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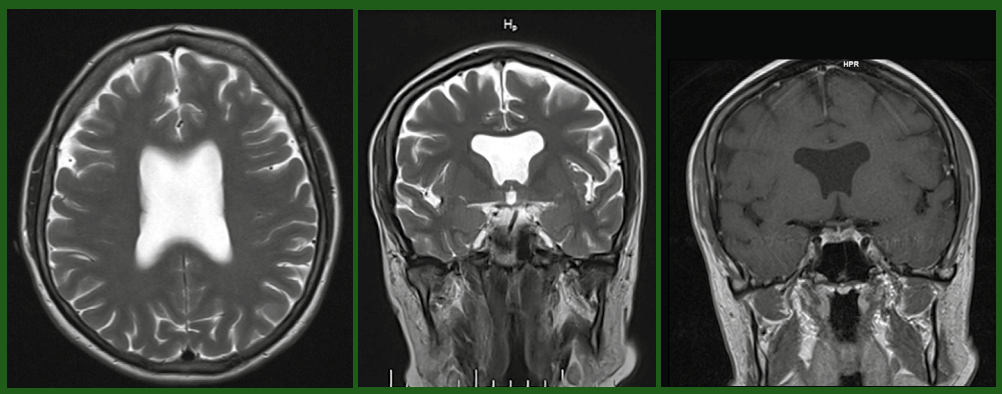

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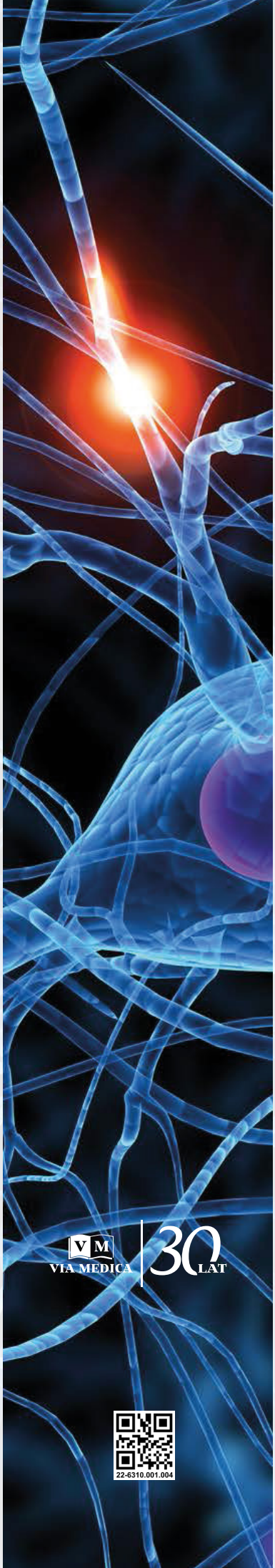

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Table of Contents

REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
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Multisystem presentation of Late Onset Pompe Disease: what every consulting neurologist should know

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ABSTRACT

Introduction. Pompe Disease is a rare, autosomal recessive, lysosomal disorder caused by deficiency of alpha glucosidase (GAA). It leads to the accumulation of glycogen in body tissues, with severe myopathy and cardiomegaly as a hallmark of the classic infantile form. Non-classical, or Late Onset Pompe Disease (LOPD) manifests after 12 months of age or in adulthood.

Material and methods. The clinical heterogeneity of LOPD causes delay in diagnosis and pharmacological treatment. In the Polish population, it is still underdiagnosed, and the time from onset to diagnosis remains a cause for concern.

Clinical implications. Although typically patients present with proximal muscle weakness, high CK or early respiratory insufficiency, they can also suffer from multiple symptoms from other organs. Patients may present with arrhythmias, vascular abnormalities including aneurysms or dilative arteriopathy, gastric or urinary symptoms, or musculoskeletal pathologies.

Results. A high index of suspicion among neurologists consulting internal medicine wards would aid early diagnosis of LOPD, while a multidisciplinary approach with the involvement of other specialists can reduce the risk of complications and improve the prognosis for LOPD patients. Patients who manifest with musculoskeletal and respiratory symptoms are prone to be diagnosed sooner than individuals with non-muscular symptoms, and therefore it is important to raise awareness of other manifestations of this disease.

Key words: LOPD, Late Onset Pompe Disease, GAA, multidisciplinary approach

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Introduction

Pompe Disease (PD, glycogen storage disease type II; OMIM # 232300) is a rare neuromuscular disease caused by mutations of the acid α-glucosidase (*GAA*) gene encoding acid maltase, transmitted as an autosomal recessive disorder. GAA deficiency leads to the accumulation of glycogen in body tissues, with a predilection for the skeletal muscles [1, 2].

The classic infantile form (Infantile Onset Pompe Disease, IOPD) presents within the first year of life, while the non-classical form, or Late Onset Pompe Disease (LOPD), becomes symptomatic between 12 months of age and late adulthood [1, 3]. IOPD has a rapidly progressive course with severe cardiomegaly, hepatomegaly and myopathy. Without pharmacotherapy, it leads to death before the second birthday [4].

LOPD is heterogeneous clinically and poses a significant diagnostic challenge, especially when pulmonary or cardiac symptoms are present before significant skeletal muscle weakness. The most common symptoms of LOPD are listed in Table 1.

The incidence of Pompe Disease is estimated at approximately 1:40,000 — 1: 60,000 [5–9]. With its unspecific phenotype, LOPD is still underdiagnosed in many populations [1, 10].

Enzyme replacement therapy (ERT) for Pompe Disease with alpha glucosidase was approved in 2006. Early treatment improves the patients' prognosis, allowing them to improve or maintain their respiratory functions and ambulation, and lowering their mortality rate [11–14].

Pompe Disease is a multisystem condition. Due to its heterogeneous disease presentation, in this article we seek

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Table 1. Most common symptoms in LOPD patients

Affected system	Most common symptoms
Laboratory findings	CK, LDH, AST, ALT elevation
Neuromuscular symptoms	Limb girdle muscle weakness Axial muscle weakness Frequent falls Difficulties in climbing stairs Myalgia Fatigue
Musculoskeletal and bones symptoms	Spine abnormalities: scoliosis, kyphosis and lumbar lordosis Rigid spine syndrome Osteoporosis and bone fractures Asymptomatic vertebral fractures
Respiratory symptoms	Sleep disruption Fatigue, excessive daytime sleepiness, nocturnal hypoventilation, orthopnoea Wheezing Morning headache Impaired coughing Frequent airway infections Dyspnoea Respiratory failure
Cardiovascular symptoms	Supraventricular arrhythmias: WPW, SVT, sick sinus syndrome or AF; In rare cases, cardiomyopathy
Gastrointestinal symptoms	Incontinence Stool urgency Diarrhoea Abdominal discomfort Cramps Early satiety Macroglossia Dysarthria Dysphagia
Urinary tract symptoms	Urinary urge incontinence Lower urinary tract symptoms
Vascular and central nervous system involvement	Dilative arteriopathy Aneurysms Ischaemic stroke Lacunar encephalopathy Subarachnoid haemorrhage Aortic stiffness

AF — atrial fibrillation; ALT — alanine transaminase; AST — aspartate aminotransferase; CK — creatine kinase; LDH — lactate dehydrogenase; LOPD — late onset Pompe Disease; SVT — supraventricular tachycardia; WPW — Wolff–Parkinson–White syndrome

to underline the importance of testing for LOPD also those patients presenting with pulmonary or cardiac symptoms.

Material and methods

We have searched PubMed for relevant manuscripts using the terms: Late Onset Pompe Disease or LOPD and cardiac; LOPD and respiratory; LOPD and gastrointestinal; LOPD Pompe and urinary, LOPD and multisystem, LOPD and multidisciplinary. Selected studies and also reviews in this area were assessed for further relevant citations. The reference lists of selected studies were searched for additional publications.

Neuromuscular symptoms

LOPD presents with slowly progressive limb-girdle muscle weakness in 78–95% of patients [15–18]. Muscle fatigue, exercise intolerance, decreased mobility, axial muscle weakness and myalgia are also frequently reported [1, 19–21].

Weakness may be preceded by myalgia [21]. Some patients complain of muscle cramps [22]. Even though muscle weakness progresses slowly, in the natural course of the disease it can lead to wheelchair dependence [17]. The distribution of muscle weakness varies, but most commonly it first involves the proximal muscles of the lower limbs and axial muscles, followed by the upper extremities and respiratory muscles (Tab. 1) [7].

Given the need for early diagnosis and treatment, a low threshold for screening for LOPD is crucial in patients with unclassified limb-girdle muscle weakness and/or with asymptomatic hyperCKemia [5, 10, 15, 19, 20, 23]. In the Polish population, we have performed screening for LOPD in a cohort of patients with limb-girdle muscle weakness and/or persistent hyperCKemia, confirming the diagnosis in 3% of patients. The reported rate is thus consistent with neighbouring European countries, where it has been reported as 2.4–4.2% [10, 15, 23].

Skeletal symptoms

Secondary to progressive muscle weakness, patients with Pompe Disease often develop spinal abnormalities, mostly scoliosis but also kyphosis and lumbar hyperlordosis, rigid spine syndrome (RSS), and also osteoporosis with the risk of bone and vertebral fractures [16, 24–29].

According to the international Pompe registry, scoliosis is found in 33% of patients with LOPD [25]. It is more common in patients who experience disease onset as children than it is in those with onset as adults. In some cases, surgical treatment is necessary to maintain sitting position and improve pulmonary function [24, 30]. Also, scoliosis has been found to occur in 62.5% of patients with Pompe Disease requiring a wheelchair and led to reduced pulmonary function [25].

Rigid spine syndrome is a limitation of the neck and trunk movements that causes postural abnormalities and increases the risk of respiratory insufficiency [31]. In most patients, severe axial muscle weakness is accompanied by mild to moderate extremity muscle weakness [16, 26]. In patients with RSS, Pompe Disease should be considered in a differential diagnosis [27, 32].

A Dutch study by van Berg et al. [29] showed that 67% of patients with Pompe Disease have decreased bone mineral density (BMD) and consequently are at higher risk of bone fractures due to osteoporosis. The authors suggested regular screening of BMD in children, patients who develop muscle weakness, and those who are wheelchair dependent and also with respiratory insufficiency.

Additionally, a study by Bertoldo et al. [33] reported a high prevalence of asymptomatic vertebral fractures in patients with LOPD even without significant deterioration of BMD (77% of 22 patients). The fractures were not related to trauma. This shows the need for routine screening for vertebral fractures in LOPD patients.

Respiratory symptoms

LOPD frequently presents with respiratory symptoms. Respiratory insufficiency may precede limb-girdle muscle weakness [16]. It has been described as the second most frequent initial symptom of the disease in 11–13% of patients [18, 34]. Respiratory problems have been reported in 33–60% of patients at diagnosis [15, 34]. In the study by van der Beek et al. [35], respiratory involvement was reported in 79% of adult patients and in 59% of children, with evident diaphragmatic involvement observed in 38% of those examined. In general, as the disease progresses, 29–72.2% of LOPD patients will need respiratory support [36–38].

Nocturnal hypoventilation leads to early sleep disruptions, excessive daytime fatigue and sleepiness, nocturnal dyspnoea, orthopnoea, wheezing and morning headache [39–41]. Also, respiratory muscle weakness impairs the coughing process, and therefore patients are prone to develop recurrent pulmonary infections with prolonged recovery periods [39]. Due to diaphragmatic involvement, dyspnoea is exacerbated in the supine position. Some patients may even be unable to maintain a supine position without ventilatory support [35, 39].

In most cases, symptoms progress slowly and patients adapt to the increasing pulmonary restriction [26]. Therefore, pulmonary infection can lead to decompensation and respiratory failure that mimics an acute event [42]. In most LOPD patients, respiratory failure is the main cause of death [21, 43]. Diaphragmatic insufficiency can be considered to be a hallmark of LOPD even early in the course of the disease [44, 45]. In the DIPPER screening study, performed to establish the incidence of LOPD disease in patients with paralysis of the diaphragm of unknown origin, 16.8% of patients were diagnosed with Pompe Disease. This underlines the need for screening for GAA deficiency in patients who initially present with pulmonary symptoms only, including diaphragm weakness [45]. It is indicated in every patient with unexplained respiratory symptoms requiring mechanical ventilation, especially when CK activity is elevated.

Spirometry with evaluation of forced vital capacity (FVC) in sitting and supine positions aids in diagnosing diaphragmatic weakness. Sitting FVC may still be normal, but a decrease of FVC > 10% in the supine position is considered significant [46, 47]. In LOPD, the FVC drop is usually more than 25% [7]. Maximal inspiratory pressure (MIP), sniff nasal inspiratory pressure (SNIP), maximal expiratory pressure (MEP), and peak cough flow (PCF) can also be useful parameters in LOPD [39]. Ultrasound testing can aid in the evaluation of diaphragm weakness [48].

Treatment with ERT prevents deterioration of respiratory function. A meta-analysis by Schoser et al. [12] shows a relative difference between treated and non-treated patients which increased over time — from 4.5% FVC after 12 months to 6% FVC after four years. LOPD patients may also benefit from inspiratory muscle training. When performed frequently and regularly, this can stabilise and/or slow down the deterioration of diaphragm weakness [49].

In addition to the involvement of respiratory muscles, glycogen may also accumulate in the airway's smooth muscles [50–52]. As a result, it can affect the trachea, bronchi and bronchioles, causing bronchomalacia and tracheomalacia and contributing to the need for mechanical ventilation [52–54]. Bronchoscopy should be considered in LOPD patients with progressive respiratory dysfunction preceding mechanical ventilation [52].

Cardiovascular symptoms

Although hypertrophic cardiomyopathy is an early, classic symptom in patients with IOPD, in LOPD by contrast it is rare [55]. There have only been a handful of case reports of hypertrophic cardiomyopathy in adults with Pompe Disease [36, 56, 57]. Cardiomyopathy improves with ERT [36]. A cardiovascular magnetic resonance study of LOPD reported only mild and non-specific cardiac abnormalities in a small group of patients [58].

The presence of rhythm disturbances varies greatly in different groups, from 2% up to 29.5% [16, 37]. Therefore, it is important to provide regular cardiac care to LOPD patients. Reported cardiac arrhythmias increase the risk of sudden death in LOPD [59]. There have been reports of supraventricular arrhythmias, such as Wolff–Parkinson–White syndrome (WPW), supraventricular tachycardia (SVT), sick sinus syndrome and atrial fibrillation [7, 37, 60–63]. WPW has been associated both with IOPD and LOPD, and is probably caused by the disruption of the annulus fibrosus [60, 63]. A short PR interval on ECG has been described in 8-10% of LOPD patients [21, 63]. Heart rhythm disorders with CKemia can precede neuromuscular symptoms [21].

Also, in 3% of the patients in a French LOPD cohort, atrioventricular blocks requiring pacemaker implantation were reported. It is important to remember that even though ERT improves cardiac function in patients with Pompe Disease, it does not seem to be effective in preventing arrhythmias [64].

Patients with LOPD require cardiac follow-up with electrocardiography, 24-hour Holter monitoring and also echocardiography, due to the potentially life-threatening complications [55, 64].

Cardiac involvement occurs also in other lysosomal storage disorders (Tab. 2).

Gastrointestinal symptoms

Symptoms from the gastrointestinal (GI) track are not life threatening, but they can affect quality of life (QoL) and tend to be underdiagnosed [65, 66].

Table 2. Cardiac manifestations in various lysosomal storage disorders

Condition (OMIM#, gene mutation, transmission mode)	Cardiac manifestations	Most common manifestation
Late Onset Pompe Disease (#232300, AR)	Supraventricular arrhythmias: WPW, SVT, sick sinus syndrome, AF; valvular heart disease. In rare cases, cardiomyopathy	Skeletal muscle weakness, hyperCKemia, respiratory insufficiency with diaphragm involvement
Danon Disease [93–98] (#300257, X-linked)	Cardiomyopathy, ventricular preexcitation, arrhythmias such as WPW, valvular heart disease, heart failure, or sudden cardiac death	Mental retardation, skeletal myopathy, hyperCKemia, cardiomyopathy
Anderson-Fabry Disease [95, 99–101] (#301500, X-linked)	Cardiomyopathy, heart failure, arrhythmias (short PR interval, bundle branch block, progressive AV conduction abnormalities), valvular heart disease — rarely haemodynamically significant, arterial hypertension	Angiokeratosis and corneal opacities, acroparesthesias, cardiac manifestations, gastrointestinal problems, renal involvement including renal failure, transient ischaemic attacks, recurrent strokes
Mucopolysaccharidoses [95, 99, 102–104] (MPS I: Hurler #607014, AR MPS I: Scheie #607016, AR MPS II: Hunter #309900, X-linked recessive MPS IIIa #252900, AR; /IIIb #252920, AR MPS IVa #253000, AR MPS VI #253200, AR)	Valvular heart disease (most commonly mitral valve involvement), cardiomyopathy, thickening of cardiac valves and large vessels, pulmonary hypertension	Accumulation of glycosaminoglycans causing cell and organ dysfunction; mental retardation, corneal clouding, growth retardation, contractures of joints, umbilical and inguinal hernias, kyphoscoliosis, hearing loss, hepatosplenomegaly
Mucolipidoses [95, 99, 105, 106] (type II #252500, AR; type III #252600, AR)	Valvular heart disease	Mental retardation, skeletal deformities, malfunction of heart, lungs, liver and spleen
Gaucher Disease [99, 107, 108] (type 1 #230800, AR, type 2 #230900, AR type 3 #231000, AR subtype IIIC #231005, AR)	Rare: pulmonary hypertension, cor pulmonale, valve involvement, myocardial calcifications	Heterogenous phenotype; organomegaly, bone abnormalities, anaemia and thrombocytopenia; in some cases, progressive neurological degeneration

AF — atrial fibrillation; AV — atrioventricular; SVT — supraventricular tachycardia; WPW — Wolff–Parkinson–White syndrome

The accumulation of glycogen in smooth muscles may cause incontinence, stool urgency, diarrhoea, abdominal discomfort, cramps and early satiety [7, 60, 67, 68]. GI symptoms are quite common. For instance, in a German study, stool urgency and diarrhoea were reported in more than half of the patients [68].

Also, due to bulbar muscle weakness, lingual weakness and macroglossia, some patients may suffer from dysarthria and dysphagia. Screening for dysphagia is important in LOPD [7, 52, 69, 70]. Patients with bulbar muscle weakness are at risk of pulmonary complications [38]. Difficulties in feeding can lead to low body mass, poor weight gain and malnutrition [60, 71].

Urinary tract symptoms

Glycogen also tends to accumulate in the smooth muscles of the genitourinary tract [52, 72].

Urinary urge incontinence has been reported in several studies, with a higher prevalence compared to the general population [68, 73].

Lower urinary tract symptoms (LUTS) have been reported in the majority of patients with LOPD [73]. A weak, dribbling, intermittent stream, post-void dribbling, an inability to stop the stream, and urinary incontinence have been commonly reported [73]. The aetiology is speculated to be either glycogen accumulation in smooth muscle cells of the bladder, or dysfunction of the autonomic nervous system and peripheral nerves [73, 74]. Urinary symptoms have a significant impact on QoL [73].

Other systems involvement

The involvement of the cerebrovascular, central and peripheral nervous systems have also been reported in LOPD. Various cerebrovascular abnormalities have been noted, with a higher incidence compared to the healthy population [7]. They may manifest as dilative arteriopathy or aneurysms and mainly involve posterior circulation, but the anterior circle can also be affected [75]. Glycogen can accumulate in the cells of vessel walls, diminishing smooth muscle tissue integrity and probably causing aneurysms or dilative arteriopathy [60, 76]. Patients need to be closely monitored to prevent rapture of the aneurysm. Restrictive arteriopathy has also been described [77]. Cases of stroke caused by intracranial aneurysms or arteriopathy [76, 78–80], and subarachnoid haemorrhage, have also been reported [81]. Vascular complications such as stroke may even be a presenting symptom of LOPD [78].

The involvement of the aorta, iliac arteries, renal arteries, and also cervical arteries has been reported [7, 82]. Accumulation of glycogen in the aorta may lead to aortic stiffness, causing hypertension [83].

Laboratory parameters

Most LOPD patients have mildly elevated serum CK level (1,000–1,500 U/L) [7, 20, 84]. In a review by Winkel et al. [18], over 90% of cases presented with elevated CK, LDH, AST and ALT.

Persistent CK elevation, more than 1.5× upper limit of normal, even in an asymptomatic person, should therefore raise a suspicion of Pompe Disease [10, 85].

Diagnosis

The recommended first step for the diagnosis of Pompe Disease is a test of the GAA activity. This is currently recommended to take the form of a screening test in patients with moderate CKemia, limb-girdle weakness, rigid spine syndrome, or diaphragm weakness, unless a clear alternative diagnosis can be made [15, 86, 87]. The evaluation of the GAA activity is usually performed from a dried blood spot sample. If the result is below the reference range, DNA testing may be performed from the same blood sample, where consented to. The detection of two mutations in the *GAA* gene confirms a Pompe diagnosis. Alternatively, GAA activity assessment in lymphocytes or in fibroblasts can be performed as a confirmatory test [9, 11].

Generally, DNA analysis is performed with PCR reactions and subsequent Sanger sequencing of all GAA coding exons. Also, an exon-flanking RT-PCR can be used to detect novel variants [88, 89]. Some mutations have been reported more frequently in different populations and locations. For example, mutation c.32–13T > G is very frequently reported in the Polish population as a heterozygous composition with missense or frameshift mutation on the other allele [10, 42]. This mutation is by far the most common in the Pompe registry, which consists mostly of Caucasians [86].

Over 400 genetic variants of Pompe Disease have been noted in the 'Pompe Disease GAA variant database' (http://www.pompevariantdatabase.nl/), which allows the prediction of a patient's phenotype after identifying disease variants of both alleles [90].

Conclusions

Pompe Disease is classified as a metabolic myopathy, but can manifest with various symptoms. Due to its unspecific phenotype and low prevalence, the time from onset to diagnosis remains a cause for concern [18, 91, 92]. Greater awareness of LOPD and a multidisciplinary approach to patients are required.

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REVIEW ARTICLE

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Surgical management of spontaneous intracranial hypotension syndrome: a literature review

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ABSTRACT

Introduction. Spontaneous intracranial hypotension (SIH) is a highly disabling but often misdiagnosed disorder. The optimal management options for patients with SIH remain uncertain. The aim of this study was to review studies reporting the management of SIH with a special emphasis on the surgical treatment of SIH including clinical trials, case series and case reports related to the issue of various neurosurgical procedures performed for SIH treatment.

Objective. The clinical outcomes of patients diagnosed with SIH treated with either only surgery or with surgery as the primary method of treatment were analysed.

Material and methods. The PubMed, Scopus and Google Scholar databases were searched according to the established criteria.

Results. The literature search revealed seven clinical trials, five case series and eight case reports regarding surgical treatment of patients diagnosed with SIH. Manuscripts reporting at least five individuals treated surgically for SIH were considered as case series. In most published articles, surgery provided clinical benefit, resulting in a success rate of 82.6–100% for complete relief of SIH symptoms.

Conclusions. Our literature review has revealed that SIH can be diagnosed reliably by MRI and cisternography. The identification of the location of SIH is mandatory for its successful surgical treatment. The clinical outcome is related to the location of SIH in the spinal canal. Most often, cerebrospinal fluid leakage occurs in the thoracic region. Surgical treatment is very effective and the obtained treatment results are complete and permanent.

Key words: spontaneous intracranial hypotension, surgery for spontaneous intracranial hypotension, cerebrospinal fluid leak, orthostatic headache

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Introduction

The syndrome of spontaneous intracranial hypotension (SIH) is a condition that results from leakage of cerebrospinal fluid (CSF) into the extradural space [1–7]. Intracranial hypotension from a CSF leak can be classified as spontaneous, iatrogenic, or traumatic. Spontaneous cases result from dural tears, a meningeal diverticulum, or CSF-venous fistulas. The only known predisposing factor for SIH is hereditary disorders of connective tissue. Increased incidence of SIH has been noted in patients diagnosed with Marfan's Syndrome, Ehlers-Danlos, and adult polycystic kidney disease [8, 9].

The most common and typical symptom of SIH is orthostatic headache that is worse in the upright position [1–7]. It should be noted that the onset of SIH symptoms can occur at a wide range of times. Symptoms may occur within seconds of becoming upright, or not until hours later. [1, 10, 11] Generally, such orthostatic headache occurs or worsens within 15 minutes of obtaining an upright position. The SIH diagnostic criteria according to the International Classification of Headache Disorders (ICHD-3, 3rd Edition) are considered guidelines for a diagnosis of SIH, and these are set out in Table 1.

Conversely, orthostatic headache can improve within minutes of recumbency, or also not for hours [1, 10, 11].

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The positional aspect of the headache may be variable and change with time. These variable characteristics of headache have been attributed to physiological compensation over time. [13]. The headache may be diffuse or localised to the frontal, temporal, or parietal regions, but the most common locations are the occipital and suboccipital regions. The headache is the direct result of the downward displacement of the brain due to loss of CSF, impending on pain-sensitive structures such as dura mater. An alternative mechanism involves compensatory dilatation of the pain-sensitive intracranial venous structures.

Besides typical orthostatic headache, SIH can also be accompanied by a variety of other symptoms. These symptoms, depending on the CSF leak, are usually categorised into four types as shown in Table 2. Posterior neck pain with neck stiffness, dizziness, nausea or vomiting are the most common symptoms, being found in c.50% of patients. These symptoms point to meningeal irritation [14–16].

Table 1. Criteria for headache attributed to low cerebrospinal fluid pressure, International Classification of Headache Disorders, 3rd edition ICHD-3 [12]

A	Any headache fulfilling criterion C
B	1 Low cerebrospinal fluid (CSF) pressure (< 60 mm CSF)
	2 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

Tinnitus with impaired balance is another common symptom of SIH. This symptom can be explained by downward displacement of eighth cranial nerve complex. Visual blurring and visual field deficits are also attributed to downward displacement of the brain. Not only optic nerves and chiasm are affected by the downward brain shift, but also other sensitive cranial nerves located at the cranial base. Cranial nerve deficits due to SIH can involve diplopia (abducens nerve dysfunction, rarely trochlear or oculomotor nerves dysfunctions), facial numbness or facial pain (trigeminal nerve dysfunction), facial weakness or facial spasm (facial nerve dysfunction), and dysgeusia (chorda tympani or glossopharyngeal nerve dysfunction) [15–20].

SIH can cause so-called spinal manifestations such as local back pain at the level of the CSF leak, radiculopathy due to stretching of cervical nerve roots, or dilatation of the epidural venous plexus. Prominent CSF leak may lead to myelopathy with subsequent quadriplegia. The most dangerous life-threatening situations related to SIH are so-called severe intracranial manifestations caused by prominent displacement of the brain. These intracranial symptoms may include a decreased level of consciousness caused by diencephalon herniation causing stupor and coma. Other rare intracranial manifestations may produce cognitive dysfunction, dementia, and parkinsonism [21, 22]. These symptoms generally improve when conservative or surgical treatment of SIH remains effective. SIH may be responsible for cerebellar haemorrhage or ataxia. A summary of different clinical manifestations of SIH is set out in Table 2.

Table 2. Clinical symptoms are segregated into four types of clinical manifestation of spontaneous intracranial hypotension

Type of symptoms of SIH syndrome	Symptoms	Structures responsible for symptoms occurrence
Generalised symptoms	Orthostatic headache	Headache is a direct result of downward displacement of brain due to loss of CSF, impending on pain-sensitive structures like dura mater, or caused by compensatory dilatation of pain-sensitive intracranial venous structures
Generalised symptoms	Neck pain or neck stiffness, dizziness, nausea, vomiting	Meningeal irritation
Cranial nerve deficits	Visual blurring and visual field deficits	Downward displacement of brain, with pressure on optic nerves and optic chiasm
Cranial nerve deficits	Diplopia	Abducens nerve dysfunction, rarely trochlear or oculomotor nerves
Cranial nerve deficits	Facial numbness, facial pain	Trigeminal nerve dysfunction
Cranial nerve deficits	Facial weakness, facial spasm	Facial nerve dysfunction
Cranial nerve deficits	Dysgeusia	Chorda tympani or glossopharyngeal nerve dysfunction
Cranial nerve deficits	Phonophobia, muffled hearing, tinnitus	Vestibulo-cochlear nerve dysfunction
Spinal symptoms	Lower back pain	Meningeal irritation at level of CSF leak
	Radiculopathy	Stretching of cervical nerve roots or dilatation of epidural venous plexus
	Myelopathy	Prominent CSF leak may cause myelopathy with subsequent quadriplegia
Severe intracranial manifestations	Cognitive dysfunction	Mild dementia or subtle cognitive dysfunction caused by chronic subdural hygromas
	Dementia	
	Parkinsonism	Moderate to severe displacement of brain with diencephalic herniation
	Ataxia	Severe cerebellar herniation may cause cerebellar haemorrhage
	Stupor	with downward displacement of tonsils
	Coma	

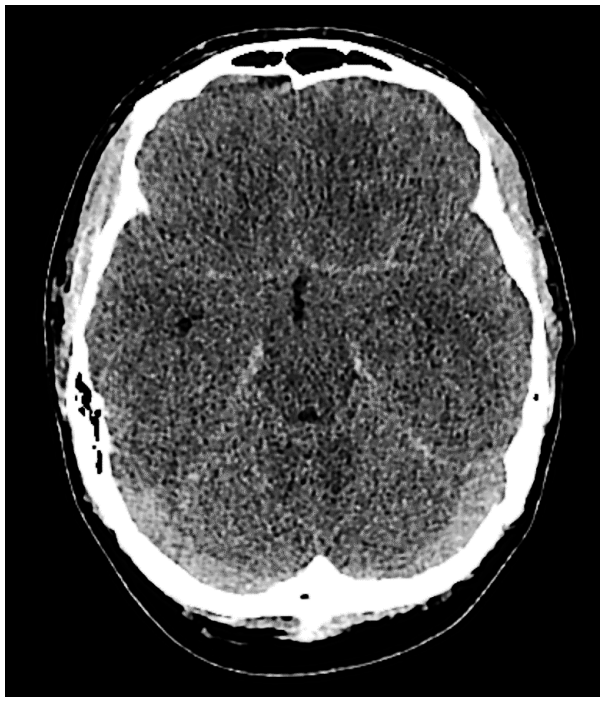

Figure 1. Computed tomography (CT) image showing increased attenuation in basal cisterns and diffuse pachymeningeal enhancement. Increased attenuation, especially in sylvian fissures, can mimic subarachnoid haemorrhage

Imaging findings in spontaneous intracranial hypotension syndrome

Computed tomography (CT) is often the first diagnostic tool performed in emergency units in patients with severe, disabling orthostatic headache. Cranial CT may show subdural fluid collection, effacement of cerebral cisterns, and downward displacement of cerebellar tonsils.

Moreover, CT may show increased attenuation in the sylvian fissures, basal cisterns, mimicking a subarachnoid haemorrhage (Fig. 1) [23]. A further diagnostic tool is magnetic resonance imaging (MRI), which is diagnostic in 80% of cases of SIH. The MRI findings are characteristic and are summarised in the mnemonic 'SEEPS', standing for: subdural fluid collections, enhancement of the pachymeninges, engorgement of venous structures, pituitary engorgement, and sagging of the brain. All these MRI findings together allow a proper and prompt diagnosis. [10, 24–29]. The MRI findings description is beyond the scope of this review article, and more information on MRI findings in SIH can be found in other review articles [30–33].

The recently described 'MRI sign' found in patients diagnosed with SIH is oedema of the corticospinal tracts in the midbrain [34]. Causes of such oedema are only speculative at present and are secondary to long-standing compression or to injury of axons within the midbrain caused by stretching along their axons [34].

Another described MRI finding is superficial siderosis detected on gradient-recalled echo or susceptibility-weighted MR imaging. Hemosiderin depositions are located on the pial surface of the brain or spinal cord as the result of chronic recurrent bleedings in the subarachnoid space. These bleedings are caused by brain sagging and stretching of superior cerebellar bridging veins or intraspinal friable vessels. The superficial brain or spinal siderosis is usually found in patients with long-standing SIH [34].

Other diagnostic tools that can help locate subtle CSF leaks include computed tomography (CT) myelogram or spinal MRI. Adjusting CT timing in brisk leaks with prompt imaging and in slow leaks with delayed imaging, can increase CSF leak detection and localisation [35]. Small ventral leaks or leaks associated with dural diverticula along root sleeves may be better localised using a dynamic CT myelogram [36]. Spinal MRI may be of value in detecting meningeal enhancement, extradural fluid collections, dilated venous structures, or meningeal diverticula. MRI myelograms, especially T2 weighted sequences or intrathecal gadolinium applications, have comparable sensitivity to a CT myelogram in localising CSF leaks [37, 38]. Yet even the aforementioned CT or MRI myelography will fail to localise the site of a CSF leak in approximately half of patients with a fistulous connection between CSF and paraspinal veins [39]. Such CT myelogram-occult CSF leaks require a more sophisticated detection method such as digital subtraction myelography (DSM). This detecting method is especially helpful in detecting CSF leaks secondary to CSF-venous fistula. Recent findings have shown a hyperattenuated paraspinal vein in close proximity to a CSF leak [24]. This so-called 'hyperdense paraspinal vein sign' represents the rapid passage of myelographic contrast into the venous system through the fistula. This finding correlates on DSM images as an opacified paraspinal vein. The recognition of this sign may be helpful in localising CSF leak (fistula) in an otherwise myelogram-occult CSF leak [39, 40].

In summary, DSM can be a very helpful diagnostic tool in high volume CSF (fistula) spinal leaks, which benefit from real-time imaging. DSM offers superior leak detection compared to a CT myelogram with an inherent time delay in ventrally located CSF venous fistulas. Even in small, brisk CSF leaks, by the time CT is performed, the contrast can spread over many levels and the exact location of the dural tear remains unknown [41, 42].

Management of spontaneous intracranial hypotension syndrome by epidural blood patching (EBP)

SIH syndrome is very often misdiagnosed, which has a profound influence on diagnostic and therapeutic management of patients with SIH. It has been observed that many cases of SIH resolve spontaneously without any specific treatment [10]. Several therapy options exist to treat patients with SIH.

Table 3. Types of CSF leak causing SIH, their characteristics on imaging studies, extradural CSF collections as well as different surgical techniques used to close these four types of CSF leak causing SIH syndrome

Leak type in spontaneous intracranial hypotension	Characterisation of leak type	Extradural CSF collection	Surgical management
Type 1a CSF leak	Ventral CSF leaks, usually related to an injury from adjacent bony abnormality	Yes	Identification of dural tear under microscopic inspection, direct repair of dural tear with sutures or placing a small muscle near dural tear with fibrin glue
Type 1b CSF leak	Posterolateral CSF leaks	Yes	Usually placing a small muscle near dural tear with fibrin glue
Type 2a CSF leak	Significant single or multiple meningeal diverticula	Yes, in 20% of cases or sometimes dilated dural sac found	Surgical treatment in cases of multiple meningeal diverticula is directed at largest diverticula Diverticula can be safely closed with small titanium aneurysm clips Direct suturing or muscle graft to directly repair CSF leak
Type 2b CSF leak	Complex meningeal diverticula or dural ectasia	Yes, in 20% of cases or sometimes dilated dural sac found	In cases of dural ectasia, coating dura with artificial dura graft
Type 3 CSF leak	Direct CSF-venous fistula	Extradural collection of CSF not present on imaging	Single venous channel may be successfully treated by applying small aneurysm clip A network of dilated veins should be treated by electrocautery to close small network veins
Type 4 CSF leak	Leaks without any dedicated spinal imaging modality and remaining otherwise intermediate as to above mentioned type	Extradural CSF collection in c.50% of cases	Lumbar dural reduction surgery performed through laminectomy (a strip of dura is resected and dural defect is closed). This manoeuvre increases intracranial CSF volume and pressure Implementation of epidural catheter

It should be noted that to date no randomised clinical trial (RCT) has been done to assess the treatment outcomes in patients with SIH [10].

Once a patient is diagnosed with MRI findings consistent with SIH, first line treatment includes conservative management such as bed rest, intravenous hydration, the use of an abdominal binder, or generous caffeine intake. An unknown percentage of SIH resolve spontaneously, so first-line conservative treatment is recommended especially for uncomplicated presentations. Patients with prominent disabling clinical signs of SIH cannot be expected to gain substantial and durable clinical benefit from conservative treatment for SIH [10].

In these cases, epidural blood patching (EBP) should be considered. EBP is performed by injecting the patient's own blood into the epidural space. It is not necessary to inject the blood at the level of the CSF leak, and the injection is typically administered in the lumbar region. The mechanism of action of an EBP injection includes compression of the thecal sac to immediately increase lumbar and intracranial pressure. Moreover, the injected blood clot over the CSF leak promotes an inflammation process that facilitates healing. Initial injection volume is from 10 to 20 mL of the patient's own blood. One third of patients undergoing this procedure achieve relief of symptoms. If the initial EBP is ineffective, a larger volume of up to 100 ml is recommended. The larger-volume EBP is usually done at two levels (one at the thoracolumbar junction and the second at the lower lumbar level). The volume of administered blood is limited by the development of local back pain or radiculopathy. Two-level large-volume blood administration forms a more stable dural tamponade, thereby sealing the CSF leak. After administration of EBP, the patient is left either in a supine, a prone or a lateral position for 30–60 minutes to allow the blood to move over many segments in the epidural space which may facilitate the sealing of the CSF leak. When several EPBs are required, a repeat procedure can be done, leaving at least a five day interval. If repeat EPBs fail to provide relief, and if the location of the CSF leak is known, targeted percutaneous placement of fibrin sealant is recommended. This is effective in one third of patients [10].

Management of spontaneous intracranial hypotension syndrome by surgery with presentation of clinical outcomes

However, in patients in whom the application of a blood patch or fibrin sealant have failed to bring SIH symptoms relief, surgical treatment is indicated [10]. Generally, surgical treatment is safe and efficacious in patients with a structural abnormality or when a focal CSF leak is precisely identified [43–45]. To perform surgical repair of a CSF, the location of the CSF level and the direction of CSF leak (i.e. ventral or dorsal to the dural sac) play the major role in choosing the surgical approach (i.e. anterior or posterior spinal approach) [1, 46–50]. Posterior CSF leaks and leaks along nerve roots are usually approached by hemilaminectomy or laminectomy [1, 6, 27, 48, 50–54].

In general, ventral CSF leaks are more challenging surgically than dorsal leaks, and the anterior or posterior approach depends greatly on the spinal CSF leak level [24, 55]. Ventral CSF

Table 4. Case reports of SIH treated by surgery

First author and year of publication	Age and gender	Clinical symptoms	Type of CSF leak	Type of diagnostic examination	Location of cerebrospinal fluid leak	Surgical approach	Follow-up in months or years	Final outcome
Davenport RJ (1995) [26]	19 F	Orthostatic headache, nausea, vomiting	Multiple diverticula Type 2b	Radioisotope cisternography	T1-T3	Epidural catheter and a saline infusion.	6 weeks and 3 months	Headache score 3–4/10
Vishteh AG (1998) [46]	32 M	Orthostatic headache	Single meningeal diverticula Type 2a CSF leak	MRI	C5-C6	Discectomy C5/C6 with osteophysectomy, dura mater closure. Dura suturing	ND*	Asymptomatic
Inamasu J (2004) [49]	41 M	Orthostatic headache	Single meningeal diverticula Type 1b	MRI and CT myelography	C1-C2	C1 laminectomy and partially C2	1 month	Asymptomatic
Witiw CD (2012) [57]	46 F	Orthostatic headache, nausea, vomiting	Single meningeal diverticula Type 1b	MRI	C4-C5	Discectomy C4/C5 with osteophysectomy, dura substituted membrane and fibrin glue	2 months	Asymptomatic
Fehnel KP (2015) [50]	34 M	Postural headaches, shoulder discomfort	Multiple meningeal diverticula Type 2b CSF leak	MRI	T9-T10	T9-T10 laminectomy	1 month	Asymptomatic
Turel MK (2018) [52]	50 F	Progressive lower-back pain, postural headaches	Multiple diverticula Type 4 CSF leak	MRI and CT myelography	T10-T11	T10-T11 laminectomy	6 weeks	Asymptomatic
Shahab S (2020) [53]	46 F	Orthostatic headache, vomiting	Type 4 CSF leak	MRI	T11-T12	Laminectomy T11-T12	2 months	8 years laer, patient is still having mild on and off headaches
Sobczyk P (2022) [48]	28 M	Orthostatic headache	Multiple meningeal diverticula Type 1b	MRI and CT	C1-C2	Laminectomy and fibrin glue	6 months	Asymptomatic

ND* — no data

leaks located at the cervical spine are approached by anterior corpectomy or discectomy [26, 56, 57]. Ventral thoracic leaks require a transdural or transpedicular approach, and ventral lumbar leaks a posterior approach between the nerve roots.

The recently defined four-grade classification system for cases of SIH may help select the most appropriate surgical management of a CSF leak. This classification system in the surgical management of SIH leaks was devised by Schievenk et al. [10]. The classification with different types of CSF leaks with preferred surgical technique utilised is presented in Table 3.

The individual case reports of surgical treatment for SIH are presented in Table 4. All patients reported in these case reports remained asymptomatic after surgery for intractable SIH symptoms [26, 46, 48–50, 52, 53, 57]. Case series and clinical studies reporting the outcomes after surgery for SIH are presented in Table 5. Most patients after neurosurgical treatment remained asymptomatic, and the successful rate for operation of SIH varied between 82.6–100% [1, 27, 43, 47, 51, 54, 56, 58–60]. Only one case series presented a successful rate of 50% for SIH symptom relief [51].

In most studies, most of the affected individuals who underwent surgery were women, and the female-to-male ratio was almost 2:1 [1, 43, 51, 54, 58–60]. The patients operated for SIH were in their fourth or fifth decades of life [1, 6, 11, 54, 59, 60]. In almost all cases, MRI was used to diagnose SIH, which remains the basic diagnostic tool [1, 5, 54, 61, 62]. Some patients were diagnosed with CT myelography [42, 47, 49, 56, 58, 59]. A typical MRI case of SIH in a patient with spontaneous CSF leak is presented in Figures 2 and 3.

Interestingly, among the reviewed cases, the most common site of CSF leak was thoracic spine, followed by cervical spine [1, 27, 43, 47–54, 56, 58–60, 63, 64].

Table 5. Clinical studies and case series reporting outcomes of surgery for SIH. Case series include at least five individuals. Studies reporting more than five individuals are considered as clinical studies. Limit on number of individuals was set arbitrarily due to relatively small number of patients treated by surgery worldwide

First author and year of publication	Number of individuals in study	Mean age of patients [yrs]	Mean follow-up in weeks	Percentage of operated patients [%]	Percentage of successful operation (asymptomatic) [%]	Percentage of unsuccessful operations (symptomatic) [%]
Schievink WI (1998) [43]	10	42.3	–	100	100	0
Eros EJ (2002) [56]	3	43	64	66.6	100	0
Farhat HI (2011) [47]	4	37	91	100	100	0
Chai CM (2014) [58]	2	54	5	100	100	0
Idrissi AL (2015) [60]	24	46	24	8	100	0
Schievink WI (2016) [1]	568	45.7	–	50.2	–	–
Beck J (2016) [67]	15	45.7	12	93.3	86.7	6.65
Beck J (2018) [27]	47	44.3	18.5	100	96	4
Wang TY (2020) [5]	20	51.3	64	83.3	90	10
Majeed K (2021) [59]	3	47.6	12	100	100	0
Kamenova M (2021) [51]	5	50.2	14.75	100	50	40
Häni L (2022) [54]	86	46.7	12	80.2	82.6	17.4

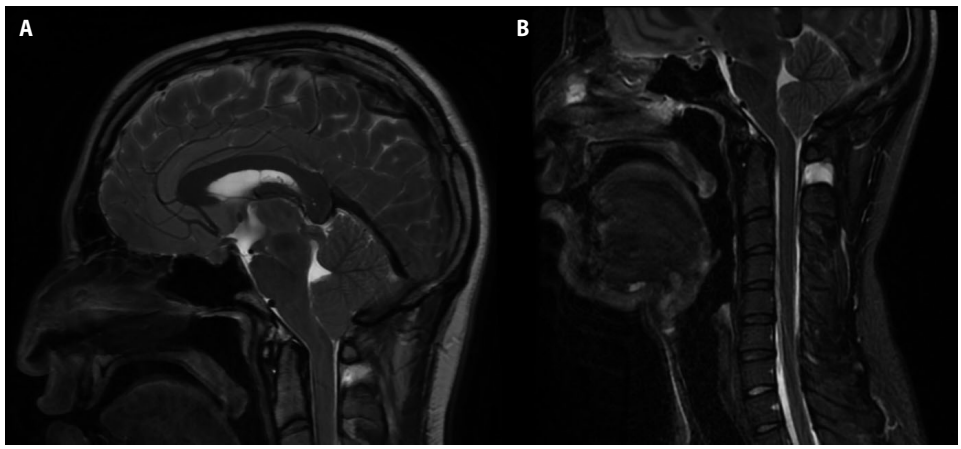

Figure 2. A. Sagittal MRI image T2-weighted sequences, showing changes in spontaneous intracranial hypotension. Lack of cerebrospinal fluid in basal cisterns and interpeduncular fossa are noticeable. **B.** Sagittal MRI image T2-weighted sequences, sagittal wedging of cerebellar tonsils into foramen magnum with confirmed CSF leak at level C1/C2 located dorsally to dural sac

Generally, surgical treatment of SIH is regarded as effective and safe [49]. It is also worth noting that none of the presented patients experienced a deterioration in their health. The sealing material used by most authors has included a fat patch, a muscle piece, fibrin glue or cyanoacrylate-based preparations. [43, 47, 57, 65]. The applied surgical treatment turned out to be a very effective method, as evidenced by the fact that more than two thirds of the patients presented with no further symptoms or complaints. As mentioned above, patients after surgery for SIH rarely complain of severe orthostatic headache or other pre-existing disabling symptoms. However, a change of pattern of headaches could indicate a rebound transient intracranial hypotension, and dural sinus thrombosis should also be considered [15, 66].

The recurrence of clinical SIH symptoms after successful surgical treatment may indicate a recurrent CSF leak [45]. It is estimated that c.10% of operated patients have recurrent CSF leaks. Outcomes studies have shown that patients with typical MRI findings for SIH and a localised CSF leak have very favourable results, in contrast to patients with normal MRI findings and multilevel spinal CSF leaks, who have worse outcomes [10]. The surgical treatment of SIH is rarely performed, as shown by this literature review, but it is very effective [48, 53, 54, 56]. However, due to the small amount of research conducted into this subject, the choice of treatment should be always individualised [48, 53].

Conclusions

SIH syndrome is very often misdiagnosed and can constitute a diagnostic challenge, although in recent times SIH syndrome has become better recognised due to the broad

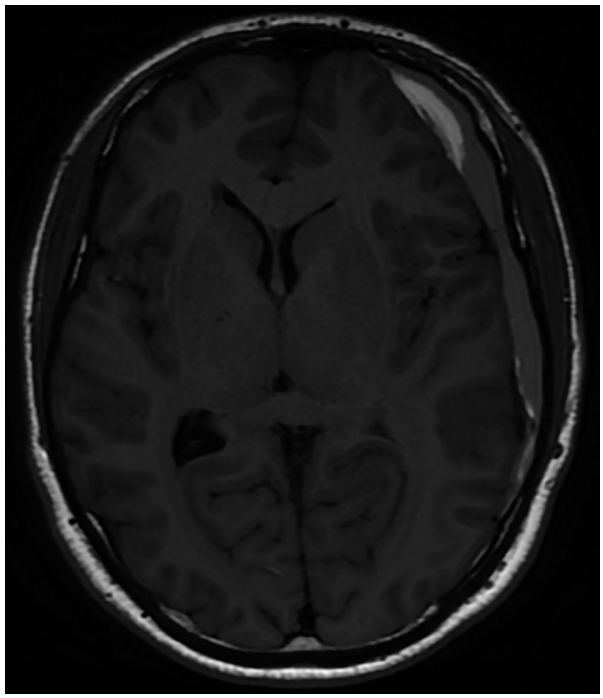

Figure 3. Axial MRI image T1-weighted sequence, showing example of subdural collection (SDC) due to SIH secondary to massive CSF leak in the cervical region

application of MR imaging. Pathological MRI findings are easily ascertained and allow proper and prompt diagnosis combined with clinical manifestations of SIH.

It should be noted that SIH syndrome is not always associated with only orthostatic headache, but can also represent a mixture of different symptoms grouped as general symptoms, cranial nerve deficits, and spinal and intracranial manifestations of SIH. Some patients require more demanding diagnostic modalities such as a CT myelogram or even a digital subtraction myelogram before a final diagnosis of SIH syndrome. An unknown number of SIH cases resolve spontaneously, and the first-line treatment for SIH, if needed, is EBP.

If the EBP fails to control the CSF leak, surgery should be reserved for symptomatic patients with a known CSF leak location. Our review has shown that different surgical approaches and methods of CSF leak sealing are safe and highly effective, and therefore surgery for SIH should not be regarded as only a 'last resort' treatment modality. There is also no doubt that the issue of the surgical treatment of SIH requires further research.

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Multi-layer reconstruction of skull base after endoscopic transnasal surgery for invasive pituitary adenomas

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ABSTRACT

Objective. To explore the efficacy of multi-layer skull base reconstruction after endoscopic transnasal surgery for invasive pituitary adenomas (IPAs).

Clinical rationale for the study. Skull base reconstruction for IPAs.

Material and methods. This retrospective analysis involved 160 patients with IPAs who underwent operations from October 2018 to October 2020. All patients were diagnosed with IPAs by pituitary enhanced magnetic resonance imaging, and all tumours were confirmed to be Knosp grades 3a, 3b, or 4. The experimental group and the control group comprised 80 patients in each, and we used different methods to reconstruct the skull base in each group. The comparison indicators included cerebrospinal fluid leakage, sellar floor bone flap (or middle turbinate) shifting, delayed healing of the skull base reconstructed tissue, nasal discomfort, and epistaxis. We used the chi-square test, and $p < 0.05$ was considered statistically significant.

Results. In the experimental group, cerebrospinal fluid leakage occurred intraoperatively in 73 patients, two of whom had cerebrospinal fluid leakage postoperatively. Brain CT 12 months postoperatively showed no sellar floor bone flap (or middle turbinate) shifting. Endoscopic transnasal checks performed seven days after surgery showed that the skull base reconstructed tissue had healed in 74 patients and had failed to heal in six. However, endoscopic transnasal checks showed that all six of these patients' pedicled nasoseptal flaps had healed well by 14 days after surgery. Other sequelae comprised nasal discomfort in four patients, and epistaxis in four. In the control group, cerebrospinal fluid leakage occurred intraoperatively in 71 patients, 14 of whom had cerebrospinal fluid leakage postoperatively. Brain CT 12 months postoperatively showed floor bone flap (or middle turbinate) shifting in 12 patients. Endoscopic transnasal checks performed seven days after surgery showed that the skull base reconstructed tissue had healed in 65 patients. In 12 patients, pedicled nasoseptal flaps had healed well by 14 days after surgery, while the remaining three patients required reoperation. Other sequelae comprised nasal discomfort in five patients, and epistaxis in six.

Conclusions. This new method of multi-layer skull base reconstruction could play an important role in endoscopic transnasal IPA surgery.

Key words: invasive pituitary adenoma, Knosp classification, multiple layers of materials, skull base reconstruction

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Introduction

Pituitary adenomas originate from the adenohypophysis, and comprise 10% of intracranial tumours, with gliomas and meningiomas being more common. Pituitary adenomas are characteristically benign, but some of them are invasive. The concept of invasive pituitary adenomas (IPAs) was first proposed by Jefferson [1] in 1940. IPAs can destroy the sellar floor and adjacent dura mater, invade the cavernous sinus, and even invade the frontal and temporal lobes. In 1993, Knosp et al. [2] proposed a classification of pituitary adenomas that is now commonly used clinically. In this classification, there are five grades based on the relationship between the pituitary adenoma and internal carotid artery on coronal magnetic resonance imaging (MRI). Grades 3a, 3b, and 4 are IPAs.

The most common surgical procedure currently used to treat IPAs is an endoscopic endonasal approach [3]. However, the invasion makes the surgical approach more complex and less likely to achieve complete (curative) resection. The more extensive procedure required to achieve complete resection of IPAs and the associated resolution of endocrine dysfunction usually result in a higher incidence of intraoperative cerebrospinal fluid leakage than occurs after excision of non-IPAs. How best to reduce the incidence of cerebrospinal fluid leakage, and other postoperative complications, thus warrants further research.

Clinical rationale for the study

This study was performed in order to explore the efficacy of skull base reconstruction for IPAs.

Material and methods

The inclusion criteria for this study were: first-time surgical treatment of an IPA; a Knosp grade 3a, 3b, or 4 IPA; no other complications such as heart disease or hepatic disease; and no history of nasal injury or surgery.

The exclusion criteria were: a history of surgery for a pituitary adenoma; a Knosp grade 1 or 2 IPA; the presence of other complications such as heart failure or cancer; and a history of nasal injury or surgery.

Information

The cohort in this retrospective study comprised 160 patients. In the experimental group, 80 patients (34 males and 46 females) ranged in age from 38 to 75 years, with a mean of 56.3 ± 10.0 years. Twenty-two of the 80 patients had growth hormone-secreting pituitary adenomas, 20 of the tumours were prolactin-secreting, 16 were adrenocorticotropic hormone-secreting, five were poly-secreting functional, and 17 were non-functional. There were 30 pituitary macroadenomas and 50 giant pituitary adenomas as defined by the pituitary adenoma volume. According to the Knosp classification (Tab. 1), 21 patients had a Knosp grade 3a tumour, 29 had a Knosp grade 3b, and 30 had a Knosp grade 4 (Fig. 1A–F). The postoperative length of stay ranged from 8 to 15 days, with a mean of 10.8 ± 1.9 days. The time required to reconstruct the skull base ranged from 40 to 60 minutes, with a mean of 51.4 ± 5.6 minutes.

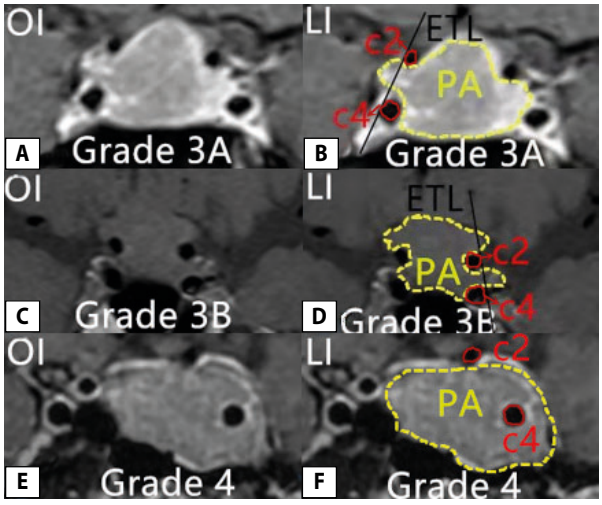

Figure 1. Pituitary adenoma of Knosp grade 3 and 4. C2 — c2 of internal carotid artery; C4 — c4 of internal carotid artery; ETL — external tangential line; LI — labelled image; OI — original image; PA — pituitary adenoma

Table 1. Knosp classification

Grade 0	Grade 1	Grade 2	Grade 3		Grade 4
			Grade 3A	Grade 3B	
Cavernous sinus is of normal shape, with enhancement of the venous plexus, and the tumour doesn't exceed the internal tangential line of c2–c4 vascular diameter.	When the tumour exceeds the cut off line of c2–c4 vascular diameter, but doesn't exceed the central line of c2–c4 vascular diameter, the venous plexus in the medial cavernous sinus disappears.	When the tumour exceeds the central line of c2–c4 vascular diameter, but doesn't exceed the external tangential line of c2–c4 vascular diameter, the upper or lower venous plexus of the cavernous sinus may disappear	When the tumour exceeds the external tangential line of c2–c4 vascular diameter, extending laterally into the upper cavernous sinus	When the tumour exceeds the external tangential line of c2–c4 vascular diameter, extending laterally into the lower cavernous sinus	The internal carotid artery in the cavernous sinus segment is completely encapsulated, resulting in internal diameter stenosis, disappearance of venous plexus in each part, and spherical outward expansion and protrusion of the superior wall and outer wall of the cavernous sinus

In the control group, 80 patients (37 males and 43 females) ranged in age from 40 to 74 years, with a mean of 56.4 ± 10.0 years. Nineteen of the 80 patients had growth hormone-secreting pituitary adenomas, 24 of the tumours were prolactin-secreting, 15 were adrenocorticotropic hormone-secreting, seven were poly-secreting functional, and 15 were non-functional. There were 32 pituitary macroadenomas and 48 giant pituitary adenomas as defined by the pituitary adenoma volume. According to the Knosp classification, 20 patients had a Knosp grade 3a tumour, 32 had a Knosp grade 3b, and 28 had a Knosp grade 4 (Fig. 1A–F). The postoperative length of stay ranged from 8 to 20 days, with a mean of 11.0 ± 2.6 days. The time required to reconstruct the skull base ranged from 35 to 55 minutes, with a mean of 50.0 ± 4.9 minutes. There was no significant difference in the above data between the two groups ($p > 0.05$) (Tab. 2). We reviewed the patients' medical records after obtaining clinical ethics committee approval.

Surgical procedure

Experimental group

Preoperative preparation

The patients fasted for 6–8 hours before the surgery.

Operative position

We performed all surgeries under general anaesthesia with the patient in a horizontal supine position. After adjusting the patient's head position so that their nostrils were oriented toward the surgeon, we used an iodine solution to disinfect the area around the nostrils three times, after which we injected iodine solution into both nasal cavities. At the same time, we marked a 4 × 3 cm oval skin flap between the patient's right knee and hip joint and disinfected it within 15 cm three times with iodine solution. We then draped the sterile area with sterile surgical towels (Fig. 2A–D).

Construction of sellar floor bone flap

Provided that the sellar floor bone had not been invaded by the pituitary adenoma, the scope of the sellar floor bone flap was determined by the findings on preoperative paranasal sinus computed tomography (CT) and pituitary MRI. First,

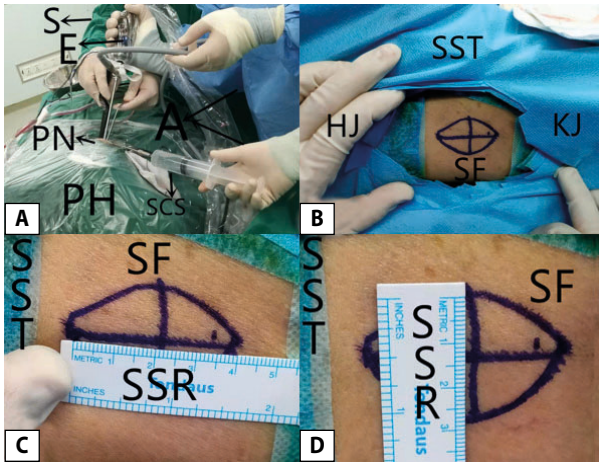

Figure 2. Operative position and skin flap. S — surgeon; E — endoscopy; A — assistant; PN — patient's nostrils; PH — patient's head; SCS — sodium chloride solution; HJ — hip joint; KJ — knee joint; SF — skin flap; SST — sterile surgical towels; SSR — sterile surgical ruler

Table 2. Patients' basic information

Information		Experimental group	Control group	P-value
Gender	M	34	37	
	F	46	43	0.750
Age		56.3 ± 10.0	56.4 ± 10.0	0.874
Hormone	GH	22	19	
	PRL	20	24	
	ACTH	16	15	
	PSF	5	7	
	NF	17	15	0.898
Pituitary adenoma volume	PMAA	30	32	
	GPA	50	48	0.871
Knosp grade	3a	21	20	
	3b	29	32	
	4	30	28	0.919
Postoperative length of stay		10.8 ± 1.9	11.0 ± 2.6	0.867
Time of reconstruction		51.4 ±5 .6	50.0 ± 4.9	0.632

M — male; F — female; GH — growth hormone; PRL — prolactin; ACTH — adrenocorticotropic hormone; PSF — poly-secretory functional; NF — non-functional; ; PMAA — pituitary macroadenomas; GPA — giant pituitary adenomas

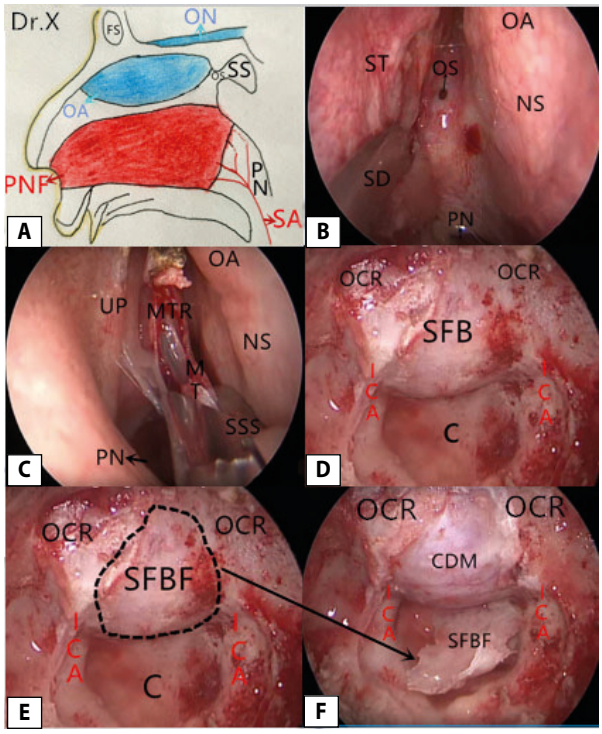

Figure 3. Making sellar floor bone flap. FS — frontal sinus; OA — olfactory area; OS — opening of sphenoid sinus; ON — olfactory nerve; PN — posterior naris; PNF — pedicled nasoseptal flap; SA — sphenopalatine artery; SS — sphenoid sinus; Dr. X — drawn by Dr. Xing; NS — nasal septum; ST — superior turbinate; SD — surgical detacher; UP — uncinate process; MTR — middle turbinate root; MT — middle turbinate; SSS — surgical scissors; OCR — optic carotid recess; SFB — sellar floor bone; C — clivus; ICA — internal carotid artery; SFBF — sellar floor bone flap; CDM — cerebral dura mater

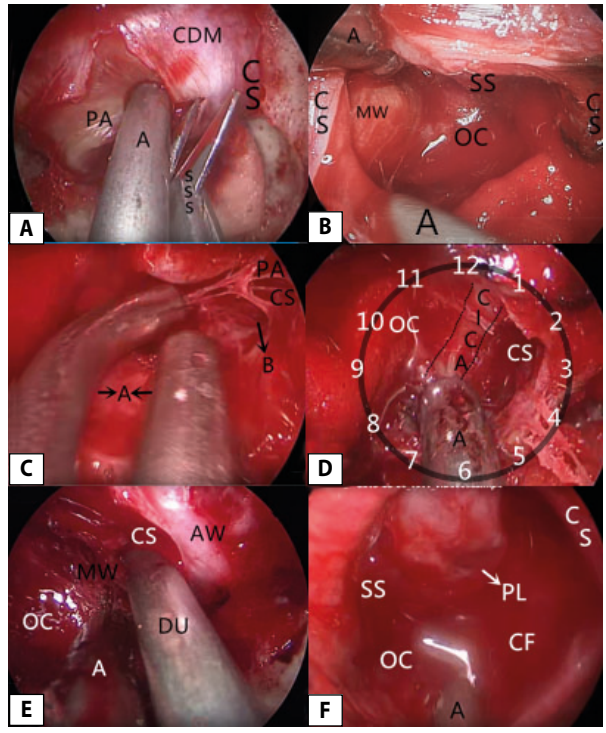

Figure 4. Resection of invasive pituitary adenoma. PA — pituitary adenoma. A — aspirator; CDM — cerebral dura mater; SSS — surgical scissors; CS — cavernous sinus; OC — operative cavity; SS — saddle septum; MW — medial wall of cavernous sinus; B — breaches of cavernous sinus; CICA — cavernous internal carotid artery; DU — Doppler ultrasound; AW — anterior wall of cavernous sinus; CF — cerebrospinal fluid; PL — point of leakage

we thinned the tissues around the sellar floor bone flap and pierced the inferior aspect of the sellar floor bone. Next, we used a Kerrison bone rongeur to remove the thinned bone and completely detach the sellar floor bone flap while protecting the entire base of the epidural saddle. Finally, we placed the sellar floor bone flap in the clivus recess until needed. On the other hand, if the pituitary adenoma had invaded the sellar floor bone and dura mater, we used a Kerrison bone rongeur to directly construct a bony window. We then used the middle turbinate to replace the sellar floor bone flap during reconstruction of the skull base (Fig. 3A–F).

Resection of IPA

In patients in whom the pituitary adenoma had invaded the dura mater, we inserted micro-scissors directly inferior to the saddle to cut that dura. While closely monitoring the pituitary adenoma capsule, we used a curette and aspirator to aspirate the pituitary adenoma and capsule in all directions, paying particular attention to the breaches in the medial walls of both cavernous sinuses (Fig. 4A–B). Given that the tumours were Knosp grades 3 or 4, one or both cavernous sinus medial walls had always been invaded (Fig. 4C). To prevent recurrence of the pituitary adenoma and achieve resolution of endocrine dysfunction, we attempted to resect the invaded medial wall(s) of the cavernous sinus simultaneously. The procedures used to resect the medial wall of the cavernous sinus were as follows.

First, we used a stripper to peel off the medial wall of the cavernous sinus in a 4-to-5-o'clock orientation (Fig. 4D) of the surgical field to fully separate the medial wall of the cavernous sinus to be resected. Second, we severed numerous dural ligaments, including the caroticoclinoid ligament, inferior parasellar ligament, and suprasellar ligament [4], by further opening the free orifice. Finally, we achieved complete separation of the medial wall of the cavernous sinus and resected it. At this stage, we used aspirators to completely clear all tumour from the cavernous sinus. We paid special attention to protecting the cavernous internal carotid artery and its branches during resection of the IPA from the cavernous sinus. Doppler ultrasound, electrophysiological monitoring, and surgery navigation were used, thus minimising rupture and bleeding of these arteries (Fig. 4E). Notably, the dural wall is thin, especially at the junction between the medial wall of the

Table 3. Grades of cerebrospinal fluid leakage

Grade 0	Grade 1	Grade 2	Grade 3
Absence of cerebrospinal fluid leak, confirmed by Valsalva manoeuvre	Small weeping leak, confirmed by Valsalva manoeuvre, without obvious, or with only small, diaphragmatic defect	Moderate cerebrospinal fluid leak, with obvious diaphragmatic defect	Large cerebrospinal fluid leak, typically created as part of extended trans-sphenoidal approach through the supra diaphragmatic or clival dura for tumour access

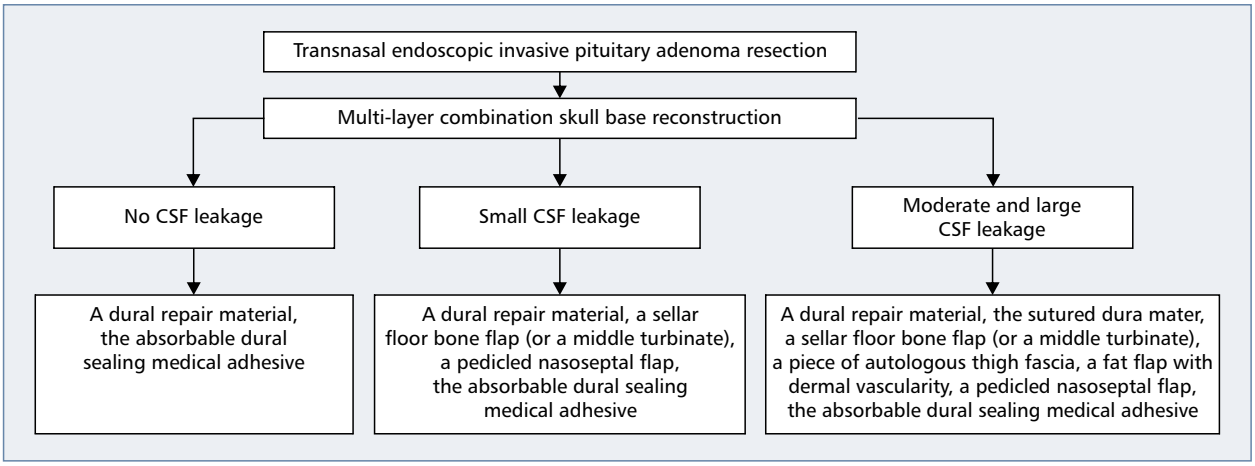

Figure 5. Reconstruction of skull base

cavernous sinus and saddle septum. Therefore, cerebrospinal fluid leakage can easily occur when performing this procedure. At this time, the Valsalva manoeuvre [5] was performed by the anaesthetist to increase the intracranial pressure to approximately 30 mmHg for identification of cerebrospinal fluid leakage (Fig. 4F). If a leak was identified, it was graded (Tab. 3). We used fluid gelatin and haemostatic gauze to stop the bleeding after resection of the IPA and then prepared for skull base reconstruction.

Reconstruction of skull base

According to the grade of cerebrospinal fluid leakage, different strategies were used to reconstruct the skull base (Fig. 5). For grade 0 cerebrospinal fluid leakage, we inserted dural repair material (Durafix; Beijing YHBIOMAX Biologic Technologies, Beijing, China) into the operative cavity inferior to the dura at the base of the saddle, and we then used an absorbable dural sealing medical adhesive (Jinan Success Biologic Technologies, China) to cover the dural repair material. For grade 1 cerebrospinal fluid leakage, a dural repair material was inserted into the tumour cavity to cover the source of the leakage, and the sellar floor bone flap was fixed by haemostatic gauze. The pedicled nasoseptal flap with the absorbable dural sealing medical adhesive was placed outside the sellar floor bone flap. For grades 2 and 3 cerebrospinal fluid leakage, we used a dural repair material, the sutured dura mater, a sellar floor bone flap (or the middle turbinate), a piece of autologous thigh fascia [6], a fat flap with dermal vascularity, a pedicled nasoseptal flap, and the absorbable dural sealing medical adhesive to reconstruct the skull base.

The specifics of our reconstruction procedure were as follows. (I) We inserted the dural repair material into the operative cavity inferior to the dura at the base of the saddle to cover any point of leakage. This dural repair material acts as a saddle septum, comprising the first layer of leak containment (Fig. 6A). (II) We usually created a double-cross slip knot [7] with the intranasal suture outside the nasal cavity to suture the dura mater. Because the dura mater was incomplete as a result of invasion or destruction by the pituitary adenoma, and shrinkage after incision, and the suturing of the dura mater mainly served as a support for the dural repair material, we did not attempt to achieve complete and tight suturing of the dura mater (Fig. 6B–C). (III) As the third layer for reconstruction of the skull base, we placed the sellar floor bone flap or the middle turbinate exterior to the dura mater. Notably, we trimmed the middle turbinate outside the nasal cavity to fit and completely cover the sellar floor defect (Fig. 6D). (IV) Next, we collected a piece of autologous thigh fascia and a fat flap with dermal vascularity from the lateral right thigh of the patient and laid it exterior to the sellar floor bone flap [8]. In accordance with the preoperative marking, we cut a 4 × 3 cm oval skin flap with a subcutaneous adipose layer between the patient's right knee and hip joint. We cut off the epidermal layer with tissue scissors, preserving the dermis layer with its subcutaneous adipose layer as a complete flap for further use. We then further explored the subcutaneous adipose layer until

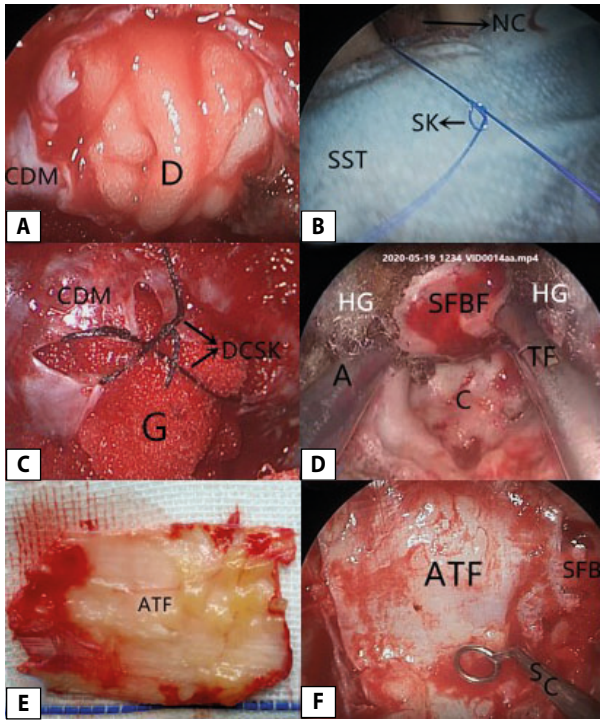

Figure 6. Multi-layer reconstruction of skull base (first four levels). D — dural repair material (Durafix); CDM — — cerebral dura mater; SST — sterile surgical towels; SK — slip knot; NC — nasal cavity; G — gelfoam; DCSK — double-cross slip knot; HG — haemostatic gauze; A — aspirator; C — clivus; SFBF — — sellar floor bone flap; TF — tissue forceps; ATF — autologous thigh fascia; SFB — sellar floor bone; SC — surgical curette

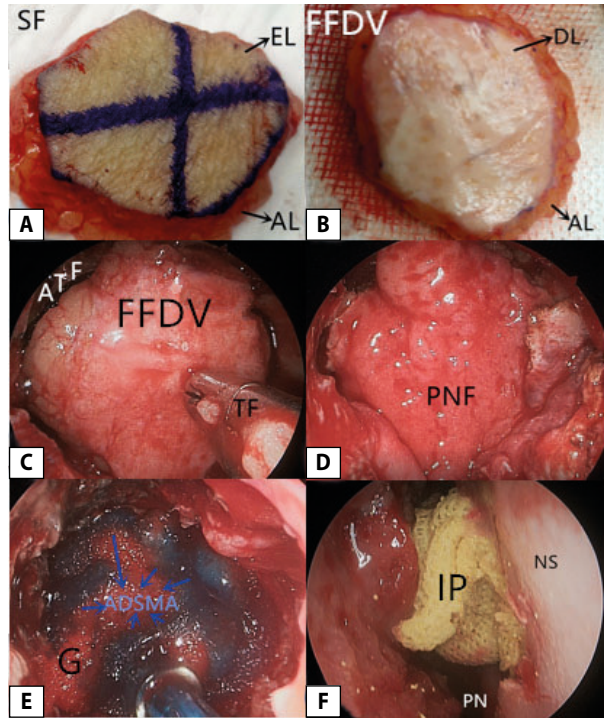

Figure 7. Multi-layer reconstruction of skull base (remaining three levels). SF — skin flap; EL — epidermal layer; AL — adipose layer; FFDV — fat flap with dermal vascularity; DL — dermis layer; ATF — autologous thigh fascia; TF — tissue forceps; PNF — pedicled nasoseptal flap; G — gelfoam; ADSMA — absorbable dural sealing medical adhesive; IP — iodoform sponges; PN — posterior naris; NS — nasal septum

we reached the muscle fascia, after which we sheared off the same size piece of fascia (4 × 3 cm), followed by suturing the incision after carefully ensuring haemostasis. We first laid the autologous thigh fascia exterior to the sellar floor bone and tried to thoroughly attach the fascia to the sellar floor bone in all directions (Fig. 6E–F). We then laid the fat flap with dermal vascularity exterior to the fascia.

Using a fat flap with dermal vascularity is an innovation developed by our department for skull base reconstruction material; this development was originally inspired by skin replantation techniques used in burn patients [9]. These flaps are waterproof, thick, and rich in blood vessels, enabling them to play a valuable role in preventing cerebrospinal fluid leakage and ensuring the success of skull base reconstruction (Fig. 7A–C). (V) The importance of a pedicled nasoseptal flap as the sixth layer for skull base reconstruction is obvious. A suitable pedicled nasoseptal flap was constructed as follows. We made an incision at the level of the opening of the right sphenoid sinus to avoid the olfactory area near the sphenoid sinus recess and the superior turbinate. Dissection then proceeded anteriorly to immediately posterior to the junction of the nasal mucosa and normal skin. Next, we dissected caudad to the inferior aspect of the nasal cavity to reach the inferior nasal passage, after which we proceeded posteriorly until the base of the nasoseptal mucosa and vascular pedicles larger than 1cm in width were visible. We then separated the pedicled nasoseptal flap from the nasal septum and placed it in the posterior nares (Fig. 7D). (VI) We used an absorbable dural sealing medical adhesive to fill the gaps around the skull base reconstructed tissue, especially in the upper quadrant of the surgical field (Fig. 7E). Regardless of which grade of cerebrospinal fluid leakage, we used two pieces of iodoform sponge to support these reconstructed materials (Fig. 7F).

Further treatment

We flushed an appropriate amount of sodium chloride solution into both nasal cavities, then removed any bone fragments before ending the operation.

Control group

The surgical procedures in the control group were the same as those in the experimental group except that the sutured dura mater was not used. A piece of autologous thigh fascia

and a fat flap with dermal vascularity were used in skull base reconstruction for moderate and large intraoperative cerebrospinal fluid leakage.

Postoperative care

In this patient cohort, we did not routinely use antibiotics. Brain CT was performed six hours, seven days, one month, six months and 12 months postoperatively, and pituitary-enhanced MRI was performed 24 hours postoperatively. According to the results of the postoperative pituitary hormone status review, we prescribed methylprednisolone or levothyroxine sodium tablets as appropriate. The pituitary hormone status was followed up every three days for one month after normal levels had been achieved. Postoperatively, all patients were asked to avoid coughing, sneezing, and the Valsalva manouevre. We administered stool softener to assist defecation. We removed the iodoform sponges seven days postoperatively after performing an endoscopy to confirm the absence of persistent leakage. We did not routinely place lumbar catheter drains.

Therapeutic evaluation

Cerebrospinal fluid leakage intraoperatively

We recorded the patients who developed cerebrospinal fluid leakage intraoperatively.

Cerebrospinal fluid leakage postoperatively

On the first postoperative day, we examined the patients for cerebrospinal fluid leakage from their nasal cavities. On the seventh postoperative day, we performed an endoscopic transnasal check to identify any cerebrospinal fluid leakage before removing the iodoform sponges. Further endoscopic transnasal checks for cerebrospinal fluid leakage were performed 14 and 28 days after surgery.

Sellar floor bone flap (or middle turbinate) shifting

We performed brain CT 6 hours, 7 days, 1 month, 6 months and 12 months postoperatively to diagnose sellar floor bone flap (or middle turbinate) shifting.

Healing of skull base reconstructed tissue

We performed endoscopic transnasal checks 7, 14, and 28 days after surgery to determine whether the skull base reconstructed tissue had healed and to identify necrosis, lack of healing, pale oedema, or any other problems with the flap.

Nasal discomfort

As soon as the patients had recovered from general anaesthesia, we asked about their nasal sensations and followed this up in all patients for 12 months, recording the number of patients who experienced nasal discomfort.

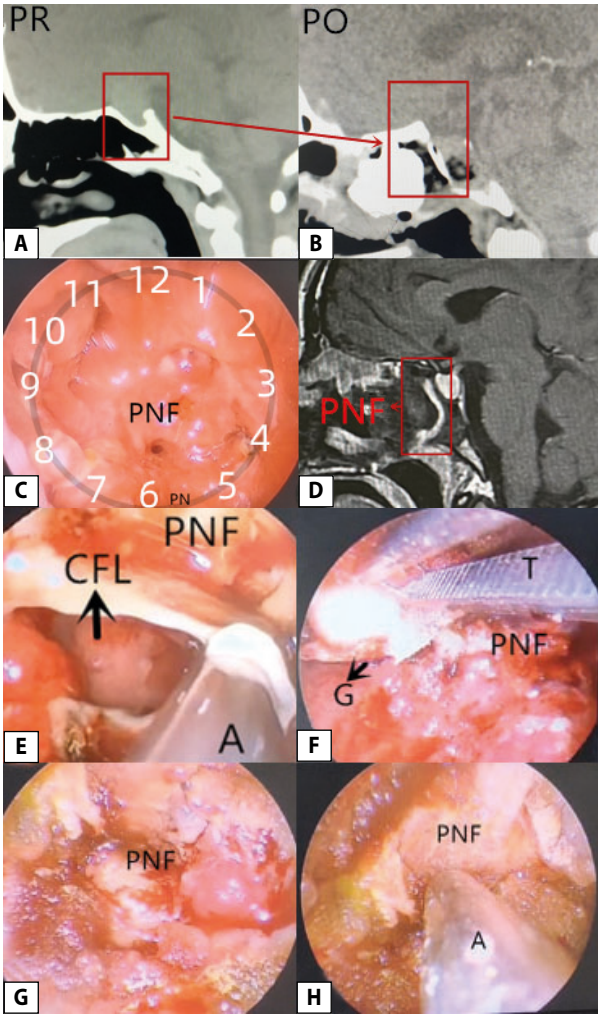

Figure 8. Postoperative CT and endoscopic transnasal check. PR — preoperative computed tomography image; PO — postoperative computed tomography image; PNF — pedicled nasoseptal flap; PN — posterior naris; CFL — cerebrospinal fluid leakage; A — aspirator; G — gelfoam; T — tweezers

Epistaxis

We recorded any episodes of epistaxis from the end of the surgery to the day of discharge from hospital.

Results

We followed all patients for one year; none were lost to follow-up. In the experimental group, intraoperative cerebrospinal fluid leakage occurred in 73 patients (91.3%), two of whom (2.5%) had cerebrospinal fluid leakage postoperatively despite the multiple layers used for skull base reconstruction. The leakage was stopped by the use of gelfoam, iodoform sponges, lumbar catheter drainage, and bed rest. No sellar floor bone flap (or middle turbinate) shifting occurred in any patients, as determined by brain CT six hours, seven days, one month, six months and twelve months postoperatively (Fig. 8A–B). Endoscopic transnasal checks performed seven days

after the surgery showed that the skull base reconstructed tissue had healed in 74 patients (92.5%) and failed to heal in six. Two of these six patients had cerebrospinal fluid leakage in the 11 o'clock orientation (Fig. 8C) of the surgical field, and were treated with gelfoam, iodoform sponges, lumbar catheter drainage, and bed rest. The pedicled nasoseptal flap of the remaining four of these patients failed to heal in the 1 o'clock orientation (Fig. 8C) of the surgical field without cerebrospinal fluid leakage, and they were treated with gelfoam, iodoform sponges, and bed rest. All three of these patients' pedicled nasoseptal flaps had healed well by the 14th postoperative day as determined by endoscopic transnasal checks. The skull base reconstructed tissue was clearly seen on the postoperative pituitary enhancement MRI, indicating survival of the skull base reconstructed tissue (Fig. 8C–H).

None of the 80 patients reported preoperative nasal discomfort. Immediately after recovering from general anaesthesia, and one year postoperatively, four patients (5.0%) reported nasal discomfort that did not affect their normal life or sleep. Although we evaluated every patient's nasal cavity before the end of the surgery and found no bleeding, four patients (5.0%) had epistaxis on the seventh postoperative day after removal of the iodoform sponges. We managed this successfully by immediately inserting inflatable haemostatic devices, after which the epistaxis resolved. In the control group, cerebrospinal fluid leakage occurred intraoperatively in 71 patients (88.8%), 14 of whom (17.5%) had cerebrospinal fluid leakage postoperatively. Brain CT one year postoperatively showed sellar floor bone flap (or middle turbinate) shifting in 12 patients (15.0%). Endoscopic transnasal checks performed seven days after surgery showed that the skull base reconstructed tissue had healed in 65 patients (81.3%) and had failed to heal in 15. In 12 of these 15 patients, the pedicled nasoseptal flaps had healed well by 14 days after surgery, whereas the remaining three patients required reoperation. Other sequelae comprised nasal discomfort in five patients (6.3%) and epistaxis in six (7.5%). We compared these two groups by the chi-square test, and the results showed a significant difference in postoperative cerebrospinal fluid leakage, sellar floor bone flap (or middle turbinate) shifting, and healing of the skull base reconstructed tissue between the two groups ($p < 0.05$). However, there was no significant difference in terms of intraoperative cerebrospinal fluid leakage, nasal discomfort, or epistaxis between the two groups ($p > 0.05$) (Tab. 4).

Table 4. Comparison of sequelae between experimental and control groups

Items	Experimental group	Control group	P-value
ICSFL	91.3%	88.8%	0.793
PCSFL	2.5%	17.5%	0.001
SFBFS	0	15.0%	0.002
SBRTH	92.5%	81.3%	0.029
ND	5.0%	6.3%	0.732
Ep	5.0%	7.5%	0.746

ICSFL — intraoperative cerebrospinal fluid leakage; PCSFL — postoperative cerebrospinal fluid leakage; SFBFS — sellar floor bone flap (or middle turbinate) shifting; SBRTH — skull base reconstructed tissue healed; ND — nasal discomfort; Ep — epistaxis

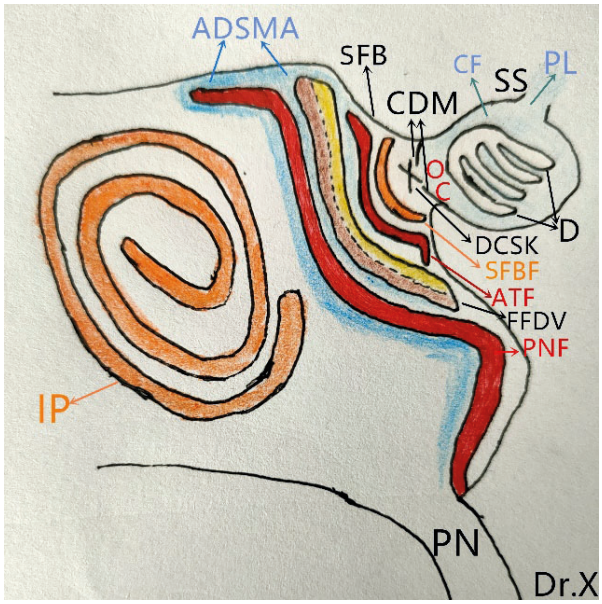

Figure 9. Illustration of multi-layer reconstruction of skull base. PL — point of leakage; SS — saddle septum; CF — cerebrospinal fluid; CDM — cerebral dura mater; SFB — sellar floor bone; OC — operative cavity; PN — posterior naris; D — dural repair material (Durafix); DCSK — double-cross slip knot; SFBF — sellar floor bone flap; ATF — autologous thigh fascia; FFDV — fat flap with dermal vascularity; PNF — pedicled nasoseptal flap; ADSMA — absorbable dural sealing medical adhesive; IP — iodoform sponges; Dr. X — drawn by Dr. Xing

Discussion

On the basis of our experience, we believe that multi-layer reconstruction of the skull base has the following advantages.

(I) Suturing the dura at the base of the saddle and the sellar floor bone flap are forms of anatomical reduction and help to preserve the integrity of the skull base.

(II) With the exception of the first layer of Durafix, the rest of the repair layers are autologous tissues, and therefore confer minimal risk of postoperative rejection and infection.

(III) In multi-layer reconstruction of the skull base, each layer makes a separate and unique contribution. Every layer contributes separately to preventing cerebrospinal fluid leakage. Multi-layer reconstruction of the skull base does not consist of a simple 'super positioning' of multiple layers, because with these layers 1 + 1 is greater than 2 (Fig. 9).

Previously published studies have revealed a c.7% incidence of postoperative cerebrospinal fluid leakage in patients with various types of pituitary adenomas in whom Hadad–Bassagasteguy [10] mucosal flaps were used for reconstruction. However, there is no independent data regarding the incidence of cerebrospinal

fluid leakage after surgery for IPAs. In our previously published article, the incidence of intraoperative cerebrospinal fluid leakage during surgeries for all kinds of pituitary adenomas (including IPAs and non-IPAs) was 43.3%, while the incidence of postoperative cerebrospinal fluid leakage was 3.3% [8].

In our current experimental group of 80 patients with IPAs, the incidence of intraoperative cerebrospinal fluid leakage was 91.3%, while the incidence of postoperative cerebrospinal fluid leakage after multi-layer reconstruction of the skull base was 2.5%. In the control group, the incidence of intraoperative cerebrospinal fluid leakage was similar to the experimental group at 88.8%; however, the incidence of postoperative cerebrospinal fluid leakage was much higher than that in the experimental group, at 17.5%. These findings indicate the role of multi-layer reconstruction of the skull base in preventing cerebrospinal fluid leakage. Multi-layer reconstruction of the skull base ensures anatomical reduction and is clearly effective in preventing sellar floor bone flap (or middle turbinate) shifting. In the experimental group, after a 1-year follow-up, the reconstructed skull bases were still stable and no sellar floor bone flap (or middle turbinate) shifting had occurred. In the control group, however, the incidence of sellar floor bone flap (or middle turbinate) shifting was 15%, with a significant difference between the two groups. Survival of the skull base reconstructed tissue is particularly critical. In the experimental group, the tissue had healed well in 92.5% of the patients by seven days after surgery as assessed by endoscopic nasal examination. According to nasal endoscopy checks 14 days after surgery, the remaining six patients achieved complete healing with gelfoam, iodoform sponges, lumbar catheter drainage (two patients), and bed rest. At seven days after surgery in the control group, the incidence of healing of the skull base reconstructed tissue was only 81.3%, and three patients even required reoperation. The incidences of nasal discomfort and epistaxis were low in both groups, and there was no significant difference. This indicates that the multi-layer reconstruction of the skull base did not cause additional damage to the patients. To further reduce patients' suffering, we need to take even greater care to minimise damage to normal tissues in the future.

In conclusion, the advantages of our multi-layer reconstruction of the skull base after transnasal endoscopic resection of IPAs include a decreased incidence of cerebrospinal fluid leakage, with no increase in the incidence of other complications.

Conflicts of interest: *None.*
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REVIEW ARTICLE

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Acute/subacute demyelinating polyneuropathy in Parkinson's Disease patients on levodopa-carbidopa intestinal gel therapy: systematic review with new case report

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ABSTRACT

Polyneuropathy (PNP) is a known complication of levodopa-carbidopa intestinal gel (LCIG) therapy of advanced Parkinson's Disease (PD). The overall prevalence of PNP in PD is estimated to be 42.1% (as shown in a review by Romagnolo et al. 2018), and the most common type is chronic axonal polyneuropathy. There is a group of acute/subacute onset demyelinating polyneuropathies, which is far less common, although it seems to be an important factor leading to the rapid discontinuation of LCIG treatment. In this systematic review, we present data on demyelinating polyneuropathy with acute/subacute onset; we identified nine papers including prospective assessments and case reports, with detailed information on 15 patients. In all patients, despite treatment with corticosteroids, intravenous immunoglobulins (IVIG) or plasma exchange (PE), the LCIG therapy was terminated. We also present a case of subacute demyelinating polyneuropathy with effective treatment and continuation of LCIG therapy.

Key words: Parkinson's Disease, levodopa-carbidopa intestinal gel, neuropathy, demyelinating polyneuropathy, acute/subacute onset

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Introduction

Parkinson's Disease (PD) is a neurodegenerative, predominantly motor disorder, manifesting with bradykinesia, tremor and rigidity. Nevertheless, it is accompanied by a broad spectrum of non-motor features [1].

Polyneuropathy in PD patients can be related to progression of the PD itself, or it can be medication- (levodopa) induced. It is predominantly of chronic sensory/sensorimotor and axonal type [2–4], and the estimated mean prevalence is 30.2% (12–55%) [5–7]. Polyneuropathy can result in severe instability and repeated falling, and therefore its identification, prevention or treatment would seem to be an important factor contributing to patients' quality of life. In patients with advanced PD undergoing levodopa-carbidopa intestinal gel (LCIG) therapy, polyneuropathy has been detected with a mean prevalence of 42.1% (13.8% to 100%) [5, 8, 9]. In the literature, a PNP diagnosis has been based on electrophysiological criteria in combination with neurological symptoms and/or validated clinical scales. The most frequent is the sensory/axonal form of neuropathy [5]. However, a substantial number of cases presenting the demyelinating form of polyneuropathy, with acute or subacute onset, have been reported as well [10–13]. The pathophysiology of this group of neuropathies seems to be different, and treatment may require a specific approach.

The aim of this study was to review the literature in order to collect data on acute and subacute demyelinating polyneuropathy during LCIG therapy in advanced PD, accompanied by a new illustrative case report.

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Material and methods

Relevant human studies in the field of PD (MeSH main topic) were searched using the PubMed and Scopus databases up to the end of December 2021 using a variety of combinations of terms used in titles and abstracts: "Duodopa", "levodopa-carbidopa intestinal gel", "LCIG", "levodopa", "neuropathy","polyneuropathy", "polyradiculoneuropathy", "Guillain-Barre syndrome", "GBS", "chronic inflammatory demyelinating polyradiculoneuropathy", and "CIDP". This search was extended to a manual search of references in order to find any papers that did not contain the search terms (and thus could not be detected by established search criteria), but nonetheless contained any information on the problem in question. The inclusion criterion was: any study containing information about patients undergoing LCIG therapy who developed demyelinating polyneuropathy of acute/subacute onset. Acute onset was defined as up to four weeks, and subacute as up to 12 weeks from the onset of symptoms. Our analysis included both publications in which it was possible to perform a detailed analysis of nerve conduction studies (NCS) parameters, and also those where a diagnosis was only based on a patient's history and clinical examination. Only original papers, systematic reviews and case reports/case series were included. PRISMA guidelines were used, and a flow diagram showing the process of identifying papers is set out at Figure 1 [14]. There were no language limitations, and papers in English and Spanish were included.

Results

Our search using the defined terms from selected databases resulted in the identification of 101 original papers. Subsequently, manual research was conducted — primarily the title research excluded papers that did not concern idiopathic PD or neuropathy as the main topic (excluded n = 47). The next step included manual abstract research in order to identify papers concerning LCIG therapy or papers with detailed information regarding conducted research in the field of neuropathy in PD (excluded n = 26). The remaining papers (n = 28) were manually screened in order to identify cases of acute/subacute demyelinating polyneuropathy with a sufficient amount of detailed information provided.

Ultimately, nine papers were identified (including one in Spanish) — four with prospective assessment [10, 12, 15, 16] and five case reports [11, 13, 17–19]. Publications were identified where such cases were only mentioned (providing an additional 33 cases) without any detailed information, and therefore they were not analysed [20–24]. Finally, the data of 15 patients was collected.

In the selected analysed case series (excluding case reports) from prospective studies, the incidence of demyelinating polyneuropathy was established at 8.9% (i.e. 9/105 pts).The analysed data was grouped into the following categories: demographic data, clinical manifestation and polyneuropathy onset, NCS and laboratory findings, LCIG dose, treatment, and outcome. All cases are presented in Table 1.

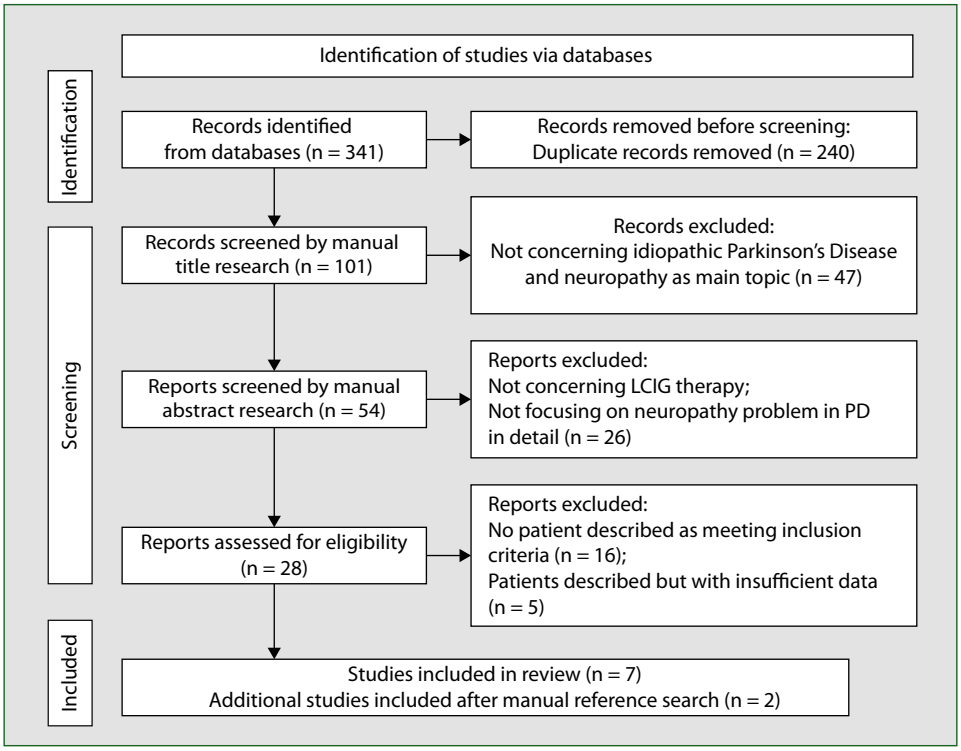

Figure 1. PRISMA flow diagram illustrating data collection process

Table 1. Summary of publications included into systematic review on acute/subacute polyneuropathy during LCIG treatment of advanced Parkinson's Disease

	Preval	PD dur	LEDD	LCIG dur	PNP onset	Diagnosis	Symptoms	Pre NCS	NCS on diag	NCS follow up	CSF	Lab	LC IG disc	Treatment	Outcome
Antonini 2007 n = 1/7	14%	Nd	Nd	7 m	1–2 w	GBS	Muscle weakness	Nd	NCS was consistent with GBS	Nd	A-c dis (protein Nd)	Nd	+	PE	"Some benefit"
Kobylecki 2012 n = 2	CR	Nd	1,740––2,240 mg	Nd	6–12 w	Demyelination	Sensory disturbances	Nd	Absent or attenuated sensory responses, reduced motor CVs, F-wave latency prolongation	Nd	No alterations	Hcy ↑ B12 N Nd	+	B12 Suppl	Improved or stabilised
Galazky 2014 n = 1	CR	5 y	2,940 mg	13 m	Sub-acute Nd	GBS/CIDP like	Paresis lower > upper, absent reflexes, sensory disturbances, gait disturbances	Nd	Mixed axonal/ demyelinating pattern	CVs improved	A-c dis protein 121 mg/dL	anti GA+ Hcy ↑ (230) B12 ↓ (136) B6 (2)↓	+	IVIG 90g/3d steroids, PE Suppl Nd	Primarily significant deterioration, > 3 m slow recovery
Galazky 2014 n = 1	CR	10 y	1,362 mg	4 m							A-c dis protein 100 mg/dL	anti GA+	+	IVIG 210 g/7d	
Merola 2014 n = 1/10	10%	Nd	Nd	4 m	Sub-acute Nd	Demyelination	Muscle weakness and sensory disturbances	No alterations	Prolonged DML, MNCB present, CMAP decreased > 30%, reduced CVs	Improvement	No alterations	Hcy N B12 N MMA N Nd	+	Suppl B12 FA	"Partial recovery"
Mancini 2014 n = 4/50	8%	13 y mean	Nd	8 m mean	1 w	Acute inflammatory	Muscle weakness, lack of tendon reflexes, sensory disturbances, inability to walk	Nd	Decrease in motor NCVs < 70%, F-wave latency prolongation	Nd	3/4 A-c dis (Protein Nd) 1/4 Nd	Hcy ↑ *vs.* no PN B12 ↓ *vs.* no PN FA ↓ *vs.* no PN Nd	Nd	Suppl Nd 2/4 IVIG 2/4 steroids Nd	IVIG 1/2 improvement, steroids 1/2 effective, 2/4 died of concurrent diseases
Uncini 2014 n = 1/15	6%	18 y	1,650 mg	4 m	1.5 w	GBS like	Tetraparesis, absent tendon reflexes, sensory disturbances	NCVs normal	Mixed axonal/demyeli-nating pattern	Improvement	A-c dis protein 148 mg/dL	Hcy N B12 (218) N FA (12.3) N anti GA–	+	Suppl B1, B12, FA PE	Motor recovery in 5 m
Merola 2016 n = 2/23	9%	Nd	Nd	4–6 m	Sub-acute Nd	Nd	Muscle weakness and sensory disturbances	No alterations	Mixed axonal/demyeli-nating pattern	Improvement	No alterations	Hcy ↑ B12 N FA N Nd	+	Suppl B12, FA	"Progressive recovery"
Pinter 2019 n = 1	CR	10 y	2620 mg	14 m	Nd	CIDP-like	Paraparesis, absent reflexes, sensory disturbances	Nd	"CIDP criteria were met"	Improvement of CMAP and motor CVs	A-c dis Protein 141 mg/dL	Nd	+	IVIG 2 × 35 g every 3 m	Motor recovery in 5 m, sensory symptoms persisted

Table 1 cont. Summary of publications included into systematic review on acute/subacute polyneuropathy during LCIG treatment of advanced Parkinson's Disease

	Preval	PD dur	LEDD	LCIG dur	PNP onset	Diagnosis	Symptoms	Pre NCS	NCS on diag	NCS follow up	CSF	Lab	LC IG disc	Treatment	Outcome
Rivero de Aguilar 2019 n = 1	CR	4 y	1,520 mg	15 m	8 w	CIDP	Tetraparesis, absent reflexes, sensory disturbances	Nd	Predominantly sensory--motor demyelinating polyneuropathy	Nd	A-c dis Protein 51 mg/dL	B12 N FA N Hcy Nd anti GA+	+	IVIG2 g/kg/5 d, methylpred-nisolone 5 g/5 d	Motor recovery in 6 m
Piekarski 2022 n = 1	CR	16 y	1,720 mg	3 m	12 w	CIDP-like	Tetraparesis, absent reflexes, sensory disturbances	Axonal bilateral lesions of peroneus and suralis	Predominantly motor-sensory demyelinating polyneuropathy	Improve-ment	A-c dis Protein 77 mg/dL	B12 ↓ FA ↓ Hcy ↑	no	Suppl B12, B1, B6, FA IVIG 2 g/ /kg/5 d + 1 g/kg/2 d	Progressive motor recovery over following months, sensory symptoms persisted

If no detailed quantitative data was available, "Nd "was used; (+) — performed with positive result; (–) — performed with negative result; ↑ — above normal values; ↓ — below normal values; a-c disc — albuminocytologic dissociation; anti GA — antibodies against gangliosides of many or unspecified type; B6 — vitamin B6 (ng/mL), N: > 4.5; B12 — vitamin B12 (pg/mL), N: 191–663; CIDP — chronic inflammatory demyelinating polyneuropathy; CMAP — compound muscle action potential; CR — case report; DML — distal motor latencies; FA — folic acid (pg/mL), N: 3.1–17.5; GBS — Guillain-Barre syndrome; Hcy — homocysteine (umol/l), N: 5–12; IVIG — intravenous immunoglobulins; MMA — methylmalonic acid; MNCB — motor nerve conduction block; N — within normal values; NCV — nerve conduction velocity; Nd — no data provided; PE — plasma exchange; Suppl — vitamin supplementation

Demographics and clinical manifestations

The most commonly reported symptoms included muscle weakness (tetra- or paraparesis), lack of tendon reflexes, paresthesia, and sensory loss. All of these were present in 11/15 patients, while in two patients only sensory symptoms were present, and for the remaining two there was no detailed information. In only 7/15 cases was detailed demographic data presented, making it impossible to draw unequivocal conclusions. The age of the patients ranged from 48 to 74 years, and the duration of PD was 5–18 years. The onset of polyneuropathy symptoms was on average 8 months (4–15 months) after the initiation of LCIG therapy. Preceding gastrointestinal infection was mentioned in one patient [18], but there was no data available in the remaining cases. Polyneuropathy onset was acute (< 4 weeks) in six cases, subacute (< 12 weeks) in eight cases (but in 5/8 only a descriptive onset was provided), and there was no data in the remaining case.

NCS findings

Due to the heterogeneous and often incomplete NCS data presented, precise interpretation or comparative analysis was impossible. For prospective studies, either only the interpretation of the result [10, 15] or average values [12, 16] are available. Detailed NCS data in the context of a case report was available in 3/5 publications, but in the remaining 2/5 only the descriptive interpretation of the study was available. In most cases, data for the baseline NCS before the diagnosis of polyneuropathy was lacking. Only in one study did we have a complete comparative list of electrophysiological parameters [18], and in two others information was provided that an NCS study had been performed [15, 16]. In the majority of cases, electrophysiological results consisted of a mixed pattern of axonal and demyelinating damage. Only in a few of them, referring to the descriptions provided by authors, were NCS results consistent with GBS/CIDP criteria [10, 13, 25]. Some authors stated that "despite the GBS/CIDP diagnosis, these results did not meet the criteria of acquired inflammatory neuropathy" [13, 18]. Follow up of NCS studies was also only partially conducted (6/9 publications) with more accurate data available only for three of these. In all of the above cases, a gradual improvement of NCV parameters was observed. Therefore, the descriptions of the type of neuropathy in Table 1 are inconsistent and we have adopted the terms used by the authors in the original descriptions (e.g. "demyelinating" "CIDP-like" etc.).

Laboratory findings

Cerebrospinal fluid (CSF) analysis showed elevated protein levels in 10/15 pts — in five cases protein levels ranged from 51 to 128 mg/dL (normal values < 45), and in the remaining five cases there was only albuminocytologic dissociation mentioned, with no quantative values. In 4/15 patients, protein levels were normal, and in the 15th patient, there was no data at all.

Serum homocysteine was described as elevated in nine patients, (accurate data was presented in three patients and ranged from 8 to 230 umol/L, normal values < 15); in two patients it was within normal values, and in the remaining four there was no data available. Vitamin B12 (B12) level was decreased in six, normal in another six, and in three patients there was no data provided. Other parameters [e.g. folic acid (FA), vitamins B6, B1, methylmalonic acid (MMA)] were scarcely provided and were not included in our analysis. Increased antiganglioside antibodies levels were occasionally reported, and were present in 3/4 patients examined.

Levodopa therapy

The levodopa-equivalent daily dose (LEDD) [26] was available for 7/15 patients on LCIG therapy, and ranged from 1,352 mg/d to 2,940 mg/d (mean 2,010 mg/day), among them three cases were related to 24-hour LCIG infusion. In one prospective study, there was no quantative data on LEDD, but patients with acute demyelinating polyneuropathy were treated with LEDD 26% higher compared to patients receiving oral therapy [16].

Treatment and outcome

LCIG therapy was discontinued in all cases. The methods of treatment applied are difficult to compare as different combinations of methods have been used for different patients (Tab. 1). Vitamin B-group supplementation (with no exact dose specified) was applied in four patients, combined with IVIG or PE or steroids in six, vitamin supplementation with IVIG or PE and steroids in one, IVIG or PE alone in three, and combined with IVIG and steroids in one case. In all, except for two patients who died due to comorbidities [12], gradual improvements were observed both clinically and electrophysiologically. For six patients detailed follow up NCS parameters were provided, in two patients there was no quantitative data, and in the other seven there was no data at all.

Clinical vignette

We here describe the case of a patient treated in our centre who developed subacute demyelinating polyneuropathy during LCIG therapy. A 66-year-old man with a 16-year history of PD, with no clinical symptoms or signs of peripheral neuropathy at baseline, developed subacute sensory-motor demyelinating polyneuropathy after the 12 weeks from the onset of therapy. There was no data on any infectious disease preceding the onset of symptoms. NCS was performed at baseline (before the initiation of LCIG as a routine procedure in our centre) and showed only a moderate decrease of conduction velocities (CV) in sural nerves with severe axonal neuropathy of both peroneal nerves and a slight decrease of CV and amplitude in both tibial nerves. Twelve weeks after the initiation of LCIG therapy, the patient started to report sensory disturbances — primarily paresthesia in the lower limbs. Over the next 12 weeks, these sensory symptoms gradually worsened with a decrease of sensation and lower limb weakness. After 12 weeks from the onset of PNP symptoms, he was admitted to hospital. On admission, he presented slight distal weakness of the upper limbs, weakness of the lower limbs significantly influencing gait (walked unassisted), and a lack of tendon reflexes. The LEDD on LCIG was 1,720 mg and this was more than 14% lower compared to the previous oral treatment (LEDD on oral medications before initiating LCIG treatment drugs was 1,980 mg). NCS showed prolonged distal latencies in median and tibial nerves (L > P) up to 5.2 ms, with decrease of CV (mean 39.5 m/s) in median and 32.5 m/s in tibial nerves (previously intact) with low frequency of F-wave and prolonged latency up to 69 ms in the left tibial nerve. The sensory responses from both sural nerves were absent, and similarly there were no sensory responses from the left median and ulnar nerves. The CSF examination showed moderately increased protein level (77 mg/dL, N < 45), B12 was 156 pg/dL (at baseline 197 pg/dL, N < 183), FA decreased to 2.83 ng/mL (at baseline 4.91 ng/mL, N < 4.5), and Hcy was above laboratory value > 50 µmol/L (at baseline 33.9 µmol/L, N < 12). Anti-ganglioside antibodies were not tested. The detailed NCS parameters are presented in Supplemental Table 1, whereas laboratory findings are presented in Supplemental Table 2.

The patient was diagnosed with CIDP-like neuropathy. The LCIG therapy was continued at the same dose of levodopa-carbidopa, vitamin supplementation (B1, B6, B12 and FA), and IVIG (sandoglobulin) was introduced (dosage 2 g per kg of body weight for five days, total dose 150 g, with repeated additional 1 g/kg after two months in two doses). Vitamin supplementation was introduced and primarily conducted in hospital simultaneously with IVIG. The detailed vitamin doses are presented in Supplementary Material 1.

The patient's condition gradually improved, and over the next three months weakness of the lower limbs disappeared with a substantial decrease of sensory disturbances. NCS parameters in motor nerves improved (the first improvement was present one month later), with no improvement in sensory nerves.

Subsequent examinations (the last one 15 months after disease onset) showed still a lack of sensory responses in upper and lower limb nerves: median, ulnar, tibial, sural, but with a persistent improvement of motor responses. Hcy levels had decreased to 15.9 µmol/L.

Discussion

The published data on acute/subacute polyneuropathy due to the LCIG therapy is inconsistent and heterogeneous and includes case reports and case series presented both retro- and prospectively (Tab. 1). In the FDA/EMA documents, there is little information about the possible adverse event that is polyneuropathy, with no differentiation made between axonal or demyelinisation. Apart from warning that precautions should

be taken against PNP, there are no recommendations as to any treatment/prevention approach.

The true prevalence of polyneuropathy (both acute/subacute and chronic) on LCIG therapy is difficult to estimate. Studies that have focused on the assessment of polyneuropathy have shown a prevalence ranging from 13.8% [9] up to 100% [8], while in multicentre studies including large groups of patients (both prospective and retrospective) specifically focusing on effectiveness and an assessment of the safety profile, the incidence of polyneuropathy has ranged from 4.5% [27] to 13% [22].

This difference is most likely due to the usage of more accurate diagnostic tools and specific clinical scales. Polyneuropathy in PD not treated with LCIG is predominantly of chronic sensory and sensorimotor axonal type, and its origin is not fully understood. There are different underlying mechanisms, mainly related to levodopa exposure due to its metabolic pathway and homocysteine formation. B-group vitamins are used as cofactors in this pathway — which may be responsible for a deficiency as an aetiology on the one hand and a neurotoxicity of homocysteine on the other [7, 12, 28–30]. On LCIG treatment, due to intrajejunal delivery, the levodopa bioavailability is higher compared to oral formulations [7, 31], something which makes the mechanism of levodopa-exposure polyneuropathy even more possible. There is also a concept on vitamin malabsorption to be considered due to the presence of levodopa gel in the intestines [32]. Gel formula can also affect gut microbiota leading to a triggering of the autoimmune response [32]. Such concepts are highly speculative, but from our point of view, their occurrence is at least possible.

Acute/subacute demyelinating neuropathy is very rare and may sometimes go unrecognised (i.e. gait deterioration may be attributed to PD progression), and there have only been 15 cases described in detail so far. There are probably more in real life as the inclusion criteria established in this review have potentially excluded many of them. In most cases, muscle weakness is the predominant symptom, with acute or subacute onset and a demyelinating pattern in NCS studies resembling Guillain-Barre syndrome (GBS), or a chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) pattern respectively.

In our new case, it was possible to compare the patient's NCS from baseline assessment at the onset of LCIG therapy, showing this was newly developed demyelinating neuropathy. His relatively fast improvement of motor deficits (and motor NCS) after IGIV treatment (four weeks after initiation) may suggest a demyelinating pattern as well. However, increased homocysteine level along with FA deficiency may suggest an underlying axonal neuropathy which was asymptomatic. Some authors have questioned the demyelinating mechanism in published cases [13, 18]. Unfortunately, due to a lack of sufficient data, in a majority of cases detailed or comparative analysis of NCS parameters is not possible.

Nevertheless, the clinical manifestation of those cases is characteristic for acquired inflammatory polyneuropathies like GBS or CIDP, and such a diagnosis has been made in almost all published cases (Tab. 1). Characteristic (but not specific) for the inflammatory neuropathies are alterations in CSF analysis of albuminocytologic dissociation — in GBS this is present in 75% of patients [33] and in CIDP in up to 90% in a typical pattern [34], but it may be lower (or even absent) in an atypical presentation e.g. Lewis-Sumner Syndrome [35]. In the presented case series, it was detected in 10/15 patients and this may suggest the immunological origin of neuropathy.

Clinical presentations of inflammatory neuropathies may vary significantly — the most characteristic (and most common) is pure symmetric motor demyelinating neuropathy, but there are also sensory and sensorimotor variants with axonal changes in NCS studies or asymmetrical presentation of both GBS and CIDP. Misdiagnosis of CIDP is common and has been reported in up to 50%, mainly in patients with an atypical presentation [36]. There are no diagnostic tools that are 100% specific, and the diagnostic approach must include clinical manifestation, NCS studies and laboratory findings. During LCIG therapy, the presence of percutaneous gastrostomy and the gel formulation of the drug affecting the gut microbiota are suspected to be the crucial factors initiating immunological response [12, 18]. Different types of anti-ganglioside antibodies could be detected in inflammatory neuropathies (GM1, GD1a, GD1b, GT1a, GQ1b, GT1b for GBS and LM1, GM1, GD1b for CIDP) [37, 38]. They were analysed in only 4/15 patients, and in three cases were detected. Therefore, it is difficult to conclude whether the underlying mechanism is of immunological origin, as the majority of case reports do not provide such information. Polyneuropathy occurred within the first 15 months of treatment and in the majority of reported cases was not preceded by an infection. Therefore, one may suspect that it was related to LCIG therapy or that this therapy was an additional factor (e.g. due to possible neurotoxicity of homocysteine) and as in our case polyneuropathy was present (but subclinical) before the LCIG therapy initiation. The baseline NCS were not performed in all presented cases. Another explanation may be a simple coincidence of LCIG therapy and GBS/CIDP, however they are (specifically CIDP) relatively rare conditions, and LCIG treatment is also offered only to a small number of PD patients. Nevertheless, demyelinating pattern in NCS and CSF-protein elevation with clinical motor or sensory/motor neuropathy presentation may suggest its immunological origin.

However, it should be mentioned that B12 deficiency may also present as demyelinating neuropathy with subacute onset. In the largest patient cohort so far, n = 66 [39] assessing neurological symptoms in vitamin B12 deficiency, NCS analysis revealed sensory/motor neuropathy which was demyelinating in 11.1%, axonal in 22.2%, and with a mixed pattern in the remaining 66.7%. The onset of symptoms was subacute or chronic symptoms were mainly sensory, but paretic symptoms were observed in four patients (13% with symptoms

of neuropathy). CSF analysis in patients with B12 deficiency shows albuminocytologic dissociation in 65% of cases [40], and therefore may be easily misdiagnosed as GBS/CIDP. Moreover, 44% of patients diagnosed with B12 deficiency with polyneuropathy symptoms had normal B12 levels with abnormal metabolite levels (homocysteine and MMA) [41].

This variable clinical presentation of B12 deficiency polyneuropathy makes the unequivocal interpretation of the neuropathy in LCIG case series even more difficult. Vitamin B12 levels were tested in 12 patients: it was decreased in six (with no accurate values provided), and in the other six was normal.

Concerning the treatment approach, LCIG was discontinued in all cases (except the one case from our centre presented in this paper). However, in one paper (n = 2 patients), LCIG treatment was terminated due to ineffectiveness of immunomodulatory treatment [11].

Supplementation of vitamins has been widely introduced as well as immunomodulatory therapy: steroids, IVIG or PE. This makes impossible the drawing of a simple conclusion on the pathological mechanism of neuropathy. Despite the different combination of treatment approaches, the treatment had a positive effect on disease symptoms in all cases, unfortunately with no data provided on NCS parameters in a majority of reports. In three patients the recovery time was described as 5–6 months, and in 6/15 patients there were performed detailed NCS control examinations, showing gradual improvement.

The authors of the publications analysed in this paper were probably aware of the fact that the NCS criteria [25] for the diagnosis of demyelinating neuropathies were not met in many cases, which is reflected in the usage of terms such as "GBS-like" or "CIDP-like" [11, 18].

In the cases presented above, regarding the clinical manifestation including acute/subacute onset, presence of paresis, laboratory findings and NCS alterations (despite not fulfilling diagnostic criteria in most cases) and the introduction of effective immunomodulatory treatment, it seems that the diagnosis of acquired demyelinating polyneuropathy of immunological origin was justified. Withdrawing LCIG therapy in advanced PD patients may result in a severe deterioration of parkinsonian symptoms. Therefore, such a decision should be made cautiously, and immunotherapy (IVIG, steroids, PE) should be offered before terminating LCIG treatment. The withdrawal of LCIG was common but difficult to understand in terms of patients' improvement on immunological therapies.

Our case report shows that continuation of LCIG therapy may result in long-term benefit, despite the temporal deterioration. The decision to maintain LCIG treatment resulted in a good control of PD motor symptoms and allowed for the introduction of intensive rehabilitation, and our patient was still independent in everyday life.

Due to the high number of neuropathy cases during LCIG treatment, we suggest that NCS studies should be performed routinely at baseline with control examinations at least every 12 months. In cases with acute/subacute deterioration of gait, and/or motor/sensory deterioration, a NCS examination should be performed on demand. In cases of demyelinating pattern, the proper immunological treatment with IVIG or steroids or PE (there are no recommendations regarding the superiority of one over another) should be offered. We do not recommend the termination of LCIG therapy (as in a majority of the presented cases), as gradual improvements were seen after immunotherapy.

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RESEARCH PAPER

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Could hyperlipidemia be a risk factor for corticobasal syndrome? — a pilot study

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ABSTRACT

Introduction. Corticobasal syndrome (CBS) is a specific clinical manifestation shared by multiple pathologies. The exact mechanism of this phenomenon remains unclear. Differential diagnosis of CBS in everyday clinical practice is challenging, as this syndrome can overlap with other entities, especially progressive supranuclear palsy Richardson-Steele phenotype (PSP-RS). Several papers have suggested a possible role of vascular pathology as a linking factor in the pathogenesis of CBS based on different neuropathologies. This paper analyses differences in the occurrence of the most common vascular risk factors such as hypertension and lipid profile with respect to dietary habits among patients who fulfill the diagnostic criteria for probable/possible CBS and PSP-RS.

Material and methods. Seventy (70) patients in total were included in the study. Exclusion criteria comprised hydrocephalus, stroke in the past, the presence of marked vascular changes in white matter defined as the presence of vascular change ≥ 1 mm in 3T MRI, medical history of hyperlipidemia or the use of drugs that could impact upon lipid metabolism before the initiation of the neurodegenerative disease, and neoplastic focuses in the central nervous system. Patients with diabetes, or with BMI exceeding 18–25, or who were smokers, or who were affected by chronic stress were also excluded. Data was analysed statistically using the Shapiro-Wilk test, the U Mann-Whitney test for group comparison, and a Bonferroni correction to control the false discovery rate (FDR).

Results. Our obtained results indicated a statistically significantly higher level of total cholesterol in the CBS group ($p = 0.0039$) without a correlation with dietary habits.

Conclusions and clinical implications. The results obtained in our study may suggest a possible role of vascular pathology in CBS development. This issue requires further research.

Key words: corticobasal syndrome, hyperlipidemia, neurodegeneration, risk factor, CBS phenotype

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Introduction

Corticobasal syndrome (CBS) is a complex of clinical symptoms highly diversified when it comes to underlying pathology. According to the recent criteria of diagnosis, it is associated with "asymmetric manifestation of limb rigidity, akinesia, limb dystonia, limb myoclonus, orobuccal or limb apraxia, cortical sensory deficit and alien limb phenomenon" [1]. Progressive supranuclear palsy is the most common atypical parkinsonism. The most common phenotype is Richardson syndrome, which is associated with oculomotor and postural instability [2]. Both these diseases are referred to as

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atypical parkinsonian syndromes. Historically, CBS has been associated with four-repeats tau pathology, otherwise known as corticobasal degeneration (CBD). With the progress in the assessment of CBS, it has been established that this clinical manifestation is related to up to half of the cases of CBD [1, 3]. CBD may also manifest as progressive supranuclear palsy syndrome (PSPS), frontotemporal dementia, Alzheimer's-like dementia, frontal behavioural-spatial syndrome or non-fluent/agrammatic variant of primary progressive aphasia [4]. The more precise assessment of CBS patients has shown that although CBD is a major pathology of CBS, it is not the only one. Post mortem examinations of other patients have revealed a surprisingly high incidence of CBS manifestations with multiple types of underlying pathologies. Examples include progressive supranuclear palsy (PSP), Pick's Disease, Lewy body Disease, TDP43 type A, Creutzfeldt–Jakob Disease, globular glial tauopathy and Alzheimer's Disease [5]. The literature has also associated CBS with pathologies based on vascular changes [3].

Despite the complicated correlation between clinical manifestation and its pathology, the main obstacle to correct diagnosis is related to overlapping clinical manifestations between CBS and other tauopathic parkinsonian syndromes, especially progressive supranuclear palsy syndromes [6]. Currently CBS is interpreted as a group of pathologies linked by the same clinical manifestation. The exact mechanism leading to a concurrent syndrome despite multiple pathologies remains unclear.

Clinical rationale for study

The most common phenotype of PSPS is PSP-Richardson Syndrome (PSP-RS), which in the vast majority of cases is related to PSP pathology [6]. The overlaps and often unclear boundaries between PSPS and CBS cause difficulties in obtaining a proper diagnosis using a clinical assessment. Among these overlaps are bradykinesia, cognitive deterioration, changes of behaviour, and postural instability [1, 2]. This has led to the introduction of a probable 4-repeat (4R)-tauopathy diagnosis [7], which combines CBD and PSP into one clinical entity.

The latest literature highlights the importance of vascular pathology in CBS development [5]. Assuming this hypothesis to be true, the aim of this study was to verify whether patients who fulfill the current diagnostic criteria for CBS diagnosis differ from patients with PSP-RS in the context of dyslipidemia severity, which is a known vascular risk factor.

Material and methods

Seventy (70) patients with atypical parkinsonism were included in the study: 51 patients with a clinical diagnosis of PSP-RS (19 females, 32 males) aged 62-83 years and 19 patients (18 females, one male) with CBS aged 57 to 87. The disease duration among all patients varied from 3 to 6 years. The clinical diagnosis was based on the recent criteria of diagnosis of PSP and CBS [1, 2]. All of the clinical examinations were performed by neurologists experienced in movement disorders between January 2017 and December 2021 in the Departments of Neurology in Warsaw and Prague. Excluded from our study were patients with hydrocephalus, who had undergone stroke, with marked vascular changes in white matter defined as presence of vascular change ≥ 1 mm, with a medical history of hyperlipidemia or the use of drugs that could impact upon lipid metabolism before the initiation of the neurodegenerative disease, and neoplastic focuses in the central nervous system. Patients with diabetes, or BMI exceeding 18–25, or who were smokers, or who were affected by chronic stress were also excluded.

Analysed data included lipid profile, presence of hypertension, and a nutrition survey of patients and caregivers involved in food preparation. This survey covered all foods consumed by the patient on three consecutive days, taking into account the portion size. On this basis, the average daily amount of kilocalories and the nutritional values taken by the patient were calculated.

The study was approved by the Bioethical Commission of the Medical University of Warsaw (AKBE/209/2021).

Laboratory testing

All of the patients included in the study underwent biochemical analysis of blood samples. The evaluation was conducted during hospitalisation in the Departments of Neurology in Warsaw or Prague. The analysis of blood samples was performed using Sysmex XT 4000i. The evaluated parameters — total cholesterol, triglycerides, high density lipoprotein (HDL), and low density lipoprotein (LDL) — were assessed automatically and compared to the hospital database of healthy volunteers.

Statistical analysis

All analysis was performed using Statistica software (version 13.1 Statsoft). Data distribution was assessed with Shapiro-Wilk test. Due to non-normal distribution, all parameters are expressed as medians (Me) with a lower (Q1) and an upper (Q3) quartile and their interquartile range (Q1–Q3). For group comparison, we used U Mann-Whitney test. Significant results are presented as box plots. We have provided a scatterplot if necessary. For a final decision with regard to statistical significance we have used corrected p-value after Bonferroni correction to control the False Discovery Rate (FDR). A calculated p value of 0.005 was considered significant.

Results

Hypertension defined as blood pressure > 140/90 mmHg was present in 76.5% of CBS and 43.6% of PSP–RS patients.

Table 1 sets out descriptive statistics for analysed groups of patients with CBS and PSP-RS; median values, Q1, Q3 and Q1–Q3 are given.

Table 1. Descriptive statistics

Parameters	CBS (N = 19) (F/M=18/1)				PSP (N = 51) (F/M = 19/32)			
	Me	Q1	Q3	Q1–Q3	Me	Q1	Q3	Q1–Q3
Lipid parameters								
Total cholesterol	213.0	197.0	239.0	42.0	179.0	160.0	205.0	45.0
HDL	47.0	42.0	55.0	13.0	50.0	39.0	58.0	19.0
LDL	128.0	88.0	154.0	66.0	104.5	86.0	136.0	50.0
TAG	95.0	87.0	107.0	20.0	98.0	77.0	117.0	40.0
Nutrition survey								
Kcal	1,800.0	1,750.0	1,835.0	85.0	1,935.0	1,825.0	2,100.0	275.0
Fat [g]	77.0	75.0	82.5	7.5	81.5	76.0	84.0	8.0
Cholesterol [mg]	225.0	206.5	242.5	36.0	248.0	200.0	279.0	79.0
Carbohydrates [g]	265.0	256.2	272.5	16.4	272.0	257.5	277.5	20.0
Protein [g]	83.8	83.0	85.6	2.6	84.3	83.0	87.0	4.0
Fibre [g]	27.0	25.0	28.0	3.0	27.0	24.0	28.4	4.4

CBS — corticobasal syndrome; HDL — high density lipoprotein; LDL — low density lipoprotein; Me — median; PSP— progressive supranuclear palsy; TAG — triglycerides; Q1 — lower quartile; Q3 — upper quartile; Q1–Q3 — interquartile range

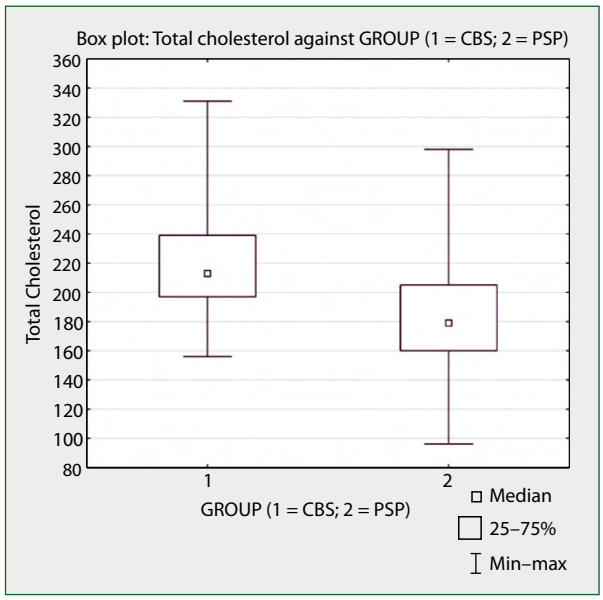

Figure 1. Comparison of median value of total cholesterol between groups
CBS — corticobasal syndrome; PSP — progressive supranuclear palsy

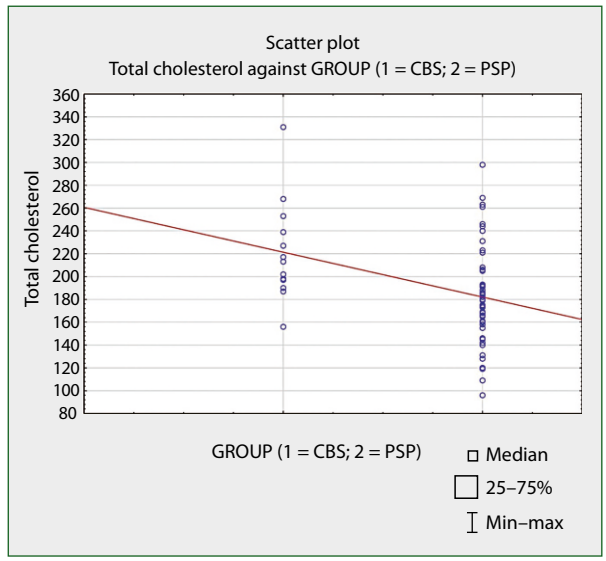

Figure 2. Scatter plot — data distribution in regard to medians differences
CBS — corticobasal syndrome; PSP — progressive supranuclear palsy

Median value of total cholesterol was significantly higher for CBS patients compared to PSP-RS patients: 213.0 *vs.* 179.0 (Fig. 1) Scatter plot also shows adequate data distribution in regard to differences in medians (Fig. 2).

Differences in median values in the rest of the analysed lipid parameters: high-density lipoprotein, low-density lipoprotein, and triacyl glycerides, in CBS and PSP-RS patients, were insignificant $p > 0.005$ (Tab. 2).

Comparison of data from the nutrition survey revealed that only the median value of total calories consumed per day differed between CBS and PSP-RS patients, and was higher in the PSP-RS group compared to CBS patients (1,935 *vs.* 1,800 kilocalories, $p = 0.0005$) (Tab. 2, Fig. 3). This could be at least partly explained by the gender inequality among the groups, with a strong female predominance in CBS.

Differences in other nutrients such as fat, cholesterol, carbohydrates, protein and fibre intake were insignificant (Tab. 2).

Discussion

Our study was affected by several limitations, most notably the lack of neuropathological examination and the screening method of lipid profile assessment, without evaluation of

Table 2. Group analysis in regard of lipid parameters and nutrition survey

Parameters	P-value for UMW test
Lipid parameters	
Total cholesterol	0.0039
HDL	0.6807
LDL	0.2101
TAG	0.9756
Nutrition survey	
Kcal	0.0005
Fat [g]	0.3410
Cholesterol [mg]	0.2041
Carbohydrates [g]	0.1653
Fibre [g]	0.9566
Protein [g]	0.3886

HDL — high density lipoprotein; LDL — low density lipoprotein; TAG — triglycerides; UMW — U Mann-Whitney test

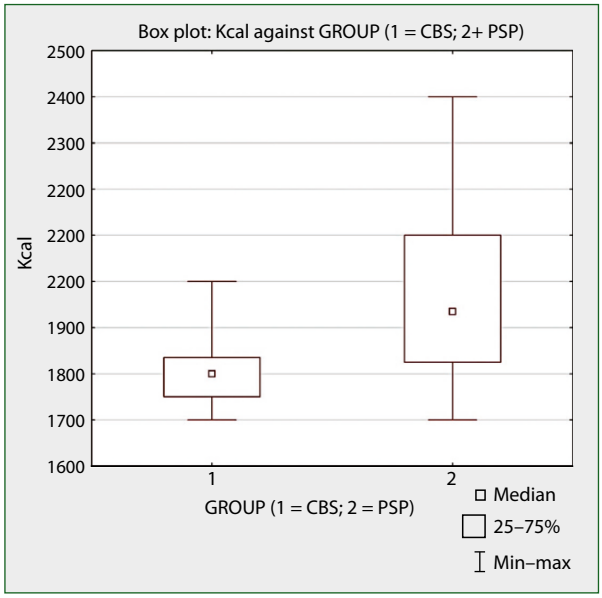

Figure 3. Comparison of data from nutritional survey
CBS — corticobasal syndrome; PSP — progressive supranuclear palsy

specific metabolism pathways, and an unequal representation of male and female patients in the PSP-RS and CBS groups, which is related to the rarity of these diseases.

However, the obtained results suggest that corticobasal syndrome may be more associated with abnormalities in the lipidic parameters than other entities. This, taking into account the fact that the cases were not verified pathologically, may reveal a possible link between vascular pathogenesis commonly described in the literature regarding corticobasal syndrome. Due to the fact that we excluded patients with vascular changes found in magnetic resonance imaging — 3T, the mechanisms may be connected also with abnormalities not evidenced in macroscopic examination.

CBS is one of the entities which are most diversified in the context of pathology, which may suggest an alternative mechanism of syndrome development [1, 3, 4]. The multiple pathologies that are likely to be associated with CBS could impact upon the results related to vascular pathogenesis in this group. In PSP-RS, about 90% cases are related to PSP pathology [8]. In CBS, our knowledge concerning the pathology is still evolving. The fact that an association between CBS and CBD is found in about 50% of cases is relatively well known. However, recent papers have shown that CBS, though associated with tauopathic pathology, may be related to vascular and Lewy body pathogenesis [9, 10] . In our work, patients with ischaemic or haemorrhagic lesions possibly detected using the resolution of MRI were excluded from the study. This issue may suggest the need to search for molecular mechanisms affecting more pronounced dyslipidemia in CBS. A cross-sectional analysis of cardiovascular risk factors and their associations with different neurodegenerative diseases indicates that this association may be restricted to AD pathology [11]; however, corticobasal syndrome often is its clinical presentation.

The association between parkinsonisms and vascular changes has been studied in various clinical entities, although in CBS it has been relatively sparingly described [12]. From the initial definition of CBS right up until today, the interpretation of the disease has continued to evolve. Currently growing interest is associated with the vascular and metabolic pathogeneses of CBS [13]. A postmortem analysis performed on 217 subjects with antemortem diagnosis of CBS revealed three patients with vascular changes [10]. Another work presented a case report of a patient with superior sagittal sinus intracranial dural arteriovenous fistula mimicking corticobasal syndrome [14]. CBS has also been described in patients with multiple ischaemic lesions [15]. The descriptions of vascular pathogenesis are generally based on relatively small numbers of patients or case reports. Hypertension is considered as a significant co-existing and preceding state in the pathogenesis of CBS and related disorders such as PSP [16]. A case report presenting a progressive course of typical CBS symptoms showed disseminated ischaemic lesions and steno-occlusion of both middle cerebral arteries [17]. The explanation for CBS's clinical manifestations requires further research.

Most papers concerning vascular pathogenesis in the context of neurodegenerative disorder have focused on Alzheimer's Disease. In 2020, the Lancet Commission on dementia prevention, intervention, and care published a list of 12 modifiable risk factors for dementia development; four of these (diabetes, hypertension, obesity, and lack of physical activity) can be considered also as vascular risk factors [18]. Dysfunction of the neurovascular unit consisting of the blood–brain barrier endothelium and surrounding smooth muscle cells, microglia, pericytes, and astrocytes, as well as abnormal

cerebral bloodflow, are associated with early cognitive decline, regardless of typically described amyloid and tau accumulation [19]. Blood–brain barrier dysfunction increases vascular impairment, causing amyloid angiopathy due to reduction of amyloid efflux [20]. Progressive vasculopathy impairs microcirculation and leads to hypoperfusion and hypoxia described in AD pathogenesis [21]. Dyslipidemia as a factor contributing to vascular pathology causes oxidative stress and inflammation, which leads to further vascular impairment and forms a vicious circle of damage and neurodegeneration. Animal studies clearly indicate that vascular dysfunction promotes neurodegeneration observed in AD-mice models [22]. The issue of neuroinflammation in tauopathies was also recently discussed in the context of PSP and CBD [23].

AD, as well as other types of dementia, are considered as being possibly correlated with vascular mechanism, although the mechanism of this association is not fully understood [24, 25]. The levels of lipids and lipoproteins were verified in a comparison of patients with AD and vascular dementia. This revealed that AD patients had lower levels of total cholesterol, TG, LDL-C, VLDL-C, Non-HDL-C, and atherosclerosis index, not only when compared to vascular dementia patients with a comparable stage of cognitive deterioration, but also compared to healthy controls [26]. Additionally, the risk of AD was not found to be correlated with familial hypercholesterolemia [27]. Although the data concerning lipidic abnormalities in AD does not indicate a concise correlation with lipidic profile, research concerning dyslipidemia in PSP has shown a correlation of LDL-C/HDL-C ratio with the PSP rating scale and the Geriatric Depression Scale. A general study on risk factors for dementia revealed that LDL is a risk factor for dementia a minimum of 10 years later [28].

Regardless of the presented lipidic profile, AD is considered an entity possibly linked with vascular pathogenesis. One paper associates a connection between maximum systolic pulse energy location and the acceleration of atherosclerosis impacted by age [29]. One theory suggests decreased brain perfusion as a factor inducing beta amyloid accumulation and further evolution to dementia [30]. Furthermore, ApoE, one of the genetic determinants of AD, is considered to be a feature correlated with decreased perfusion [31].

A possible association between lipid metabolic changes and parkinsonism has also been described in the context of Parkinson's Disease and deep brain stimulation therapy (DBS) [32]. The authors indicated that the DBS group was characterised by increased BMI and TG levels and decreased HDL-C levels.

Clinical implications/future directions

Our results, though affected by certain limitations, may serve as reference points in the discussion concerning vascular factors leading to CBS phenotype. The lack of significant vascular changes in MRI suggests that the abnormalities may not be captured in macroscopic evaluation. The outcome of this study may be beneficial in the context of future therapies dedicated to certain entities. Our results suggest that research concerning the exact pathogenesis of CBS phenotype requires further development.

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RESEARCH PAPER

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Functional improvement of young children with cerebral palsy treated with integrated/intensive rehabilitation and botulinum toxin injections

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ABSTRACT

Introduction. Patients with cerebral palsy (CP) present mobility limitations altering their activity and participation in social life. The aim of this study was to assess changes in Gross Motor Function Classification System (GMFCS) and Functional Mobility Scale (FMS) in children with CP who received repeated BoNT-A injections within a rehabilitation treatment over a five-year follow-up period.

Material and methods. This retrospective, observational study included 200 consecutive children with bilateral CP (GMFCS I–IV). Annual assessments of the five-year follow-up period were analysed.

Results. The mean age of the patients at the beginning was 32.23 months (± 6.96). The GMFCS level improved in 67 (33.5%) ($p < 0.001$) and worsened in four (2%) children. In children with GMFCS III and IV levels, improvement was observed in 50% and 40%, respectively. FMS 5 and 50 metres improved in 54% and 52.5% of children respectively.

Conclusions. Our study showed a significant, positive effect of integrated treatment on functional mobility in patients with CP.

Key words: cerebral palsy, integrated rehabilitation, botulinum toxin-A, mobility, gross motor function

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Introduction

Cerebral palsy (CP) describes "a group of permanent disorders of the development of movement and posture causing activity limitations, which are attributed to nonprogressive disturbances in the developing foetal or infant brain" [1]. Cerebral palsy is one of the most common causes of motor disability in children [2].

In children with CP, limited activity directly affects the level of functioning in daily activities and may cause problems that make it difficult to engage in daily life and determine participation restrictions [3].

The Gross Motor Function Classification System (GMFCS) is a five-level classification that describes the gross motor function in children with cerebral palsy. The extended and revised version takes into consideration also children from 12 to 18 years of age and draws attention to personal and environmental factors [4, 5]. The GMFCS is strongly associated with mobility care and domestic life. The fact that also in this study such a strong relationship was found between the GMFCS and mobility, supports the use of the GMFCS to classify a child's mobility performance [6].

GMFCS is known for its stability but it is not an outcome assessment tool. Generally, children stayed at the same GMFCS level from 1–2 years up to 6–12 years of age. Based on Canadian population studies, it has been shown that children with spastic CP on average reach 90% of their motor function at approximately five years of age, then there is a plateau in further motor development at about seven years, and children in GMFCS Groups III, IV, and V suffer a decline through adolescence [7–9].

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The Functional Mobility Scale (FMS) is a reliable scale for classifying functional mobility in children covering three distances, 5, 50 and 500 metres, including assistive devices that the child might use to cover a certain distance [10, 11]. The FMS is sensitive to detect change after intervention e.g. surgery [10].

Opheim et al. [12] showed that adults with bilateral spastic CP and higher levels of GMFCS demonstrate a greater risk of deterioration of their gait function than those with less intensive disorders and better gross motor skills. The authors give the cause of overload resulting from excessive load on the motor system to meet social and environmental requirements.

In light of the above, the process of rehabilitation of children and adolescents with cerebral palsy should be focused on achieving the highest possible functional level allowing for full participation in social and professional life.

Over the past three decades, botulinum toxin type A (BoNT-A) has become established as an important treatment modality for hypertonia in children with CP. The biggest breakthrough in the therapy of children with CP was the introduction of multi-level injections of botulinum toxin type A (BoNT-A) as a part of a multimodal rehabilitation process which include physiotherapy and orthoses, among a range of other treatments. Such an integrated approach brings measurable results and changes the natural course of the disease [13, 14]. The answer to the question of the long-term impact of BoNT-A treatment plus physiotherapy on gross motor function in long term is still unclear [15].

The aim of this study was to assess changes in functional mobility for the distances of 5 and 50 metres in patients with cerebral palsy who received repeated botulinum toxin-A (BoNT-A) injections within a rehabilitation treatment over a five-year follow-up period. Moreover, stability of GMFCS in assessed population was observed.

Material and methods

Settings and inclusion criteria

This was a retrospective, single-centre, observational study conducted in the Mazovian Neuropsychiatry Centre in Zagórze, Poland. The retrospective study included 200 consecutive children with CP treated with BoNT-A injections and an integrated rehabilitation programme from February 2004 to August 2019, who met all of the inclusion and none of the exclusion criteria. The inclusion criteria were: (1) children diagnosed with bilateral CP, spastic type; (2) children between the ages of 2 and 4 years at the beginning of the observation; (3) children who had GMFCS level I to IV before first injection; (4) gait assessment and medical records available for 5 years of follow-up; and (5) gait assessment performed before, or at least three months after, each BoNT-A injection. Exclusion criteria included: (1) other forms of CP especially with predominantly dyskinetic type; (2) children who had GMFCS level V; and (3) orthopaedic procedures performed due to CP.

BoNT-A treatment and rehabilitation programme

During the follow-up period, all children underwent BoNT-A injections, an individual physiotherapy programme and used ankle foot orthosis (AFO). BoNT-A most often was administered once or twice a year; patients received from 5 to 10 injections during the observation period. Total doses per session varied from 20 μ/kg to 30 μ/kg for ABOBoNT-A or from 10 μ/kg to 20 μ/kg for OnaBoNT-A. During the five-year treatment period, children could receive both toxins, and in the majority multilevel injections were performed. The treatment scheme was developed by the authors based on our experience and available recommendations [13, 14]. Hip flexors and adductors, knee flexors, and foot plantar flexor muscles were usually selected for the treatment based on detailed assessment including: muscle tone, range of motion, strength, and gait analysis. Injections were administered under mild sedation, and ultrasound as a guidance method was used. The physiotherapy programme was planned individually for each child and was intended to achieve their specific functional goals, which were set across all components of the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) [16]. Therapists during the intensive physiotherapy period used this model to select the measurement tools, goal setting and evaluation of the outcomes. Functional goals were defined to structure the therapy process. Goals focused on functional mobility, comprising the activities of daily living which were established with children and parents. Goals were set on the five SMART principles: specific, measurable, achievable, realistic, and time-bound [17, 18]. The long-term goals of physical therapy aimed to improve the child's mobility and independence during daily living activities and related participation in social life. The short-term goals were focused on body structure level and included improving passive and active range of motion, muscle strength and selective motor control [19, 20]. The inpatient rehabilitation ranged from one to four three-week stays per year, and usually took place 2–4 weeks after BoNT-A injection. Physiotherapy included individual and group training, lasting an average of 120 minutes per day. Physiotherapists used analytical therapy techniques as well as functional and task-oriented training approaches. Additionally, during each intensive physiotherapy period, the children had aquatic therapy, occupational therapy, speech therapy, and therapeutic horse-riding [21]. After evaluating the outcomes, the children and caregivers were given guidance on which exercises and activities they should focus on during community-based rehabilitation between intensive physiotherapy periods. Community rehabilitation ranged from two to five times per week and was conducted in kindergarten, school, or at home for all assessed children. All patients used rigid or semirigid ankle foot orthoses (AFO) along with proper footwear. AFO were tuned individually based on ground reaction vector visualisation. The purpose of orthotic management was to improve

gait parameters and movement patterns. 169 (84.5 %) children wore AFO 5-8 hours per day, while 31 (15.5%) wore them for less than five hours daily.

Outcome measures

The objective of the analysis was to document the long-term changes in FMS in the presented group; additionally, changes in GMFCS were analysed. GMFCS describes a child's or youth's abilities and limitations in gross motor function based on self-initiated movement with particular emphasis on sitting, transfers, and mobility. According to the general guidelines, children classified at level I walk fully independently, while those whose gross motor function is assessed at level V are dependent on assistive technology and the assistance of a caregiver. Accurate determination of the current level of gross motor function was possible due to detailed descriptions of five functional levels referring to specific age groups, which were divided as follows: up to 2 years of age, 2 to 4 years of age, 4 to 6 years of age, 6 to 12 years of age and 12 to 18 years of age [5]. The FMS (Functional Mobility Scale) classifies functional mobility in children over distances of 5, 50 and 500 metres and includes assistive devices requisite to cover a certain distance. The indicated distances play a largely informative role, because the most important element is the environmental factor. The functional mobility over distances of 5, 50 and 500 metres represents mobility at home, in the school environment including the playground, and outdoors e.g. in a shopping centre or high street. A mobility rating of 6 describes complete independence when a child walks on various surfaces and has the ability to overcome obstacles. If a child uses sticks, crutches or a walking frame, the FMS scores would be 4, 3 and 2, respectively. A score of 1 describes a child who uses a wheelchair and can make some steps supported by a caregiver [10, 22].

Data collection procedure

A treatment, casting, physiotherapy, orthoses, GMFCS level and FMS score for 5 and 50 metres was collected from medical records, structured interviews, corridor tests and goal assessment charts based on GAS methodology, conducted on the first and last days of each intensive physiotherapy period by therapists working in the Neurorehabilitation Department. From the available measurements, those that were made at about annual intervals were selected to show the dynamics of changes. Additionally, GMFCS level and FMS score was reassessed based on two-plane clinical video recordings performed in all children. For the purposes of this study, data from assessments prior to, or at least three months after, injection of BoNT-A were analysed for a 5-year period. All assessors involved in the study were well trained and had many years of experience. Due to the retrospective nature of this study, including the analysis of medical records, no application was submitted to the Bioethics Committee for research and scientific use of the obtained results. The authors (MB, WP) are employees of the Neurorehabilitation Department and took part in the treatment of the assessed group in the past.

Statistical analysis

All calculations were performed using the R statistical package, version 3.6.0. The level of significance was $\alpha = 0.05$. The statistical significance of differences in the assessment of patients over the five-year follow-up period was assessed using the Friedman test. In the case of a significant Friedman test result, a post hoc analysis of these results was performed using the Wilcoxon test with the Bonferoni correction when multiple assessments were presented for the follow-up period.

Results

The study group consisted of 120 males and 80 females aged from 24 to 46 months. The mean age was 32.23 months (± 6.96). Before the treatment, six (3%) children were rated at GMFCS level I, 96 (48%) at GMFCS II, and 72 (36 %) and 26 (13%) at GMFCS levels III and IV respectively (Tab. 1).

During a five-year follow-up period, 71 (35.5%) children changed the level of their GMFCS, of which the majority, 67, improved, and four deteriorated (Tab. 2). The results were statistically significant ($p < 0.001$). The highest numbers of improvements were observed in children with GMFCS III and IV levels, with an improvement in 32 (50%) and nine (40%) respectively. Post hoc analysis revealed significant differences in the GMFCS between all assessments except 2–3, 3–4, 3–6 and 5–6. 54% of patients improved mobility measured with FMS at the 5 m distance (Tab. 3). The number of children rated 6 increased from three (1.5%) to 29 (14.5%), whereas the number of patients rated 1 decreased from 77 (38.5%) to seven (3.5%) (Tab. 1). In 48 of the patients (24%), the rating increased by 1, while in 22 (11%) and 32 (16%) patients the ratings increased by 3 and 4, respectively. Similar results were obtained for the 50 m distance (Tab. 3). Also, at this distance, there was a decrease in the number of children rated 1 from 79 (39.5%) to seven (3.5%) and an increase in those rated 6 from three (1.5%) to 27 (13.5%). 45 patients (22.5%) improved by one point, 24 (12%) by three points, and 32 (16%) by four points according to the FMS scale (Tab. 1). All changes on functional mobility between the first and last assessments were statistically significant ($p < 0.001$). For both distances, post hoc analysis showed significant differences in the assessment of the patient's functional mobility between all assessments except 3–4, 4–5, 4–6 and 5–6.

Discussion

Our long-term, retrospective study showed a positive effect of the applied treatment on the motor development of children with cerebral palsy. Gross motor skills and mobility have changed significantly over the course of five years of observation. The majority of children showed either stability

Table 1. Percentages (numbers) of patients reaching specified FMS score and GMFCS level before treatment and during annual follow-up assessments. P-values indicating a statistically significant result are in bold

	Score/ /level	Baseline	After one year	After two years	After three years	After four years	After five years	
FMS 5 metres	1	38.5% (N = 77)	19% (N = 38)	9% (N = 18)	4.5% (N = 9)	3.5% (N = 7)	3.5% (N = 7)	**(p < 0.001)**
	2	8.5% (N = 17)	18% (N = 36)	17.5% (N = 35)	15% (N = 30)	14.5% (N = 29)	13.5% (N = 27)	
	3	0% (N = 0)	0% (N = 0)	0% (N = 0)	0% (N = 0)	0% (N = 0)	0% (N = 0)	
	4	2.5% (N = 5)	4% (N = 8)	9% (N = 18)	13.5% (N = 27)	13% (N = 26)	13.5% (N = 27)	
	5	49% (N = 98)	57% (N = 114)	57.5% (N = 115)	55.5% (N = 111)	54% (N = 108)	55% (N = 110)	
	6	1.5% (N = 3)	2% (N = 4)	7% (N = 14)	11.5% (N = 23)	15% (N = 30)	14.5% (N = 29)	
FMS 50 metres	1	39.5% (N = 79)	19.5% (N = 39)	10% (N = 20)	5% (N = 10)	3.5% (N = 7)	3.5% (N = 7)	**(p < 0.001)**
	2	7.5% (N = 15)	17.5% (N = 35)	16.5% (N = 33)	14.5% (N = 29)	14.5% (N = 29)	13.5% (N = 27)	
	3	0% (N = 0)	0% (N = 0)	0% (N = 0)	0% (N = 0)	0% (N = 0)	0% (N = 0)	
	4	2.5% (N = 5)	4.5% (N = 9)	9% (N = 18)	13.5% (N = 27)	13.5% (N = 27)	13.5% (N = 27)	
	5	49% (N = 98)	56.5% (N = 113)	58% (N = 116)	56.5% (N = 113)	55% (N = 110)	56.5% (N = 113)	
	6	1.5% (N = 3)	2% (N = 4)	6.5% (N = 13)	10.5% (N = 21)	13.5% (N = 27)	13% (N = 26)	
GMFCS	I	3% (N = 6)	3% (N = 6)	7.5% (N = 15)	11.5% (N = 23)	14.5% (N = 29)	14% (N = 28)	**(p < 0.001)**
	II	48% (N = 96)	56% (N = 112)	56.5% (N = 113)	54.5% (N = 109)	54.5% (N = 109)	55% (N = 110)	
	III	36% (N = 72)	28% (N = 56)	24.5% (N = 49)	22.5% (N = 45)	20.5% (N = 41)	20.5% (N = 41)	
	IV	13% (N = 26)	13% (N = 26)	11.5% (N = 23)	11.5% (N = 23)	10.5% (N = 21)	10.5% (N = 21)	

FMS — Functional Mobility Scale; GMFCS — Gross Motor Function Classification System

Table 2. Change in GMFCS level over 5-years follow up period

GMFCS	Change	Percentage (number) of patients
	Improvement by one level	33.5% (N = 67)
	No change	64.5% (N = 129)
	Deterioration by one level	2% (N = 4)

GMFCS — Gross Motor Function Classification System

Table 3. Change in FMS 5 and FMS 50 score over 5-years follow up period

Distance	Change	Percentage (number) of patients
FMS 5 metres	Increase	54% (N = 108)
	No change	46% (N = 92)
FMS 50 metres	Increase	52.5% (N = 105)
	No change	47.5% (N = 95)

FMS — Functional Mobility Scale

of mobility or a change to less assistance required. The GMFCS classification level changed for 71 (35.5%) patients, of whom 67 (33.5%) improved by one degree, and four (2%) deteriorated, also by one degree. Children with GMFCS level III who had been able to walk on flat surfaces with the help of a hand-held device before starting the treatment were the largest group in which an improvement in motor skills was observed: 36 of them (50%) achieved the ability to walk without assistance. The second largest group in which a change in GMFCS level was observed were patients classified at level II. After five years, almost 25% of these patients were able to walk independently without any limitations. In the smallest group of 26 patients classified as level IV before the treatment, a change was observed in nine (41%).

Improvement from level IV to III means that a patient can walk independently using a hand-held support device. This significantly changes the quality of life because children and adolescents from level IV require physical assistance or a powered device support. They function for most of the day in a sitting position, exercising the ability to walk only for short distances with a walking frame and under supervision [5, 7].

The results for the rest of the patients reflected the motor development curves, remaining unchanged. Population-based studies indicate that GMFCS level may change over time for a certain percentage of children with cerebral palsy [23]. Palisano et al. [24] assessed the stability of levels in a group of 610 Canadian children and found that 73% of children remained at the same GMFCS level throughout the observation period. Similarly, Alriksson-Schmidt et al. [25] examined the stability of GMFCS levels in 736 children from Sweden and showed that 74% of the participants received the same GMFCS level at their first and their last registered follow-up. However, it is worth emphasising that these studies concerned the entire population of children with cerebral palsy. If we narrow the criteria, in the entire population studied by Alriksson-Schmidt et al. [25] there were 297 children with diplegia, of whom only 11% improved their motor skills (level change to a lower level) and 15% worsened (level change to a higher level). Another register-based study from the Stockholm region of Sweden on 768 children with at least two GMFCS ratings, showed that as many as 616 children (80%) were rated at the same

level in the first and the last assessments [26]. In studies of specific interventions, authors have demonstrated the stability of GMFCS after a single-event multilevel surgery [9], and hip reconstructive surgery [27]. Ailon et al. [28] assessed the long-term effects of selective dorsal rhizotomy. Ten of 44 (23%) assessed children improved by one level. These children were evenly distributed between GMFCS II, III, and IV. Dursun et al. [29] showed that at least 40% of patients with CP with a diverse clinical picture have the potential to improve GMFCS levels after using botulinum toxin in combination with an intensive rehabilitation programme. These results are the closest to those observed in our study. Longitudinal changes in the functional mobility of patients over a distance of 5 and 50 metres correspond to mobility at home and in a school environment. Based on the conducted analyses, a statistically significant ($p < 0.001$) difference of the results obtained for both distances, between the subsequent tests and the first and the last test were demonstrated. 54% of patients improved over the 5m distance, of whom 16% improved by as much as four levels. The group of children with the highest rating (6 — functioning completely independently on all surfaces without the use of any supporting device or assistance) increased from three (1.5%) during the first assessment to 29 (14.5%) during the last. The number of patients rated at 1, i.e. who were able to make only a few steps with the help of another person or using a walking frame, systematically decreased: from 77 (38.5%) during the first assessment to seven (3.5%) during the last. For the 50m distance, 52.5% of children improved, including 16% of patients who improved by four levels. Also, for this distance, a decrease in the number of patients graded 1 from 79 (39.5%) to seven (3.5%) was observed. 40 children changed level after the first year of treatment, regardless of age. This may suggest the role of applied therapy. For five years, an increase in the number of patients with the highest FMS score (6) from three (1.5%) up to 26 (13%) was observed. For functional reasons, an increase in mobility measured at 50 m is particularly important because it allows patients to move around in their environment, e.g. at school. Very few publications presenting a similar follow-up period can be found in the available literature. In a retrospective study by Harvey et al. [11], the authors observed changes in FMS in some patients over a five-year follow-up period after multilevel surgery and intensive postoperative rehabilitation. In 156 patients (GMFCS I–III), with an average age of 11 years and one month (6–19), the changes were most common in the group of patients classified at GMFCS level III. There was an increase in FMS 5m and FMS 50m in 51% and 34%, respectively, and a decrease in 16% and 15% of children. In the group of children with GMFCS I, II, an improvement in FMS 5m and FMS 50m was observed in 18% and 20%, and deterioration in 6% and 14% of children respectively.

Our study showed a significant, positive, effect of integrated treatment on gross motor function and mobility in patients with CP. Moreover, the study showed that children with CP can change GMFCS level over the course of treatment. Improvement was especially observed in patients with higher mobility impairment. An important factor responsible for the significant improvement in the parameters described in our study may be physiotherapy combined with BoNT injections and appropriately prescribed and tuned orthotics [30–32]. An individually planned therapy programme based on tasks aimed at achieving clearly set goals also seems to be crucial [33].

The main strength of this study is the homogenous group of young children with bilateral spastic cerebral palsy treated in one centre with a standardised intensive therapy programme. Other strengths include the experienced therapists who had extensive training in the application of the assessments used in the study, and detailed reassessment based on video recordings. Limitations of the study include the retrospective design and the lack of a control group, which could potentially introduce bias. Another limitation is the absence of a standard of home therapy.

Clinical implications/future directions

The results of this study encourage the use of integrated rehabilitation and BoNT-A injections to improve gross motor skills and mobility in children with spastic bilateral cerebral palsy. Future studies would benefit from incorporating validated, patient-centred outcome measures focused on life satisfaction and quality of life. It will also be important to assess whether improvements in mobility are sustained and persist over longer periods of time, i.e. until adolescence or adulthood.

Conflicts of interest/funding: *Marcin Bonikowski was an investigator in Allergan, Ipsen studies, and received research support from Ipsen, Allergan, and personal fees for consultancy and speaking from Ipsen and Allergan. Weronika Pyrzanowska was a sub-investigator in Ipsen studies, and received personal fees for speaking from Ipsen and Allergan.*

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Cognitive impairment in chronic migraine compared to pseudotumor cerebri

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ABSTRACT

Introduction. We aimed to define the prevalence of objective cognitive impairment in a group of chronic migraineurs, and to define how migraineurs with cognitive impairment differed from those without impairment, and in doing so to compare cognitive impairment in chronic migraine to another chronic headache-related disorder already associated with cognitive impairment (i.e. pseudotumor cerebri syndrome).

Objectives. Cognitive impairment in migraine, especially chronic migraine, has been too little studied. Only a few studies have been done, demonstrating that cognitive impairment exists in chronic migraineurs. It is not known how this compares to other headache-related conditions.

Material and methods. We administered a cognitive battery consisting of the National Adult Reading Test, Mini-Mental Status Examination, Digit Span, Boston Naming Test, Rey Auditory Verbal Learning Test, Trail Making Test, Controlled Oral Word Association, and Category Fluency. Cognitive impairment was defined as mild single-domain with one test score, and mild multi-domain with two scores more than two standard deviations below the mean for age-, gender-, and education-adjusted norms. The data from this study was compared to our previously published population of patients with pseudotumor cerebri syndrome.

Results. One hundred prospectively recruited patients with chronic migraine were enrolled. Fifty-seven patients had normal cognitive profiles. Forty-three patients demonstrated mild cognitive impairment, and more than half (n = 24) showed impairment in multiple cognitive domains. Migraineurs with multi-domain impairment had higher pain intensity, shorter duration of disease, were taking narcotics, had more impaired vision-related mental health scores, and worse social health scores. We found an association between objective cognitive impairment and subjective perception of impairment only when controlling for pain. We found no associations with depression and topiramate use. The mean composite cognitive Z score was no different in chronic migraineurs and patients with pseudotumor cerebri.

Conclusions and clinical implications. Most chronic migraineurs have normal cognitive profiles, but a large proportion of them do experience mild cognitive impairment, especially in multiple domains. The impairment seen in migraine is similar to that in pseudotumor cerebri syndrome, which has already been associated with mild cognitive impairment. Cognitively impaired migraineurs are different from non-impaired/less impaired migraineurs in several ways, which may be an important factor in influencing their migraine treatment.

Key words: migraine, cognition, impairment, pseudotumor cerebri syndrome

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Introduction

The experience of chronic pain has multiple biopsychosocial implications, only one of which is cognitive impairment. The negative effects of chronic pain on general cognition, learning and memory, attention, information processing, and executive function have been well studied [1]. Cognitive dysfunction has also been implicated in migraine. Migraineurs perceive cognitive dysfunction during all phases of the complex migraine cycle [2]. Multiple studies have confirmed the presence of reversible, objective cognitive impairment during a migraine (pain) attack, with negative effects on executive function, processing speed, working memory, visuospatial processing, attention, and/or verbal learning similar to the impairments seen in chronic (non-headache) pain [3, 4]. Worse cognitive performance on some tasks has been linked to increasing migraine frequency, so it is not surprising that chronic migraineurs, who have more attacks, have been found to have greater cognitive impairment compared to episodic migraineurs [5, 6].

Most patients with pseudotumor cerebri syndrome (PTCS) experience headache. The headache phenotype is varied, but most often it resembles migraine or probable migraine [7], Similar to patients with migraine, patients with PTCS report subjective cognitive dysfunction, and have demonstrated objective impairment in multiple cognitive domains including learning and memory, attention, processing speed, reaction time, visuospatial memory, and executive functioning [8–14]. Objective cognitive impairment has been found in our previous large sample of patients with PTCS to correlate with headache severity and headache-related disability but not with measures intrinsic to intracranial pressure (i.e. opening pressure, papilloedema grade, and visual function) [14].

This introduces the idea that the cognitive impairment seen in PTCS may be similar to impairment experienced in any other headache or chronic pain disorder including chronic migraine. This relationship has not previously been explored.

The aims of our study were therefore to: 1) define the prevalence of objective cognitive impairment in a group of chronic migraineurs and define associated factors; and 2) compare the cognitive profiles of patients with chronic migraine to our previously reported sample of patients with PTCS [14].

Clinical rationale for study

Cognitive impairment in migraine, especially chronic migraine, is understudied. Only a few studies have been done, demonstrating that cognitive impairment exists in chronic migraine [6, 15]. It is not known how cognitive impairment in chronic migraine compares to other headache-related conditions.

Material and methods

Patient selection

One hundred patients with chronic migraine were recruited prospectively during new or existing appointments at The Johns Hopkins Headache Centre (n = 96) or from elective inpatient admission to the hospital affiliated with the headache centre, for the treatment of chronic migraine (n = 4) between November 2014 and May 2015. Chronic migraine was diagnosed by the neurologists or nurse practitioner of the Headache Centre according to the criteria set out by the International Classification of Headache Disorders, 3rd edition, beta version (i.e. headache occurring on 15 or more days per month for more than three months, and which on at least eight days per month has the features of migraine) [16]. Sample size was determined by the number of consecutive patients meeting the inclusion criteria, who consented to cognitive testing during the recruitment period. Patients with mental health conditions under treatment, e.g. depression, were included and the depression was examined in our linear regression model for the following reasons.

Depression and mood have been shown to have no impact on objective cognitive impairment in migraine [6, 17]. Furthermore, mental health conditions are extremely common in chronic migraine. The incidence of depression in migraineurs ranges from c.9% to almost 50% especially in chronic migraineurs, and anxiety affects more than half of migraineurs [18]. Keeping in mind this high incidence, excluding these conditions would have drastically reduced our sample size, something which we felt would have compromised our study in the light of previously demonstrated null relationships. Study patients had no neurological disorders aside from chronic migraine.

Patients with the following conditions were excluded: episodic migraine (< 14 headache days per month), pseudotumor cerebri syndrome, previously diagnosed cognitive impairment, non-native English speakers, patients with language impairment, and patients with hearing impairment.

History

Patients were asked to self-report the following information: age, gender, education, headache characteristics, and duration of headache disorder. Medical records were reviewed by the author (OF) for history of sleep apnoea, and the current use of narcotics, acetazolamide, and topiramate. Our historical search was tailored to factors common between chronic migraine and pseudotumor cerebri management.

Examination

A single physician (OF) tested visual acuity using a retro illuminated Early Treatment Diabetic Retinopathy Study chart and corresponding LogMAR values were recorded. Colour vision was tested using Hardy-Rand-Rittler plates.

Participant-completed questionnaires

All participants were asked to complete self-administered questionnaires including: the Headache Impact Test (HIT-6), a six item scale to assess headache-related disability which yields a range from 36 (no disability) to 78, where

a score of 60 or more is considered severe headache-related disability [19]; the Numerical Rating Pain Scale (NRS) where 0 indicates the absence of pain and 10 represents the most intense pain possible; the STOP-Bang screening tool for sleep apnoea, in which the presence of three or more characteristics indicates a high risk for the condition [20]; the Prospective and Retrospective Memory Questionnaire (PRMQ) to assess for subjective memory failures in everyday situations, where scores range from 16 to a maximum impairment of 80, with the mean in normal adults being 39 [21]; the National Eye Institute Visual Function Questionnaire (VFQ 39) to assess vision-related disability [22]; and two scales measuring quality of life in neurological disorders, the Neuro-QOL v1.0 Ability to participate in social roles and activities-Short Form and the Neuro-QOL v1.0 Depression-Short Form [23]. The Ability to participate in social roles and activities-Short Form is an 8-item scale yielding raw scores in the range 8 to 40, with higher scores indicating better (desirable) self-reported social health. The Depression-Short Form is an 8-item scale yielding raw scores in the range 8 to 40 with higher scores indicating worse (undesirable) self-reported emotional health. For scoring, raw scores from both scales are converted to T-scores according to published tables [23]. All questionnaires were scored by a single physician (OF).

Data from the HIT-6, NRS, STOP-Bang, and PRMQ was missing in three patients, from the VFQ 39 in four patients, from the Ability to participate in social roles and activities-Short Form in 18 patients, and from the Depression-Short form in 17 patients. The PRMQ was self-completed by the patients prior to initiation of the objective cognitive testing.

Cognitive testing

All participants were assessed using a battery of cognitive tests administered in a private room of the clinic or hospital by the same physician (OF) and the same test instructions were used during all sessions. The tests included: 1) National Adult Reading Test in English (NART) to estimate premorbid intelligence [24]; 2) Mini Mental Status Examination (MMSE); 3) Digit Span repetition, forward to test attention and backward to test working memory and executive function [25]; 4) Boston Naming Test (BNT) for confrontational naming [26]; 5) Rey Auditory Verbal Learning Test (RAVLT), a test of verbal memory, learning and retrieval [27]; 6) Trail Making Test (TMT), part A for psychomotor speed and part B for executive function [28]; 7) Controlled Oral Word Association task for letters CFL (COWA) to assess phonemic fluency and executive function [29]; and 8) Category fluency (animals) to test semantic fluency and memory [30].

Raw test scores were converted to standardised Z scores based on published norms for healthy adults and were adjusted for age, gender, and education. Impairment was defined as a Z score below two standard deviations (SD). Mild cognitive impairment (MCI) single-domain was defined as an impaired score in any one cognitive domain (not restricted to the memory domain), compared to age-, gender-, and education-adjusted norms. MCI multi-domain was defined as impaired performance in two or more domains. We also determined a composite cognitive Z score from the mean of tests 2 to 8 inclusive [31]. The rationale for our definition of MCI was previously detailed in our earlier work defining cognitive impairment in pseudotumor cerebri syndrome [14].

Patients with pseudotumor cerebri syndrome

A very similar research protocol was used to recruit patients with PTCS at the Centre for Cerebrospinal Fluid Disorders at Johns Hopkins Hospital between August 2009 and May 2015. This protocol and results were published previously [14]. The data pertaining to the patients with chronic migraine was collected separately, but the two groups were compared for the purpose of this study.

Statistical analysis

To compare the characteristics between chronic migraineurs without objective cognitive impairment, with MCI single-domain and with MCI multi-domain, one-way ANOVA tests or Kruskal-Wallis tests were used for continuous variables, and chi-square tests or Fisher's exact tests were used for categorical variables. For post-hoc pairwise comparisons, Tukey's HSD tests and Dunn's tests were used for continuous variables and chi-square tests or Fisher's exact tests with Bonferroni correction were used for categorical variables. Simple linear regression models with robust standard error estimates were carried out respectively to evaluate the association between the composite cognitive Z score and the baseline factors that could predict cognitive dysfunction. A multiple linear regression model was generated using backward-stepwise selection with candidate predictors selected based on $p < 0.2$ from the simple linear regression models. We forced NRS to be included as a term in the multiple linear regression model to control for the impact of active severe headache on cognition.

To compare the characteristics between patients with chronic migraine and patients with PTCS, two sample t-tests or U Mann-Whitney test were used for continuous variables, and chi-square tests or Fisher's exact tests were used for categorical variables. Statistical analysis was performed using Stata 17.0 software (StataCorp LLC). A p value of 0.05 or less was considered statistically significant.

Institutional review board approval

This study was approved by the Johns Hopkins Medical Institutions' Institutional Review Board. All patients gave written informed consent for participation. This study was performed in accordance with the ethical principles stated in the Declaration of Helsinki. No formal prospective protocol was registered.

Results

Demographics

One hundred patients with chronic migraine were enrolled. Baseline characteristics of the sample, divided into groups without, with MCI single-domain, and with MCI multi-domain, are set out in Table 1. Chronic migraineurs with MCI multi-domain had fewer years of education than migraineurs without impairment, but otherwise there were no demographic differences.

The chronic migraine sample was compared to our previously published sample of 101 patients with pseudotumor cerebri syndrome [14]. Given the inherent risk factors common to most patients with pseudotumor cerebri syndrome (i.e. younger reproductive-age women with elevated body mass index), there were multiple baseline differences between the two groups. These are set out in Table 2.

Objective cognitive impairment in chronic migraine and clinical characteristics

All one hundred enrolled patients with chronic migraine completed the full cognitive battery. Nearly 60% (n = 57) of the patients had normal cognitive performance when compared to published age-, gender-, and education-adjusted norms. Forty-three per cent demonstrated MCI, specifically 19% (n = 19) in a single domain, and 24% (n = 24) in multiple domains (Tab. 1).

There were no differences in the self-perception of cognitive impairment, with PRMQ scores not differing between any of the groups. Interestingly, the mean PRMQ score in migraineurs with the highest level of impairment (MCI multi-domain) was 39.8, which is consistent with the mean in normal healthy adults (Tab. 1) [21].

Migraineurs with MCI multi-domain had higher headache intensity as measured by NRS at the time of testing compared to migraineurs with no MCI (p = 0.044), though all had severe headache-related disability as measured by the HIT-6 scale (p = 0.55). Migraineurs with MCI multi-domain had significantly shorter duration of disease compared to the patients without impairment (p = 0.004) (Tab. 1).

We investigated these counterintuitive results further using linear regression models, and we found a trend of decreasing headache intensity with longer duration of disease, presented in Figure 1. With each increasing year of disease, we saw a 0.07 drop in NRS (headache intensity) (95% CI:

Table 1. Demographics and clinical characteristics of chronic migraineurs with and without cognitive impairment

	N	Without objective cognitive impairment	With MCI single-domain	With MCI multi-domain	P- value
		N = 57	N = 19	N = 24	
Demographics					
Age (mean ± SD)		42.1 ± 11.6	40.1 ± 14.9	36.5 ± 13.8	0.21
Female (%)		51 (89.5%)	13 (68.4%)	21 (87.5%)	0.11
Education, yrs (mean ± SD)		16.1 ± 2.1*	15.2 ± 2.5	13.8 ± 1.7*	< 0.001
Clinical characteristics					
BMI kg/m^2 (mean ± SD)		28.6 ± 7.5	27.1 ± 4.8	28.6 ± 5.6	0.68
Sleep apnoea (% yes)		10 (17.5%)	1 (5.3%)	3 (12.5%)	0.45
STOP BANG (mean ± SD)	2:1	2.13 ± 1.54	1.89 ± 0.83	2.13 ± 1.60	0.82
Headache intensity, NRS (mean ± SD)	2:1:0	3.72 ± 2.79*	3.50 ± 3.19	5.46 ± 3.02*	0.036
HIT-6 Score (mean ± SD)	2:1:0	64.3 ± 6.0	63.8 ± 5.0	65.8 ± 9.0	0.55
Duration of disease, yrs (median, IQR)		21.0 (5.0, 30.0)*	6.0 (3.0, 27.0)	4.5 (1.0, 15.0)*	0.003
VA (mean ± SD)	1:0:0	0.02 ± 0.09	0.05 ± 0.12	0.02 ± 0.12	0.64
CV (median, IQR)	1:0:0	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)	10.0 (10.0, 10.0)	0.83
Total VFQ39 (median, IQR)	2:1:1	92.0 (83.7, 96.8)	95.2 (87.1, 96.2)	89.8 (73.7, 93.7)	0.095
VFQ Mental Health (median, IQR)	2:1:1	95 (85, 100)*	100 (85, 100)	90 (50, 95)*	0.036
VFQ Ocular Pain (mean ± SD)	2:1:1	75 (50, 100)	81.3 (62.5, 100)	75 (37.5, 87.5)	0.26
Depression SF T-Score (mean ± SD)	6:4:7	49.1 ± 7.0	46.6 ± 8.5	49.9 ± 7.9	0.41
Social Health SF T-Score (mean ± SD)	7:4:7	43.9 ± 6.2*	43.6 ± 8.2	39.4 ± 5.4*	0.050
PRMQ (mean ± SD)	2:1:0	37.0 ± 10.1	35.6 ± 13.3	39.8 ± 14.3	0.50
Narcotics use (% yes)		14 (24.6%)	0 (0%)*	8 (33.3%)*	0.010
Acetazolamide use (% yes)		1 (1.8%)	0 (0%)	1 (4.2%)	0.68
Topiramate use (% yes)		14 (24.6%)	7 (36.8%)	10 (41.7%)	0.11

BMI — body mass index; CV — colour vision; HIT-6 — Headache Impact Test 6 score; MCI — mild cognitive impairment; NRS — Numerical Rating Pain Scale; PRMQ — Prospective and Retrospective Memory Functioning Questionnaire score; SF — short form; VA — visual acuity; VFQ39 — Visual Function Questionnaire score
*Pairwise difference statistically significant for p < 0.05

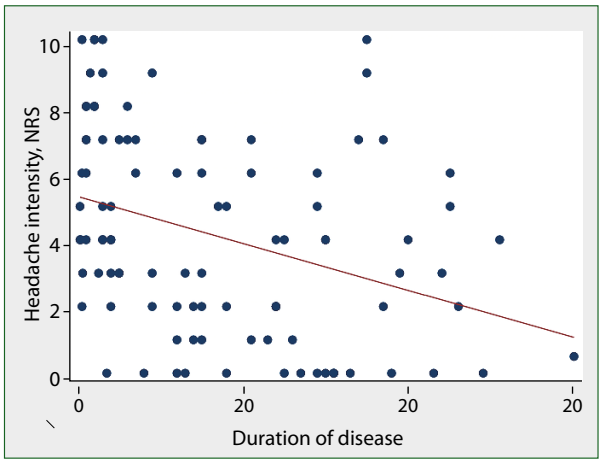

Figure 1. Relationship between duration of chronic migraine and headache severity at time of testing as measured by numerical rating scale (NRS)

–0.107, –0.034, p < 0.001). However, controlling for NRS and analysing the regression of composite Z score on duration, we found that duration of disease was still statistically significant (beta coefficient = 0.016, p < 0.001) meaning that factors other than improving pain intensity must be at play.

Eight of the 24 patients (33.3%) with MCI multi-domain were taking narcotics compared to none of the patients with MCI single-domain (p = 0.017). Topiramate use did not differ significantly among the groups (p = 0.11) (Tab. 1).

The average Depression-Short Form T-score for all three groups, i.e. no MCI, MCI single-domain, and MCI multi-domain, was 46.6–49.9 (p = 0.41), indicating that the self-reporting of depression symptoms was similar to that of the general adult population. Migraineurs with MCI multi-domain experienced the greatest vision-related mental health impairment, as indicated by the lowest median VFQ39 Mental Health subscale (p = 0.036). This was despite no statistical differences in the mean visual acuity, colour vision, or ocular pain among the three groups. Finally, migraineurs with MCI multi-domain had the lowest (worst) mean T-score when grading social health as measured by the Ability to participate in social roles and activities-Short Form (p = 0.050) (Tab. 1).

Simple regression models agreed with the above findings. We found a negative association between composite cognitive score and NRS (beta coefficient = –0.069, p = 0.022). We found positive associations between composite cognitive Z score and duration of education, duration of disease, vision-related quality of life, and social health (beta coefficients = 0.136, 0.018, 0.016, 0.036, p = < 0.001, p = < 0.001, p = < 0.001, p = 0.002, respectively). These relationships remained statistically significant in our multiple linear regression model controlling for NRS. There was no relationship between composite cognitive Z score and narcotics use. PRMQ was negatively associated with composite cognitive score only when controlling for NRS in the multiple linear regression model (see Supplementary materials).

Objective cognitive impairment in chronic migraine compared to pseudotumor cerebri

The 100 patients with chronic migraine were compared to our previously studied sample of 101 patients with pseudotumor cerebri syndrome. Overall, there was no difference in the mean composite cognitive Z score between these two separate populations. Patients with pseudotumor syndrome had worse performance on the BNT, RAVLT recognition portion, and Trails B compared to patients with chronic migraine. Chronic migraineurs performed worse on RAVLT i.e. total recall. Performances did not differ on the MMSE, digit span, retention, and delayed recall portions of RAVLT, Trials A, COWA and Category fluency between the two groups. This is set out in Table 2.

Discussion

This is one of few studies to have measured objective cognitive impairment in a group of chronic migraineurs, and this is the first study to compare cognition in chronic migraine to a different chronic headache-related condition (PTCS) and vice versa. Only patients with chronic migraine (> 15 headache days per month) were included, and fortunately the majority had normal cognitive profiles. When MCI occurred in chronic migraine, it tended to be in multiple domains. The patients with MCI multi-domain had higher levels of pain at the time of testing, the shortest duration of disease, and had the highest proportion of narcotics use compared to patients with MCI-single domain or patients with no impairment at all. Patients with MCI multi-domain had worse vision-related mental health and social health scores compared to the cognitively normal group of migraineurs. We found a relationship between subjectively reported cognitive impairment and objectively tested impairment, but only when controlling for headache intensity. We also found no relationship between cognitive impairment and self-reported symptoms of depression.

Our results agree with several other studies that have found cognitive impairment in chronic migraine. Ferreira et al. studied 30 chronic migraineurs compared to 30 controls without migraine, finding they had worse performance on tests of general cognitive ability (Montreal Cognitive Assessment), language (verbal fluency), visuospatial skills (clock drawing) and attention (Stroop test) [15]. Latysheva et al. studied 144 chronic migraineurs alongside 44 episodic migraineurs, finding significantly worse performance in multi-domain cognitive function as measured by the Digital Symbol Substitution Test, and verbal memory as measured by the RAVLT total recall. We also found our chronic migraineurs had the most impairment in the total recall subsection of the RAVLT, and notably more than the group with PTCS. Unlike our study, they found no correlation between self-reported subjective cognitive impairment and objective cognitive impairment [6]. It is possible that migraineurs in higher levels of pain perceive themselves as more cognitively impaired, because we only

Table 2. Comparison of chronic migraine cohort to pseudotumor cerebri cohort: demographics, clinical characteristics, and results of cognitive battery

	PTCS	Chronic migraine	P-value
	N = 101	N = 100	
Demographics			
Age (mean ± SD)	34.0 ± 8.9	40.4 ± 12.9	< 0.001
Female (% yes)	92 (91.1%)	85 (85.0%)	0.18
Education, yrs (mean ± SD)	14.3 ± 2.4	15.4 ± 2.3	0.001
Clinical characteristics			
BMI kg/m^2 (mean ± SD)	36.2 ± 8.4	28.4 ± 6.6	< 0.001
Sleep apnoea (% yes)	18 (17.8%)	14 (14.0%)	0.46
STOP BANG (mean ± SD)	2.47 ± 1.46	2.08 ± 1.44	0.064
Headache intensity, NRS (mean ± SD)	6.91 ± 2.39	4.11 ± 2.99	< 0.001
HIT-6 Score (mean ± SD)	61.5 ± 10.8	64.6 ± 6.7	0.018
Duration of disease, yrs (median, IQR)	1.00 (0.25, 2.00)	13.0 (3.0, 28.0)	< 0.001
VA (mean ± SD)	0.00 ± 0.14	0.03 ± 0.10	0.15
CV (median, IQR)	10.0 (9.75, 10.0)	10.0 (10.0, 10.0)	0.007
Total VFQ39 (median, IQR)	80.4 (71.0, 90.6)	92.0 (82.3, 96.1)	< 0.001
General Health VFQ (mean ± SD)	59.0 ± 18.5	62.2 ± 22.0	0.28
General Vision VFQ (median, IQR)	80.0 (70.0, 85.0)	85.0 (72.5, 95.0)	< 0.001
VFQ Ocular Pain (median, IQR)	62.5 (37.5, 75.0)	75.0 (50.0, 100.0)	< 0.001
VFQ Near Activities (median, IQR)	86.3 (70.8, 95.8)	91.7 (79.2, 100.0)	0.047
VFQ Distance Activities (median, IQR)	83.3 (66.7, 91.7)	95.8 (83.3, 100.0)	< 0.001
VFQ Social Functioning (median, IQR)	100.0 (83.3, 100.0)	100.0 (100.0, 100.0)	0.002
VFQ Mental Health (median, IQR)	75.0 (50.0, 90.0)	95.0 (82.5, 100.0)	< 0.001
VFQ Role Difficulties (median, IQR)	87.5 (62.5, 100.0)	100.0 (81.3, 100.0)	0.001
VFQ Driving (median, IQR)	83.3 (66.7, 91.7)	83.3 (66.7, 100.0)	0.54
VFQ Colour Vision (median, IQR)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	0.31
VFQ Peripheral Vision (median, IQR)	75.0 (50.0, 100.0)	100.0 (75.0, 100.0)	< 0.001
PRMQ (mean ± SD)	39.4 ± 13.6	37.4 ± 11.8	0.29
Narcotics use (% yes)	10 (9.9%)	22 (22.0%)	0.019
Acetazolamide use (% yes)	50 (49.5%)	2 (2.0%)	< 0.001
Topiramate use (% yes)	9 (8.9%)	31 (31.0%)	< 0.001
Cognitive testing			
Composite cognitive Z score (mean ± SD)	–0.25 ± 0.80	–0.24 ± 0.85	0.93
MMSE (mean ± SD)	–0.51 ± 1.46	–0.63 ± 1.26	0.52
Forward Digit Span (mean ± SD)	0.82 ± 1.38	1.15 ± 1.32	0.084
Backward Digit Span (mean ± SD)	–0.28 ± 1.09	–0.30 ± 1.09	0.91
BNT (median, IQR)	–0.68 (–2.82, 0.12)	–0.33 (–1.41, 0.64)	0.008
RAVLT — Total Recall (median, IQR)	–0.20 (–1.10, 0.60)	–0.80 (–1.50, 0.27)	0.015
RAVLT Retention (mean ± SD)	–0.31 ± 1.26	–0.38 ± 1.18	0.71
RAVLT Delayed Recall (mean ± SD)	–0.25 ± 1.24	–0.35 ± 1.23	0.56
RAVLT Recognition (median, IQR)	0.52 (0.21, 0.90)	0.21 (–0.30, 0.81)	0.032
Trails A (median, IQR)	0.28 (–0.24, 0.73)	0.48 (–0.30, 0.95)	0.19
Trails B (median, IQR)	–0.78 (–2.29, 0.22)	–0.28 (–1.32, 0.86)	0.007
COWA (mean ± SD)	–0.16 ± 1.17	–0.26 ± 1.07	0.55
Category Fluency — Animals (mean ± SD)	–0.23 ± 1.08	–0.29 ± 1.01	0.67

BMI — body mass index; BNT — Boston Naming Test; COWA — Controlled Oral Word Association task; CV — colour vision; HIT-6 — Headache Impact Test 6 score; MMSE — Mini Mental Status Examination; NRS — Numerical Rating Pain Scale; PRMQ — Prospective and Retrospective Memory Functioning Questionnaire score; PTCS — pseudotumor cerebri syndrome; RAVLT — Rey Auditory Verbal Learning Test; VA — visual acuity; VFQ39 — Visual Function Questionnaire score

found this relationship in a multiple linear regression model controlling for headache intensity.

We found that chronic migraineurs with higher levels of headache pain at the time of testing exhibited greater levels of cognitive impairment. The two studies mentioned above did not assess headache intensity, so a direct comparison cannot be made. However, cognitive impairment in episodic migraine has been related to attack severity in the past [4].

Earlier works found no relationship between mood, depression, and objective cognitive performance in migraineurs [6, 17] despite the high association of psychiatric comorbidities with migraine [18].

The relationship that we identified between cognitive impairment and shorter duration of disease is counterintuitive, but is not new as Rist and Kurth also demonstrated [32]. The effect of duration is especially curious because the migraine brain is different in many ways, including in structural and functional areas related to cognition (hippocampus, parahippocampal gyrus, and orbitofrontal cortex) [33]; migraineurs with a higher frequency of headaches have been found to have smaller hippocampal volumes compared to those with lower frequency headaches [34] and migraineurs to have a higher degree of white matter lesion burden over time [35].

One would think that the cumulative effect of recurrent attacks over time would cause greater cognitive impairment, and greater negative neuroplasticity, but in our study the longer duration of disorder had a positive outcome. We did find that migraineurs with longer duration of chronic migraine had lower pain scores, but duration of disease still had an independent positive correlation with cognition, after adjusting for pain scores. The reason for this is not known. It is possible that migraineurs with longer disease duration have learned better coping skills over the years, although the similar severe headache-related disability scores among cognitively normal as opposed to cognitively impaired groups would argue against this. It is also possible that migraineurs with longer duration of disease have had higher healthcare use over the years, and thus have had more frequent opportunities for intervention on modifiable risk factors for cognitive impairment (e.g. hypertension, a sedentary lifestyle, and smoking). We can only hypothesise this because these factors were not studied.

A very interesting and novel finding was our association of cognitive impairment with vision-related mental health, especially considering normal visual activity and colour vision. Migraineurs have already been reported to have significant reductions in visual quality of life, especially in chronic migraine, with similar impairment to neuro-ophthalmic disorders such as optic neuritis and myasthenia gravis [36]. This impairment is predominantly related to dry eye, but also to photophobia [37].

Finally, we demonstrated, for the first time, that chronic migraineurs have a similar level of cognitive impairment to patients with PTCS, a condition already known to cause cognitive impairment in young women otherwise not at risk for cognitive decline. Our previous study reported that cognitive impairment in PTCS was related to headache intensity and headache-related disability, which is similar to what we found in our latest study, though headache-related disability did not yield any associations for the chronic migraine group. Many patients with PTCS meet the diagnostic criteria for chronic migraine. Our results support the notion that the similar cognitive impairments seen in both conditions are, at least in part, migraine-related.

Our study has several limitations. Firstly, the patients were recruited from a tertiary referral headache centre, so it is very likely that our sample was more significantly disabled compared to chronic migraineurs seeking care from primary care or general neurology clinics. Secondly, we did not perform any follow up cognitive testing to investigate the reversibility of impairment after making positive changes (i.e. withdrawing opiates, controlling acute pain). A longitudinal study is needed to determine if these deficits are reversible with improvement in migraines, but is beyond the scope of our current study. Thirdly, our migraineurs differed in many baseline characteristics compared to our earlier sample of patients with PTCS.

Conclusions, clinical implications and future directions

While most chronic migraineurs have normal cognitive profiles, multi-domain mild cognitive impairment is indeed present in a large proportion of patients, supporting the notion that migraine is an "invisible" disability. This should be recognised when chronic migraineurs need extra help, for example at work or school. We have identified several modifiable factors comorbid with cognitive impairment in chronic migraineurs — pain intensity, narcotics use, worse vision-related quality of life, and worse social health. Improved acute headache relief, avoidance of narcotics, special measures to help with visual disability (e.g. lubricating drops for dry eye, and tinted lenses for photosensitivity), and functional restoration programmes aimed at helping migraineurs to be more active in the community may be particularly important in migraineurs who experience cognitive impairment. Improved headache prevention, e.g. with the initiation of onabotulinumtoxinA or monoclonal antibodies directed against calcitonin gene related peptide or its receptor, could be used to both reduce acute headache severity and reduce the need for analgesics such as narcotics [38, 39]. In our clinical experience, patients with chronic migraine often worry that they are developing a neurodegenerative disease when they experience migraine-related cognitive impairment.

Our study serves to validate their symptoms, and provides information on the scope of disability caused by migraine, as well as pointing to several, highly modifiable, risk factors for improvement.

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Steroid-responsive encephalopathy in autoimmune thyroiditis (SREAT) as a differential diagnosis of Creutzfeldt-Jakob Disease

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ABSTRACT

Introduction. Steroid-responsive encephalopathy in autoimmune thyroiditis (SREAT) is characterised by a wide range of neuropsychiatric symptoms and elevated thyroid antibodies. SREAT can mimic sporadic Creutzfeldt-Jakob Disease (sCJD) and distinguishing between both entities is important because SREAT responds to corticosteroids.

Material and methods. Data of patients reported to the National Reference Centre for the Surveillance of CJD in Göttingen, Germany between August 1994 and October 2008 was retrospectively reviewed. In the case and control groups, 49 patients had SREAT and 48 had sCJD with elevated thyroid antibodies.

Results. Antibodies against thyroid peroxidase were the most common antibodies in both SREAT (86%) and sCJD (88%), followed by antibodies against thyroglobulin (SREAT, 63.3%; sCJD, 39.6%; $p = 0.020$) and TSH-receptor-antibodies (SREAT, 14.3%; sCJD, 2.1%; $p = 0.059$).

Epileptic seizures were observed more frequently in the SREAT group (SREAT, 44.9%; sCJD, 12.5%; $p < 0.001$). Dementia (SREAT, 61.2%; sCJD, 100%; $p < 0.001$), ataxia (SREAT, 44.9%; sCJD, 89.6%; $p < 0.001$), visual impairment (SREAT, 22.4%; sCJD, 50%; $p = 0.005$), extrapyramidal disorder (SREAT, 32.7%; sCJD, 60.4%; $p = 0.006$), myoclonus (SREAT, 38.8%; sCJD, 81.3%; $p < 0.001$) and akinetic mutism (SREAT, 6.1%; sCJD, 37.5%; $p < 0.001$) were observed more frequently in sCJD.

Cerebrospinal fluid (CSF) pleocytosis was observed more frequently in SREAT patients (SREAT, 33.3%; sCJD, 6.4%; $p = 0.001$), as was a pathological increase in protein concentration (SREAT, 68.8%; sCJD, 36.2%; $p = 0.001$).

Conclusions. In a case of encephalopathy, the diagnosis of SREAT should also be considered in suspected cases of CJD so as to be able to start corticosteroid treatment quickly.

Key words: steroid-responsive encephalopathy (SREAT), Hashimoto encephalopathy (HE), sporadic Creutzfeldt-Jakob Disease (sCJD), diagnostic criteria

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Introduction

Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) is a rare disorder first described in 1966 by Brain et al. as Hashimoto's encephalopathy in a 48-year-old patient with a known Hashimoto's thyroiditis [1]. Since then, more than 300 cases have been published worldwide, mostly in the form of individual case reports [2]. The estimated overall prevalence is 2.1 per 100,000 subjects [2], although the disease may be underdiagnosed. The aetiology of SREAT has not yet been established. The previous models have so far been based on observations and speculative conclusions rather than experimental or histological evidence [3]. Despite different aetiology models, there is consistently a significant

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clinical improvement under glucocorticoid therapy. Due to the lack of diagnostic criteria, SREAT remains a diagnosis of exclusion. The diagnosis of SREAT is currently based on a broad range of unspecific neuropsychiatric symptoms, elevated thyroid antibodies, and a good response to immunosuppressive treatment [3]. On the other hand, a recent study argues that a "good response to corticosteroid treatment" should not be considered a necessary criterion, since such a response is only achieved in 32% of patients [4].

Elevated thyroid antibodies have also been described in Creutzfeldt-Jakob Disease (CJD), which belongs to a family of fatal neurodegenerative diseases collectively known as human transmissible spongiform encephalopathies [3, 5]. One of the most crucial differences between the two diseases is that SREAT responds to corticosteroids, whereas CJD leads to death within a few months. Distinguishing between SREAT and CJD is very important, since they can show some similarities, in particular in clinical symptoms and cerebrospinal fluid (CSF) findings, especially in the early phase of CJD [6, 7].

The present study aims to investigate the differences between SREAT and sporadic Creutzfeldt-Jakob Disease (sCJD), considering clinical appearance, laboratory findings, imaging, and the courses of both diseases.

Material and methods

The approval of the ethics committee for the study 'Investigation of the epidemiology, early diagnosis and molecular pathology of human spongiform encephalopathies' was obtained (application number 11/11/93, votes of the ethics committee of November 4, 1993, September 18, 1996, September 12, 2002). Since 1 June, 1993, all suspected cases of CJD have been reported nationwide across Germany to the National Reference Centre for CJD in Göttingen. In the present retrospective case-control study, cases with the diagnosis of SREAT were identified by reviewing the data of the patients reported to the National Reference Centre for CJD between August 1994 and September 2008. The diagnosis of SREAT was confirmed in all cases according to the following criteria [8]: unexplained, recurrent episodes with epileptic seizures, myoclonus, focal neurological deficits, or psychiatric disorders; increased thyroid antibodies; very good response to corticosteroids; and no evidence of metabolic, paraneoplastic, infectious or other causes. The control group consisted of confirmed and probable sCJD patients according to the 1998 criteria of the World Health Organisation (WHO) [9], and at least one elevated thyroid antibody was detected in all cases. Patients with unclear diagnoses and sCJD patients without elevated thyroid antibodies were excluded from the study. The descriptive statistical analysis of the data was carried out using Statistical Program System for Social Sciences (SPSS) version 21.0. The $\chi 2$ test statistic and the independent samples t-test were used for the group difference analysis. The medians, means, standard deviations, and percentages are reported for the case and control groups.

Results

A total of 97 individuals were included in the study. Of these, 49 were patients with a SREAT diagnosis forming the case group, and 48 were patients with a confirmed or probable sCJD diagnosis forming the control group. The median age of the SREAT and sCJD groups were 60 years (range 47 to 72.5) and 65.5 years (range 62 to 71.75), respectively ($p = 0.055$). Women were more frequently affected by both diseases than men (female: male; SREAT: 71%: 29%; CJD: 75%: 25%). The median disease duration for sCJD was six months. These results are comparable with data reported in the literature, highlighting that our control group was representative. The duration of SREAT could not be determined since patients usually improved clinically very quickly after the initiation of steroid therapy, and also the exact duration was not provided in patient records in many cases. A detailed overview of the cohort is set out in Table 1.

Thyroid function

Information on thyroid function was available for 48 SREAT and 43 sCJD patients. There was no difference between the two groups regarding thyroid dysfunction ($p = 0.152$). At the time when the neurological or psychiatric symptoms first appeared, the majority of the participants in both groups were euthyroid, while 31.2% of the SREAT and

Table 1. Distribution of case and control groups according to selected criteria

	Case group (SREAT) (n = 49)	Control group (confirmed/probable sCJD) (n = 48)	P-value
Age (years)	60 [47–72.5]	65.5 [62–71.75]	0.055[1]
Gender			0.691[2]
Women	35 (71)	36 (75)	
Men	14 (29)	12 (25)	
Duration of illness (months) Median [IQR]	could not be captured	6 [4–12]	

[1]U Mann-Whitney test; Median [IQR]
[2]Pearson's chi-square; n (%)

Table 2. Thyroid function

	Case group (SREAT) (n = 48)	Control group (confirmed/probable sCJD) (n = 43)	P-value
Euthyroid	29 (60.4)	28 (65.1)	0.152[1]
Hypothyroid	15 (31.2)	13 (30.2)	
Euthyroid, THRT	5 (10.4)	10 (23.3)	
Hypothyroid, subclinical	4 (8.3)	3 (7)	
Hypothyroid	4 (8.3)	0	
Hypothyroid, unclassifiable	2 (4.2)	0	
Hyperthyroid	4 (8.3)	2 (4.7)	

[1]Fisher-Freeman-Halton exact test; n (%)
THRT: Thyroid hormone replacement therapy

Table 3. Thyroid antibodies

	Case group (SREAT) (n = 49)	Control group (confirmed/probable sCJD) (n = 48)	P-value
TPO	42 (85.7)	42 (87.5)	0.796[1]
anti-Tg	31 (63.3)	19 (39.6)	**0.020**[1]
TR-Ab	7 (14.3)	1 (2.1)	0.059[2]
only TPO	17 (34.7)	28 (58.3)	**0.036**[3]
only anti-Tg	5 (10.2)	5 (10.4)	
only TR-Ab	0	1 (2.1)	
TPO+ anti-Tg	20 (40.8)	14 (29.2)	
TPO+ TR-Ab	1 (2)	0	
TPO+ anti-Tg+ TR-Ab	4 (8.2)	0	

[1]Pearson's chi-square; n (%)
[2]Fisher's exact test; n (%)
[3]Fisher-Freeman-Halton exact test; n (%)
anti-Tg — antibodies against thyroglobulin; TPO — antibodies against thyroid peroxidase; TR-Ab — TSH-receptor-antibodies

30.2% of the sCJD cases were hypothyroid. We note that five of the SREAT, and 10 of the sCJD, patients were in a clinically euthyroid condition due to being on thyroid hormone replacement therapy (THRT) at the time of the investigation. Hyperthyroidism was observed in four of the SREAT and two of the CJD cases. 22 of the SREAT and 11 of the sCJD patients were diagnosed with Hashimoto's thyroiditis (HT) (p = 0.692). Table 2 provides an overview of thyroid function.

An increase in at least one of the thyroid antibodies in the blood was the inclusion criterion for the present study. Antibodies against thyroid peroxidase (TPO) were the most common thyroid antibodies observed in both patient groups (SREAT 86%; sCJD 88%), followed by antibodies against thyroglobulin (anti-Tg) (SREAT: 63.3%; sCJD: 39.6%; p = 0.020) and TSH-receptor-antibodies (TRAb) (SREAT: 14.3%; sCJD: 2.1%; p = 0.059). While anti-TPO alone was commonly observed in sCJD (sCJD: 58.3%; SREAT: 34.7%), the combination of anti-TPO and anti-Tg was more common in SREAT (SREAT: 40.8%; sCJD: 29.2%, p = 0.036). A detailed overview of the thyroid antibodies is presented in Table 3.

Symptoms

Cognitive deficits were the most frequently observed initial clinical symptoms in both groups, followed by balance and coordination disorders and depressive symptoms. Epileptic seizures, headaches, and impaired consciousness as initial symptoms were observed more frequently in the SREAT group than in the sCJD group. In contrast, we observed visual impairment more frequently in sCJD cases. A detailed overview is presented in Table 4.

During the entire course of the diseases, significant differences were observed between the two groups in the occurrence of dementia, ataxia, myoclonus, akinetic mutism, and epileptic seizures. The symptoms are set out in Table 5 according to their frequency.

Findings in cerebrospinal fluid

Analysis of the CSF showed significantly more pleocytosis in SREAT patients (SREAT 33.3%) *vs.* sCJD 6.4%; p = 0.001). The comparison of the quantitative data (SREAT: n = 46; sCJD: n = 40) showed on average a slight pleocytosis

Table 4. Symptom frequencies at onset of disease

	Case group (SREAT) (n = 49)	Control group (confirmed/probable sCJD) (n = 48)	P-value
Visual impairment	0	5 (10.4)	**0.005**[1]
Hallucinations	1 (2)	0	
Myoclonus	0	1 (2.1)	
Seizures	5 (10.2)	0	
Balance and coordination disorders	8 (16.3)	14 (29.2)	
Cephalgia	3 (6.1)	0	
Depressive symptoms	8 (16.3)	14 (29.2)	
Cognitive deficits	13 (26.5)	17 (35.4)	
Disturbed state of consciousness	5 (10.2)	0	
Paresis	2 (4.1)	1 (2.1)	
Tremor	1 (2)	1 (2.1)	
Reduced/disturbed speech production	1 (2)	0	
Sensory disturbance	2 (4.1)	2 (4.2)	

[1]Fisher-Freeman-Halton exact test; n (%)

Table 5. Symptom frequencies during entire course of disease

	Case group (SREAT) (n = 49)	Control group (confirmed/probable sCJD) (n = 48)	P-value
Dementia	30 (61.2)	48 (100)	**< 0.001**[1]
Ataxia	22 (44.9)	43 (89.6)	**< 0.001**[2]
Visual impairment	11 (22.4)	24 (50)	**0.005**[2]
Pyramidal disorder	24 (49)	29 (60.4)	0.258[2]
Extrapyramidal disorder	16 (32.7)	29 (60.4)	**0.006**[2]
Myoclonus	19 (38.8)	39 (81.3)	**< 0.001**[2]
Akinetic mutism	3 (6.1)	18 (37.5)	**< 0.001**[2]
Epileptic seizures	22 (44.9)	6 (12.5)	**< 0.001**[2]
Hallucinations	17 (34.7)	16 (33.3)	0.888[2]

[1]Fisher's exact test; n (%)
[2]Pearson's chi-square; n (%)

(mean: 8.1/μL; median [IQR]: 2 [1–7]/μL) for the SREAT (p=0.009). Likewise, a pathological increase in the protein concentration in the CSF was observed significantly more in the SREAT cases (SREAT 68.8% *vs.* sCJD 36.2%; p = 0.001). The average total protein in the CSF was significantly increased in the SREAT collective (mean: 1,256 mg/L; median [IQR]: 569 [410–1,264] mg/L; p = 0.004) (SREAT: n = 43; sCJD: n = 38). Oligoclonal bands were found in only 7/39 SREAT and 4/42 CJD patients (Tab. 6).

Evaluation of the 14-3-3 protein showed a statistically significant detection of 14-3-3 in sCJD patients compared to SREAT patients (p < 0.001). 14-3-3 protein showed a sensitivity of 87.5% and a specificity of 70.4% regarding sCJD. Other CSF proteins such as tau protein, beta-amyloid (ßA), neuron-specific enolase (NSE), and S100 protein were observed as pathologically more frequently in sCJD cases. Statistically significant differences were observed between the two groups in all protein types, except for ßA (Tab. 7).

EEG

Only one SREAT patient had an EEG showing typical changes for sCJD, the periodic sharp-wave complexes, although it was no longer detectable at the second examination. The EEG examination showed a sensitivity of 46.8% and a specificity of 96% regarding sCJD.

Cranial Magnetic Resonance Imaging (cMRI)

Available cMRI recordings (in total 48 patients; 24 SREAT and 25 sCJD) were re-evaluated by a neuroradiologist. The cMRI examination regarding the signal hyperintensities

Table 6. Number of cells and protein concentration in CSF

	Case group (SREAT) (n = 48)	Control group (confirmed/probable sCJD) (n = 47)	P-value
Pleocytosis	16 (33.3)	3 (6.4)	**0.001**[1]
Total protein	33 (68.8)	17 (36.2)	**0.001**[1]

[1]Pearson's chi-square; n (%)

	Case group (SREAT)	Control group (confirmed/probable sCJD)	P-value
Pleocytosis (/μL)	2 [1–7]	1 [1–2]	**0.009**[1]
Total protein (mg/L)	569 [410–1264]	433 [329–600]	**0.004**[1]

[1]U Mann-Whitney test; Median [IQR]

Table 7. Liquor proteins

	Case group (SREAT) (n = 24)		Control group (confirmed/probable sCJD) (n = 25)		P-value
Negative	31 (68.9)		0		**< 0.001**[3]
Positive	11 (24.4)		42 (87.5)		
Positive → Negative	2 (4.4)		0		
Negative → Positive	0		6 (12.5)		
Infectious/Not evaluable	1 (2.2)		0		
	Case group (SREAT)		**Control group (confirmed/probable sCJD)**		**P-value**
	Total	Pathological	Total	Pathological	
Tau	24	3 (12.5)	36	35 (97.2)	**< 0.001**[1]
ßA	23	4 (17.4)	24	8 (33.3)	0.210[1]
NSE	16	2 (12.5)	22	20 (90.9)	**< 0.001**[1]
S100	8	2 (25)	9	9 (100)	**0.002**[2]

ßA — beta-amyloid; NSE — neuron-specific enolase; S100 — S100 protein; Tau — tau protein;
[1]Pearson's chi-square; n (%)
[2]Fisher's exact test; n (%)
[3]Fisher-Freeman-Halton exact test; n (%

of the basal ganglia was observed more frequently in sCJD with 84%, whereas this was only observed in about a third of the SREAT patients (p-value < 0.001). Cortical changes were observed in 84% of the sCJD and 50% of the SREAT patients. Hyperintensity in the frontal cortex was the most frequently observed change in both patient groups. On the other hand, hyperintensities on the frontal (p = 0.007), parietal (p = 0.010), and temporal cortex (p = 0.019) occurred significantly more in the sCJD cases. In contrast to the cerebral cortex, the hyperintensities in the white matter in the sense of leukoencephalopathy were observed almost identically in both groups (SREAT: 71%; sCJD: 72%). However, there were significant differences in white matter morphology. Areal changes were observed in SREAT cases. In contrast, the sCJD cases showed more scattered changes. Another non-specific change, atrophy, was observed more frequently in sCJD than in SREAT. However, the difference was not significant. MRI images with all T2, Flair, and DWI weightings were available from five SREAT patients and five sCJD patients. Cortical hyperintensities were detectable in all sCJD patients with DWI. In contrast, hyperintensities in white matter were detectable in all patients in both the sCJD and SREAT groups with flair and T2 weighting. Statistical analysis was not carried out due to the small numbers.

The study radiologist correctly classified the MRI images in 88% of the sCJD cases, but was only able to make the diagnosis of SREAT in 41.7% of the SREAT cases.

Discussion

To the best of our knowledge, this is the largest cohort of adult SREAT patients in the literature, which also compared the disease with sCJD in many ways and showed some differences between both diseases, which may help to distinguish SREAT from sCJD in early and in late stages. In our study, the median age of the SREAT and sCJD groups were 60 years

Table 8. MRI

	Case group (SREAT) (n = 24)	Control group (confirmed/probable sCJD) (n = 25)	P-value
Cortex			
Frontal	8 (33.3)	18 (72)	**0.007**[1]
Cing. Gyr.	8 (33.3)	14 (56)	0.111[1]
Parietal	2 (8.3)	10(40)	**0.010**[1]
Temporal	4 (16.7)	12 (48)	**0.019**[1]
Insula	5(20.8)	10 (40)	0.146[1]
Occipital	0	2 (8)	0.490[2]
Hippoc.	4 (16.7)	6 (24)	0.725[2]
White matter			
Scattered	7 (29.2)	16 (64)	**0.033**[3]
Areal	11 (45.8)	3 (12)	
Scattered and areal	3 (12.5)	2 (8)	
Basal ganglia	7 (29.2)	21 (84)	**< 0.001**[1]
Thalamus	1 (4.2)	7 (28)	**0.049**[2]
Cerebellum	3 (12.5)	10 (40)	**0.029**[1]
Atrophy			
Global	6 (25)	10 (40)	0.531[3]
Focal	2 (8.3)	3 (12)	
Correctly evaluated by radiologist	10 (41.7)	22 (88)	**0.001**[1]

[1]Pearson's chi-square; n (%)
[2]Fisher's exact test; n (%)
[3]Fisher-Freeman-Halton's test; n (%)

(range 47 to 72.5) and 65.5 years (range 62 to 71.75), respectively (p = 0.055), and women were more often affected by both diseases than men (female: male; SREAT: 71%/29%; sCJD: 75%/25%). These results agree with the literature. However, SREAT has been observed in younger patients (52 years) in the literature [10, 11]. The fact that the patients in our SREAT group consisted of suspected sCJD cases may explain this difference between our results and the literature.

Both hypothyroidism and hyperthyroidism can affect brain function [12]. However, the present study showed that the majority of patients in both groups were euthyroid, in line with the literature [3, 11, 13, 14]. The increased thyroid antibodies are currently a diagnostic criterion for SREAT, whereby HT is not necessarily — not even often — associated with SREAT [8]. Our study also showed no difference in the presence of HT between the two diseases. These results might indicate that SREAT and sCJD cannot be distinguished regarding the presence of autoimmune thyroiditis or thyroid dysfunction. This might further imply that SREAT is not a consequence of dysthyroidism. The role of antibodies in the pathogenesis of the disease is also not yet clear. Many authors have considered the antibodies to be innocent bystanders, whereas other researchers believe that the increase of autoantibody levels is proportional to the activity of the disease and that their level decreases after treatment with corticosteroids [3]. In line with the literature, anti-TPO was the most common antibody not only in SREAT but also in sCJD [13, 15, 16], while anti-TG is observed more commonly in SREAT patients. In clinical terms, it is noteworthy that the sole occurrence of anti-TPO for sCJD and the combination of anti-TPO and anti-TG rather speaks for SREAT. A high prevalence of antibodies in the entire population as well as in sCJD cases makes it difficult to use the antibodies as markers [5, 16, 17]. However, a conclusion based on incidence frequencies does not rule out a causal connection of thyroid antibodies in disease processes.

SREAT has a wide range of symptoms such as stroke-like episodes, with transient focal neurological deficits, with or without cognitive defects, and variably combined with epileptic seizures and deterioration of cognitive functions up to dementia with associated reduced vigilance [18]. We observed CJD-typical symptoms such as dementia, myoclonus, and ataxia to occur more frequently in the SREAT relative to the cases reported in the literature while epileptic seizures were less frequent. This might be because our initial cohort consisted of suspected CJD cases. The symptom frequency in our sCJD sample agrees with the literature [19, 20]. It might be suggested that the occurrence of epileptic seizures and the disturbed state of consciousness as initial symptoms speak in favour of SREAT, and visual disturbances as initial symptoms are distinguishing features of sCJD.

Although cognitive deficits are the most common initial symptom in both diseases, they are observed more frequently in sCJD than in SREAT. In the course of the diseases, the distinction between the two in terms of symptom frequency becomes clearer. An epileptic seizure is a characteristic of SREAT while symptoms such as dementia, ataxia, visual disturbances, extrapyramidal disorders, myoclonus, and akinetic mutism are decisive indicators of sCJD, even if the thyroid antibodies have been detected.

Inflammatory changes in the CSF might support the hypothesis that cerebral vasculitis causes SREAT. Detection of 14-3-3 protein in the CSF is a good marker for differentiating between the two diseases, as the protein is detected more frequently in sCJD. Due to the occurrence of false positive or false negative results, we recommend a follow-up CSF analysis after two weeks in case of doubt. In patients under the age of 60 with epileptic seizures, 14-3-3 protein and total protein in CSF should be examined. The absence of 14-3-3 protein, a pathologically increased protein concentration in the CSF, and pleocytosis are indicators for SREAT.

Regarding the EEG changes, the periodic sharp-wave complexes stand out as one of the characteristic features of sCJD, making it a reliable feature to distinguish from SREAT. In our sample, there was only a single SREAT patient with periodic sharp-wave complexes, where such changes disappeared for the same patient in a second EEG examination, indicating that it might have been a false positive. Thus, we recommend an EEG follow-up for cases with an unclear diagnosis.

Neuroimaging has been shown in the literature to provide markers for SREAT and sCJD. SREAT has been described as correlating with changes in cMRI and biopsy evidence of vasculitis [21]. DWI was also shown to be more effective in capturing the characteristics of the disease than FLAIR weighting for displaying cortical hyperintensities [22–24]. Supporting literature, our observations of symmetrical signal elevations of the basal ganglia in the cMRI, and hyperintensities in the frontal, parietal, and temporal cortex being higher in sCJD cases, all highlight that these changes can be used to differentiate sCJD from SREAT. On the other hand, cMRI changes in the white matter in SREAT cases were areal, while sCJD cases showed more scattered changes. This finding might indicate a vascular genesis of SREAT and can be used to differentiate SREAT from sCJD. Further confirming the literature, we observed that DWI was better than FLAIR weighting for displaying cortical hyperintensities, especially in the sCJD group, while still being observable in the SREAT group. Our results further highlighted the reverse to be the case for the hyperintensities in the white matter in the sense of leukoencephalopathy, as FLAIR and T2 weighting provided a better representation than DWI for both groups. This result demonstrates the proper use case for these three imaging modalities in cortical grey matter as well as white matter tissue. However, it should not be forgotten that only five patients with the three weightings were examined in both groups. The differentiation between the two diseases based on the cMRI images was largely possible because the study radiologist was able to correctly classify the cMRI images in 88% of the CJD cases, whereas he was only able to correctly diagnose SREAT in 41.7% of cases.

In summary, our results show that SREAT patients are younger than sCJD patients, and the combination of anti-TPO and anti-Tg is more frequently observed in SREAT patients. While headaches and disturbances of consciousness were more common as initial clinical symptoms in SREAT, epileptic seizures were observed both as initial symptoms and during the course of the disease. Pleocytosis and pathological elevation of protein concentration in CSF were common features in SREAT patients. Areal white matter changes were observed in the cMRI of SREAT, in contrast to more scattered white matter changes in sCJD.

A clinical picture of relapsing encephalopathy caused by stroke-like episodes, seizures, myoclonus, and neuropsychiatric disorders, especially in a young patient, should warrant an examination for SREAT. Since most of the patients with SREAT are euthyroid, thyroid antibodies should be systematically tested in all patients with unexplained encephalopathy. Early diagnosis of SREAT and rapid initiation of corticosteroid therapy can often lead to seizure control when anti-epileptic drugs are ineffective [15]. Plasma exchange has also been described in the literature for the treatment of SREAT when steroids are ineffective in the short term or when patients cannot tolerate the side effects of steroids [25]. Because a good corticosteroid response was a necessary criterion for SREAT in our study, all SREAT patients had a good corticosteroid response, which was not the case in sCJD cases. Therefore, corticosteroid therapy is worth trying if SREAT is suspected as the differential diagnosis of CJD.

Although to the best of our knowledge the current study presents the largest cohort examination on SREAT vs sCJD, the rarity of SREAT imposed an inherent limitation on the sample size of our study. Retrospective data collection, variable times for follow-up examinations, and patient data coming from different laboratories, were all further limitations, which calls for a prospective study to further validate the results presented here and elsewhere in the literature.

Determining the pathogenesis of SREAT requires detailed experimental and immunopathological studies to demonstrate the relevance of the thyroid antibodies.

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RESEARCH PAPER

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Prevalence of polyneuropathies among systemic sclerosis patients and impact on health-related quality of life

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ABSTRACT

Introduction. Systemic sclerosis (SSc) is a chronic rheumatic disease that affects multiple organ systems, including the peripheral nervous system. However, studies into the involvement of polyneuropathies (PNP) have shown inconsistent results. The aim of this study was to determine the prevalence of small (SFN) and large (LFN) fibre neuropathy among SSc patients and the impact on health-related quality of life (HRQoL).

Material and methods. The study enrolled 67 patients with diagnosed SSc. The severity of neuropathic symptoms was evaluated using shortened and revised total neuropathy scoring criteria. Nerve conduction studies were used for LFN, and quantitative sensory testing was used to evaluate SFN. Neuropathic pain was evaluated using a Douleur Neuropathique en 4 questionnaire, and the severity of anxiety symptoms was assessed using a Generalised Anxiety Disorder-7 scale. The Health Assessment Questionnaire-Disability Index was used to assess HRQoL. Previous data on antinuclear autoantibodies (ANA) test results was obtained. Statistical analysis was performed using SPSS software.

Results. LFN was diagnosed in 47.8% (n = 32/67) and SFN in 40.3% (n = 27/67) of the subjects. ANA positivity was not associated with the presence of LFN/SFN. The severity of neuropathic pain had a significant correlation with anxiety symptoms ($r = 0.61$, $p < 0.001$), the severity of neuropathy symptoms ($r = 0.51$, $p < 0.001$) and HRQoL ($r = 0.45$, $p < 0.001$). The severity of neuropathy symptoms correlated with HRQoL ($r = 0.39$, $p = 0.001$).

Conclusions. We demonstrated that PNP are found in almost all SSc patients. Also, SFN is as common as LFN. Additionally, we found that the severity of neuropathy symptoms and neuropathic pain are both associated with a worse HRQoL.

Key words: systemic sclerosis, large fibre neuropathy, small fibre neuropathy, neuropathic pain, anxiety, health-related quality of life

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Introduction

Systemic sclerosis (SSc), also known as scleroderma, is a rare chronic rheumatic disease characterised by immune activation, widespread vascular damage, and progressive fibrosis [1, 2]. The hallmark of this disease is thickening and hardening of the skin, but other organ systems are also commonly affected, leading to considerable morbidity and mortality. Many patients complain about one or more symptoms of gastroesophageal reflux disease, but more severe upper and lower gastrointestinal tract involvement can be associated with malnutrition. Restricted joint mobility, arthritis, renal failure, heart and pulmonary complications are the main causes of morbidity and mortality in the course of SSc [2]. Additionally, the peripheral nervous system can also be affected [3]. Neurological involvement includes both

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compression (e.g. trigeminal neuropathy, carpal tunnel syndrome, ulnar nerve entrapment) and non-compression (e.g. sensorimotor neuropathy, sensory ataxic neuropathy, multiple mononeuropathies) neuropathies [4].

Neuropathy was previously thought to be a less common SSc finding [5]. However, recent studies have shown that neurological involvement is fairly common. The prevalence of peripheral neuropathy in SSc ranges from 17% [6] to 40% [7], with a pooled prevalence close to 30% [3, 4]. Probably due to the rarity of the disease, the methods used in these studies and the characteristics of the study groups, the results differ and the extent of peripheral nervous system involvement remains unclear. Moreover, there are only a few studies on polyneuropathy that have differentiated small (SFN) from large fibres (LFN). To the best of our knowledge, no nationwide study of peripheral nervous system disorders among SSc patients has previously been carried out in the Baltic countries.

As a chronic systemic disease, SSc affects patients' health-related quality of life (HRQoL), with a number of problems associated with decreased functional status and increased disability [8, 9]. It is unclear whether HRQoL has a direct association with SSc or nervous system involvement, as other factors such as anxiety and neuropathic pain can worsen patients' HRQoL.

The aim of this study was to define the prevalence of SFN and LFN among patients with SSc, based on a population-wide cohort in Latvia, and to identify factors associated with LFN or SFN development. Additionally, we aimed to identify the effects of LFN and SFN, the severity of neuropathic pain, and anxiety symptoms related to HRQoL.

Material and methods

Materials

This study was performed on Latvian patients diagnosed with SSc in accordance with the American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) criteria [10] who were diagnosed or consulted in the period from 1 January 2016 to 30 September 2021 at either of Latvia's adult university hospitals: Riga Eastern Clinical University Hospital and Pauls Stradins Clinical University Hospital. In total, 109 SSc patients were assessed for participation and 67 (54 women and 13 men, age range 23 to 83 years) were enrolled in the study.

Methods

According to the ACR/EULAR criteria [10], patients were assessed for skin thickening on the fingers, fingertip lesions, telangiectasia, abnormal nailfold capillaries, interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), Raynaud phenomenon (RP), and SSc-related autoantibodies. Disease duration was determined based on the occurrence of the first non-Raynaud's phenomenon symptom. The general severity of cutaneous involvement was assessed using the modified Rodnan skin score (mRSS) [11]. Additionally, all subjects were asked regarding specific therapy use (e.g. cyclophosphamides) and common health conditions (e.g. diabetes, thyroid diseases) that are known to be causative for peripheral neuropathy. Previous data on antinuclear autoantibody (ANA) test results was obtained. ANA tests were performed on peripheral blood serum by indirect immunofluorescence using HEp-2 ANA indirect fluorescent antibody (IFA) assays [12].

Enrolled subjects underwent a uniform evaluation of the peripheral nervous system. Firstly, patients were screened using the shortened and revised total neuropathy scoring criteria (srTNS) [13], which consists of three symptom extension components (numbness, tingling, and neuropathic pain) and two objective testing components (tendon reflex and vibration sensibility). Next, the patients were examined using nerve conduction studies (NSC) by a certified neurophysiology expert. Nerve conduction studies were performed on both motor and sensory conduction according to the polyneuropathic examination protocol. Each patient underwent bilateral upper extremities NCS (motor and sensory components of ulnar and median nerves) and bilateral lower extremities NCS (motor component of peroneal and tibial nerves and sensory components of a sural nerve) for nerve conduction latency, amplitude, and velocity. Those subjects who had abnormal NCS results according to the normal values used in Latvian clinical practice [14, 15] in more than one attribute in two separate nerves were diagnosed as having large fibre polyneuropathy. Quantitative sensory testing (QST) was performed in the subjects with normal NSC results in order to evaluate small fibre function for possible abnormalities [16]. Thermal (warm, cold, painful warm/painful cold) sensations were checked. Stimuli were applied to the thenar region of the hands and the dorsal surface of the feet. QST results were compared to normative data, and those subjects who had abnormal values in two separate extremities were diagnosed as having small fibre polyneuropathy.

Additionally, all enrolled subjects completed the Latvian version of the Douleur Neuropathique en 4 (DN4) [17] questionnaire to assess neuropathic pain, the Generalised Anxiety Disorder-7 (GAD-7) [18] scale to assess anxiety symptoms, and the Health Assessment Questionnaire-Disability Index (HAQ-DI) [19] to assess HRQoL. Those patients scoring four or more points on the DN4 questionnaire were defined as having neuropathic pain. More than four points on the GAD-7 questionnaire indicates an increased risk of generalised anxiety. The eight scores of the eight sections of the HAQ-DI were added together and divided by eight to provide the functional disability index.

Statistical analysis

Statistical analysis was performed using SPSS 27.0 software (SPSS Inc., Chicago, IL, USA). Data normality was assessed using histograms and the Kolmogorov-Smirnov test.

Table 1. Clinical characteristics of SSc subjects with and without peripheral neuropathy

Characteristic	No neuropathy (n = 8; 11.9%)	Large fibre neuropathy (n = 32; 47.8%)	Small fibre neuropathy (n = 27; 40.3%)
Median age	62.5 (IQR, 9.25)	66.5 (IQR, 10.50)	57.0 (IQR, 17.50)
Female sex	8 (100%)	24 (75%)	22 (81.5%)
Male sex	0	8 (25%)	5 (18.5%)
Age at scleroderma onset	46.5 ± 15.4	51.0 ± 13.8	40.7 ± 17.4
Median duration of SSc	15.0 (IQR, 13.50)	19.5 (IQR, 17.25)	12.0 (IQR, 13.50)
Scleroderma subtype			
Limited	5 (62.5%)	23 (71.9%)	22 (81.5%)
Diffuse	3 (37.5%)	9 (28.1%)	5 (18.5%)
Median Rodnan score	11.0 (IQR, 14.50)	6.0 (IQR, 10.0)	4.0 (IQR, 10.0)
Antinuclear antibodies	7 (87.5%)	26 (81.3%)	21 (77.8%)
Anti-centromere		*Data not shown*	
Anti-SCL70		*Data not shown*	
Speckled		*Data not shown*	
Nucleolar		*Data not shown*	
Homogenous		*Data not shown*	
Median TNS	2.0 (IQR, 3.50)	7.0 (IQR, 5.25)	0 (IQR, 3.50)
Median DN4 score	3.0 (IQR, 3.50)	4.0 (IQR, 6.0)	3.0 (IQR, 7.5)
Median GAD-7 score	8.0 (IQR, 13.0)	4.5 (IQR, 10.25)	5.0 (IQR, 7.50)
Median HAQDI score	0.81 (IQR, 1.47)	1.63 (IQR, 1.72)	0.63 (IQR, 1.56)
Without risk factors	5 (62.5%)	18 (56.3%)	20 (74.1%)
With risk factors	3 (37.5%)	14 (43.8%)	7 (25.9%)
Treatment with cyclophosphamide	1 (12.5%)	9 (28.1%)	6 (22.2%)
Treatment with chemotherapy	2 (25%)	2 (25%)	0
Diabetes mellitus	0	0	1 (3.7%)
Thyroid diseases	0	3 (9.4%)	2 (3.7%)
Chronic renal diseases	0	4 (12.5%)	3 (3.7%)

TNS — total neuropathy score; DN4 — douleur neuropathique 4; GAD-7 — general anxiety disorder-7; HAQDI — Health Assessment Questionnaire Disability Index

For comparison between groups, the Kruskal-Wallis H test, Spearman's rank-order correlation and Fisher's exact tests were used. P values < 0.05 were considered significant.

Ethical approval

This study was approved by the Ethics Committee of Riga Stradiņš University [Nr. 22-2/481/2021]. All subjects were informed about the rationale and goals of the study, signed an informed consent form, and gave their permission for anonymised publication of their clinical information.

Results

The median age of the study group was 64 years (IQR, 12.0). Out of 67 enrolled patients, 54 (80.6%) were female and 13 (19.4%) were male. The median age at the onset of SSc was 47 (IQR, 19.5) years and the median duration of disease was 16 (IQR, 15.0) years. 52.2% of subjects had the limited subtype of SSc (n = 35/67), while 47.8% had the diffuse type (n = 32/67). A description of the SSc groups divided by the presence of polyneuropathy and its type is set out in Table 1.

Based on the NCS evaluation, LFN was identified in almost half of the SSc individuals (47.8%, n = 32/67). Furthermore, the majority of individuals who did not have LFN showed signs of SFN, evaluated by QST (40.3%, n = 27/67); only 11.9% (n = = 8/67) of the subjects did not fulfil any criterion for SFN or LFN. A comparison of the clinical features, as well as neuropathy risk factors between these three groups, is set out in Table 1.

To identify the aetiology of the peripheral nervous system involvement in SSc, we analysed the prevalence of neuropathy risk factors among the SSc patients. Neuropathy risk factors as

a possible secondary cause were defined in 35.8% of subjects (n = 21/59). These included treatment with cyclophosphamides, chemotherapy, diagnosed diabetes mellitus, thyroid disorders, and chronic renal disease [20–22]. However, the same risk factors were present in 37.5% (n = 3/8) of individuals without neuropathy and there was no difference in risk factor prevalence among the subjects with LFN, with SFN, or without neuropathy ($p > 0.05$). Because we understood that the small number of SSc patients without polyneuropathy affected the statistical power of the given result, we further analysed other factors that could explain the presence of LFN or SFN.

There were no associations between the presence of LFN or SFN and sex ($p = 0.32$), age ($p = 0.63$), disease duration ($p = 0.64$), severity of cutaneous involvement ($p = 0.19$), subtype of SSc ($p = 0.73$), or ANA positivity ($p = 0.91$), nor with any specific subtype of ANA ($p = 0.93$) (ANA subtype data not shown).

LFN patients had higher TNS scores [median TNS = 7.0 (IQR, 5.25)] than SFN patients [median TNS = 0 (IQR, 3.5)] and also higher than subjects without neuropathy [median TNS = 2.0 (IQR, 3.5)], but the difference was not statistically significant ($p = 0.37$).

There were no significant differences between LFN/SFN and the severity of neuropathic pain ($p = 0.46$), anxiety symptoms ($p = 0.75$), or HRQoL ($p = 0.68$). However, the severity of neuropathic pain had a significant correlation with anxiety symptoms ($r = 0.61$, $p < 0.001$), the severity of neuropathy symptoms ($r = 0.51$, $p < 0.001$), and HRQoL ($r = 0.45$, $p < 0.001$). Additionally, the severity of neuropathy symptoms had a moderately strong correlation with HRQoL ($r = 0.39$, $p = 0.001$).

Discussion

In this study, we performed a detailed evaluation of large and small fibre polyneuropathy in a large cohort of SSc patients from Latvia. By systematically analysing both LFN and SFN, we identified that the prevalence of peripheral neuropathy in SSc patients is very high, affecting ~90% of patients. Even though some subjects had possible secondary causes (risk factors) for their neuropathy, we did not find any significant differences between individuals with polyneuropathy and those without, although the second group of patients was not big enough to make a firm conclusion of neuropathy to be developed independently of known risk factors.

Additionally, we found that neuropathic pain is common among SSc patients and that neuropathic pain has a significant correlation with the total neuropathic score and the severity of anxiety symptoms. While the presence of LFN or SFN did not reach statistical significance, neuropathy-related symptoms (both neuropathic pain and severity assessed by the TNS) affected SSc patients' HRQoL.

Our study revealed a higher prevalence of polyneuropathy in SSc than has been found in other studies, but only a few studies have performed as detailed and targeted an evaluation of the peripheral nervous system as we have. Furthermore, the materials and methods used in those studies provide a large range of results. A recent systematic review of 113 studies [4] showed a pooled prevalence of neuropathy involvement in 27.37% of cases, including 26% (n = 556/2,143) with SFN and 10.8% (n = 231/2,143) with LFN when neuropathies were assessed based on small and large fibres.

However, the titles and abstracts were not selected according to strict criteria regarding evaluated neuropathies, including all works where peripheral neuropathy was reported by symptoms and clinical examination, nerve conduction studies or other detection tools. LFN was observed in many studies on isolated or multiple mononeuropathies [23–30], and confirmatory diagnostic tests differed depending on the design of the study. Some studies performed electrophysiological examinations [27, 28, 31], while others used imaging techniques [23, 26, 32], biopsy [26, 30] or other methods. Only a few studies showed similar results to our study. One study on the role of ultrasound imaging in the evaluation of peripheral nerves in SSc [32] showed sensory disturbances revealed by clinical examination in 40% (n = 10/25) of subjects, but the imaging modalities used (ultrasound, computer tomography, magnetic resonance) revealed abnormalities in 7/10 patients. However, a peripheral nervous system examination was performed only on median and ulnar nerves, observing compression neuropathies. We believe that the high prevalence of LFN can be explained by the fact that we were working with a relatively large study group and that all subjects were evaluated using both clinical symptoms and electrophysiological methods, where motor and sensory components were studied on several nerves of each extremity.

Our study suggests that small fibre abnormalities are common in SSc, and that neurological events appear in almost all SSc patients, with the predominant involvement of small fibres, although there are limitations on assessing small fibre function. As mentioned above, in a recent systematic review of peripheral neuropathy in SSc [4], the prevalence of SFN was more than double that of LFN. In our study, SFN was less prevalent than LFN; even so, of those subjects who did not show abnormalities by NCS, only eight had normal QST results. The high prevalence of SFN may be associated with skin changes due to SSc, but there was not a significant difference between the severity of cutaneous involvement and the presence of SFN.

The diagnosis of SFN can be challenging because the diagnostic criteria for SFN are not yet fully established. This lack of standardised diagnostic criteria for SFN may indeed have implications on our research in terms of the definition of SFN, since our study subjects were defined to have SFN solely based on their QST results [33, 34]. We did not detect specific gene mutations for transthyretin familial amyloid polyneuropathy as a rarer underlying cause of SFN and LFN [35, 36]. Neither were autoantibodies in SFN tested, for example antisulfatide and anti-plexin antibodies, which could be specific for small fibre neuropathies and may be a key pointer towards explaining the high frequency of small fibre polyneuropathies in our study [37].

We speculate that the autoimmune nature of polyneuropathy could justify immunomodulatory therapy use such as plasma exchange for those SSc patients who show neuropathic symptoms [38, 39]. Thus more specific examinations of possible autoantibodies should be performed as the next stage of research.

Our study assessed neuropathic pain in SSc patients and showed that LFN and SFN subjects have a tendency towards higher DN4 scores, with no direct association with the severity of neuropathic pain, but a significant association between neuropathic pain and the severity of neuropathy symptoms where both affect SSc patients' HRQoL. Neuropathic pain occurs in many rheumatic diseases and neuropathic pain is thought to be more prevalent in these patients than in the general population [40]. A Danish nationwide cross-sectional registry survey (DANBIO) on pain and pain mechanisms in patients with inflammatory arthritis showed neuropathic pain in 20% of rheumatic arthritis patients, 28% of psoriatic arthritis patients, and 21% of spondylarthritis patients [41]. The prevalence and severity of neuropathic pain in SSc patients is not well-studied and is not yet established. One cross-sectional study on neuropathic pain in SSc patients showed that neuropathic pain was significantly higher in SSc patients compared to control subjects (56.2% *vs.* 13.3%) [42]. In our study, we assessed the severity of neuropathic pain by the DQ4 in all study participants. Only 18 subjects (26.87%) scored zero points on the DQ4. We found neuropathic pain to have an important impact on SSc patients' HRQoL, but it is unclear whether neuropathic pain affects HRQoL independently of, or in relation with, a higher severity of neuropathy symptoms. Moreover, our study supports the concept of neuropathic pain being associated with the severity of anxiety symptoms, showing significance between the DN4 and GAD-7 scores [43].

The main limitation of this study was the size of our study group. Although we enrolled 67 out of 109 SSc patients who were examined at Latvia's university hospitals over the course of 5.75 years, we believe that more statistical significance would be found with a larger study group. The small number of SSc patients is explained by the rarity of the disease and Latvia's small population. Another limitation was the small fibre function being assessed by QST only. To clarify the involvement of SFN, a skin punch biopsy should be performed to measure epidermal nerve fibre density (ENFD), since the results of such a biopsy can provide more objective diagnostic data for defining SFN.

Conclusions

We demonstrated an unexpectedly high prevalence of polyneuropathy in Latvian SSc patients, showing that the peripheral nervous system is affected in almost all patients. Moreover, we found SFN to be as common as LFN. Another important finding in our study is that the severity of neuropathy symptoms and neuropathic pain were both associated with a higher health-related disability index, indicating worse HRQoL. The presence of polyneuropathy was not associated with known risk factors. Therefore it is necessary to seek other reasons for the presence of SFN and LFN in SSc patients, possibly associated with specific antibodies.

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Olfactory dysfunction in patients with Wilson's Disease

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ABSTRACT

Introduction. Many neurodegenerative disorders are associated with olfactory dysfunction (OD), but little is known about OD in Wilson's Disease (WD). We evaluated olfactory function in patients with WD.

Material and methods. OD was examined in 68 patients with WD and 70 sex- and age-matched healthy controls using subjective testing with 'Sniffin Sticks'. Threshold discrimination identification (TDI) score and its three components (odour detection threshold, discrimination, and identification) were assessed.

Results. Compared to controls, patients with WD had a significantly weaker sense of smell in terms of TDI ($p < 0.01$), odour discrimination ($p < 0.01$), and identification ($p < 0.01$), but not in terms of odour detection threshold ($p = 0.27$). Patients with predominantly neurological symptoms were characterised by greater OD by TDI ($p < 0.01$), odour detection threshold ($p = 0.01$), and discrimination ($p = 0.03$). The presence of pathological lesions ($p = 0.04$) in brain magnetic resonance imaging and generalised brain atrophy ($p = 0.02$) predisposed to worse TDI.

In the WD group, weak inverse correlations between age and TDI score ($r = –0.27$), odour detection threshold ($r = –0.3$), and discrimination ($r = –0.3$) were found. Male gender was a risk factor for abnormal TDI in both WD and controls (both $p = 0.02$).

Conclusions. Patients with WD, particularly older individuals, more frequently had OD than healthy volunteers. Predominantly neurological symptoms, and the presence of typical brain MRI changes, predisposed patients with WD to smell disorders.

Key words: Wilson's Disease, olfactory dysfunction, Sniffin Sticks, olfaction

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Introduction

Olfactory dysfunction (OD) is a frequently observed sensory symptom associated with various neurodegenerative disorders, including Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease and hereditary ataxia [1–4]. Recently, a link between OD and SARS-CoV-2 infection has been described [5]. Olfaction is transmitted by olfactory nerve fibres which pass the cribriform plate to enter the olfactory bulb, then proceed to the olfactory tract and olfactory striae to reach the olfactory cortex (piriform cortex, amygdala and entorhinal cortex). The olfactory cortex has numerous connections with the orbitofrontal cortex, insula, amygdala, and cerebellum, which are organised as an olfactory network [6].

Wilson's Disease (WD) is an autosomal recessive disorder of copper metabolism, caused by mutations in the copper transporting ATPase (ATP7B) that is responsible for excess copper excretion by hepatocytes. WD results in copper accumulation and subsequent clinical symptoms in various organs, but particularly in the liver and brain. Symptoms usually appear between the ages of five and 35. Most frequent is hepatic presentation (50–60% of cases) ranging from elevated

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liver enzymes to liver cirrhosis and, rarely, acute liver failure. Neurological symptoms (up to 40% of patients) include movement disorders such as dystonia, tremor, bradykinesia, chorea associated with dysphagia, dysarthria, drooling, and gait and posture disturbances [7–9].

OD is of interest in many diseases, but there is little data regarding OD in WD. As early as the 1990s, patients with WD pointed out a possible olfactory deficit in a patients' newsletter [10]. Some patients, but not others, were unable to perceive certain bad odours. To date, only three studies have evaluated smell impairment [11, 12] or identification [13] in WD. Currently, smell dysfunction evaluation is based on functional assessment of global odour identification.

Identifying specific smells that are less perceived by patients with WD would allow for the development of more specific diagnostic olfactory tests for WD.

The aim of this study was to evaluate the sense of smell in patients with WD and in a comparable control group, including the odour detection threshold and the ability to identify and discriminate odours, and to define which smells are poorly identified by patients with WD.

Material and methods

Participants

Patients with WD plus sex- and age-matched healthy controls were prospectively enrolled in this study before the COVID-19 pandemic. All WD patients were treated at the Second Department of Neurology, Institute of Psychiatry and Neurology in Warsaw, Poland. Key eligibility criteria were: a confirmed diagnosis of WD (Leipzig score of 4 or more points) [14], signed informed consent, and the ability to participate in smell testing. WD patients were classified according to the predominant clinical symptoms (neurological or hepatic form) or the absence of clinical symptoms (asymptomatic or symptomatic) as described previously [15]. Data was also collected on patient demographics, the presence of Kayser-Fleischer rings, treatment type (i.e. d-penicillamine or zinc sulfate) and duration, smoking, and alcohol consumption. All participants were interviewed and physically examined to rule out any conditions that can cause OD, such as nasal polyposis, allergic rhinitis, acute or chronic rhinosinusitis, previous nasal or paranasal surgery, or recent upper airway tract infections. The control group comprised healthy volunteers with no history of neurological or hepatic diseases or smell problems.

Magnetic resonance imaging (MRI)

An MRI examination was performed in sagittal, frontal and transverse sections in spin echo (SE) and fast spin echo (FSE) sequences, with resulting T1-, T2-weighted and Flair images. The obtained MRI results were evaluated for the presence of hypointense or hyperintense focal lesions in T1- and T2-weighted sequences in typical WD structures including: globi pallidi, putamen, caudate nuclei, thalamus, cerebellum, and pons. The presence of atrophy dilation of lateral ventricles, dilation of cerebral sulci, and subarachnoid space) was assessed in the T1-weighted sequence.

Evaluation of olfactory function

Olfactory function assessment was performed using a 'Sniffin Sticks' subjective test (Heinrich Burghart GmbH, Germany) [16, 17], comprising an assessment of odour detection threshold, and the discrimination and identification of odours. The individually evaluated fragrances or odourless substances were placed in spongy buds in tightly closed plastic frames (the so-called 'sticks'). A 3–5-minute interval was maintained between the subsequent parts of the test. Fifteen minutes before the start of the test, the subjects refrained from consuming liquid or solid food, smoking cigarettes, or chewing gum.

Tests were performed as described previously [16]. In brief, the olfactory detection threshold test consisted of the determination of the fragrance threshold for phenylethyl alcohol (PEA) or butanol. Sixteen butanol solutions were used for this test. In each sample, three sticks ('triplets') were presented, one containing n-butanol, and the other two containing solvent. The triplets were presented at intervals of approximately 30 seconds. The results ranged from 1 to 16, where the higher the score, the lower (i.e. better) the olfactory threshold. The discrimination test consisted of distinguishing one stick with a different scent from two sticks with the same scent. Sixteen triplets were used for the test. The result of the test was the sum of all correctly differentiated smells, ranging from 0 to 16. The odour identification test involved identifying 16 common odours. After presenting the stick, the patient selected a fragrance from a list of four different fragrances. The sticks were presented at 30-second intervals. The test result was the sum of correctly identified smells and ranged from 0 to 16.

The threshold discrimination identification (TDI) score was the sum of the results of the odour detection threshold, plus the discrimination and identification tests. A TDI total score of 15 or below indicated anosmia, a score of 16–30 indicated hyposmia, and a score above 30 indicated normosmia [17]. The room in which the test was carried out was air-conditioned and quiet; the person tested had their eyes closed or covered for the duration of the test. During the test, the investigator used odourless disposable gloves.

This study was approved by the Bioethical Committee of the Institute of Psychiatry and Neurology, Warsaw, Poland.

Statistical analysis

Calculations were carried out using Statistica v.10 (Stat Soft Inc., Tulsa, OK, USA). Data was presented as numbers with percentages or means with standard deviations (SD).

The preliminary correlation analysis was carried out by examining the significance of differences in mean or median values for individual parameters in the WD group and the healthy volunteer group. For factors measured on continuous

scales and to assess the differences in the impact of the factors, the Wilcoxon rank sum test was applied. For factors measured on nominal scales, the relationship between the variables was tested in the system of contingency tables, using the chi-square test, or Fisher's exact test. Analysis of the correlations between TDI, odour detection threshold and odour discrimination parameters and clinical parameters were performed using the Spearman's rank correlation coefficient. For multiple comparisons, hypothesis testing was performed using the Bonferroni correction (the p-value divided by the total number of pairwise comparisons) to correct for the possibility that in multiple comparisons the null hypothesis would be rejected by chance. $P < 0.05$ was considered to be statistically significant.

Results

In total, 68 patients with WD were enrolled, including 35 women and 33 men. The control group consisted of 70 age- and gender-matched healthy volunteers. The demographics of the evaluated groups are set out in Table 1.

The average age of the WD patients at the time of study recruitment was 29.1 ± 9.4 years, and the age at diagnosis of WD was 27.0 ± 8.9 years. The presence of Kayser-Fleischer rings was confirmed in 46 (68%) patients. None of the patients reported smell problems. However, this was not verified by objective methods.

Neurological examination and MRI

At the time of the olfactory examination, 36 (51.5%) patients had no significant deviations from the normal state in the neurological examination; 32 (47%) had neurological symptoms; and one (1.5%) was asymptomatic. Among neurological forms, rigidity was diagnosed in four (13%) patients, tremor in 15 (48%), rigidity-tremor in seven (22.5%), and dystonic form in five (16%) patients.

MRI was performed on 63 patients. In 27 (42.9%) patients, no focal pathological lesions were found. In 9 (14.3%) patients, lesions were found in only one structure, while 27 (42.9%) patients had pathological lesions in at least two brain structures.

Evaluation of smell in WD patients and healthy volunteers

Statistically significant differences were found between the tested groups, with reduced TDI, discrimination, and identification in WD patients compared to controls (all $p < 0.01$), but there was no significant difference in odour detection threshold (Table 2).

A comparison of correct answers (%) in the identification test between the study groups is set out in Table 3. Significant differences were noted between the groups for the target fragrances of banana, lemon, turpentine, cloves, pineapple, rose, and aniseed, with reduced identification in the WD *vs.* controls in each case. The least frequently identified fragrance in both groups was the smell of apples.

Patients with predominantly neurological symptoms were identified by greater smell disorders in terms of TDI ($p < 0.01$), odour detection threshold ($p = 0.01$), and discrimination ($p = 0.03$) compared to patients with predominantly liver-related symptoms (data not shown).

Table 1. Demographic and clinical characteristics of patient and control groups

	Wilson's Disease (n = 68)	Healthy volunteers (n = 70)	P-value*
Gender, female, n (%)	35 (51.47%)	45 (64.29%)	0.71
Age at study recruitment, mean ± SD (years)	35.1 ± 12.0	34.7 ± 10.6	0.95
Latency between disease onset and smell test, mean ± SD (years)	8.1 ± 9.8	–	
Latency between WD diagnosis and smell test, mean ± SD (years)	6.1 ± 9.8	–	
Treatment			
Treatment duration, median (95% CI), years	6.06 (8.38–11.79)	–	
D-penicillamine, n (%)	36 (53%)	–	
Zinc sulfate, n (%)	32 (47%)	–	
Use of tobacco and alcohol			
Smoking, n (%)	17 (25%)	11 (15.71%)	0.17
Alcohol consumption, n (%)	7 (10.61%)	20 (29.85%)	0.01
Clinical symptoms of WD at study recruitment			
Hepatic symptoms, n (%)	35 (51.47%)	–	
Neurological symptoms, n (%)	32 (47.05%)	–	
Asymptomatic, n (%)	1 (1.47%)	–	
Kayser-Fleischer ring, n (%)	46 (68%)	–	

CI — confidence interval; SD — standard deviation; WD — Wilson's Disease
*P-value was calculated using chi-square test for comparisons of number of correct answers between Wilson's Disease patients and healthy volunteers

Table 2. Values of total result of olfactory test (threshold detection identification) and its individual components in study groups (scores)

Parameter (mean ± SD)	Wilson's Disease (n = 68)	Healthy volunteers (n = 70)	P-value*
Threshold detection identification	28.41 ± 4.42	32.91 ± 2.80	0.00
Odour detection threshold	5.80 ± 1.59	6.04 ± 1.61	0.27 (NS)
Odour discrimination	11.23 ± 2.60	13.60 ± 1.34	0.00
Odour identification	11.37 ± 2.13	13.27 ± 1.31	0.00

NS — not significant; SD — standard deviation
After Bonferroni correction, all except odour detection threshold were statistically significant
*P-value was calculated using chi-square test for comparisons of number of correct answers between Wilson's Disease patients and healthy volunteers

Table 3. Comparison of correct answers (%) in identification test in study groups

Target fragrance	Other fragrances "to choose"	Wilson's Disease, n (%)	Healthy volunteers, n (%)	P-value*	P-value* after Bonferroni correction
Orange	Blackberry, strawberry, pineapple	57 (83.8)	62 (88.6)	0.42	NS
Skin	Smoke, glue, grass	39 (57.4)	49 (70.0)	0.12	NS
Cinnamon	Honey, vanilla, chocolate	39 (57.4)	54 (77.1)	0.13	NS
Mint	Chives, fir, onion	65 (95.6)	68 (97.1)	0.62	NS
Banana	Coconut, walnut, cherry	51 (75.0)	67 (95.7)	0.00	0.008
Lemon	Peach, apple, grapefruit	27 (39.7)	40 (57.1)	0.04	NS
Liquorice	Cherry, green mint, cake	53 (77.9)	55 (78.6)	0.15	NS
Turpentine	Mustard, rubber, menthol	27 (39.7)	44 (62.9)	0.01	NS
Garlic	Onions, sauerkraut, carrots	62 (91.2)	69 (98.6)	0.05	NS
Coffee	Paper, wine, smoke	67 (98.5)	68 (97.1)	0.58	NS
Apple	Melon, peach, orange	20 (29.4)	29 (41.4)	0.14	NS
Cloves	Pepper, cinnamon, mustard	54 (79.4)	65 (92.9)	0.02	NS
Pineapple	Pear, plum, peach	40 (58.8)	57 (81.4)	0.04	NS
Rose	Camomile, raspberry, cherry	52 (76.5)	66 (94.3)	0.003	0.048
Aniseed	Rum, honey, fir	46 (67.6)	66 (94.3)	0.00	0.002
Fish	Bread, cheese, ham	67 (98.5)	70 (100)	0.31	NS

*P-value was calculated using chi-square test for comparisons of number of correct answers between Wilson's Disease patients and healthy volunteers

Relation between demographic and clinical data and occurrence of olfactory disorders

In the group of WD patients, there was a weak inversely proportional correlation between the age of the patient and the TDI result ($r = -0.27$), their odour detection threshold ($r = -0.3$), and their odour discrimination ($r = -0.3$) (all $p < 0.05$). This relationship was not observed in the group of healthy volunteers.

Worse results were obtained in men *vs.* women in both groups. Among men *vs.* women with WD, there were statistically significantly worse TDI results ($p = 0.02$), odour detection threshold results ($p = 0.03$), and a trend towards worse odour identification ($p = 0.087$). Similarly, in the group of healthy volunteers, men obtained a statistically significantly lower TDI result ($p = 0.02$), and were less able to identify smells than women ($p = 0.003$).

There was no statistically significant correlation between the presence of Kayser-Fleischer rings and the occurrence of OD in TDI ($p = 0.5$) and its components [olfactory threshold ($p = 0.98$), discrimination ($p = 0.31$), and identification ($p = 0.86$)].

Abnormal brain MRI with the presence of pathological lesions ($p = 0.04$) characteristic for WD, including the globus pallidus ($p = 0.02$) and/or the putamen ($p = 0.048$), and generalised brain atrophy ($p = 0.02$) predisposed to a worse TDI.

There was no effect of the type of treatment (d-penicillamine *vs.* zinc sulfate) on the TDI score ($p = 0.4$) or on the individual components of the olfactory test [olfactory threshold ($p = 0.16$), discrimination ($p = 0.91$), and identification ($p = 0.45$)].

There were no significant differences in the result of the TDI score ($p = 0.39$) and its components [olfactory threshold ($p = 0.82$), discrimination ($p = 0.27$), and identification ($p = 0.21$)] between smokers and non-smokers.

Only seven (10.61%) patients with WD and 20 (29.85%) from the control group declared alcohol consumption. Due to these small numbers, we were unable to reliably assess the influence of alcohol consumption on olfactory parameters.

Discussion

In this relatively large cohort of patients with WD and healthy volunteers, WD was associated with OD, particularly as related to odour discrimination and identification. The exact mechanism of OD in WD is unclear, but it is possible that copper deposits may impair the structural, regulatory, and catalytic functions of the enzymes, receptors, transporters, and other proteins [18]. In WD, there is neuronal loss and atrophy in the thalamus and lenticular nucleus (structures involved in odour processing), as well as in the other parts of the basal ganglia [19].

Although patients with a neurological presentation of WD typically develop extrapyramidal symptoms [8], other subclinical abnormalities have also been reported in motor-evoked potentials reflecting pyramidal tracts damage [20], somatosensory, auditory and visually-evoked potentials [21], visual pathways [22] and blink reflex [23]. Our study supports other reports which have suggested that, additionally, olfactory tracts may be affected in WD patients [11–13].

Our results are consistent with the findings of Mueller et al., who observed a significant decrease in olfactory function in 24 WD patients compared to a control group in a study using Sniffin Sticks [11]. Similarly, a study by Chen et al., using a simplified Chinese version of the University of Pennsylvania Smell Identification Test, demonstrated that patients with WD had lower smell identification skills compared to a control group [12]. Obtained average values of the odour discrimination and identification test in the studied control group were comparable to the standards adopted for many European and Asian countries [17, 24, 25].

Comparing the ability to identify smells by WD patients and healthy volunteers in the studied group, the most visible deficiencies in the WD group concerned the identification of aniseed, banana, pineapple, rose, turpentine, lemon, and cloves. These results are partly consistent with those presented in an abstract by Carvalho et al. [13]. When assessing the identification of smells using Sniffin Sticks in 64 patients with WD and 60 people from a control group, they found the most significant differences between the groups concerned the identification of mint, banana, lemon, aniseed, and fish [13].

However, in our study, the smells of fish, coffee and mint were equally well identified by both groups. In our work, the least frequently identified fragrance in both the group of patients and the healthy control group was apples, which is consistent with reports from Turkish [26], German [1], and Belgian populations [27].

In our study, patients with dominant neurological symptoms scored much worse in TDI, odour detection threshold and odour discrimination compared to patients with dominant hepatic symptoms. Similar results were published by Mueller et al., where 13 WD patients with neurological symptoms obtained much worse olfactory results compared to 11 patients with WD-induced liver damage only [11]. Similarly to our results, the greatest differences concerned the odour detection threshold and odour discrimination, with no differences found in the ability to identify odours.

In our cohort, the presence of brain MRI changes typical for WD (in globi pallidi, putamen and generalised brain atrophy) resulted in poorer olfactory function in WD patients. This is not consistent with Mueller et al., who did not find significant correlations between OD and the presence of lesions by MRI (n = 24) or abnormalities of glucose metabolism by positron emission tomography (n = 21) [11]. In men with the neurological form, cerebellar atrophy and a trend indicating cerebral atrophy have been found to be more common [28]. However, to date, these differences have not been linked to OD.

Analysing the influence of age on the sense of smell in WD patients, we found a slight inverse proportional correlation with TDI, olfactory threshold score, and discrimination. No such relationship was found in the control group. Structural changes within the olfactory tract must be mentioned when discussing the reasons for age-related olfactory impairment, beginning with changes in the olfactory epithelium along with a decrease in the number of olfactory receptors [29], through the olfactory bulb, and ending with weaker age-dependent olfactory cortex activation [30].

According to most authors, the odour detection threshold increases with age [16, 31], although other authors [32] have recorded comparable odour detection thresholds between young people and healthy elderly people without cognitive impairment. Similarly, it has been found that the ability to discriminate odours is weaker in older people, and particularly so in males [33].

Women may have a better ability overall to identify odours. A meta-analysis by Sorokowski et al. [34] demonstrated that in every analysed aspect of olfactory function, i.e. odour detection threshold, discrimination and identification, women performed better than men. Similarly, in our study, women were less likely to present with OD than men. Additionally, there were more women in the control group, which may explain why smell appeared to be better in the control group. According to the literature review by Doty and Cameron, sex hormones are not the only factors determining the differences in smell sensation between women and men [35]. Other factors affecting smell may include those concerning the impact of the monthly cycle and pregnancy on the sense of smell, and whether the neuroendocrine changes are specific and concern only selected types of smells. Another meta-analysis of 13 studies found that the odour detection threshold is significantly lower in the fertile phase compared to the non-fertile phase of the monthly cycle [36]. However, we did not investigate the effects of the menstrual cycle or the use of contraceptives on the sense of smell.

We did not find a relationship between the tested olfactory parameters and cigarette smoking, either in WD patients or healthy volunteers. Results of studies assessing the impact of cigarette smoking on smell sensation are inconsistent. A meta-analysis of 11 studies showed a higher risk of OD in

current but not former smokers [37]. Çengel Kurnaz et al. [38] demonstrated that olfactory functions were affected by both active and passive smoking. Smoking had the greatest impact on the odour detection threshold, followed by identification and discrimination [38].

Finally, our study was conducted before the COVID-19 pandemic. The prevalence of olfactory deficits worldwide in COVID-19 patients has been estimated to be 22.2% [39]. A similar study to ours, being conducted currently, may have been biased by the effects of COVID-19 on WD patients, or patients who suffered from COVID-19 would have to have been disqualified from participating. This also limits the usefulness of performing routine smell testing in WD patients. Moreover, this would not change the methods of routine diagnosis and treatment in this group of patients.

Limitations of study

The main limitation of our study is that not all patients, and none of the healthy volunteers, had a brain MRI. Hence, we cannot exclude any potential subclinical/preclinical lesions. Moreover, olfactory tracts in the central nervous system involve multiple anatomical structures and functional connectivity, and these complex interrelations and connections make it difficult to define the observed OD to any specific brain structures.

Conclusions

Patients with WD, particularly males and older individuals, often experience OD even if they are unaware of it. Predominant neurological symptoms and the presence of typical brain MRI changes may predispose WD patients to smell disorders.

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Incidental diagnosis of septo-optic dysplasia in an adult: a case report

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To the Editors

Septo-optic dysplasia (SOD) is a rare, congenital central nervous system malformation syndrome. It is equally prevalent in males and females, with a reported incidence of 1.9–2.5 per 100,000 live births. Most reported cases are diagnosed in childhood or early adolescence. The diagnosis of SOD is a clinical one that can be made when two or more features of the classical triad of optic nerve hypoplasia, disorders of the hypothalamo-pituitary axis, and agenesis of midline brain structures, are present. There is wide variation in the severity of clinical features. Seizures, developmental delay and cerebral palsy are the most frequent neurological presentations [1, 2]. There is a paucity of data regarding the incidence and clinical features of subtle variants of SOD in adult patients.

We here present the case of a patient who was diagnosed with SOD in the sixth decade of her life. This is, to the best of our knowledge, the first report of an SOD patient with migraine-like headaches as the only neuro-ophthalmological SOD manifestation.

A 56-year-old female was referred to neurological care for severe recurrent headaches of a few weeks' duration. Splitting and diffuse headaches had appeared on the second day of COVID-19 infection. The pain was strong and bilateral and changed its character within a few days. In the emergency department, the patient reported a tension-type, bifrontal headache having lasted for several weeks. There was no evidence of meningitic or encephalitic involvement. The pain met the criteria of the International Headache Society for headaches attributed to systemic viral infection [3, 4]. The patient experienced head traumas at the ages of 17 and 35. She had a history of trigeminal neuralgia, hypercholesterolemia, depression, insulin resistance, obesity and a 40-year history of migraine headaches. The pulsating, severe headache attacks, lasting less than 24 hours, started when she was 17. Symptoms included nausea and vomiting. There were 2–3 attacks per year, but they disappeared in the post-menopausal period. There was also a history of pubertal delay and menstrual irregularity. The patient had been treated using rosuvastatin, metformin, spironolactone, moclobemide, semaglutide, 17-beta-oestradiol and dydrogesterone. There were no abnormalities on the neurological assessment. Funduscopic examination revealed small optic discs suggesting optic nerves hypoplasia. The ophthalmological assessment revealed no other changes. Brain magnetic resonance imaging (MRI) showed abnormalities of the midline structures: agenesis of septum pellucidum, hypogenesis of corpus callosum, falx and optic chiasm (Fig. 1). Electroencephalographic (EEG) activity showed groups of synchronous theta and delta waves, most pronounced over the left occipital, parietal and posterior temporal areas on normal background activity (Fig. 1). Endocrine testing revealed prolactin dysfunction (4.36 ng/mL; normal: 5.18–26.53 ng/mL). *De novo* headache resolved in the patient within one month, and was interpreted as post

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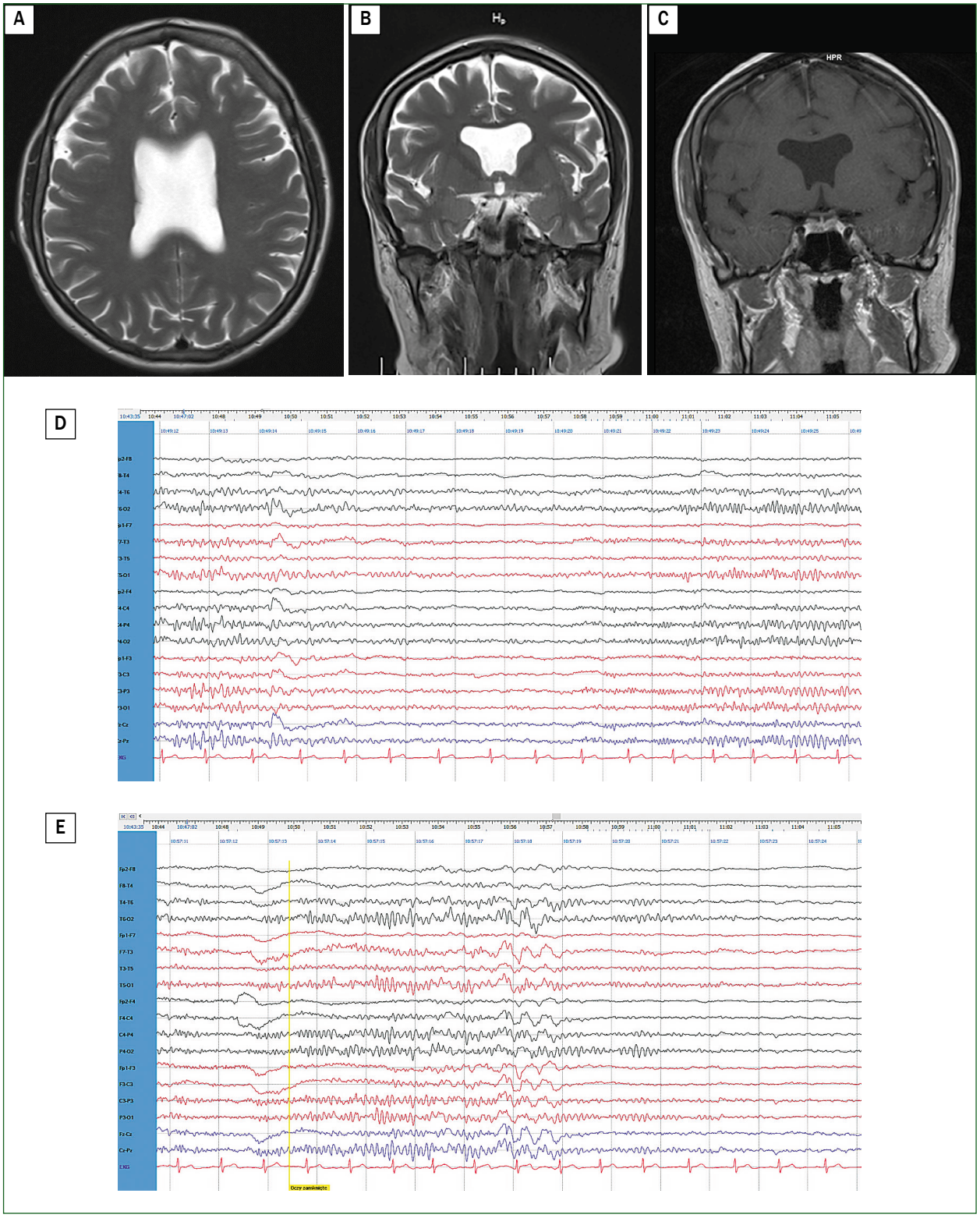

Figure 1. Septo-optic dysplasia. Brain magnetic resonance imaging (MRI); **A.** Axial T2- and **B.** coronal T2-weighted sequences show agenesis of midline structures; **C.** Coronal T1-weighted sequence shows optic chiasm hypoplasia. **D**, **E.** Electroencephalographic (EEG) activity: groups of synchronous theta and delta waves most pronounced over left occipital, parietal and posterior temporal areas on normal background activity

Coronavirus disease-19 headache. The diagnosis of SOD was established.

Less than 50% of SOD patients present all three of the classical triad of features [1, 2]. In the presented patient, two of the triad were present: midline abnormalities of the brain (hypogenesis of septum pellucidum and corpus callosum), and optic nerves hypoplasia.

The precise causes of SOD remain unknown. The phenotypic penetration is highly variable. A combination of genetic predisposition and prenatal exposure to environmental factors are believed to play major roles in its occurrence. The specific genes most frequently involved in the development of SOD are: HESX1, SOX2, SOX3 and OTX2. Very rare familial cases have been described, mostly with autosomal recessive inheritance. Genetic abnormalities have been identified in less than 1% of patients. Whole-exome sequencing (WES) of our patient revealed no pathogenic variants in the 150 genes, according to the Human Phenotype Ontology, associated with septo-optic dysplasia (HP:0100842), absent septum pellucidum (HP:0001331), and optic nerve hypoplasia (HP:0000609).

Some environmental factors (drugs, hormones, alcohol abuse, young maternal age) may play a significant role in the aetiology of SOD. According to the presented patient, there had been no drugs, hormones or alcohol abuse in her mother's history. The mother was aged 39 on the day of the patient's delivery.

Ophthalmological symptoms are the earliest that can be identified in SOD patients. Visual impairment accounts only for 23% of overall reported symptoms [1, 2]. The presented patient had no visual disturbances.

Hypopituitarism is the most commonly reported feature of SOD. Although there was a history of pubertal delay and menstrual irregularity in our patient, she was not diagnosed because of those features. There is no data regarding obesity in SOD adult patients. Its prevalence in SOD children appears to be up to 44% [1, 2]. The presented patient had a history of obesity since adolescence.

Headache affects almost half of patients in the acute phase of COVID-19. As in the presented patient, it begins early in the symptomatic phase and is bilateral of a moderate to strong intensity. The frequent phenotypes are migraine or tension-type headache patterns [3, 4]. The presented patient reported that the headache during the COVID-19 infection had a different pattern to that of previous ones. To the best of our knowledge, the presented patient is the first reported patient diagnosed with SOD in adulthood with migraine-like headaches as the only neuro-ophthalmological presentation.

The clinical features of SOD are very heterogeneous. Most data relates to patients diagnosed in their childhood or early adolescence. Only a few reports are dedicated to adults, and we found only one that presented the incidental diagnosis of a subtle variant of SOD in an adult. This was a patient with a history of migraine headaches and congenital left monocular blindness who was diagnosed with SOD in the fourth decade of his life. A review of this patient's medical record showed no note of endocrine abnormality, developmental delay, or neurological impairment other than left monocular blindness [5].

In our case, there was a history of endocrine abnormalities (pubertal delay, menstrual irregularity) and obesity. The patient was diagnosed with insulin resistance and optic nerve hypoplasia. There was no history of ophthalmological problems or developmental delay. The patient we here present has expanded our understanding of the phenotype of subtle variants of SOD which are diagnosed in adults.

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Left ventricular non-compaction cardiomyopathy and ischaemic stroke

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To the Editors

Non-compaction cardiomyopathy is a rare congenital myocardial disorder that results due to the arrest of left ventricle compaction during embryogenesis. Other terms such as "spongy myocardium" or "persistent embryonic myocardium" have been used, but most frequently this disorder is known as left ventricle non-compaction or non-compaction cardiomyopathy [1].

The 'compaction' of the spongy myocardium (with a trabecular appearance) is during weeks 5–8 of embryogenesis, and the interruption of this process leads to persistence of these trabeculations continuous with ventricular cavity and a cessation of the communication with epicardial circulation [2]. More than 40 genes coding for sarcomeric, cytoskeletal, ion channels and desmosomal proteins have been identified in this disorder [3].

Atrial fibrillation, decreased systolic function and intratrabecular thrombus formation found in the left ventricle are common clinical features of left ventricular non-compaction, and can be involved in thromboembolic events [2]. These events can be stroke, transient ischaemic attack, mesenteric, myocardial and renal infarction, or peripheral embolism [4].

We here report the case of a 47-year-old man who was admitted to the neurological department for sudden onset of weakness in left limbs and slurred speech of 3.5 hours' duration. On admission, the patient showed no signs for mesenteric, myocardial, renal or peripheral embolisation. He had a history of alcohol drinking and cigarette smoking, without any additional vascular risk factors. His father had died young due to myocardial infarction.

The neurological examination revealed left hemi-sensory deficits and left-sided hemiparesis (strength was 3+/5 on the left hand and 4+/5 on the left foot, and the Babinski reflex was extensor on the left and flexor on the right), oculocephalic deviations to the right, and dysarthria with an NIHSS score of 6 points. The CT scan performed in the emergency department revealed an acute hyperdense thrombus in M1-M2 segments of right middle cerebral artery. The ASPECTS score was 9 points. The routine blood exam was unremarkable. Thrombolysis with Alteplase was performed, and the NIHSS score during hospitalisation decreased to 3 points.

The cerebral MRI performed two days after thrombolysis confirmed ischaemic lesions in the right middle cerebral artery territory and a small contralateral parietal lesion (Fig. 1A–C). We did not identify cervical or intracranial atherosclerosis.

The cardiovascular investigations such as transthoracic echocardiography revealed an obvious trabecular aspect of the left ventricle, with an EF (ejection fraction) < 20% (Fig. 1D–E). Stöllberger echocardiographic criteria [5] and Paterick criteria [6] for left ventricular non-compaction were met.

Stöllberger et al. [5] defined the echocardiographic criteria for LVNC as: three or more trabeculations protruding from the LV endocardial border in end-diastole; trabeculations are moving synchronously with the compacted myocardium; these trabeculations are non-compacted part of the two-layered

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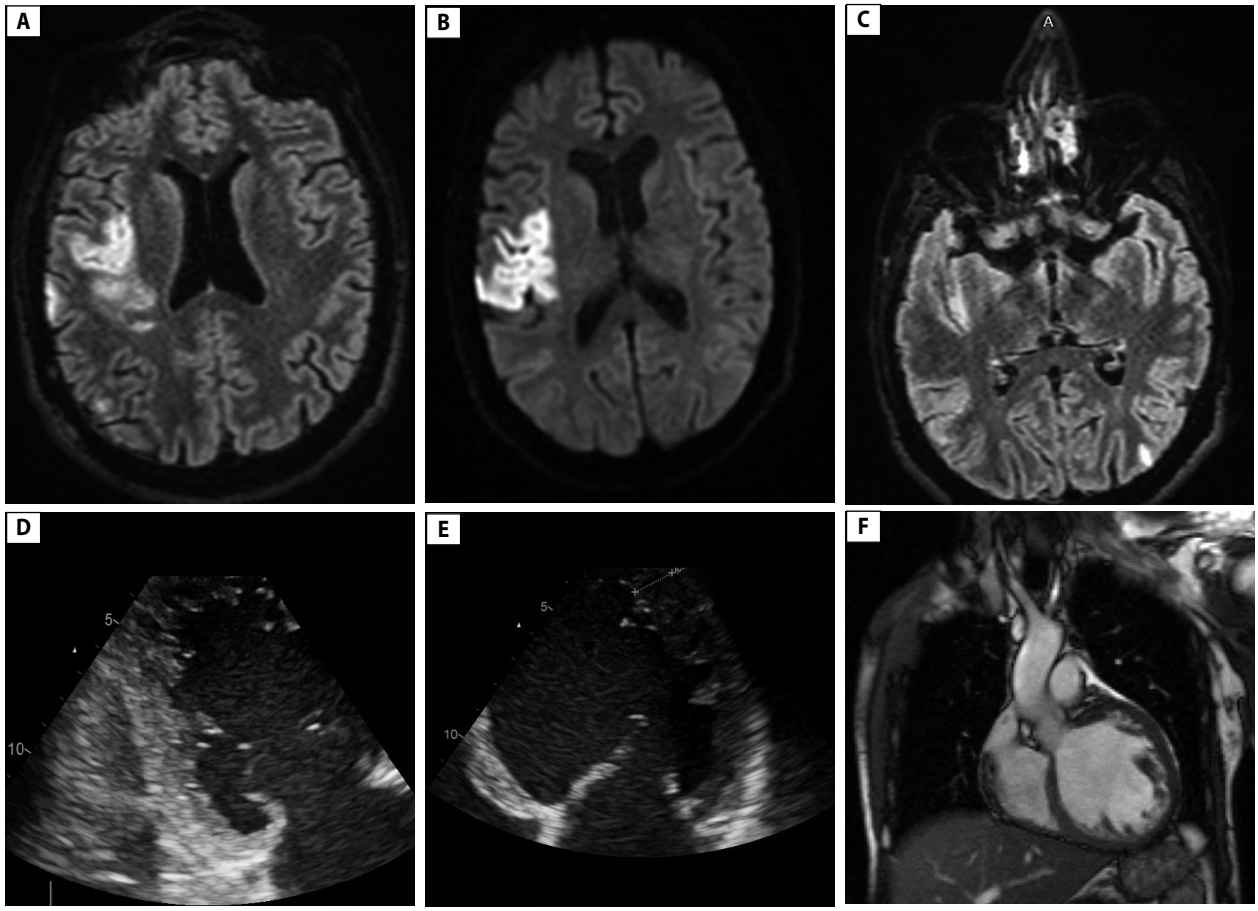

Figure 1. A. axial FLAIR: high signal in right MCA territory; **B.** Axial diffusion: confirming acute right superficial MCA ischaemic stroke; **C.** Axial FLAIR: small left parietal area with high signal; **D.** Echocardiography: apical two-chamber view: > 3 prominent trabeculations with deep intertrabecular recesses (Stöllberger criterion) [5]; **E.** Apical four-chamber view, end-diastole, left ventricle zoom, 2-layered myocardium with non-compaction/compaction ratio = 1.3 cm/0.7 cm = 1.85 (Paterick criterion: ratio > 2) [6]; **F.** Cardiac MRI: myocardial non-compaction of left ventricle

myocardial structure; and perfusion of the intertrabecular spaces from the ventricular cavity is present at end-diastole on colour-Doppler echocardiography.

According to Paterick et al., the echocardiographic criteria for LVNC are: an evaluation of the trabeculations' sizes (non-compacted myocardium NC) in relation to compacted (C) wall thicknesses in multiple imaging windows; identification of the bilayered myocardium (C and NC), in the short-axis views at the mid- and apical levels, and in the apical 2- and 4-chamber and apical long-axis views; thicknesses of the C and NC sections of the myocardium are best measured in the short-axis views at end-diastole, with NC/C ratio > 2 being diagnostic of LVNC; and abnormal ventricular function and abnormal myocardial mechanics, along with the above noted features, to diagnose LVNC cardiomyopathy [6].

A cardiac MRI was performed, confirming the diagnosis of non-compaction cardiomyopathy (Fig. 1F).

In the literature, we found common opinions about complications, but there was a lack of consensus in specific guidelines about the type of anticoagulation needed for secondary ischaemic stroke prevention.

Non-compaction cardiomyopathy may remain undiagnosed until adulthood when complications like cardiac arrhythmias, cardiac failure, thromboembolic events or sudden death can be seen. The management of this disorder is dependent on clinical manifestations. The treatment is addressed to cardiac failure management, comprising an implantable defibrillator or, in some cases, cardiac transplant [2].

Because this cardiac disorder has a low prevalence, there have been no large randomised trials regarding the clinical management of this disorder, especially regarding the anticoagulation treatment [4].

According to the American Heart Association 2021 guidelines for secondary stroke prevention, five randomised trials have evaluated the effects of antithrombotic therapy on clinical outcome, including stroke, in patients with heart failure and reduced LV EF in sinus rhythm.

The WARCEF trial (Warfarin *vs.* Aspirin in Reduced Cardiac Ejection Fraction) documented no benefit of warfarin therapy compared to acetylsalicylic acid at a mean follow-up of 3.5 years for the primary outcome (i.e. death, ischaemic stroke, or intracranial haemorrhage), although patients on warfarin

had reduced incidence of stroke, particularly patients with an EF ≥ 15. The only randomised trial evaluating the benefit of DOACs (dabigatran) in stable patients after LVAD (Left Ventricular Assist Device) implantation was halted prematurely because of an excess of thromboembolic events [7].

In our case, we supposed that cardio-embolic mechanism was implicated in the stroke aetiology (supported also by imaging examination), and we decided to start the treatment with DOACs.

Some studies have recommended routine anticoagulation for primary thromboembolic prevention in left ventricular non-compaction, while others have suggested anticoagulation when systolic dysfunction (EF < 40%), atrial fibrillation, or intracardiac thrombus exist [8]. In our patient, prolonged cardiac monitoring put into place post-treatment did not reveal atrial fibrillation or any other cardiac arrhythmia.

Hypertrabeculation and affected left ventricular function predispose patients to cerebrovascular events, and the data from the literature recommends oral anticoagulation when such a diagnosis is confirmed.

Because this is a rare disease, evidence-based recommendations for preventing thromboembolic events in this disorder are not well established. The utility of echocardiography can be considered to estimate the duration of anticoagulation [2, 8].

New insights into understanding the genetic aetiology and the utility of screening relatives are promising areas for further research. It would be most valuable to establish consensus guidelines [8].

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SARS-CoV-2 infection complicated by neuro- or psycho-COVID

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To the Editors

We read with interest the review article by Czarnowska et al. on the effects of SARS-CoV-2 on the nervous system [1]. The pathophysiology of neuro-COVID has been explained by a systemic immune reaction against the virus (platelet activation, thrombocytopenia, leukocyte activation, overproduction of inflammatory pro-aggregating cytokines, endothelial dysfunction, complement system activation, mast cell activation), microglial activation, cerebral hypoxia, or neuro-invasion of the virus via the olfactory tract, invasion of the virus into the central nervous system via haematogenous pathways, and disruption of the blood brain barrier allowing leukocytes carrying SARS-CoV-2 to enter the brain (the so-called 'Trojan horse' mechanism) [1]. The authors concluded that cerebrovascular disease is the most common neurological complication of SARS-CoV-2 infection [1]. The review article is excellent, but we feel it has limitations and raises concerns that should be discussed.

Specifically, we disagree with the subheading 'Neurological symptoms' and the heading given to Table 2: 'Neurological symptoms during acute/post-acute stage of infection in large analyses of patients hospitalised due to COVID-19' [1]. Contradicting these captions, this section and this Table actually discuss neurological disorders rather than neurological symptoms.

With regard to neurological diseases, the spectrum of neuro-COVID is much broader than discussed in the review. The neurological complications of SARS-CoV-2 infection not included in the review are: immune encephalitis, cerebellitis, acute disseminated encephalomyelitis (ADEM), acute, haemorrhagic, necrotising encephalitis (AHNE), pontine myelinolysis, cerebral vasculitis including giant cell arteritis, ventriculitis, hypophysitis, intracerebral bleeding, demyelinating disorders (multiple sclerosis, neuromyelitis optica (NMO) spectrum disorder, myelin-oligodendrocyte glycoprotein (MOG) associated disease), reversible, cerebral vasoconstriction syndrome (RCVS), Wernicke encephalopathy, transverse myelitis, mono- or polyneuritis cranialis including optic neuritis, Parsonage-Turner syndrome, lumbosacral plexitis, myasthenia gravis, myositis, and rhabdomyolysis [2].

Since the review article is entitled 'Impact of SARS-CoV-2 on the nervous system', we contend that psychiatric sequelae of SARS-CoV-2 infection should also have been included and discussed. In addition to 'altered mental state', 'anxiety', 'sleep disorders', and 'decreased mood', patients suffering a SARS-CoV-2 infection may also, or instead, develop delirium, isolated hallucinations, mania, akinetic mutism, psychosis, eating disorders, or autism spectrum disorders [3].

We disagree with the notion that cerebral hypoxia occurs due to SARS-CoV-2 infection [1]. Hypoxic brain damage has rarely ever been documented by cerebral MRI in COVID-19 patients, and where it does occur it is usually in patients with severe COVID-19 requiring prehospital bystander resuscitation. In-hospital COVID-19 patients with respiratory failure are usually given timely oxygenation by non-invasive

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means or invasive means by mechanical ventilation. Furthermore, cerebral hypoxia does not explain peripheral nervous system complications after SARS-CoV-2 infection.

In summary, this interesting study has some shortcomings that call into question the results and their interpretation. Addressing these weaknesses would strengthen the conclusions and thereby improve the study.

The spectrum of neuro- and psycho-COVID is broader than has been commonly assumed. Discussing the effects of SARS-CoV-2 on the central and peripheral nervous systems requires taking into consideration the full spectrum of neurological and psychiatric sequelae in order to shed more light on the possible underlying pathophysiological mechanisms.

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RESPONSE TO LETTER
TO THE EDITORS

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Response to the Letter to the Editors on the article reviewing the complex subject of 'Impact of SARS-CoV-2 on the nervous system'

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To the Editors

We are most grateful to Mehri et al. for their comments on the review we have prepared discussing the various impacts of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the nervous system [1, 2]. However, we would like to address a few minor limitations mentioned in their letter for the sake of clarification.

In the presented review, we set out the current state of knowledge on the particle of SARS-CoV-2, and we discussed what may have led to such a wide spread of the novel coronavirus. Most of the manuscript is dedicated to the various theories as to how the virus approaches the nervous system, and to discussing potential neuropathology mechanisms. The clinical impact of SARS-CoV-2 is further described, albeit to a lesser extent.

The first minor matter pointed out are the headings of section 7 and Table 2. We agree that the term "symptoms" does not fully reflect the content of these sections. Therefore, we suggest "symptoms and disorders" would be more appropriate.

The second limitation mentioned by Mehri et al. is an insufficient explanation of post-COVID disorders and the possible psychiatric sequelae of SARS-CoV-2 infection. We thank the letter's authors for their expansion of the list of possible post-infectious symptoms. We agree with most of them.

However, we cannot fully agree that either multiple sclerosis or myelin-oligodendrocyte glycoprotein associated disease are direct consequences of SARS-CoV-2 infection. There is no data supporting such a statement. These particular disorders are more likely to be triggered by an infectious agent, or their first manifestation may appear in post-infectious conditions.

Moreover, the potential of stimulating autoimmune activity is moderate in multiple sclerosis patients, as the relapse rate during the infection, and for several months after, has not yet proven to be higher [3]. Therefore, the neurological incidences following COVID-19 cannot be classified altogether, as they have been by the authors of the letter.

The pathomechanism behind such a broad presentation of neurological and psychiatric symptoms following COVID-19 is as yet unknown, and is probably multifactorial. However, some hypotheses have been presented. Persistent symptoms may be a consequence of numerous factors beyond the ones described in our review, e.g. a reduction in cerebrospinal fluid flow (reduced removal of brain metabolites); triggered and sustained neuroinflammation (activation of microglia, autoimmunisation, autoimmune mimicry); and impaired neurotransmission (e.g. GABAergic) [4].

Mehri et al. disagree with the impact of hypoxia on the central nervous system. However, they have focused only on direct damage to the CNS (seen in neuroimaging). Our review clearly states that the matter is much more complex, and that not only can acute hypoxia affect the CNS, but so also can prolonged oxygen deficit. A cascade of events may lead to indirect injury (e.g. injury to the blood-brain barrier) [5].

Furthermore, the authors claim that hypoxia does not explain peripheral damage to the nervous system, but it must be emphasised that several mechanisms lead to neurological deficits in SARS-CoV-2 infection. This matter is discussed in other sections of our review.

We did not state that hypoxia was the only factor causing neurological complications in COVID-19 patients.

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