it is the first symptom of the disease. The pathomechanism of the metastasising tendency of some tumours to the mandible is not yet fully understood. One hypothesis is that it may be due to the large amount of red bone marrow in the mandible, which favours the formation of tumour cell emboli [3]. Lung cancer very rarely causes NCS. The three most common malignancies associated with NCS are breast cancer (40.4%), lymphomas (20.5%), and prostate cancer (6.6%) [4–8].

A quick diagnosis allows cancer to be detected at an earlier stage and appropriate treatment to begin. In c.40% of patients with previously diagnosed cancer, NCS is the first symptom of disease progression or recurrence [3–5]. It is worth emphasising that a disseminated neoplastic process can cause simultaneous damage to many cranial nerves [9], and in such cases must be differentiated from facial onset sensor and motor neuropathy syndrome (FOSMN). Examination of the cerebrospinal fluid with the assessment of cytology and flow cytometry may be helpful in differential diagnosis [9, 10].

The prognosis is good if NCS is due to dental causes — then the symptoms may disappear if the causative agent is

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removed, and there is no permanent damage to the mental nerve. In oncological patients, symptoms of mental neuropathy are a very poor prognostic factor, with an average survival of c.6 months [6–8].

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Intraparenchymal pericatheter cyst: a rare but important manifestation of cerebrospinal shunt failure

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Key words: intraparenchymal pericatheter cyst, cerebrospinal shunt, intracranial hypertension, shunt failure

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To the Editors

Ventriculoperitoneal (VP) shunt is one of the most commonly performed procedures in neurosurgery, and is used in a variety of diseases including hydrocephalus and idiopathic intracranial hypertension (pseudotumor cerebri).

Shunt failure is a frequent problem, with up to 1/3 VP shunts failing within 12 months after placement, and 50% of patients requiring shunt revision during the first six years. Among the most prevalent complications are shunt blockage and infection [1]. Intraparenchymal pericatheter cyst is a rare complication of a shunt procedure, and is mostly seen in children [1, 2].

We present the case of a four-year-old girl with a history of type 1 Chiari malformation, who had been submitted to VP shunt and median suboccipital craniectomy two years before the current admission, at which she had been suffering from persistent generalised headache and recurrent vomiting of three days' duration. On clinical examination, she presented neck stiffness, without any other meningeal signs or focal neurological deficits. Laboratory studies, including inflammatory parameters, were unremarkable. Blood and cerebrospinal fluid (CSF) cultures were sterile.

On admission, head computed tomography (CT) scan showed a large hypodense subcortical area surrounding the proximal (ventricular) catheter of VP shunt (Fig. 1, G). To better characterise this finding, a brain magnetic resonance imaging (MRI) was obtained. This revealed a well-defined, homogenous cystic lesion surrounding the proximal catheter with signal similar to CSF in all sequences (hyperintense on T2-weighted with attenuation on T2/FLAIR, and hypointense on T1), facilitated diffusion, and adjacent extensive vasogenic oedema. No enhancement was observed on T1 post-gadolinium sequence. This lesion was associated with moderate locoregional mass effect (Fig. 1, A-F). A retrospective analysis of the initial brain CT showed that the proximal catheter was disconnected from the valve of the VP shunt, suggesting shunt failure (Fig. 1, H).

Based on the clinical and radiological features, the diagnosis of intraparenchymal pericatheter cyst due to VP shunt dysfunction was established. Shunt revision was performed, with gradual clinical improvement over the following days. Follow-up CT scan after two months revealed near-complete resolution of the intraparenchymal pericatheter cyst, without symptomatic recurrence.

The occurrence of pericatheter CSF oedema and intra-parenchymal pericatheter cyst has been associated with CSF shunt dysfunction, due to outflow increased resistance or obstruction [1, 3, 4].

The exact pathogenesis of pericatheter collections remains unclear. The pressure differential between the intraventricular CSF and brain parenchyma is thought to be the main reason for CSF flow into the parenchyma. Two possible pathways in the formation of pericatheter CSF collections have been hypothesised: either via the fenestrations on the proximal segment of the proximal (ventricular) catheter, or via backwards flow along the channel that was created during its insertion (focal weakness in the ependymal surface) [2–5]. It appears that CSF is not able to flow back to the ventricular system due to a one-way valve mechanism, leading to the gradual development of

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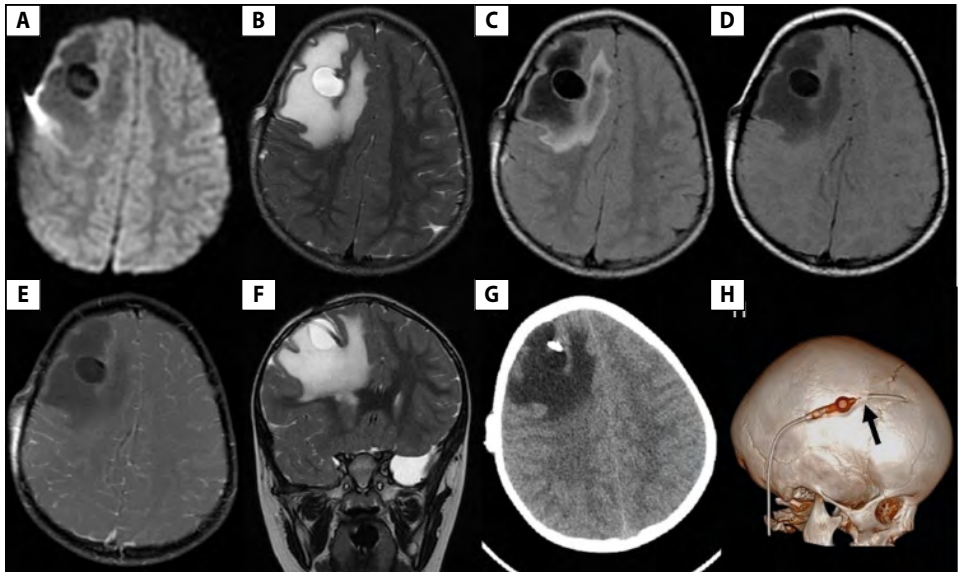

Figure 1. Brain magnetic resonance imaging (MRI) study in axial [DWI (A), T2 FSE (B), T2/FLAIR (C), T1 SE (D), T1 FatSat after intravenous gadolinium injection (E)] and coronal [T2 FSE (F)] views, demonstrating a homogenous, well demarcated cystic intraparenchymal pericatheter lesion with signal similar to CSF in all MRI sequences, without diffusion restriction, and associated with surrounding frontal vasogenic oedema. No enhancement was observed on post-gadolinium T1 fat-saturated sequence €. On axial non-enhanced head computed tomography (CT) (G), there was a large hypodense subcortical area adjacent to proximal catheter compatible with finding presented on MRI. 3D CT bone reconstruction (H) depicted disconnection between proximal catheter and valve of ventriculo-peritoneal shunt (*black arrow*)

pericatheter oedema and cyst (with or without ventriculomegaly) [4]. Pathologically, this lesion is a pseudocyst, given the absence of an epithelialised wall [2].

These intraparenchymal cysts are often preceded by pericatheter CSF oedema. The progression of CSF oedema to a cyst depends on various physiological factors such as the acuteness of shunt obstruction, the tautness of the ventricular wall, the degree of pericatheter gliosis, and the compliance of brain parenchyma [4]. Brain consistency at the time of the shunt might explain the higher incidence in the paediatric population, whose parenchyma is softer and more compliant [2, 4]. Astrogliosis often develops along the shunt catheter regardless of prior pericatheter haemorrhage or local radiotherapy, promoting pericatheter cysts [5].

Brain MRI plays an important role in differential diagnosis, mainly with tumours, infections (cerebritis and/or abcess) and ischaemic strokes. On MRI, these pericatether lesions have thin-wall cysts with CSF signal in all sequences, often associated with low attenuation and high T2/FLAIR signal in the surrounding parenchyma, consistent with vasogenic oedema. The lack of enhancement after contrast injection and diffusion restriction can be very useful in differential diagnosis [1–3, 5]. Additionally, in some cases, VP shunt nuclear scintigraphy (usually with Indium-111 disodium pentetate tracer) can be performed to evaluate the patency and function of the VP system [1].

Management of these patients remains controversial. Shunt revision is recommended, even though there have been a few cases in the literature treated with a conservative surgical approach (cyst aspiration).

Pericatheter cyst is a rare VP shunt complication, and is more commonly seen in children. The pathogenesis remains unclear but is thought to be multifactorial. Imaging studies, such as MRI and CT, have an important role to play in the diagnosis of these lesions, improving the management of these patients.

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LETTER TO THE EDITORS

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This Letter is accompanied by Response, see page 142

Cerebral amyloid angiopathy associated with Alzheimer's Disease: two pathologies from a single peptide?

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Keywords: amyloid, brain, angiopathy, Alzheimer's Disease

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To the Editors

We read with interest the extensive and thorough ahead-of-print review article entitled 'Updates on pharmacological treatment for Alzheimer's Disease' [1]. This article addresses the compelling issue — not only medical/scientific, but also social and cost/benefit — of pharmacological therapies to slow/block the progressive organisation of β-amyloid peptide (Aβ) deposits in Alzheimer's Disease (AD), their specific molecular targets, and the major related phase III and IV clinical trials.

One aspect that is not addressed is the frequent coexistence of AD and other β-amyloid deposition pathologies, which could, at least hypothetically, benefit equally from the aforementioned anti-amyloid therapies.

Below, we briefly report a histological case arising in this context.

A 78-year-old woman presented with new-onset dementia and sudden loss of left-side motor skills. Radiology showed a haemorrhage with marked signal reduction in the right parietal lobe, with contrast enhancement of uncertain significance, whether inflammatory or neoplastic: for this reason, surgery was performed.

Microscopy revealed thickened and hyalinised vessels (Fig. 1a) that were positive for Congo red histological staining (Fig. 1b) and Aβ immunohistochemical staining (Fig. 1c), leading to the diagnosis of cerebral amyloid angiopathy (CAA). The surrounding tissue also showed microbleeds (Fig. 2a) and scattered so-called 'red motor neurons' (Fig. 2b), which are hypoxic consequences of CAA [2], and were likely to be the cause of the clinically observed motor impairment. However, the aforementioned Aβ immunohistochemistry also highlighted coexisting microscopic AD morphology with typical extravascular deposits, both diffuse and focal (Fig. 1c), justifying the neurological condition of dementia.

The accumulation of Aβ in the brain can lead to several diseases, including CAA and AD. Whereas in CAA Aβ is deposited in the vascular wall, in AD it accumulates at the extravascular parenchymal level or intracytoplasmically in neurons in the form of tangles. These different Aβ depositions would be the result of different pathways, but with common initial steps, which is why the two diseases often co-occur [3, 4]. It is estimated that c.48% of AD cases have co-existing CAA [5].

The coexistence of CAA and AD is often suspected clinically, and the fact that it can be documented histologically supports this thesis, as well as that of a common aetiopathogenesis. However, despite the existence of important data [2–5], it is still not fully understood why some individuals develop only CAA, some others only AD, and in still others, as in the present case, both CAA and AD coexist.

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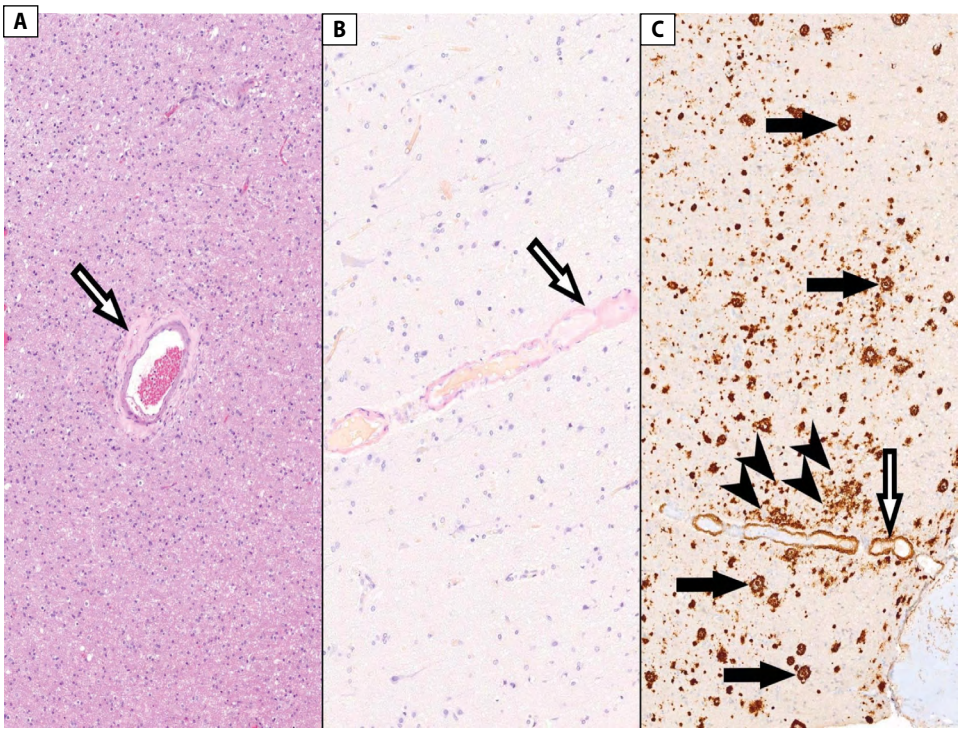

Figure 1. Photomicrographs of cerebral tissue with amyloid angiopathy (CAA): (a) view of an intraparenchymal blood vessel with hyaline wall thickening (arrow) suspicious for amyloid deposition (haematoxylin and eosin, 10×); (b) Congo red staining showing pink amyloid deposition (arrow, 20×); (c) β-amyloid immunohistochemistry showing Alzheimer's Disease deposits: besides confirmed positivity in vessel wall (white arrow), further multiple intraparenchymal/extravascular positivities are highlighted, both in focal/targetoid form (black arrows) and as diffuse deposits (black arrowheads, 10×)

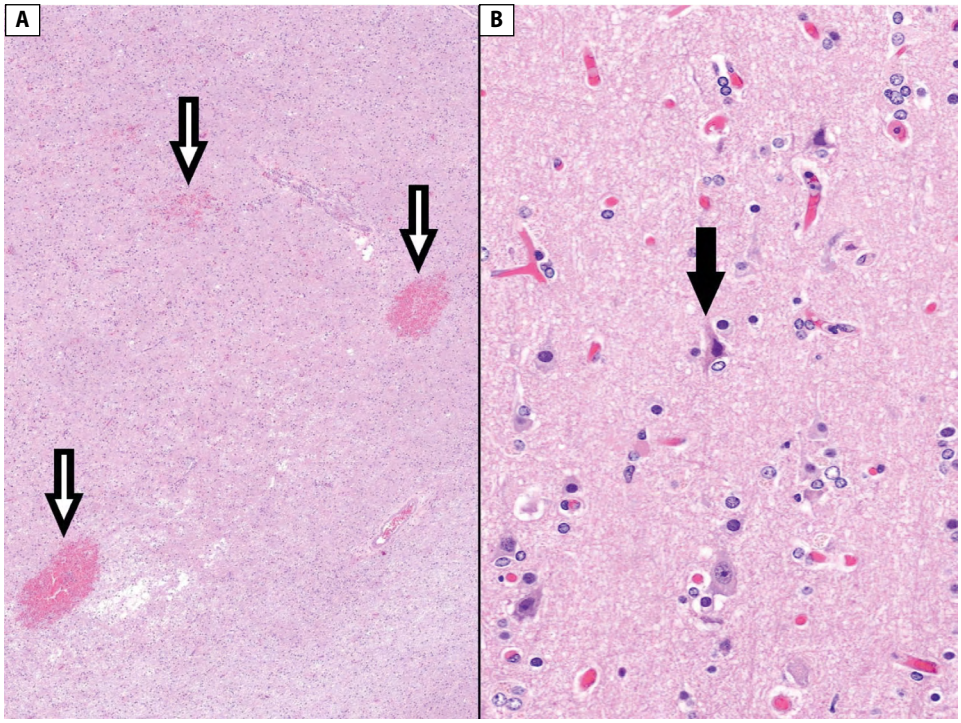

Figure 2. Photomicrographs of surrounding brain tissue: (a) intraparenchymal microbleeds (white arrows) (haematoxylin and eosin, 4×); (b) so-called 'red neurons' (black arrow), a morphological feature of neuronal hypoxic distress CAA-related (haematoxylin and eosin, 40×)

The case described does not represent a novelty of Aβ deposition brain lesions, but it helps to reflect, also in a histological/topographical sense, that the consideration of anti-amyloid therapies should be placed in a broader context than AD, although AD is certainly its most important chapter in terms of incidence, prevalence, morbidity, mortality, and cost to society.

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RESPONSE TO LETTER
TO THE EDITORS

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This Response accompanies
a Letter, see page 139

Updates on pharmacological treatment for Alzheimer's disease: response to Letter to the Editors

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To the Editors

The past two years have brought major advances to the treatment landscape of Alzheimer's disease (AD). Once a disease with mediocre symptomatic treatment, AD will soonhave three disease-modifying therapies available (aducanumab, lecanemab, and donanemab). This journal recently published my review of the pharmacological advances in AD treatment [1]. In their Letter to The Editors, Gaggero et al. noted that my review did not discuss treatment of cerebral amyloid angiopathy (CAA) despite its high concurrence with AD [2]. Herein, I discuss evidence regarding the risk and potential benefit of treating CAA with monoclonal antibodies directed against amyloid-β (Aβ).

Amyloid-related imaging abnormality (ARIA) is a well-documented adverse effect of anti-amyloid therapies that manifests with edema (ARIA-E) and/or haemorrhage (ARIA-H). ARIA is usually asymptomatic, but can be life-threatening and has been observed in virtually all trials of monoclonal antibodies directed against Aβ. Numerous trials of anti-amyloid therapies have failed to demonstrate significant efficacy, but have taught us that certain patient characteristics, such as APOEε4 allele homozygosity, as well as imaging features suggestive of CAA, increase one's risk of developing ARIA.

CLARITY AD was the first non-disputed positive phase III clinical trial of an anti-amyloid monoclonal antibody to treat AD [3]. To minimise the occurrence of ARIA, CLARITY AD excluded individuals with any of the following: > 4 microhaemorrhages (≤ 10 mm at greatest diameter); ≥ 1 macrohaemorrhage (> 10 mm at greatest diameter); or superficial siderosis [3]. The donanemab trial also adopted these exclusion criteria [4]. Despite effectively excluding individuals with known CAA, ARIA-H still occurred in 17.3% of patients in the treatment arm of CLARITY AD [3]. Fortunately, only six individuals receiving lecanemab were symptomatic.

Despite the demonstrable benefit of anti-amyloid therapies in AD, there is no compelling evidence supporting their use in CAA due to the lack of positive primary outcomes in phase III clinical trials. Even theoretical efficacy is lacking, because potential study enrollees with imaging features of CAA were excluded from the only positive AD clinical trials due to their increased risk of developing ARIA-H. Cummings et al. recently published appropriate use guidelines for lecanemab, and recommended adopting the same inclusion/exclusion criteria of CLARITY AD when deciding which patients should be offered lecanemab [5].

Monoclonal antibodies directed against Aβ may be an effective therapeutic approach for CAA, but require additional study. Aβ40 is the primary amyloid isoform of CAA as opposed to Aβ42 in AD. Ponezumab is a monoclonal antibody directed against Aβ40, and a recent phase II clinical trial demonstrated safety and tolerability but did not meet efficacy criteria [6]. Like other amyloidoses (e.g. transthyretin amyloidosis), alternatives to monoclonal antibodies may be more effective for treating CAA.

In conclusion, there is much work to be done before a CAA treatment is ready for the clinic.

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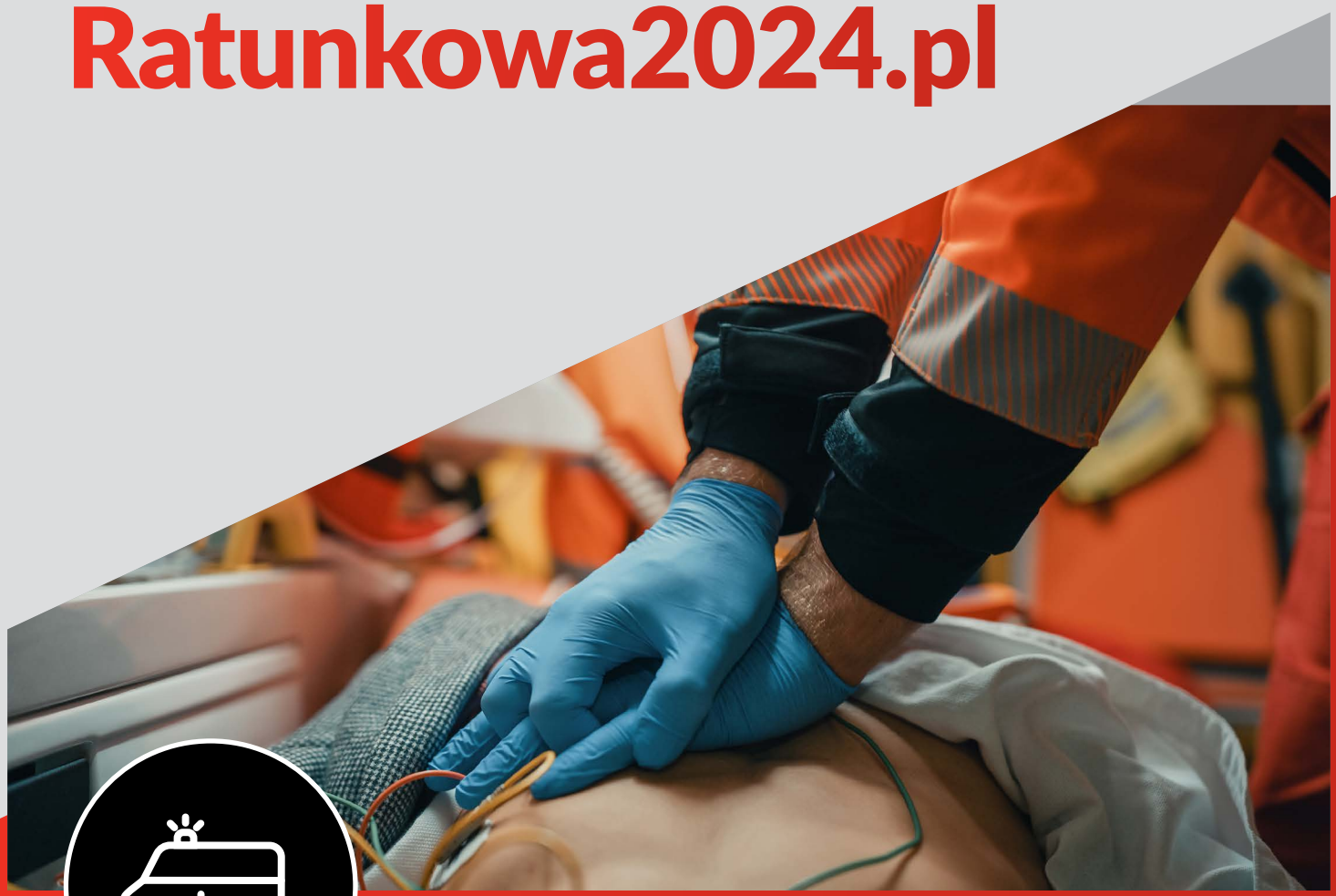

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