Neurologia i Neurochirurgia Polska, 2023, vol. 57, no. 4

NEUROLOGIA I NEUROCHIRURGIA POLSKA

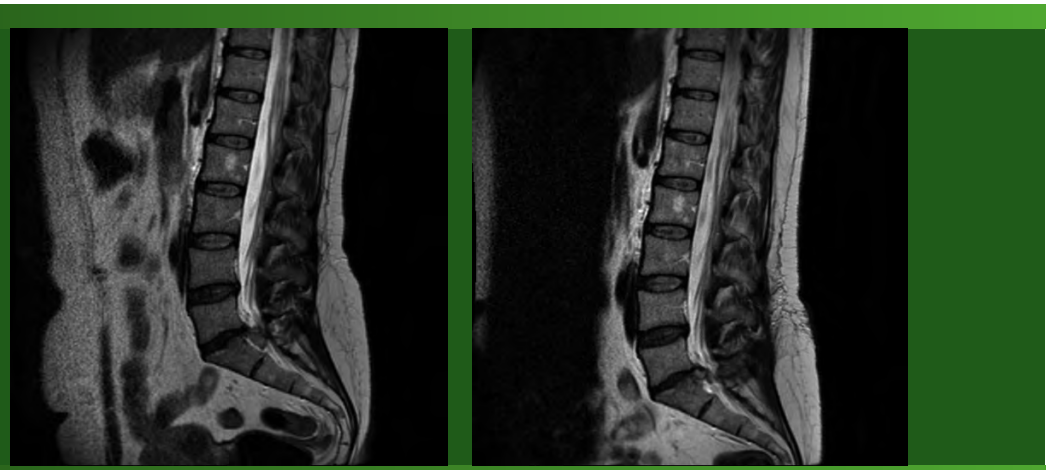
POLISH JOURNAL OF NEUROLOGY AND NEUROSURGERY

The Official Journal of Polish Neurological Society

2023, vol. 57, no. 4

Impact Factor: 2.9

Ministry of Education and Science • Polish 140



Established: 1938

VIA MEDICA

ISSN: 0028-3843
e-ISSN: 1897-4260

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Published by: VM Media Group sp. z o.o.

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Neurologia i Neurochirurgia Polska (ISSN: 0028-3843, e-ISSN: 1897-4260) is published 6 times a year by VM Media Group sp. z o.o.

Editorial address: VM Media Group sp. z o.o.
ul. Swietokrzyska 73, 80–180 Gdansk,
tel: (+48 58) 320 94 94, fax: (+48 58) 320 94 60
www.journals.viamedica.pl/neurologia_neurochirurgia_polska,
e-mail: editorialoffice@pjnns.viamedica.pl

Journal has an international indexation in CrossRef, Chemical Abstracts, DOAJ, EBSCO, EMBASE, Google Scholar, Index Copernicus, MEDLINE/PubMed, OpenMed, Polish Medical Library, Polish Ministry of Education and Science, Polish Scientific Bibliography, Science Citation Index Expanded, Scopus.

Current Impact Factor of Neurologia i Neurochirurgia Polska (2022) is 2.9

The Journal has been included in the register of journals and proceedings of international conferences published by Polish Ministry of Education and Science on July 17th, 2023 with 140 points awarded.

Editorial policies and author guidelines are published on journal website:
www.journals.viamedica.pl/neurologia_neurochirurgia_polska

Cover photo: Michał Sobstyl et al. Large left disc sequestration at level of L5/S1 before and after right-sided microdiscectomy (see figure on page 333)

22-6129.004.001

NEUROLOGIA I NEUROCHIRURGIA POLSKA

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EDITORIAL NOTE

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DOI: 10.5603/pjnns.97095

ISSN: 0028-3843, e-ISSN: 1897-4260

Latest bibliometrics of Polish Journal of Neurology and Neurosurgery

Zbigniew K. Wszolek[1], Łukasz Stolarczyk[2], Jarosław Sławek[3, 4]

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At the end of June, *Clarivate Analytics*™ (CA) released the 2023 Edition of *Journal Citation Reports*, which included important changes. Each Web of Science Core Collection journal was given a *Journal Impact Factor* (JIF). Journals indexed in the *Arts and Humanities Citation Index* and the *Emerging Sources Citation Index* received JIFs for the very first time, meaning that c.9,000 additional titles were included in the JIF calculation for 2022. CA introduced this new policy in order to widen representation of journals from different fields and to provide better journal assessments.

The second, albeit minor, change introduced by CA this year relates to simplifying the calculation of JIF to just the first decimal place (previously it was to three decimal places). CA anticipates that this move will eliminate a false sense of precision in JIF presentation, and encourage users to consider other bibliometrics and descriptive data in journal assessments.

The 2022 JIF for the Polish Journal of Neurology and Neurosurgery (PJNNS, Neurologia i Neurochirurgia Polska) has significantly increased, as illustrated in Figure 1. The current JIF is 2.9 points, an increase of nearly 0.7 points when compared to the 2021 JIF. The 5-year JIF has also increased by almost 0.2 points. The three most cited articles that contributed to these increases are listed in Table 1. Not surprisingly, two of them deal with topics related to SARS-CoV-2 infection. All three are from Polish authors.

Another bibliometric measure that we are highlighting here is the *Journal Citation Indicator* (JCI), which uses

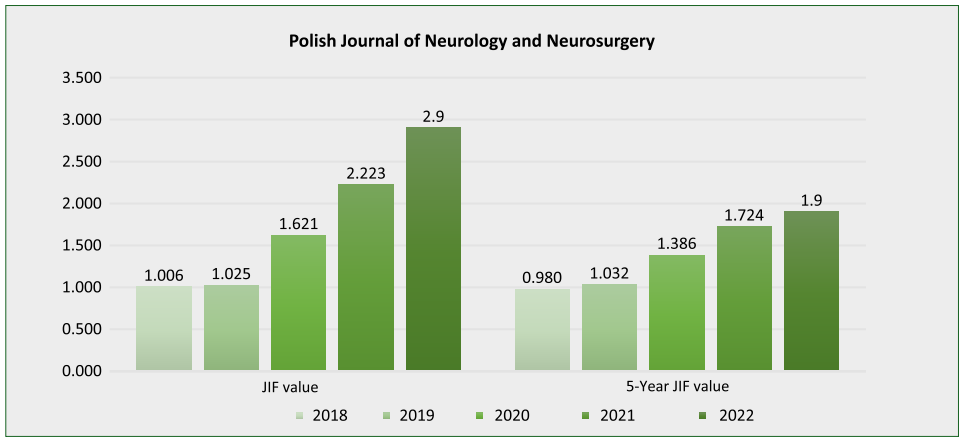

Figure 1. Illustration of increases in *Journal Impact Factor* (JIF) and 5-Year JIF for PJNNS from 2018 to 2022. Data from *Clarivate Analytics*™

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Table 1. Three most cited manuscripts published in PJNNS that contributed to calculation of 2022 *Journal Impact Factor*

First author	Title	Number of citations	Reference
Czarnowska A.	Clinical course and outcome of SARS-CoV-2 infection in multiple sclerosis patients treated with disease-modifying therapies — the Polish experience	17	[1]
Nojszewska M.	COVID-19 mRNA vaccines (Pfizer-BioNTech and Moderna) in patients with multiple sclerosis: a statement by a working group convened by the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society	9	[2]
Malinowski Ł.	Genetics of Parkinson's disease in the Polish population	9	[3]

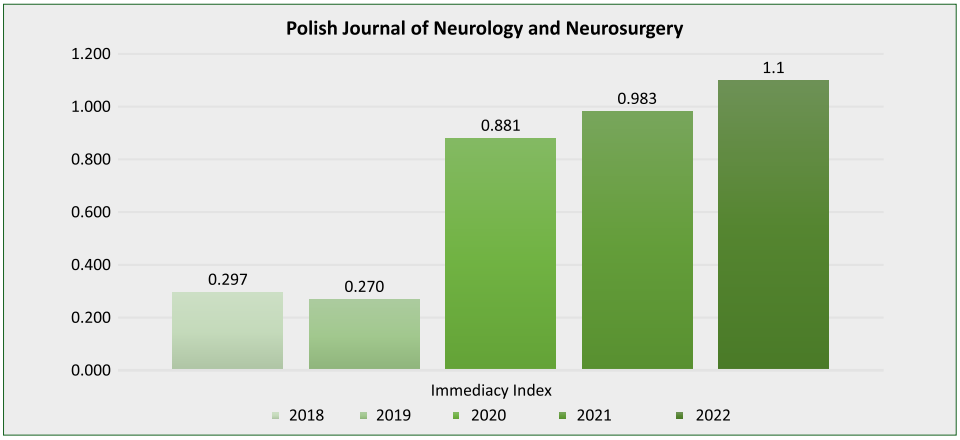

Figure 2. Increases in *Immediacy Index* of PJNNS from 2018 to 2022. Data from *Clarivate Analytics*™

Table 2. Three most cited manuscripts published in PJNNS that contributed most to 2022 *Immediacy Index*

First author	Title	Number of citations	Reference
Madetko N.	Platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio may reflect differences in PD and MSA-P neuroinflammation patterns	8	[4]
Szejko N.	Cannabis-based medicine in treatment of patients with Gilles de la Tourette syndrome	6	[5]
Bratosiewicz-Wąsik J.	Neuro-COVID-19: an insidious virus in action	5	[6]

a category-normalised calculation. The JCI of PJNNS has been systematically increasing, from the initial assessment of 0.26 points in 2017 to the current 0.56 points. In 2022, both indices improved, allowing PJNNS to change its position from Q4 to Q3 in the Web of Science 'Clinical Neurology' category.

The *Immediacy Index* (II) of PJNNS has increased as well. The II is a measure of the topicality of published articles that are cited in the same year as their publication. The steady increase of PJNNS's II is depicted in Figure 2. The three most cited articles that contributed to the growth of the 2022 II are presented in Table 2.

The editors thank all authors and reviewers of PJNNS for their continued support of our journal. We welcome any suggestions and comments as to how we might further improve the international standing of PJNNS.

References

1. Czarnowska A, Brola W, Zajkowska O, et al. Clinical course and outcome of SARS-CoV-2 infection in multiple sclerosis patients treated with disease-modifying therapies - the Polish experience. Neurol Neurochir Pol. 2021; 55(2): 212–222, doi: 10.5603/PJNNS.a2021.0031, indexed in Pubmed: 33856686.
2. Nojszewska M, Kalinowska A, Adamczyk-Sowa M, et al. COVID-19 mRNA vaccines (Pfizer-BioNTech and Moderna) in patients with multiple sclerosis: a statement by a working group convened by the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society. Neurol Neurochir Pol. 2021; 55(1): 8–11, doi: 10.5603/PJNNS.a2021.0016, indexed in Pubmed: 33555604.
3. Milanowski ŁM, Ross OA, Friedman A, et al. Genetics of Parkinson's disease in the Polish population. Neurol Neurochir Pol. 2021;

55(3): 241–252, doi: 10.5603/PJNNS.a2021.0013, indexed in Pubmed: 33539026.

4. Madetko N, Migda B, Alster P, et al. Platelet-to-lymphocyte ratio and neutrophil-tolymphocyte ratio may reflect differences in PD and MSA-P neuroinflammation patterns. Neurol Neurochir Pol. 2022; 56(2): 148–155, doi: 10.5603/PJNNS.a2022.0014, indexed in Pubmed: 35118638.
5. Szejko N, Saramak K, Lombroso A, et al. Cannabis-based medicine in treatment of patients with Gilles de la Tourette syndrome. Neurol Neurochir Pol. 2022; 56(1): 28–38, doi: 10.5603/PJNNS.a2021.0081, indexed in Pubmed: 34708399.
6. Bratosiewicz-Wąsik J. Neuro-COVID-19: an insidious virus in action. Neurol Neurochir Pol. 2022; 56(1): 48–60, doi: 10.5603/PJNNS.a2021.0072, indexed in Pubmed: 34642927.

INVITED EDITORIAL

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 4, pages: 332–334
DOI: 10.5603/PJNNS.a2023.0052

ISSN: 0028-3843, e-ISSN: 1897-4260

Reoperations for degenerative spinal disease in Poland reported to the National Health Fund over 12 months with estimation of reoperation rate and of risk factors associated with reoperations

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I read with great interest the article by Słowiński et al. entitled: 'Risk factors for reoperation after surgical treatment for spinal disease in Poland: a nationwide retrospective study of 38,953 hospitalisations'. The authors of this study have analysed and discussed the state of play regarding the practice of surgical treatment of degenerative spine disease (DSD) in Poland reported to the National Health Fund (NHF) over a 12-month period.

The authors did not only touch upon the problems associated with the neurosurgical treatment of DSD in Poland, they also presented this issue in a broader context that will be unfamiliar to neurosurgeons or orthopaedic surgeons. The sheer numbers of surgical procedures for DSD in Poland illustrate how large is the burden placed on doctors of many specialisms and on our NHF. The authors stated that, in 2014, 68,000 hospitalisations for DSD were reported in Polish hospitals. A total of 1,001,000 DSD patients were treated, and 2,004,000 medical consultations were provided. All these consultations, medical treatments, and neurosurgical operations including reoperations, were reimbursed by the NHF.

The issue of reoperations for DSD is a timely topic because spinal surgeries constitute the majority of neurosurgical operations performed in many neurosurgical departments across Poland. The practice of neurosurgical treatment of DSD is growing, and in the coming years this will pose not only a medical challenge, but also a financial burden for our NHF (Fig. 1). An increasing trend for spinal surgeries is also being observed in many other countries [1–4].

The authors of this study found that in 2018, 38,953 neurosurgical operations for DSD were performed. Reoperations reported within 365 days of hospital discharge affected a total of 3,942 operated patients (10.12%). They established the risk factors for reoperations to include female sex (female-to-male ratio 1.34:1), age at surgery (mean age of reoperated patients 56.66, mean age of other patients 53.24), and multiple comorbidities (from 8.81% in a group of patients without comorbidities to 15.31% in a group of patients with at least three comorbidities). The highest reoperation rate for comorbidities was reported for patients with severe malnutrition (24%), lymphomata and haematological cancers (21.13%), and also obesity (15.11%), depression (14.76%), peripheral vascular diseases (14.54%), arthropathies and connective tissue diseases (14.15%), and neurological diseases (14.71%).

The identification of the above-mentioned comorbidities may be of practical significance in selecting and counselling potential candidates for surgery due to DSD. Regarding the facility profile, those surgeries performed in orthopaedic departments had the highest reoperation rate (11.65%) compared to neurosurgical departments (8.27%) and clinical centres (8.51%). The study revealed unexpected effects of other studied variables on the reoperations rate, which included surgeries with implants, as well as emergency admission and duration of hospital stay. The highest reoperation rate was identified for hospitalisation lasting 1–2 days (12.37%), then for emergency admission (9.33%). Surgeries involving an implant (6.6%) and hospitalisation lasting 4–7 days (6.25%) had the lowest reoperation rates.

Variables that reduced the likelihood of reoperation were shown to include: place of residence (lower for rural areas than urban areas), surgery with an implant compared to surgery without, performance of the primary surgery in a neurosurgical department, and longer hospital stay compared to one-day surgery.

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Received: 29.06.2023 Accepted: 17.07.2023 Early publication date: 25.07.2023

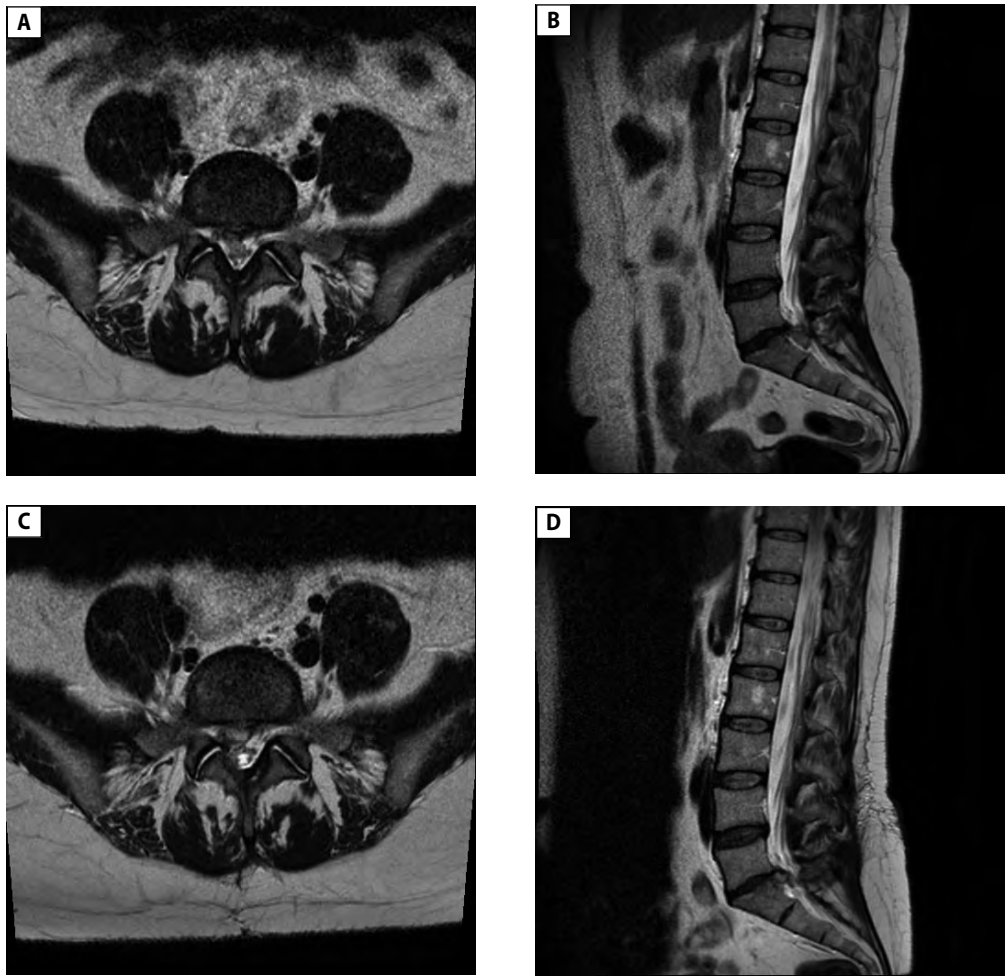

Figure 1. Axial (**A**) and sagittal (**B**) magnetic resonance images show large left disc sequestration at level of L5/S1. Postoperative axial (**C**) and sagittal (**D**) magnetic resonance images depict recurrent herniated disc two months after right-sided microdiscectomy

In my opinion, this is the first Polish study which has systematically elaborated on the reoperation rate after spine surgery in Poland, taking into account so many variables [3, 4]. There have been a few studies, but the literature related to this issue is still scarce in Poland as it is worldwide [5–8]. Furthermore, the authors claim that there is still a need for the establishment of a national spine surgery registry in Poland. However, a few Polish medical institutions already provide medical data to the EUROSPINE International Spine Registry (Spine Tango), founded in 2002 [9].

The establishment of true risk factors for reoperations is a highly important goal, and this may help to reduce the incidence of reoperations for DSD in the future. This approach will, undoubtedly, lead to a reduction of the costs associated with repeated hospitalisations and reoperations reimbursed by the NHF. The search for ways to reduce reoperations is urgent [10, 11].

This study provokes some concerns regarding the true incidence of the reoperations rate throughout one year in Poland. The data provided in this study refers only to the services reimbursed by the NHF. The services funded by private non-public funds are not included. The inclusion criterion set by the authors was 365 days to a reoperation; yet some reoperations are performed later than 12 months. Thus, the final annual rate for the reoperations of DSD is probably underestimated in this study.

My second concern regarding this study relates to non-reported truly reoperation-associated variables including the anatomical site of operation (e.g. cervical, thoracic or lumbar spine), the surgical approach adopted (anterior *vs.* posterior), and any underlying spine pathology (e.g. spinal stenosis, instability, spinal disc herniation) as well as the experience of a surgeon built up over years of clinical practice. If the reoperation rate was to be considered in the scope of primary spinal operation, the reoperation ratio could be estimated according to the type of first spinal surgery performed.

Nevertheless, this study remains a good basis for comparative studies in the future, and may become a benchmark for subsequent studies regarding truly surgical-associated variables of the operation/reoperation ratio for DSD in Poland and beyond.

References

1. Kobayashi K, Ando K, Nishida Y, et al. Epidemiological trends in spine surgery over 10 years in a multicenter database. Eur Spine J. 2018; 27(8): 1698–1703, doi: 10.1007/s00586-018-5513-4, indexed in Pubmed: 29435653.
2. Helseth Ø, Lied B, Heskestad B, et al. Retrospective single-centre series of 1300 consecutive cases of outpatient cervical spine surgery: complications, hospital readmissions, and reoperations. Br J Neurosurg. 2019; 33(6): 613–619, doi: 10.1080/02688697.2019.1675587, indexed in Pubmed: 31607163.
3. Baranowska A, Baranowska J, Baranowski P. Analysis of Reasons for Failure of Surgery for Degenerative Disease of Lumbar Spine. Ortop Traumatol Rehabil. 2016; 18(2): 117–129, doi: 10.5604/15093492.1205004, indexed in Pubmed: 28155820.
4. Flakiewicz J, Wicentowicz Z, Sklepowicz A. Reoperations in lumbar discopathies. Neurol Neurochir Pol. 1992; Suppl 1: 156–160, indexed in Pubmed: 1407291.
5. Adamson T, Godil SS, Mehrlich M, et al. Anterior cervical discectomy and fusion in the outpatient ambulatory surgery setting compared with the inpatient hospital setting: analysis of 1000 consecutive cases. J Neurosurg Spine. 2016; 24(6): 878–884, doi: 10.3171/2015.8.SPINE14284, indexed in Pubmed: 26849708.
6. McGirt MJ, Godil SS, Asher AL, et al. Quality analysis of anterior cervical discectomy and fusion in the outpatient versus inpatient setting: analysis of 7288 patients from the NSQIP database. Neurosurg Focus. 2015; 39(6): E9, doi: 10.3171/2015.9.FOCUS15335, indexed in Pubmed: 26621423.
7. Le Huec JC, Seresti S, Bourret S, et al. Revision after spinal stenosis surgery. Eur Spine J. 2020; 29(Suppl 1): 22–38, doi: 10.1007/s00586-020-06314-w, indexed in Pubmed: 31997016.
8. Machado GC, Ferreira PH, Harris IA, et al. Effectiveness of surgery for lumbar spinal stenosis: a systematic review and meta-analysis. PLoS One. 2015; 10(3): e0122800, doi: 10.1371/journal.pone.0122800, indexed in Pubmed: 25822730.
9. Spine Tango Annual Report 2020; EUROSPINE, the Spine Society of Europe. Uster-Zürich, Switzerland. 2020.
10. Wei FL, Zhou CP, Liu R, et al. Management for lumbar spinal stenosis: A network meta-analysis and systematic review. Int J Surg. 2021; 85: 19–28, doi: 10.1016/j.ijsu.2020.11.014, indexed in Pubmed: 33253898.
11. Yavin D, Casha S, Wiebe S, et al. Lumbar Fusion for Degenerative Disease: A Systematic Review and Meta-Analysis. Neurosurgery. 2017; 80(5): 701–715, doi: 10.1093/neuros/nyw162, indexed in Pubmed: 28327997.

REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 4, pages: 335–343
DOI: 10.5603/PJNNS.a2023.0044

ISSN: 0028-3843, e-ISSN: 1897-4260

Role of orexin in pathogenesis of neurodegenerative parkinsonisms

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ABSTRACT

Introduction. The pathogenesis of parkinsonisms is not fully understood. Among possible factors which may influence the course of neurodegenerative diseases, endocrine abnormalities may be interpreted as having been underevaluated.

State of the art. Growing interest is associated with the role of neuropeptides such as orexin. Orexin is a neuropeptide produced by orexigenic neurons in the lateral parts of the hypothalamus and is linked with excitement, wakefulness and appetite. An extended analysis of this neuropeptide might answer whether changes in the metabolism of orexin is more likely to be a cause or a consequence of neurodegeneration.

Clinical significance. Orexin is a neuropeptide produced by orexigenic neurons in the lateral parts of the hypothalamus and is linked with excitement, wakefulness and appetite. The aim of this study was to discuss the role of this factor and its abnormalities in the pathogenesis and course of parkinsonian syndrome.

Future directions. Understanding the role of orexin in these diseases may be interpreted as an important feature in evolving therapeutical methods. Further evaluation based on larger groups of patients is required.

Key words: parkinsonism, orexin, Parkinson's disease, hypothalamus, PSP

(*Neurol Neurochir Pol 2023; 57 (4): 335–343*)

Introduction

Parkinsonisms are a relatively wide group of diseases of which Parkinson's disease (PD) is the most common. Among other entities associated with this group, dementia with Lewy bodies (DLB) and atypical parkinsonisms such as progressive supranuclear palsy (PSP), corticobasal syndrome (CBS) and multiple system atrophy (MSA) can be mentioned. The pathogenesis of these diseases is not fully verified [1–3]. However, growing interest is associated with the impact of endocrine abnormalities. Dopamine, of which a deficiency is characteristic for Parkinson's disease (PD), is an important neurotransmitter that regulates hormone secretion. Due to the fact that both normal hormonal cells and tumour cells have receptors for dopamine, it can be assumed that abnormal levels of dopamine associated with Parkinson's disease, as well as with its treatment, could potentially cause endocrine disorders.

Endocrine abnormalities in parkinsonisms

Currently, there are few prospective publications on long-term treatment with dopamine agonists and its effect on hormonal balance [4–7]. Based on the literature, in untreated patients diagnosed with Parkinson's disease, there are no

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Received: 26.03.2023 Accepted: 06.06.2023 Early publication date: 18.07.2023

significant disorders in the basal secretion of anterior pituitary hormones- prolactin [8], thyroid-stimulating hormone [8], luteinsing hormone [9], and follicle-stimulating hormone [9]. The role of hormones contributing to non-motor PD symptoms is not fully understood, although a study has indicated cortisol and melatonin to be possible factors impacting upon these elements of clinical manifestation of PD [10]. In the context of melatonin, sleep disturbances and gastrointestinal dysfunction have been described as features negatively correlated with plasma melatonin concentrations [11].

Furthermore, Aziz et al. [8] found normal levels of growth hormone and IGF-1 in untreated patients with Parkinson's disease in morning tests. However, in the testing of the nocturnal secretion of growth hormone, Bruno et al. observed its lower values, which could be more related to age and concomitant diseases than to PD [12]. Secondarily, hormonal imbalance in patients with PD may result from treatment with dopamine agonists rather than prior disease pathology. A significant decrease in prolactin concentration and increased secretion of growth hormone have been observed with unchanged concentrations of insulin-like growth factor (IGF-1), suggesting peripheral resistance to growth hormone in PD patients on dopaminergic medication [7]. Not all dopaminergic drugs cause endocrine abnormalities to the same extent. Among the drugs having the least effect on hormones are the non-ergoline dopaminergic agents, e.g. pramipexole, ropinirole, and rotigotine [13]. Currently, the significance of the hormonal disorders described above in patients with PD is unclear. However, it cannot be ruled out that they have an impact on the occurrence or intensification of non-motor symptoms of this disease, such as autonomic, neuropsychiatric, cognitive disorders, sleep disorders or weight loss.

Orexin in parkinsonisms

Growing interest is associated with the role of neuropeptides such as orexin. Orexin is a neuropeptide linked with excitement, wakefulness and appetite [14]. It is produced by orexigenic neurons located in the hypothalamus. It is a group of neuropeptides of two main types — orexin-A (OXA) and orexin-B (OXB) [14], which are derived from the same prepro-orexin precursor by proteolytic processing [15]. Preproorexin is composed of 130 amino acids and the first beginning of OXA and OXB. Mature OXA is a peptide with 33 amino acids ~3.5 kDa, having two disulfide bonds [16], while OXB is a 28 amino acid peptide with mass of 2.9 kDa, and contains two α-helices which are connected by an elastic loop [17]. Orexin receptors, including orexin 1 receptor (OX_1R) and orexin 2 receptor (OX_2R), belong to G protein-coupled receptors (GPCR) [18–20].

Ox_1R and Ox_2R are found in the brain and central nervous system [21] but OXA is more lipophilic and stable than OXB. OXA is also detectable in the cerebrospinal fluid (CSF) as it crosses the blood–brain barrier and rapidly enters the brain by simple diffusion. In contrast, OXB is rapidly degraded in the serum before entering the CNS [22, 23].

The distribution of these two receptors overlaps, but certain regional differences can be observed. For example, OX_1R is more intensively expressed in the ventromedial nucleus of the hypothalamus, cortical areas, and the nucleus of the bed of the striatum terminal and hippocampus, while OX_2R expression is more pronounced in the cerebral cortex, anterior pretectal nucleus, and the nucleus accumbens (NAc) [24, 25]. The NAc is the projection area of dopaminergic neurons that are present in the VTA. Both receptors are conserved in mammals. Human OX_1R and OX_2R have 94% and 95% resemblance to rat OX_1R and OX_2R, respectively. Both human receptors consist of 425 and 444 amino acids, respectively [26].

The affinity to orexigenic receptors varies depending on the type of orexin [27]. Its impact is based on inducing orexin 1 and orexin 2 receptors. Orexin-A is generally associated with stimulating orexin 1 receptor, Orexin-B is not linked with a majorly affected receptor [28].

Orexin is evaluated in various entities. Its deviated levels may be observed in physiological conditions such as pregnancy and various pathological states [29]. Narcolepsy is among the main entities associated with the abnormalities within orexin neurons [30]. Orexin abnormalities are associated with multiple pathologies, although the mechanism of deterioration varies. In the most common tauopathy, Alzheimer's disease (AD), the progressive deterioration of orexin neurons is associated with developing sleep abnormalities. It is hypothesised that in AD sleep may be affected by abnormalities in orexin regulations, which may be linked with tau and beta-amyloid secretion, accumulation and clearance [31]. Orexin is related with abnormalities in parkinsonisms, although it is not known whether the factor is one of the causes of, or rather a consequence of, the pathological pathways observed in the diseases [32, 33]. In diseases affected by Lewy bodies such as PD or DLB, the pathology selectively affects the regions of the hypothalamus, among which can be mentioned orexin/ /hypocretin neurons, tuberomammillary nucleus and lateral tuberal nucleus [34, 35]. Among neurological diseases with abnormalities in the orexinergic system can be mentioned PD, atypical parkinsonisms, Huntington's disease, AD and multiple sclerosis [36]. In some of these diseases, as with PD, abnormalities of the levels of orexin are associated with disease severity [37]. The role of orexin in parkinsonism has been studied for more than 20 years (Tab. 1).

Orexin in synuleinopathic parkinsonian syndromes

From previous studies, it is known that orexinergic neurons are significantly affected by Parkinson's disease (PD). Fronczek et al. [38] showed that in patients with PD, the number of orexinergic neurons is decreased in the hypothalamus, while the concentration of OXA in the CSF and the frontal cortex is reduced. In addition, studies in animal models have shown that

Table 1. Abnormalities associated with orexin in parkinsonisms*

Disease	Clinical features
Synucleinopathic parkinsonian syndromes	– excessive daytime sleepiness – anxiety – cognitive deterioration** – dysautonomia – inverse correlation between levels of orexin and duration of morbidity
Tauopathic parkinsonian syndrome	– inverse correlation between levels of orexin and duration of morbidity

*Based on literature summarised in paragraph "endocrine abnormalities in parkinsonisms"
**Questionable data concerning dementia with Lewy bodies

the greater the damage to orexinergic neurons, the greater the decrease in the level of orexin in the cerebrospinal fluid [39].

Orexin as possible neuroprotective agent

Studies on PD animal and cell models have provided data suggesting a neuroprotective effect of orexin on dopaminergic neurons; orexin-A reduced MPP+-induced damage by increasing the expression of hypoxia-inducible factor 1α. Feng et al. [40] showed that hypoxia-inducible factor 1 alpha (HIF1-α) is deficient in PD as a result of mitochondrial dysfunction, while administration of orexin-A leads to a significant neuroprotective effect on dopaminergic neurons through activation of HIF-α. Orexin-A attenuated 6-hydroxydopamine toxicity [41] and lowered MPTP-induced loss of dopaminergic neurons in the substantia nigra in mice [42]. Therefore, it can be hypothesised that neurodegeneration of orexigenic neurons observed in PD may accelerate further damage of other brain structures.

Brain-derived neurotrophic factor (BDNF) promotes neuroprotection and neuroregeneration [43]. In animal models of PD, BDNF enhances the survival of dopaminergic neurons, and improves dopaminergic neurotransmission and motor performance. OXA increases BDNF protein levels in dopaminergic neurons in PD by reducing tyrosine hydroxylase (TH) and upregulating BDNF in the substantia nigra. This is mainly mediated by OX_1R [44, 45].

Research has shown that mRNA expression of BDNF is downregulated in the substantia nigra, and inhibition of BDNF expression leads to loss of dopaminergic neurons in the substantia nigra of PD patients [46–48]. Epidemiological studies have shown that lower levels of BDNF in serum were associated with cognitive and motor impairments in PD patients [49–51].

These studies may suggest a role for orexin-A deficiency in the progression of PD, as well as explaining the link between narcolepsy-like symptoms in PD as both dopamine and orexin influence the regulation of the sleep pattern by activating the midbrain and thalamocortical pathways [52].

Orexin in context of narcolepsy-like symptoms

Ylikoski et al. [53] reported a high correlation between the occurrence of symptoms of narcolepsy and REM sleep behaviour disorder (RBD) among PD patients. Interestingly, many symptoms of PD and narcolepsy are shared: excessive daytime sleepiness, REM sleep abnormalities, sleep paralysis, hypnagogic hallucinations, and cataplexy. This phenomenon could be, at least partially, explained by progressive loss of orexigenic neurons in the process of neurodegeneration which causes orexin deficiency similar to that in narcolepsy with cataplexy. Ylikoski et al. concluded that narcolepsy-like symptoms in PD patients are secondary to PD itself as there is no evidence suggesting that patients with narcolepsy have a higher risk of developing PD. Genetic analysis revealed the existence of 38 genes shared in PD and narcolepsy gene sets [54] mainly associated with locomotion, circadian circle, sleep, learning and memory. The correlation of narcolepsy-like symptoms with orexin deficiency could potentially have a therapeutic impact in the future; currently animal studies indicate the usefulness of orally administered TAK-994 (OX2R agonist) in ameliorating narcolepsy-like symptoms in narcolepsy mouse models [55].

Orexin in context of body metabolism

Further studies on animal models have shown that orexin is an important link between sleep and body metabolism, as sleep deprivation leads to increased food intake and induction of catabolism [56]. It is known that orexin is responsible for stimulating food intake as a result of inhibiting autonomic digestive reactions. Orexigenic neurons are inhibited by leptin and food intake, while ghrelin and hypoglycaemia activate these neurons. The use of a high-protein and amino acids diet may affect the hyperpolarisation of orexigenic neurons and block glucose-induced activations of orexigenic neurons [57]. The association between the impact of food intake, the role of orexin and PD has not yet been explored. One study indicated links between reward functions and orexin, as the abnormalities within this mechanism may be linked with drug-craving, which is commonly described as a feature of dopaminergic dysregulation [58]. On the other hand, food intake by be affected by the dysregulation of striatal dopamine D2/D3 receptors. In this mechanism, the impact of orexin was found to be inducing depressive behaviours in animal models [59]. These mechanisms show examples of possible and indirect pathways leading to food intake disruptions.

Orexin in context of other neurotransmitters

Both orexin receptors are involved in stimulating various neurotransmitters that are associated with the activation of the central nervous system such as monoamine neurons (serotonin, histamine, norepinephrine and dopamine), and cholinergic neurons in the basal forebrain [60]. Therefore, orexin receptor mutations lead to sleep disorders. Yamanaka et al. [61] showed that activation of OX_2R by orexin leads to wakefulness mediated by the neurotransmitter histamine, as antihistamine blocks the excitatory effects of orexin, while activation of OX_1R by orexin leads to wakefulness through the neurotransmitter norepinephrine. Decreased CSF orexin levels have been documented in

patients with narcolepsy, and are indeed now considered one diagnostic criterion for diagnosing narcolepsy.

Orexin in contest of daytime sleepiness

A work based on the examination of three patients did not show abnormalities in the level of orexin-A among patients with PD and excessive daytime sleepiness. The group was affected by several limitations apart from the number of patients, among which could be mentioned the diverse ages of the patients — 52 to 69, and the fact that treatment duration varied from 0.5 to 5 years. All of the patients received dopamine agonists — pramipexole and pergolide, factors increasing their vulnerability to daytime sleepiness [62]. On the other hand, a study based on a larger group of patients revealed an association between reduced orexin levels in ventricular CSF and daytime sleepiness in advanced PD [63]. The impact of orexin in parkinsonian syndromes is not limited to sleep disturbances. The lack of an effect between orexin levels and daytime sleepiness in PD patients is still unclear, but many factors may be at play. Firstly, it may be a discrepancy between the measurements of the CSF of the spinal cord and the ventricular CSF [64]. The next explanation could be a deficiency in other neurotransmitters besides orexin. PD and parkinsonian syndromes are neurodegenerative diseases in which broad neuronal systems are impaired, including not only orexin fibres, but also acetylcholine, serotonin, and norepinephrine neurons. These neurotransmitters also play an important role in sleep/wake mechanisms [30, 65]. Confirmation of this thesis came from a paper by Rey et al., which showed the possible involvement of midbrain noradrenergic and dopaminergic neurons on the sleep/wake state via thalamocortical pathways [66]. In addition, the arrangement of orexin fibres in the hypothalamic and brainstem nuclei that are damaged in PD may contribute to the dysfunction of the orexin system. Therefore, CSF orexin levels are poorly correlated with clinical sleep disturbance in PD [30].

Orexin in context of dementia

Orexin-B transferred intracerebroventricularly in MPTP parkinsonian mice resulted in the reduction of dopaminergic neuron degeneration. Orexin B application was correlated with improvements in spontaneous activity and motor coordination [67]. Additionally, the impact of Orexin-A is different in dementias. In dementia with Lewy bodies (DLB), the cognitive function is not correlated with its levels in the cerebrospinal fluid, whereas the correlation is maintained in AD [68–70]. In parkinsonian syndromes it is considered as a factor affecting sleep abnormalities [71]. In a study examining PD patients with REM Behaviour Disorder (RBD), PD without RBD and idiopathic RBD, no significant decrease in the levels of orexin compared to healthy controls was observed [72]. The lack of differences between the groups was accompanied by similar results of Tumour Necrosis Factor alpha in the serum and cerebrospinal fluid.

Increased levels of plasma orexin-A have been detected in entities preceding neurodegenerative disease, as in mild cognitive impairment with Lewy bodies [73]. In PD, increased levels of orexin-A have been correlated with anxiety, cognitive and non-motor symptom scales [74]. Similar results have been observed in DLB, although in DLB with cognitive fluctuation or parkinsonisms the levels of orexin-A were decreased when contrasted with healthy controls. Plasma orexin-A was found to be correlated with cognitive and motor features in MCI-Lewy bodies and DLB [73]. The abnormalities regarding orexin in DLB were also interpreted as a differentiating feature in AD and DLB in females, as its levels were decreased in this synucleinopathy when compared to tauopathy [75].

Role of orexin in autonomic nervous system

Orexin neurons are connected with multiple structures involved in autonomic functions such as presympathetic neural cells inter alia in rostral ventrolateral and ventromedial medulla, raphe nuclei, noradrenergic cells in the pons, paraventricular nucleus of the hypothalamus, nucleus ambiguus, dorsal motor nucleus of the vagus nerve, and solitary tract nucleus [76]. Orexin has an impact on the sympathetic cardiovascular system causing an increase of blood pressure (BP), heart rate (HR) and renal sympathetic nerve activity [76]. Animal studies have indicated that orexin is involved in the cardiovascular stress response that is sympathetic excitation and in baroreflex and chemoreflex responses [76], although this is a rather minor role focused on potentiating and controlling other inputs, as HR and BP variability are preserved in animals with orexin signalling dysfunction [76].

It is possible that a similar mechanism may be involved in orthostatic hypotension observed in patients with PD and especially multiple system atrophy (MSA). Animal studies suggest orexin signalling is necessary in cardiovascular regulation during sleep [77]. Although the impact of orexin on cardiovascular system and sympathetic regulation is evident in animal studies, it is unwise to extend these results to humans as there are no methods enabling a direct assessment of orexin activity applicable for human participants. Another animal study indicates that transgenic rats with a minimal number of orexigenic neurons have decreased response to B-blockers, impaired R-R interval regulation, and heart hypotrophy [78].

Some data supports a hypothesis concerning the role of orexin in the fight-or-flight response — e.g: orexin administration causes an increase in cardiovascular and respiratory activity and analgesia [79]. Interestingly, in a mouse model, the suppression of baroreceptor reflex was visible only during the defence response, while it remained normal at rest [80]. Orexigenic neurons, but not orexin peptides, are involved in stress-induced hyperthermia in a mouse model, which indicates the role of other neurotransmitters in this process [81]. Orexin neurons are sensitive to changes in pH and CO_2 concentration; acidosis causes its excitation and an

increase in autonomic respiration rate regulation, whereas alkalosis reduces their firing rate and causes a decrease in respiratory activity [82].

Orexin in tauopathic parkinsonian syndromes

A study evaluating orexin in PD, DLB, CBS and PSP revealed an inverse correlation between levels of orexin and duration of morbidity in PSP and its lack in other examined diseases [83]. The authors hypothesised that orexin may be a feature of neurodegeneration in PSP [83]. Information concerning the role of orexin in PSP has been relatively briefly described. One of the cases revealed orexin-A in undetectable levels in the CSF in a 74-year-old patient with probable PSP [84]. The authors assessed the neuropathological changes in PSP as neurofibrillary tangles in the hypothalamus as being associated with deviated orexin neurotransmission.

Orexin in other entities

The role of orexin-A has also been evaluated in MPTP parkinsonian mice. This work showed an association between BDNF and impacting OX1R receptors [85]. Orexin-A was found to have a neuroprotective role. Apart from sleep disorders, orexin has been found to be a factor decreasing the severity of motor impairments and deficits in memory updating [86]. The recent development of pharmacological orexin antagonists provides a good avenue for therapy in this field, which also has potential in neurodegeneration [87, 88]. The mechanism of orexin inhibition is associated with beta-amyloid accumulation [89]. Dual orexin antagonists block the association of the wakefulness-promoting neuropeptides orexin A and orexin B, with their location and receptor sites. Currently, two orexin receptor antagonists (suvorexant and lemborexant) are approved for the treatment of insomnia.

These drugs bind reversibly to both receptors (OX1R and OX2R) and inhibit the activation of the arousal system; thereby facilitating the induction and maintenance of sleep [90–92], although lemborexant has a stronger inhibitory effect on OX2R than OX1R compared to suvorexant which could increase non-REM sleep. Lemborexant binds to and rapidly dissociates from orexin receptors, unlike other orexin receptor antagonists which usually dissociate slowly, which will make it easier to fall asleep and reduce the risk of drowsiness the next day.

Suvorexant is generally well tolerated, but it has a lesser effect on the neurophysiology of sleep compared to benzodiazepines (traditional hypnotics). However its efficacy requires additional validation [93, 94]. A few studies have reported rare, but significant, side-effects of suvorexant in the treatment of insomnia disorder in Parkinson's patients. These include sleep paralysis, abnormal dreams, over-sedation, the acute worsening of depressive symptoms, REM sleep behavioural disorder and suicidal thoughts [95–97]. Confirmation of the above comes from a paper by Tabota et al., which presented a 72-year-old patient with PD in whom administration of 15 mg suvorexant induced both nightmares and abnormal behaviour during sleep, whereas he did not exhibit such dream enactment behaviour when not taking suvorexant [98].

However, no papers have yet addressed the therapeutic potential of lemborexant in PD patients.

Orexin antagonists are among the methods of therapy in this field. The mechanism of orexin inhibition is associated with decreased beta-amyloid plaque formation [89]. A study has shown that physiological levels of orexin A in the CSF are linked with excessive daytime sleepiness [99]. This study revealed that the level of orexin-A in CSF was similar to the one observed among geriatric patients, decreased in comparison with AD, and increased in comparison with frontotemporal lobe dementia [99].

Orexin as a factor in anti-parkinsonian medication

Interestingly, the orexinergic neurons may be reduced as an effect of anti-parkinsonian medication. The role of ropinirole is not fully understood, however the authors of one study suggested a possible association between impacting dopaminergic receptors and inhibiting excitatory activities of the neurons correlated with orexin [100]. The impact of anti-parkinsonian drugs on orexigenic receptors is not fully understood. A work on the role of levodopa revealed its antinoceptive function in colonic distension by stimulating D2 dopamine receptor and inducing endogenous brain orexin [101].

Conclusions

The main question regarding abnormalities of orexin levels in the context of parkinsonisms is whether the factor is more of an inductor, a consequence of neurodegeneration, or simply a neutral feature.

In the context of vigilance and sleep deviations in this group of diseases, the possible interference of orexin may play a role. The ambiguous results of analyses of orexin levels in parkinsonian entities may suggest that the role is diverse, possibly depending more on the stage of the disease than the type of parkinsonism.

The often contradictory outcomes of studies may suggest an undetectable feature or that the significance of orexin in parkinsonisms may be questionable. Moreover, the majority of studies have been affected by a lack of sleep-specific data as well as of polysomnographic data, a sleep questionnaire, and circadian rhythm data. Such detailed analysis would be helpful in obtaining possibly more effective methods of treatments. The findings concerning orexin in parkinsonisms lacking evidence-based treatment as atypical parkinsonisms seem additionally striking. More research in this field is required.

Conflicts of interest: *None.*
Funding: *None.*

References

1. Figura M, Friedman A. In search of Parkinson's disease biomarkers — is the answer in our mouths? A systematic review of the literature on salivary biomarkers of Parkinson's disease. Neurol Neurochir Pol. 2020; 54(1): 14–20, doi: 10.5603/PJNNS.a2020.0011, indexed in Pubmed: 32003440.
2. Madetko N, Migda B, Alster P, et al. Platelet-to-lymphocyte ratio and neutrophil-tolymphocyte ratio may reflect differences in PD and MSA-P neuroinflammation patterns. Neurol Neurochir Pol. 2022; 56(2): 148–155, doi: 10.5603/PJNNS.a2022.0014, indexed in Pubmed: 35118638.
3. Alster P, Madetko N, Friedman A. Neutrophil-to-lymphocyte ratio (NLR) at boundaries of Progressive Supranuclear Palsy Syndrome (PSPS) and Corticobasal Syndrome (CBS). Neurol Neurochir Pol. 2021; 55(1): 97–101, doi: 10.5603/PJNNS.a2020.0097, indexed in Pubmed: 33315235.
4. Díaz F, Liberman C, Chariá P. Patients with Parkinson disease: functional analysis of dopamine receptors by bromocriptine-thyrotropin-releasing hormone test. Rev Med Chil. 1991; 119(3): 252–257, indexed in Pubmed: 1842116.
5. Eisler T, Thorner MO, MacLeod RM, et al. Prolactin secretion in Parkinson disease. Neurology. 1981; 31(10): 1356–1359, doi: 10.1212/wnl.31.10.1356, indexed in Pubmed: 6810204.
6. Daniel JS, Govindan JP, Kamath C, et al. Newer dopaminergic agents cause minimal endocrine effects in idiopathic Parkinson's disease. Clin Med Insights Endocrinol Diabetes. 2014; 7: 13–17, doi: 10.4137/CMED.S14902, indexed in Pubmed: 24855402.
7. Schaefer S, Vogt T, Nowak T, et al. German KIMS board. Pituitary function and the somatotrophic system in patients with idiopathic Parkinson's disease under chronic dopaminergic therapy. J Neuroendocrinol. 2008; 20(1): 104–109, doi: 10.1111/j.1365-2826.2007.01622.x, indexed in Pubmed: 18081558.
8. Aziz NA, Pijl H, Frölich M, et al. Diurnal secretion profiles of growth hormone, thyrotrophin and prolactin in Parkinson's disease. J Neuroendocrinol. 2011; 23(6): 519–524, doi: 10.1111/j.1365-2826.2011.02134.x, indexed in Pubmed: 21466597.
9. Lake MG, Krook LS, Cruz SV. Pituitary adenomas: an overview. Am Fam Physician. 2013; 88(5): 319–327, indexed in Pubmed: 24010395.
10. van Wamelen DJ, Wan YM, Ray Chaudhuri K, et al. Stress and cortisol in Parkinson's disease. Int Rev Neurobiol. 2020; 152: 131–156, doi: 10.1016/bs.irn.2020.01.005, indexed in Pubmed: 32450994.
11. Li L, Zhao Z, Ma J, et al. Elevated plasma melatonin levels are correlated with the non-motor symptoms in parkinson's disease: a cross-sectional study. Front Neurosci. 2020; 14: 505, doi: 10.3389/fnins.2020.00505, indexed in Pubmed: 32508583.
12. Bruno OD, Danilowicz K, Manavela M, et al. Long-term management with octreotide or cabergoline in ectopic corticotropin hypersecretion: case report and literature review. Endocr Pract. 2010; 16(5): 829–834, doi: 10.4158/EP09286.CR, indexed in Pubmed: 20497940.
13. Schilling JC, Adamus WS, Palluk R. Neuroendocrine and side effect profile of pramipexole, a new dopamine receptor agonist, in humans. Clin Pharmacol Ther. 1992; 51(5): 541–548, doi: 10.1038/clpt.1992.60, indexed in Pubmed: 1350237.
14. Khalil H, Alomari MA, Khabour OF, et al. Relationship of circulatory BDNF with cognitive deficits in people with Parkinson's disease. J Neurol Sci. 2016; 362: 217–220, doi: 10.1016/j.jns.2016.01.032, indexed in Pubmed: 26944151.
15. Gotter AL, Webber AL, Coleman PJ, et al. International Union of Basic and Clinical Pharmacology. LXXXVI. Orexin receptor function, nomenclature and pharmacology. Pharmacol Rev. 2012; 64(3): 389–420, doi: 10.1124/pr.111.005546, indexed in Pubmed: 22759794.
16. Nitkiewicz A, Smolinska N, Maleszka A, et al. Localization of orexin A and orexin B in the porcine uterus. Reprod Biol. 2012; 12(2): 135–155, doi: 10.1016/s1642-431x(12)60082-5, indexed in Pubmed: 22850467.
17. Wong KKY, Ng SYL, Lee LTO, et al. Orexins and their receptors from fish to mammals: a comparative approach. Gen Comp Endocrinol. 2011; 171(2): 124–130, doi: 10.1016/j.ygcen.2011.01.001, indexed in Pubmed: 21216246.
18. de Lecea L, Kilduff TS, Peyron C, et al. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci USA. 1998; 95(1): 322–327, doi: 10.1073/pnas.95.1.322, indexed in Pubmed: 9419374.
19. Sakurai T, Amemiya A, Ishii M, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell. 1998; 92(4): 573–585, doi: 10.1016/s0092-8674(00)80949-6, indexed in Pubmed: 9491897.
20. Soya S, Sakurai T. Evolution of orexin neuropeptide system: structure and function. Front Neurosci. 2020; 14: 691, doi: 10.3389/fnins.2020.00691, indexed in Pubmed: 32754010.
21. Xu TR, Yang Y, Ward R, et al. Orexin receptors: multi-functional therapeutic targets for sleeping disorders, eating disorders, drug addiction, cancers and other physiological disorders. Cellular Signalling. 2013; 25(12): 2413–2423, doi: 10.1016/j.cellsig.2013.07.025.
22. Azeez IA, Del Gallo F, Cristino L, et al. Daily fluctuation of orexin neuron activity and wiring: the challenge of "chronoconnectivity". Front Pharmacol. 2018; 9: 1061, doi: 10.3389/fphar.2018.01061, indexed in Pubmed: 30319410.
23. Kastin AJ, Akerstrom V. Orexin A but not orexin B rapidly enters brain from blood by simple diffusion. J Pharmacol Exp Ther. 1999; 289(1): 219–223, indexed in Pubmed: 10087007.
24. Trivedi P, Yu H, MacNeil DJ, et al. Distribution of orexin receptor mRNA in the rat brain. FEBS Lett. 1998; 438(1-2): 71–75, doi: 10.1016/s0014-5793(98)01266-6, indexed in Pubmed: 9821961.
25. Marcus JN, Aschkenasi CJ, Lee CE, et al. Differential expression of orexin receptors 1 and 2 in the rat brain. J Comp Neurol. 2001; 435(1): 6–25, doi: 10.1002/cne.1190, indexed in Pubmed: 11370008.
26. Spinazzi R, Andreis PG, Rossi GP, et al. Orexins in the regulation of the hypothalamic-pituitary-adrenal axis. Pharmacol Rev. 2006; 58(1): 46–57, doi: 10.1124/pr.58.1.4, indexed in Pubmed: 16507882.
27. Al-Kuraishy HM, Abdulhadi MH, Hussien NR, et al. Involvement of orexinergic system in psychiatric and neurodegenerative disorders: A scoping review. Brain Circ. 2020; 6(2): 70–80, doi: 10.4103/bc.bc_42_19, indexed in Pubmed: 33033776.
28. Wang C, Wang Q, Ji B, et al. The orexin/receptor system: molecular mechanism and therapeutic potential for neurological diseases. Front Mol Neurosci. 2018; 11: 220, doi: 10.3389/fnmol.2018.00220, indexed in Pubmed: 30002617.
29. Bastianini S, Berteotti C, Lo Martire V, et al. A critical role of hypocretin deficiency in pregnancy. J Sleep Res. 2014; 23(2): 186–188, doi: 10.1111/jsr.12107, indexed in Pubmed: 24772478.
30. Ogawa T, Kajiyama Y, Ishido H, et al. Decreased cerebrospinal fluid orexin levels not associated with clinical sleep disturbance in Parkinson's disease: A retrospective study. PLoS One. 2022; 17(12): e0279747, doi: 10.1371/journal.pone.0279747, indexed in Pubmed: 36584130.
31. Dauvilliers Y. Hypocretin/orexin, sleep and Alzheimer's disease. Front Neurol Neurosci. 2021; 45: 139–149, doi: 10.1159/000514967, indexed in Pubmed: 34052817.

32. Cersosimo MG, Benarroch EE, Raina GB. Lewy bodies in the olfactory system and the hypothalamus. Handb Clin Neurol. 2021; 182: 235–244, doi: 10.1016/B978-0-12-819973-2.00016-2, indexed in Pubmed: 34266595.
33. Alster P, Madetko-Alster N, Migda A, et al. Sleep disturbances in progressive supranuclear palsy syndrome (PSPS) and corticobasal syndrome (CBS). Neurol Neurochir Pol. 2023; 57(3): 229–234, doi: 10.5603/PJNNS.a2023.0019, indexed in Pubmed: 36928793.
34. Stanojlovic M, Pallais JP, Kotz CM. Inhibition of orexin/hypocretin neurons ameliorates elevated physical activity and energy expenditure in the A53T mouse model of Parkinson's disease. Int J Mol Sci. 2021; 22(2), doi: 10.3390/ijms22020795, indexed in Pubmed: 33466831.
35. Gan J, Chen Z, Han J, et al. Orexin-A in patients with Lewy body disease: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2021; 12: 765701, doi: 10.3389/fendo.2021.765701, indexed in Pubmed: 34867809.
36. Wang Q, Cao F, Wu Y. Orexinergic system in neurodegenerative diseases. Front Aging Neurosci. 2021; 13: 713201, doi: 10.3389/fnagi.2021.713201, indexed in Pubmed: 34483883.
37. Emamzadeh FN, Surguchov A. Parkinson's disease: biomarkers, treatment, and risk factors. Front Neurosci. 2018; 12: 612, doi: 10.3389/fnins.2018.00612, indexed in Pubmed: 30214392.
38. Fronczek R, Overeem S, Lee SYY, et al. Hypocretin (orexin) loss in Parkinson's disease. Brain. 2007; 130(Pt 6): 1577–1585, doi: 10.1093/brain/awm090, indexed in Pubmed: 17470494.
39. Drouot X, Moutereau S, Nguyen JP, et al. Low levels of ventricular CSF orexin/hypocretin in advanced PD. Neurology. 2003; 61(4): 540–543, doi: 10.1212/01.wnl.0000078194.53210.48, indexed in Pubmed: 12939433.
40. Feng Ya, Liu Te, Li XQ, et al. Neuroprotection by Orexin-A via HIF-1α induction in a cellular model of Parkinson's disease. Neurosci Lett. 2014; 579: 35–40, doi: 10.1016/j.neulet.2014.07.014, indexed in Pubmed: 25038418.
41. Pasban-Aliabadi H, Esmaeili-Mahani S, Abbasnejad M. Orexin-A protects human neuroblastoma SH-SY5Y cells against 6-hydroxydopamine-induced neurotoxicity: involvement of PKC and PI3K signaling pathways. Rejuvenation Res. 2017; 20(2): 125–133, doi: 10.1089/rej.2016.1836, indexed in Pubmed: 27814668.
42. Liu MF, Xue Y, Liu C, et al. Orexin-A exerts neuroprotective effects via OX1R in Parkinson's disease. Front Neurosci. 2018; 12: 835, doi: 10.3389/fnins.2018.00835, indexed in Pubmed: 30524223.
43. Chmielewska N, Szyndler J, Makowska K, et al. Looking for novel, brain-derived, peripheral biomarkers of neurological disorders. Neurol Neurochir Pol. 2018; 52(3): 318–325, doi: 10.1016/j.pjnns.2018.02.002, indexed in Pubmed: 29478670.
44. Sheng Q, Xue Y, Wang Y, et al. The subthalamic neurons are activated by both Orexin-A and Orexin-B. Neuroscience. 2018; 369: 97–108, doi: 10.1016/j.neuroscience.2017.11.008.
45. Bubser M, Fadel JR, Jackson LL, et al. Dopaminergic regulation of orexin neurons. Eur J Neurosci. 2005; 21(11): 2993–3001, doi: 10.1111/j.1460-9568.2005.04121.x, indexed in Pubmed: 15978010.
46. Howells DW, Porritt MJ, Wong JY, et al. Reduced BDNF mRNA expression in the Parkinson's disease substantia nigra. Exp Neurol. 2000; 166(1): 127–135, doi: 10.1006/exnr.2000.7483, indexed in Pubmed: 11031089.
47. Porritt MJ, Batchelor PE, Howells DW. Inhibiting BDNF expression by antisense oligonucleotide infusion causes loss of nigral dopaminergic neurons. Exp Neurol. 2005; 192(1): 226–234, doi: 10.1016/j.expneurol.2004.11.030, indexed in Pubmed: 15698637.
48. Fumagalli F, Racagni G, Riva MA. Shedding light into the role of BDNF in the pharmacotherapy of Parkinson's disease. Pharmacogenomics J. 2006; 6(2): 95–104, doi: 10.1038/sj.tpj.6500360, indexed in Pubmed: 16402079.
49. Angelucci F, Peppe A, Carlesimo GA, et al. A pilot study on the effect of cognitive training on BDNF serum levels in individuals with Parkinson's disease. Front Hum Neurosci. 2015; 9: 130, doi: 10.3389/fnhum.2015.00130, indexed in Pubmed: 25852518.
50. Khalil H, Alomari MA, Khabour OF, et al. Relationship of circulatory BDNF with cognitive deficits in people with Parkinson's disease. J Neurol Sci. 2016; 362: 217–220, doi: 10.1016/j.jns.2016.01.032, indexed in Pubmed: 26944151.
51. Wang Yu, Liu H, Zhang BS, et al. Low BDNF is associated with cognitive impairments in patients with Parkinson's disease. Parkinsonism Relat Disord. 2016; 29: 66–71, doi: 10.1016/j.parkreldis.2016.05.023, indexed in Pubmed: 27245919.
52. Asai H, Hirano M, Furiya Y, et al. Cerebrospinal fluid-orexin levels and sleep attacks in four patients with Parkinson's disease. Clin Neurol Neurosurg. 2009; 111(4): 341–344, doi: 10.1016/j.clineuro.2008.11.007, indexed in Pubmed: 19097685.
53. Ylikoski A, Martikainen K, Sarkanen T, et al. Parkinson's disease and narcolepsy-like symptoms. Sleep Med. 2015; 16(4): 540–544, doi: 10.1016/j.sleep.2014.12.010, indexed in Pubmed: 25770044.
54. Chunduri A, Crusio WE, Delprato A. Narcolepsy in Parkinson's disease with insulin resistance. F1000Res. 2020; 9: 1361, doi: 10.12688/f1000research.27413.3, indexed in Pubmed: 34745571.
55. Ishikawa T, Hara H, Kawano A, et al. TAK-994, a novel orally available brain-penetrant orexin 2 receptor-selective agonist, suppresses fragmentation of wakefulness and cataplexy-like episodes in mouse models of narcolepsy. J Pharmacol Exp Ther. 2023; 385(3): 193–204, doi: 10.1124/jpet.122.001449, indexed in Pubmed: 37001988.
56. Kaneko K, Yoshikawa M, Ohinata K. Novel orexigenic pathway prostaglandin D2-NPY system — involvement in orally active orexigenic δ opioid peptide. Neuropeptides. 2012; 46(6): 353–357, doi: 10.1016/j.npep.2012.10.003, indexed in Pubmed: 23141054.
57. Palomba L, Silvestri C, Imperatore R, et al. Negative regulation of leptin-induced reactive oxygen species (ROS) formation by cannabinoid CB1 receptor activation in hypothalamic neurons. J Biol Chem. 2015; 290(22): 13669–13677, doi: 10.1074/jbc.M115.646885, indexed in Pubmed: 25869131.
58. Mahler SV, Smith RJ, Moorman DE, et al. Multiple roles for orexin/hypocretin in addiction. Prog Brain Res. 2012; 198: 79–121, doi: 10.1016/B978-0-444-59489-1.00007-0, indexed in Pubmed: 22813971.
59. Chen B, Xu J, Chen S, et al. Dysregulation of striatal dopamine D2/D3 receptor-mediated by hypocretin induces depressive behaviors in rats. J Affect Disord. 2023; 325: 256–263, doi: 10.1016/j.jad.2023.01.031, indexed in Pubmed: 36638964.
60. Almeneessier AS, Alzoghaibi M, BaHammam AA, et al. The effects of diurnal intermittent fasting on the wake-promoting neurotransmitter orexin-A. Ann Thorac Med. 2018; 13(1): 48–54, doi: 10.4103/atm.ATM_181_17, indexed in Pubmed: 29387256.
61. Yamanaka A, Tsujino N, Funahashi H, et al. Orexins activate histaminergic neurons via the orexin 2 receptor. Biochem Biophys Res Commun. 2002; 290(4): 1237–1245, doi: 10.1006/bbrc.2001.6318, indexed in Pubmed: 11811995.

62. Overeem S, van Hilten JJ, Ripley B, et al. Normal hypocretin-1 levels in Parkinson's disease patients with excessive daytime sleepiness. Neurology. 2002; 58(3): 498–499, doi: 10.1212/wnl.58.3.498, indexed in Pubmed: 11839864.
63. Drouot X, Moutereau S, Nguyen JP, et al. Low levels of ventricular CSF orexin/hypocretin in advanced PD. Neurology. 2003; 61(4): 540–543, doi: 10.1212/01.wnl.0000078194.53210.48, indexed in Pubmed: 12939433.
64. Compta Y, Santamaria J, Ratti L, et al. Cerebrospinal hypocretin, daytime sleepiness and sleep architecture in Parkinson's disease dementia. Brain. 2009; 132(Pt 12): 3308–3317, doi: 10.1093/brain/awp263, indexed in Pubmed: 19858078.
65. Távora DG, de Bruin VM, Lopes Gama R, et al. The nature of excessive sleepiness and sudden sleep onset in Parkinson's disease. Sleep Sci. 2014; 7(1): 13–18, doi: 10.1016/j.slsci.2014.07.020, indexed in Pubmed: 26483896.
66. Rye DB. The two faces of Eve: dopamine's modulation of wakefulness and sleep. Neurology. 2004; 63(8 Suppl 3): S2–S7, doi: 10.1212/wnl.63.8_suppl_3.s2, indexed in Pubmed: 15505137.
67. Bian K, Liu C, Wang Y, et al. Orexin-B exerts excitatory effects on nigral dopaminergic neurons and alleviates motor disorders in MPTP parkinsonian mice. Neurosci Lett. 2021; 765: 136291, doi: 10.1016/j.neulet.2021.136291, indexed in Pubmed: 34666119.
68. Shimizu S, Takenoshita N, Inagawa Y, et al. Positive association between cognitive function and cerebrospinal fluid orexin a levels in Alzheimer's disease. J Alzheimers Dis. 2020; 73(1): 117–123, doi: 10.3233/JAD-190958, indexed in Pubmed: 31744010.
69. Inagawa Y, Shimizu S, Takenoshita N, et al. Association between cerebrospinal fluid Orexin A level and severity of rapid eye movement sleep behaviour disorder in dementia with Lewy bodies. Psychogeriatrics. 2021; 21(1): 128–130, doi: 10.1111/psyg.12618, indexed in Pubmed: 33145889.
70. Matsumoto S, Tsunematsu T. Association between sleep, Alzheimer's, and Parkinson's disease. Biology (Basel). 2021; 10(11), doi: 10.3390/biology10111127, indexed in Pubmed: 34827122.
71. Kumar S, Behl T, Sehgal A, et al. Exploring the role of orexinergic neurons in parkinson's disease. Neurotox Res. 2021; 39(6): 2141–2153, doi: 10.1007/s12640-021-00411-4, indexed in Pubmed: 34495449.
72. Yuan Y, Zhang Y, Cheng Y, et al. Cerebrospinal fluid TNF-α and orexin in patients with Parkinson's disease and rapid eye movement sleep behavior disorder. Front Neurol. 2022; 13: 826013, doi: 10.3389/fneur.2022.826013, indexed in Pubmed: 35250828.
73. Gan J, Liu S, Chen Z, et al. Elevated plasma orexin-a levels in prodromal dementia with Lewy bodies. J Alzheimers Dis. 2022; 88(3): 1037–1048, doi: 10.3233/JAD-220082, indexed in Pubmed: 35723094.
74. Huang S, Zhao Z, Ma J, et al. Increased plasma orexin-A concentrations are associated with the non-motor symptoms in Parkinson's disease patients. Neurosci Lett. 2021; 741: 135480, doi: 10.1016/j.neulet.2020.135480, indexed in Pubmed: 33161104.
75. Wennström M, Londos E, Minthon L, et al. Altered CSF orexin and α-synuclein levels in dementia patients. J Alzheimers Dis. 2012; 29(1): 125–132, doi: 10.3233/JAD-2012-111655, indexed in Pubmed: 22207004.
76. Grimaldi D, Silvani A, Benarroch EE, et al. Orexin/hypocretin system and autonomic control: new insights and clinical correlations. Neurology. 2014; 82(3): 271–278, doi: 10.1212/WNL.0000000000000045, indexed in Pubmed: 24363130.
77. Bastianini S, Silvani A, Berteotti C, et al. Sleep related changes in blood pressure in hypocretin-deficient narcoleptic mice. Sleep. 2011; 34(2): 213–218, doi: 10.1093/sleep/34.2.213, indexed in Pubmed: 21286242.
78. Murakami M, Ohba T, Kushikata T, et al. Involvement of the orexin system in sympathetic nerve regulation. Biochem Biophys Res Commun. 2015; 460(4): 1076–1081, doi: 10.1016/j.bbrc.2015.03.157, indexed in Pubmed: 25849891.
79. Kuwaki T. Orexin (hypocretin) participates in central autonomic regulation during fight-or-flight response. Peptides. 2021; 139: 170530, doi: 10.1016/j.peptides.2021.170530, indexed in Pubmed: 33741478.
80. Zhang W, Sakurai T, Fukuda Y, et al. Orexin neuron-mediated skeletal muscle vasodilation and shift of baroreflex during defense response in mice. Am J Physiol Rehul Integr Comp Physiol. 2006; 290(6): R1654–R1663, doi: 10.1152/ajpregu.00704.2005, indexed in Pubmed: 16410401.
81. Kuwaki T. Thermoregulation under pressure: a role for orexin neurons. Temperature (Austin). 2015; 2(3): 379–391, doi: 10.1080/23328940.2015.1066921, indexed in Pubmed: 27227052.
82. Barnett S, Li A. Orexin in respiratory and autonomic regulation, health and diseases. Compr Physiol. 2020; 10(2): 345–363, doi: 10.1002/cphy.c190013, indexed in Pubmed: 32163209.
83. Yasui K, Inoue Y, Kanbayashi T, et al. CSF orexin levels of Parkinson's disease, dementia with Lewy bodies, progressive supranuclear palsy and corticobasal degeneration. J Neurol Sci. 2006; 250(1–2): 120–123, doi: 10.1016/j.jns.2006.08.004, indexed in Pubmed: 17005202.
84. Hattori Y, Hattori T, Mukai E, et al. Excessive daytime sleepiness and low CSF orexin-A/hypocretin-I levels in a patient with probable progressive supranuclear palsy]. No To Shinkei. 2003; 55(12): 1053–1056, indexed in Pubmed: 14870576.
85. Liu MF, Xue Y, Liu C, et al. Orexin-A exerts neuroprotective effects via OX1R in Parkinson's disease. Front Neurosci. 2018; 12: 835, doi: 10.3389/fnins.2018.00835, indexed in Pubmed: 30524223.
86. Tabikh M, Chahla C, Okdeh N, et al. Parkinson disease: Protective role and function of neuropeptides. Peptides. 2022; 151: 170713, doi: 10.1016/j.peptides.2021.170713, indexed in Pubmed: 34929264.
87. Musiek ES, Holtzman DM. Mechanisms linking circadian clocks, sleep, and neurodegeneration. Science. 2016; 354(6315): 1004–1008, doi: 10.1126/science.aah4968, indexed in Pubmed: 27885006.
88. Cedernaes J, Osorio RS, Varga AW, et al. Candidate mechanisms underlying the association between sleep-wake disruptions and Alzheimer's disease. Sleep Med Rev. 2017; 31: 102–111, doi: 10.1016/j.smrv.2016.02.002, indexed in Pubmed: 26996255.
89. Kang JE, Lim MM, Bateman RJ, et al. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science. 2009; 326(5955): 1005–1007, doi: 10.1126/science.1180962, indexed in Pubmed: 19779148.
90. Dubey AK, Handu SS, Mediratta PK. Suvorexant: The first orexin receptor antagonist to treat insomnia. J Pharmacol Pharmacother. 2015; 6(2): 118–121, doi: 10.4103/0976-500X.155496, indexed in Pubmed: 25969666.
91. Hopkins CR. ACS chemical neuroscience molecule spotlight on Suvorexant. ACS Chem Neurosci. 2012; 3(9): 647–648, doi: 10.1021/cn300086a, indexed in Pubmed: 23024835.
92. Beuckmann CT, Suzuki M, Ueno T, et al. In vitro and in silico characterization of lemborexant (E2006), a novel dual orexin

receptor antagonist. J Pharmacol Exp Ther. 2017; 362(2): 287–295, doi: 10.1124/jpet.117.241422, indexed in Pubmed: 28559480.
93. Rhyne DN, Anderson SL. Suvorexant in insomnia: efficacy, safety and place in therapy. Ther Adv Drug Saf. 2015; 6(5): 189–195, doi: 10.1177/2042098615595359, indexed in Pubmed: 26478806.
94. Schroeck JL, Ford J, Conway EL, et al. Review of safety and efficacy of sleep medicines in older adults. Clin Ther. 2016; 38(11): 2340–2372, doi: 10.1016/j.clinthera.2016.09.010, indexed in Pubmed: 27751669.
95. Hatano M, Kamei H, Inagaki R, et al. Assessment of switching to suvorexant versus the use of add-on suvorexant in combination with benzodiazepine receptor agonists in insomnia patients: a retrospective study. Clin Psychopharmacol Neurosci. 2018; 16(2): 184–189, doi: 10.9758/cpn.2018.16.2.184, indexed in Pubmed: 29739132.
96. Sutton EL. Profile of suvorexant in the management of insomnia. Drug Des Devel Ther. 2015; 9: 6035–6042, doi: 10.2147/DDDT.S73224, indexed in Pubmed: 26648692.
97. Petrous J, Furmaga K. Adverse reaction with suvorexant for insomnia: acute worsening of depression with emergence of suicidal thoughts. BMJ Case Rep. 2017; 2017, doi: 10.1136/bcr-2017-222037, indexed in Pubmed: 29066641.
98. Tabata H, Kuriyama A, Yamao F, et al. Suvorexant-Induced dream enactment behavior in Parkinson disease: a case report. J Clin Sleep Med. 2017; 13(5): 759–760, doi: 10.5664/jcsm.6600, indexed in Pubmed: 28212694.
99. Baumann CR, Dauvilliers Y, Mignot E, et al. Normal CSF hypocretin-1 (orexin A) levels in dementia with Lewy bodies associated with excessive daytime sleepiness. Eur Neurol. 2004; 52(2): 73–76, doi: 10.1159/000079749, indexed in Pubmed: 15256827.
100. Michinaga S, Hisatsune A, Isohama Y, et al. An anti-Parkinson drug ropinirole depletes orexin from rat hypothalamic slice culture. Neurosci Res. 2010; 68(4): 315–321, doi: 10.1016/j.neures.2010.08.005, indexed in Pubmed: 20727917.
101. Okumura T, Nozu T, Kumei S, et al. Levodopa acts centrally to induce an antinociceptive action against colonic distension through activation of D2 dopamine receptors and the orexinergic system in the brain in conscious rats. J Pharmacol Sci. 2016; 130(2): 123–127, doi: 10.1016/j.jphs.2016.01.007, indexed in Pubmed: 26883457.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 4, pages: 344–351
DOI: 10.5603/PJNNS.a2023.0038

ISSN: 0028-3843, e-ISSN: 1897-4260

Multiple sclerosis and autoimmune diseases — a case control study

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ABSTRACT

Introduction. Multiple sclerosis (MS) is one of the most common autoimmune diseases worldwide, and various autoimmune comorbidities have been reported with MS. The aim of this study was to estimate the prevalence of autoimmune disease co-morbidity in patients with MS and their relatives in a Polish population.

Material and methods. In this retrospective multicentre study, we investigated a group of patients with MS, and their relatives, in terms of age, gender, and the presence of simultaneous autoimmune diseases such as Graves's disease, Hashimoto's thyroiditis, type 1 diabetes mellitus, myasthenia gravis, psoriasis, ulcerative enteritis, Crohn's disease, coeliac disease, rheumatoid arthritis, autoimmune hepatitis and systemic lupus erythematous.

Results. This study included 381 patients with MS, of whom 52.23% were women. 27 patients (7.09%) had at least one autoimmune disease. The most common comorbidity was Hashimoto's thyroiditis (14 patients). 77 patients (21.45%) had relatives with an autoimmune disease, of which the most common was Hashimoto's thyroiditis.

Conclusions. Our study revealed that the probability of autoimmune diseases co-occurring in patients with MS, and in their relatives, is higher and we found the greatest risk to be for Hashimoto's thyroiditis.

Key words: multiple sclerosis, autoimmune disease, comorbidity, prevalence

(*Neurol Neurochir Pol 2023; 57 (4): 344–351*)

Introduction

Due to their increasing incidence and chronic nature, autoimmune diseases (AID) pose a growing challenge to modern medicine. Although autoimmune diseases can affect virtually any organ, the tropism to the nervous system, endocrine system, and connective tissue is particularly manifested.

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system. The disease has three clinical forms: relapsing-remitting (RRMS), primary progressive (PPMS), and secondary progressive (SPMS) [1]. There are approximately 2.8 million patients with MS worldwide, mainly in Europe and countries with Caucasian populations i.e. the United States, Australia, and northern Asia [2, 3]. MS is an autoimmune disease that results from complex interactions between genetic and environmental factors. The fact that it shares susceptibility genes with other autoimmune diseases raises the question of whether MS is associated with a higher incidence of these diseases than in the general population. In autoimmune diseases, abnormal humoral and cellular responses to one's own antigens play a role. This can lead to the co-occurrence of different autoimmune diseases in the same patient [4]. As with other

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Received: 22.11.2022 Accepted: 10.05.2023 Early publication date: 21.06.2023

autoimmune diseases, MS is more common in females, with a peak incidence between the ages of 20 and 40, and there is a tendency to remission during pregnancy and intensification during the postpartum period.

Several studies on this issue have been published, with contradictory results. Some have shown an increased incidence of autoimmune diseases in patients with MS [5, 6], while others claim that these results are related to the more frequent reporting of symptoms by patients with MS [7, 8]. To the best of our knowledge, no study on the co-occurrence of autoimmune diseases in patients with MS and their relatives in a Polish population has yet been published. We hope that the conclusions from this study will draw attention to the problem of the co-occurrence of autoimmune diseases with MS.

Material and methods

In this retrospective multicentre study, we assessed the prevalence of autoimmune diseases in patients with MS diagnosed according to the 2010 McDonald criteria, and in their relatives. Patients recruited for the study came from Polish MS treatment centres in Bydgoszcz, Białystok, Zabrze, Szczecin and Rzeszów. Expanded Disability Status Score (EDSS) was evaluated by neurostatus-certified neurologists dealing with MS patients on a daily basis. The questionnaire asked about autoimmune diseases such as diabetes, myasthenia gravis, Hashimoto's thyroiditis, Graves's disease, psoriasis, ulcerative enteritis, Crohn's disease, coeliac disease, rheumatoid arthritis, systemic lupus erythematosus, and autoimmune hepatitis both in patients with MS and in their first- and second-line relatives. First-line relatives were defined as the patient's parent, sibling or child, and as such they share c.50% of the patient's genes. Second-line relatives share 25% of a patient's genes and the term encompasses uncles, aunts, nephews, nieces, grandparents, grandchildren, half-siblings and cousins twice removed.

Each eligible patient was asked to complete a standard questionnaire for the diagnosis of autoimmune diseases.

Statistical analyses were performed with the use of MedCalc (version 15.8). P values less than or equal to 0.05 were considered statistically significant. Data distribution was determined by a d'Agostino-Pearson test. The values were reported as either means ± standard deviation (SD) for normally distributed variables or medians with 95% confidence interval (CI) for variables without normal distribution. Fisher's exact test was used to examine associations between sex, presence of AID comorbidity and AID in first- and/or second-line relatives. Clinical characteristics (i.e. age, age at diagnosis, disease duration and EDSS) were checked for mutual correlation with Kendall rank correlation coefficient, then compared between the two sexes and subgroups of patients with and without: comorbid AID, first-line relatives with AID, second-line relatives with AID and first- or second-line relatives with AID. To compare normally distributed variables, a t-test was employed. For non-normal data distribution and ordinal variables, a Mann-Whitney U test was used instead. Subsequently, logistic regression models were calculated, enter and stepwise (significance level to enter the model: 0.10, level to remain: 0.05) to determine the variables with the greatest contribution to the EDSS scores.

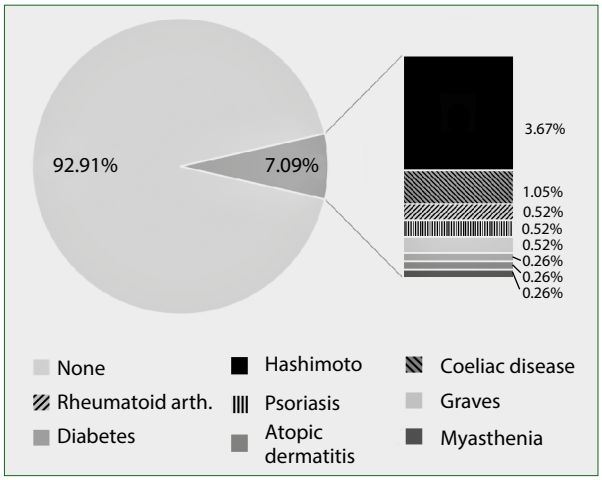

Figure 1. Concurrent AID prevalence in study cohort. In study cohort, female patients were more likely to have a concurrent AID (RR = 3.2, p = 0.01)

This study was approved by the Bioethics Committee of the Nicolaus Copernicus University in Toruń, number KB 438/2017 and all patients signed an informed consent form to participate in the study.

Results

Prevalence of AIDs in MS patients and their families

The study involved 381 patients, including 199 females with a mean age of 41.3 years (range: 19–70) and median EDSS of 1.75 (range: 1.5–2.0), and 182 males with a mean age of 40.7 years (range: 21–69) and median EDSS of 2.0 (range: 2.0–2.5). The median disease duration was 8 (range: 7–9) years in males and 6 (range: 5–7) years in females.

Twenty seven patients with MS (7.09%) had at least one additional autoimmune disease: 14 (3.7%) patients had Hashimoto's thyroiditis, four (1.05%) had coeliac disease, two (0.52%) had rheumatoid arthritis, two (0.52%) had psoriasis, two (0.52%) had Graves's disease, one (0.26%) had diabetes type 1, one (0.26%) had atopic dermatitis, and one (0.26%) had myasthenia gravis (Fig. 1).

Seventy seven patients (21.45%) had a family history of AID. Twenty patients (5.17%) had a first- or second-line relative with Hashimoto's thyroiditis, 17 (4.39%) rheumatoid arthritis, 12 (3.10%) type 1 diabetes mellitus, 14 (3.62%) MS, nine (2.33%) psoriasis, seven (1.81%) Graves's disease, and four (1.03%) another autoimmune disease (coeliac disease, colitis ulcerosa, systemic lupus erythematosus, or autoimmune hepatitis) (Fig. 2, 3).

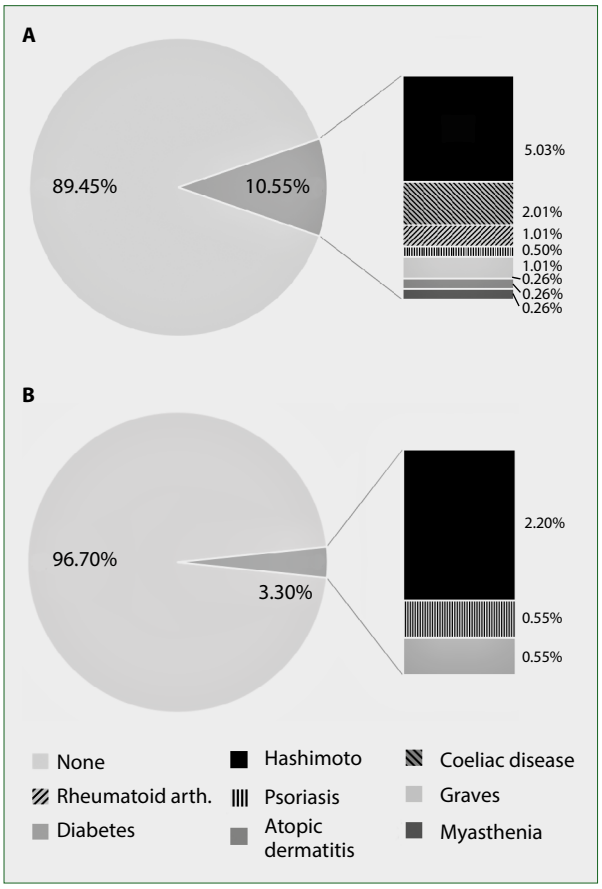

Figure 2. A. Concurrent AID prevalence in study cohort, females. **B**. Concurrent AID prevalence in study cohort, males

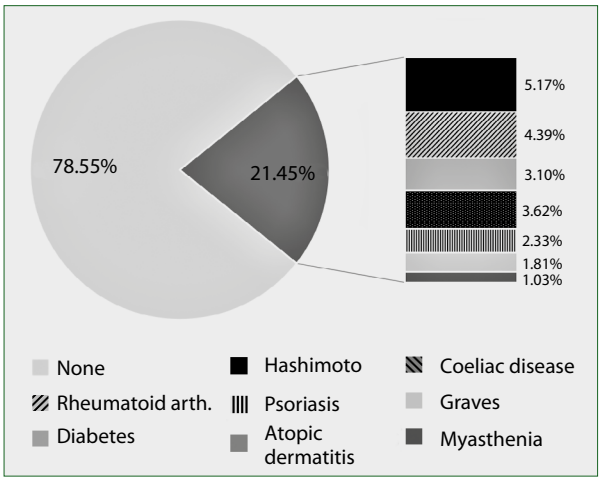

Figure 3. AIDs in first- and/or second-line relatives of MS patients

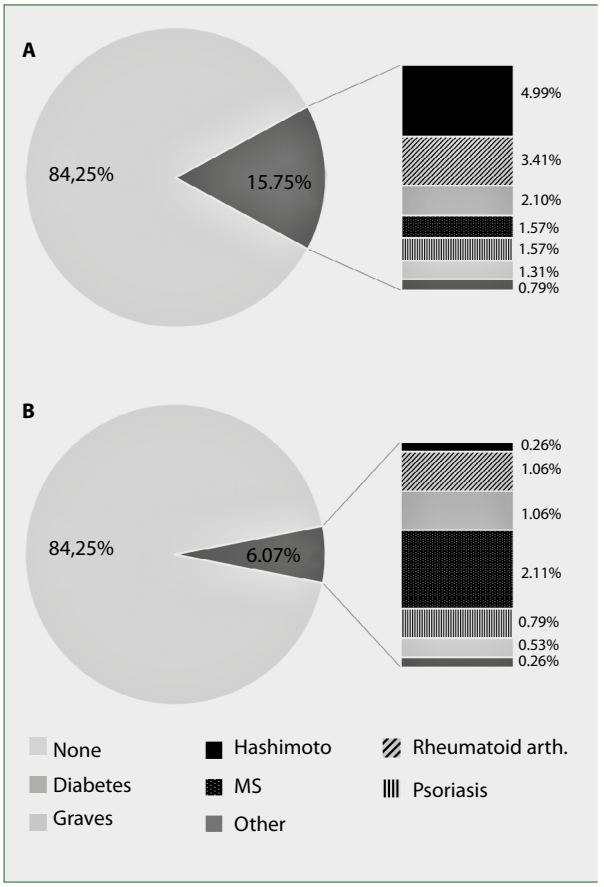

Figure 4. A. AIDs in first-line relatives of MS patients. **B.** AIDs in second-line relatives of MS patients

Overall, AIDs in first-line relatives were more than twice as frequent as in second-line relatives (Fig. 4), with the particular exception of MS which was reported in second-line relatives of eight patients (2.11%) but in first-line relatives of only six patients (1.57%). However, recall bias cannot be ruled out.There was no statistically significant association between sex and a family history of AID. Multiple sclerosis patients with first-line relatives affected by AIDs were themselves more likely to have an additional AID [relative risk (RR) = 2.7] (p = 0.01).

Clinical characteristics of MS patients with concurrent AID and family history of AID

Gender

Median EDSS was higher in males than in females [2.0 (95% CI 2.0–2.5) *vs.* 1.5 (95% CI 1.5–2.0)] (p = 0.018), but disease duration was longer in males as well [8(7–9) *vs.* 6(5–7), p = 0.0005]. In the study cohort, disease duration correlated positively with EDSS (Kendall tau: 0.134, p = 0.0009), although less than age (Kendall tau: 0.208, p < 0.0001) (Fig. 5).

Women did not differ significantly from men in either current age or age at onset of symptoms.

Personal history of concurrent AID

Patients with other AIDs did not differ from those with only MS in terms of EDSS, age, age at onset of symptoms, or disease duration. No gender-specific associations between these characteristics and AIDs were noted (Fig. 2).

Table 1. Significant contributors to Expanded Disability Status Score (EDSS) score in logistic regression models

Outcome	Significance level	Variable	Coefficient	Variable p
EDSS ≥ 2	< 0.0001	Sex (♂)	1.2587	< 0.0001
		Age	0.0459	0.0014
EDSS ≥ 3	< 0.0001	Sex (♂)	1.5319	< 0.0001
		Age	0.0462	0.0020
EDSS ≥ 4	< 0.0001	Sex (♂)	0.9861	0.0404
		Duration	0.1059	0.0026
		Age	0.0520	0.0062
♀ EDSS ≥ 3	0.0320	Duration	0.1394	0.0391
♀ EDSS ≥ 5	0.0024	Duration	0.4530	0.0440
♂ EDSS ≥ 2	0.0197	Age	0.0532	0.0034
♂ EDSS ≥ 3	0.0061	Age	0.0498	0.0024
♂ EDSS ≥ 4	0.0005	Age	0.0570	0.0054
		Duration	0.1015	0.0109
♂ EDSS ≥ 5	0.0258	Age	0.0778	0.0259

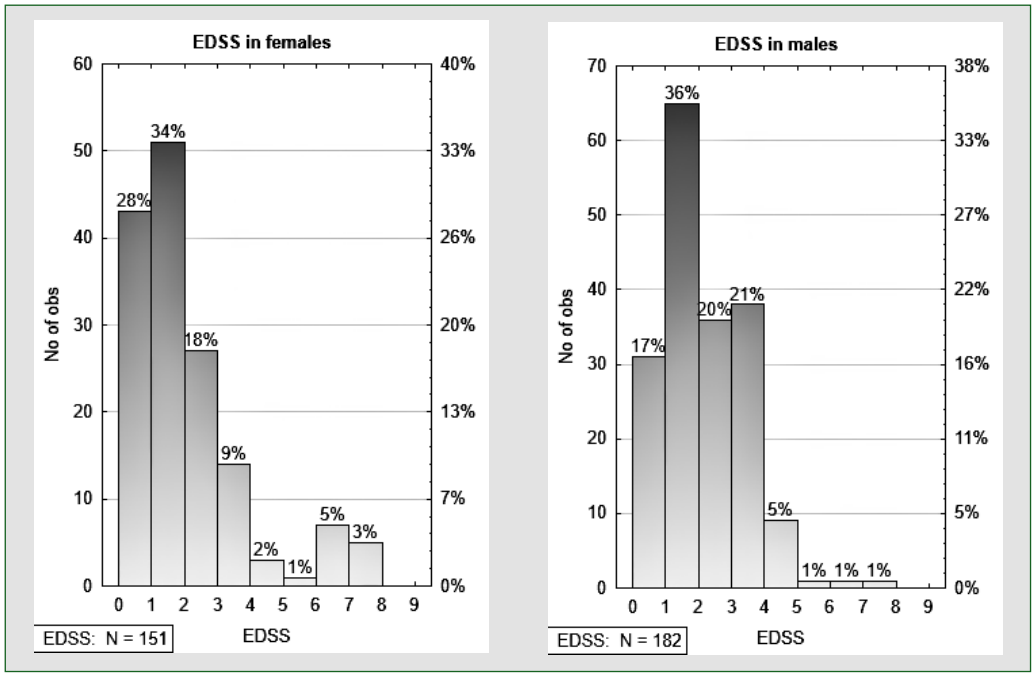

Figure 5. Expanded Disability Status Score (EDSS) by gender

Family history of AID

There was no significant difference in age, age at disease onset, or disease duration between patients with and without AID-affected relatives, regardless of the degree of kinship. However, those with a first-line relative with an AID had lower EDSS scores [1.5(1.5–2.0) *vs.* 2(2.0–2.5), p = 0.0346]. This effect was more evident among female patients [1.5(1.07–1.5) *vs.* 2.0(2.0–2.5), p = 0.007) was not present among males (Fig. 6). No similar associations were shown for patients with and without second-line relatives affected by AIDs.

EDSS predictors in MS patients

In logistic regression analysis, only sex (male), age (older) and disease duration (longer) remained as predictors of EDSS (Tab. 1). On the contrary, no association with additional AID or family history of AID was preserved in the models.

Discussion

Multiple sclerosis is a chronic disease of the central nervous system that is mainly mediated by T lymphocytes specific

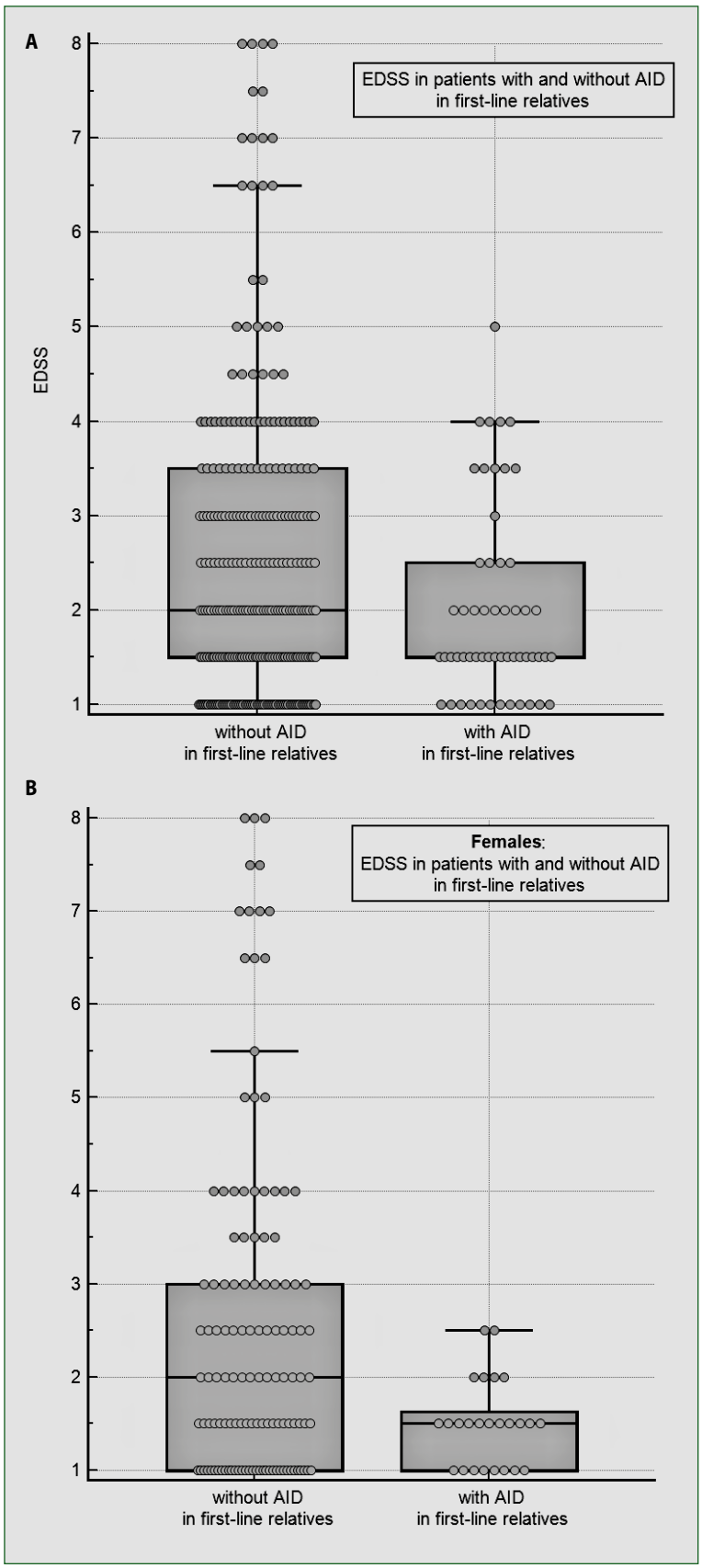

Figure 6. A. Expanded Disability Status Score (EDSS) with and without autoimmune disease (AID) in first-line relatives. **B**. Expanded Disability Status Score (EDSS) with and without autoimmune disease (AID) in first-line relatives

to neuronal antigens. It seems that genetic susceptibility may play a key role here. AIDs may result from the loss of tolerance of one's own tissues. Although the mechanisms underlying impaired tolerance have not been fully understood, deficits in the functioning of regulatory T lymphocytes is one possibility [9]. The coexistence of other AIDs and MS has been described in the literature. But what influence the presence of another AID has on the course of MS is not yet fully understood [10]. It is known that another AID can develop after a diagnosis of MS. And immunomodulatory therapy alone can have an impact on the incidence of other diseases in patients [10–13].

This study assessed the impact of the presence of an additional AID in MS patients and in their first- and second-line relatives on the clinical course of MS. The risk of developing another AID in the studied patients was also assessed.

Our results revealed that patients with MS and without a concomitant AID did not differ in terms of EDSS score compared to those with a concurrent AID. A similar study, carried out on a smaller group of patients, revealed that the mean EDSS was 1.62 ± 1.12 in patients with MS and another AID, compared to the control group, where EDSS was 3.33 ± 1.89 [10]. The authors suggested that MS may coexist with other AIDs, and their presence may modify the course of the disease.

Zéphir et al. [14] presented 66 patients with MS and concomitant enteritis. These patients had a milder course of the disease compared to patients with isolated MS.

These findings reveal that the problem of the coexistence of AIDs is not uncommon, and understanding their development in patients with MS and their relatives could help to better understand the pathomechanisms of AIDs, which may be useful in future prognoses.

Patients who had a first-line or a second-line relative with an AID were more likely to be in the low EDSS group (0–2.5), 80% in the first-line and 78% in the second line, respectively.

As research shows, family history is a frequent contributory factor in a wide variety of autoimmune disorders. Type 1 diabetes may serve as a well-studied example. In more than 14% of patients with type 1 diabetes, at least one first- or second-line relative also suffered from this disease. This shows how important it is to evaluate patients comprehensively and to conduct an in-depth interview on the burden of other diseases in the family [15].

In our study, the presence of an additional AID in patients with MS did not result in more frequent inclusion in the group with low EDSS. However, the presence of such a disease in a first- or second-line relative resulted in a better course of the disease. It is possible that the coexistence of an AID in relatives and patients with MS could predispose them to a milder course of the disease.

A study in Sweden revealed that the relative risk of MS was 1.21 when the parents were diagnosed with any AID. That study was based on a multigenerational registry of diseases. Alleles associated with MS so far do not fully explain the familial occurrence of MS. On the other hand, the Swedish authors revealed a shared family risk of MS with amyotrophic lateral sclerosis and asthma, which may suggest a common genetic basis [16].

In another publication by authors from Italy, the risk of MS in relatives of patients with MS was 1.9%. The male gender of the affected patient, the female gender of the relative, and the number of family members with an AID, all significantly increased the risk of MS in other relatives. It follows that gender may be of great importance in the risk of developing AID. On the other hand, in our study, there was no correlation between gender and disease progression expressed by belonging to a group with low, medium, and high EDSS.

It seems that establishing similar registries of co-occurring AID and MS in other countries, including Poland, would contribute to the holistic care of patients with MS.

In the presented study, the risk of developing another AID among patients with MS was 10.5%. The greatest risk was found for Hashimoto's thyroiditis. Similarly, patients with type 1 diabetes also have the highest risk of developing Hashimoto's thyroiditis [15].

We observed the least frequent co-occurrence of MS and myasthenia. Danikowski et al. [9] presented possible common mechanisms of the development of these diseases based on the loss of regulatory T lymphocytes. Other AIDs that have been noted have been rheumatoid arthritis, coeliac disease, psoriasis, atopic dermatitis, and Graves's disease. In this study, systemic lupus erythematosus (SLE) was not found in any of the patients although, according to previous studies, it is very often passed on in the family. There is a 10.3 times greater risk of developing SLE among first-degree relatives of patients with SLE. Moreover, regardless of the degree of relationship, people with a family history of SLE have been found to have a greater risk of developing other AIDs, including rheumatoid arthritis, autoimmune thyroid disease, MS, and others [17].

Another study carried out by Fanouriakis et al. [19] showed that patients with concurrent SLE and MS may have mild SLE with mostly dermal, mucosal, and musculoskeletal symptoms. After an average of four years of observation, the authors concluded that the coexistence of these two diseases does not seem to be associated with a severe phenotype of either [18].

There have been few reports on interactions between AIDs, one example being the relationship between colitis and primary sclerosing cholangitis. The coexistence of these diseases is almost always manifested by mild colitis.

On the one hand, the additional burden of another AID is a significant problem for a patient with MS. On the other, it may predict a milder course of the underlying disease.

It is unclear whether the two coexisting AIDs interact with each other. The mechanism of the coexistence itself is difficult to explain [10, 20–22]. It is possible that exposing patients to more antigens may result in greater immune tolerance and a milder course of MS. A more severe activation of regulatory

T lymphocytes and anti-inflammatory cytokines is another hypothesis explaining a milder course of disease in patients with two concurrent AIDs [23–27].

Weiner et al. [28] observed that the progressive course of the disease was more frequent in patients with isolated MS. In the presented study however, patients in the high EDSS group had a comorbid AID more often than not.

This study has several limitations. Firstly, the different forms of MS were not considered separately. Moreover, further research should take into account the immunomodulatory drugs used, because some of the therapies may impair the balance of the immune system and initiate the development of other AIDs [10].

Also, MRI examinations and radiological progression were not compared between patients with and without an additional AID. A clinical evaluation based on EDSS alone may be insufficient.

The analysis of the presence of AIDs among relatives could facilitate the prognostication in patients with MS. It is possible that the coexistence of another disease could improve the prognosis.

Further studies on a larger group of patients are necessary in order to assess the significance of the presented results. In the future, it may be possible to link the analysis of family burdens with the assessment of the presence of specific genes.

A concomitant AID may play a role in the body's tolerance to autoantigens. Further research involving more detail, including MRI and body fluid biomarkers, should be carried out to assess the immune system of patients with MS plus another coexisting AID.

Conflict of interests: *None.*
Funding: *None.*

References

1. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis. Neurology. 2014; 83(3): 278–286, doi: 10.1212/wnl.0000000000000560, indexed in Pubmed: 24871874.
2. Atlas of MS 2020 — Epidemiology report. https://www.msif.org/resource/atlas-of-ms-2020/ (22.10.2022).
3. Goris A, Epplen C, Fiten P, et al. Analysis of an IFN-gamma gene (IFNG) polymorphism in multiple sclerosis in Europe: effect of population structure on association with disease. J Interferon Cytokine Res. 1999; 19(9): 1037–1046, doi: 10.1089/107999099313262, indexed in Pubmed: 10505747.
4. Belniak E, Stelmasiak Z, Papuć E, et al. Multiple Sclerosis Therapy Consensus Group. Escalating immunotherapy of multiple sclerosis — new aspects and practical application. J Neurol. 2004; 251(11): 1329–1339, doi: 10.1007/s00415-004-0537-6, indexed in Pubmed: 15592728.
5. Dobson R, Giovannoni G. Autoimmune disease in people with multiple sclerosis and their relatives: a systematic review and meta-analysis. J Neurol. 2013; 260(5): 1272–1285, doi: 10.1007/s00415-012-6790-1, indexed in Pubmed: 23315260.
6. Barcellos LF, Kamdar BB, Ramsay PP, et al. Clustering of autoimmune diseases in families with a high-risk for multiple sclerosis: a descriptive study. Lancet Neurol. 2006; 5(11): 924–931, doi: 10.1016/S1474-4422(06)70552-X, indexed in Pubmed: 17052659.
7. Roshanisefat H, Bahmanyar S, Hillert J, et al. Shared genetic factors may not explain the raised risk of comorbid inflammatory diseases in multiple sclerosis. Mult Scler. 2012; 18(10): 1430–1436, doi: 10.1177/1352458512438240, indexed in Pubmed: 22419672.
8. Disanto G, Ramagopalan SV. Multiple sclerosis and co-morbid autoimmune disease: the final nail in the coffin? Mult Scler. 2012; 18(10): 1370–1371, doi: 10.1177/1352458512440833, indexed in Pubmed: 23014625.
9. Danikowski KM, Jayaraman S, Prabhakar BS. Regulatory T cells in multiple sclerosis and myasthenia gravis. J Neuroinflammation. 2017; 14(1): 117, doi: 10.1186/s12974-017-0892-8, indexed in Pubmed: 28599652.
10. Sahraian MA, Owji M, Naser Moghadasi A. Concomitant multiple sclerosis and another autoimmune disease: Does the clinical course change? Clin Neurol Neurosurg. 2016; 150: 92–95, doi: 10.1016/j.clineuro.2016.09.003, indexed in Pubmed: 27614222.
11. Ramos-Casals M, Perez-Alvarez R, Diaz-Lagares C, et al. BIOGEAS Study Group. Autoimmune diseases induced by biological agents: a double-edged sword? Autoimmun Rev. 2010; 9(3): 188–193, doi: 10.1016/j.autrev.2009.10.003, indexed in Pubmed: 19854301.
12. Ramos-Casals M, Brito-Zerón P, Soto MJ, et al. Autoimmune diseases induced by TNF-targeted therapies. Best Pract Res Clin Rheumatol. 2008; 22(5): 847–861, doi: 10.1016/j.berh.2008.09.008, indexed in Pubmed: 19028367.
13. Perez-Alvarez R, Pérez-de-Lis M, Ramos-Casals M, et al. BIOGEAS study group. Biologics-induced autoimmune diseases. Curr Opin Rheumatol. 2013; 25(1): 56–64, doi: 10.1097/BOR.0b013e32835b1366, indexed in Pubmed: 23114587.
14. Zéphir H, Gower-Rousseau C, Salleron J, et al. CFSEP, GETAID and EPIMAD Groups. Milder multiple sclerosis course in patients with concomitant inflammatory bowel disease. Mult Scler. 2014; 20(8): 1135–1139, doi: 10.1177/1352458513515081, indexed in Pubmed: 24326672.
15. Goworek M, Madej A, Suwała S. The prevalence of autoimmune diseases in patients with type 1 diabetes and in their relatives. Diabet Klin. 2013; 2(1): 9–13.
16. Hemminki K, Li X, Sundquist J, et al. Risk for multiple sclerosis in relatives and spouses of patients diagnosed with autoimmune and related conditions. Neurogenetics. 2009; 10(1): 5–11, doi: 10.1007/s10048-008-0156-y, indexed in Pubmed: 18843511.
17. Ulff-Møller CJ, Simonsen J, Kyvik KO, et al. Family history of systemic lupus erythematosus and risk of autoimmune disease: Nationwide Cohort Study in Denmark 1977-2013. Rheumatology (Oxford). 2017; 56(6): 957–964, doi: 10.1093/rheumatology/kex005, indexed in Pubmed: 28339674.
18. Fanouriakis A, Mastorodemos V, Pamfil C, et al. Coexistence of systemic lupus erythematosus and multiple sclerosis: prevalence, clinical characteristics, and natural history. Semin Arthritis Rheum. 2014; 43(6): 751–758, doi: 10.1016/j.semarthrit.2013.11.007, indexed in Pubmed: 24332007.
19. Loftus EV, Harewood GC, Loftus CG, et al. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. Gut. 2005; 54(1): 91–96, doi: 10.1136/gut.2004.046615, indexed in Pubmed: 15591511.

20. Yamamoto-Furusho J. Innate immunity in inflammatory bowel disease. World Gastroenterol. 2007; 13(42): 5577, doi: 10.3748/wjg.v13.i42.5577.
21. Wraith DC, Nicholson LB. The adaptive immune system in diseases of the central nervous system. J Clin Invest. 2012; 122(4): 1172–1179, doi: 10.1172/JCI58648, indexed in Pubmed: 22466659.
22. Hedegaard CJ, Krakauer M, Bendtzen K, et al. T helper cell type 1 (Th1), Th2 and Th17 responses to myelin basic protein and disease activity in multiple sclerosis. Immunology. 2008; 125(2): 161–169, doi: 10.1111/j.1365--2567.2008.02837.x, indexed in Pubmed: 18397264.
23. Fontoura P, Garren H, Steinman L. Antigen-specific therapies in multiple sclerosis: going beyond proteins and peptides. Int Rev Immunol. 2005; 24(5-6): 415–446, doi: 10.1080/08830180500379655, indexed in Pubmed: 16318989.
24. Bernard CC, Johns TG, Slavin A, et al. Myelin oligodendrocyte glycoprotein: a novel candidate autoantigen in multiple sclerosis. J Mol Med (Berl). 1997; 75(2): 77–88, doi: 10.1007/s001090050092, indexed in Pubmed: 9083925.
25. Bar-Or A, Vollmer T, Antel J, et al. Induction of antigen-specific tolerance in multiple sclerosis after immunization with DNA encoding myelin basic protein in a randomized, placebo-controlled phase 1/2 trial. Arch Neurol. 2007; 64(10): 1407–1415, doi: 10.1001/archneur.64.10.nct70002, indexed in Pubmed: 17698695.
26. Garren H, Garren H, Robinson WH, et al. BHT-3009 Study Group. A DNA vaccine for multiple sclerosis. Expert Opin Biol Ther. 2008; 8(10): 1539–1550, doi: 10.1517/14712598.8.10.1539, indexed in Pubmed: 18774921.
27. Van der Aa A, Hellings N, Medaer R, et al. T cell vaccination in multiple sclerosis patients with autologous CSF-derived activated T cells: results from a pilot study. Clin Exp Immunol. 2003; 131(1): 155–168, doi: 10.1046/j.1365-2249.2003.02019.x, indexed in Pubmed: 12519400.
28. Weiner HL. A shift from adaptive to innate immunity: a potential mechanism of disease progression in multiple sclerosis. J Neurol. 2008; 255 Suppl 1: 3–11, doi: 10.1007/s00415-008-1002-8, indexed in Pubmed: 18317671.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 4, pages: 352–362
DOI: 10.5603/PJNNS.a2023.0040

ISSN: 0028-3843, e-ISSN: 1897-4260

Risk factors for reoperation after surgical treatment for degenerative spinal disease in Poland: a nationwide retrospective study of 38,953 hospitalisations

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ABSTRACT

Introduction. Degenerative spinal disease (DSD) is one of the most common musculoskeletal conditions and a leading cause of sickness absence. It also contributes significantly to the global burden of disease. The aim of this study was to assess the frequency of reoperation after surgical treatment of DSDs in Poland, and to identify risk factors for reoperation.

Material and methods. A retrospective analysis of hospitalisations for DSD in 2018 that were reported to Poland's National Health Fund (NHF) was performed. Reoperations reported within 365 days of hospital discharge were identified. Demographic factors and multimorbidities were included in the analysis. A logistic regression model was then performed to assess risk factors for reoperations.

Results. In 2018, 38,953 surgical hospitalszations for DSD were reported. A total of 3,942 hospitalised patients (10.12%) required reoperation within 365 days. Patients requiring reoperation were predominantly female (female-to-male ratio 1.34:1) and elderly (mean age of reoperated patients 56.66 years, mean age of other patients 53.24). The percentage reoperated upon correlated with multiple diseases (from 8.81% in the group of patients without comorbidities to 15.31% in the group of patients with three or more comorbidities). The risk of reoperation was most increased by comorbid depression, neurological diseases, obesity, and older age. The risk of reoperation was reduced by instrumented spinal surgery, surgery in a neurosurgical unit, and hospitalisations other than same-day surgery.

Conclusions. Reoperations within a year after DSD surgical treatment are common. Identifying risk factors for reoperation, including those related to the presence of comorbidities and the phenomenon of multimorbidity, can be an important tool in reducing reoperation rates.

Key words: degenerative spinal disease, multimorbidity, reoperation, risk factors, spinal surgery

(*Neurol Neurochir Pol 2023; 57 (4): 352–362*)

Introduction

Degenerative spinal disease (DSD) is one of the most common musculoskeletal disorders and the leading cause of sickness absenteeism. It also contributes significantly to the global burden of disease. The results of the 2017 Global Burden of Disease Study indicate that low back pain remains the leading cause of disability worldwide [1]. DSD significantly reduces a patient's quality of life due to its generation of pain, reduction in physical function, and chronic course. The treatment of DSD patients represents a heavy burden on the healthcare system, including primary healthcare, specialised outpatient

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Received: 4.12.2022 Accepted: 17.03.2023 Early publication date: 22.06.2023

healthcare, inpatient treatment and rehabilitation. Low back pain, which was the most common clinical manifestation of DSD in 2000 in the United Kingdom, was found to be the most common single cause of sickness absenteeism in that country, accounting for 12.5% of all days of incapacity for work [2].

According to an analysis of the causes of sickness absenteeism in Poland in 2012–2016, conducted by the Social Insurance Institution, musculoskeletal and connective tissue disorders (which include DSD) were the second cause of sickness absenteeism after pregnancy, childbirth, and puerperium. Those spinal conditions accounted for 15.3% of total days of absenteeism, showing a marked increase in the years analysed. The lifetime prevalence of complaints associated with DSD is estimated to be up to 80% [2]. The point prevalence rate and annual prevalence rate for low back pain in the general population are estimated to be 18.3% and 38%, respectively [3]. According to analyses conducted as part of the Maps of Health Needs project in 2014, 462,000 cases of DSD were reported in Poland. The reported DSD incidence rate was 1.2% and the reported DSD prevalence rate (cases reported from 2009 to 2014) was 9.2%. In 2014, 68,000 hospitalisations for DSD were reported in Polish hospitals. A total of 1,001,000 DSD patients were treated and 2,004,000 medical consultations were provided. This data refers to services reimbursed by the National Health Fund of Poland (NHF); it does not include services funded from other sources (non-public funds), and is therefore an underestimation of the final rates in Poland.

DSD is the most common reason for spinal surgery [4, 5]. Given the type of lumbar spine pathology in surgically treated patients, the most common indications for surgery in the world include degenerative disc disease (discopathy), spinal canal stenosis, and spondylolisthesis, respectively [6]. Data obtained from the Maps of Health Needs project showed that in Poland, out of 68,000 hospitalisations of DSD patients, hospitalisations combined with surgical treatment comprised 50.1%. Surgical treatment can reduce pain and improve quality of life and overall fitness in many patients. However, it is associated with a risk of complications and adverse events. Surgeries performed for DSD are the most frequently performed surgeries of all.

The effectiveness and safety of surgical treatment for DSD are affected by the eligibility of the patient for surgery, their general health status (i.e. medical risk factors), the experience and knowledge of their surgeon, the type of medical equipment in their treatment centre, their postoperative care, and the quality of rehabilitation [7]. Additional factors include psychological, social, economic and occupational determinants of the patient.

Given the prevalence of DSD and its social and economic consequences, it is crucial to monitor the quality of treatment for DSD. The reoperation rate is one indicator of the quality of treatment in surgery. Reoperation is defined as a subsequent, unplanned surgical intervention. This may involve surgical intervention at the same site, at a different site but due to the same condition, or repair of complications resulting from the initial surgical procedure [8]. Reoperation *per se* is strongly predictive of surgical complications in spinal surgery [9]. An additional burden of other health problems (multimorbidity) may carry an increased risk of surgical failure in DSD patients, including the need for reoperation. According to the World Health Organisation's definition, multimorbidity means the co-occurrence of two or more chronic health problems in one person [10]. Multimorbidity is considered a potentially important adverse predictor in DSD patients treated with surgery, although few publications have investigated this topic. Their interpretations and, above all, references to specific outcomes, are impeded by the fact that different authors use different methods to assess multimorbidity, and their analyses cover a wide range of degenerative spinal disorders (e.g. spinal disc herniation, spinal stenosis, spondylolisthesis) treated with various surgical techniques. Overall health status before surgery is a predictor of the clinical outcome of surgery and of patient satisfaction [9–13].

There have been very few studies on reoperation after spinal surgery in Poland [7, 14–16], so the literature is still scarce. However, some Polish medical institutions provide data to EUROSPINE's International Spine Registry (Spine Tango), founded in 2002 [5]. It should also be noted that there was a specifically Polish registry for monitoring spinal surgical treatment known as Polspine [17]. Unfortunately, due to concerns about the protection of personal data and Poland's General Data Protection Regulation introduced in 2018, the platform and data collection has been stopped, so there is still a need for an active national spinal surgery registry in Poland.

This study aims to evaluate the reoperation rate after surgical treatment for DSD in Poland, and to identify risk factors for reoperation, including comorbidities and other variables.

Material and methods

Study organisation and eligibility criteria

This study is a retrospective analysis of adult patients operated on for DSD in 2018 in Poland. The study group was identified as consisting of patients hospitalised with a principal diagnosis of DSD defined by ICD-10 codes in accordance with the International Statistical Classification of Diseases and Related Health Problems ICD-10: M43.1, M47, M48, M50, M51, or M53 with extensions. Next it was verified whether the patient's hospitalisation was reported using one of diagnosis-related group (DRG) codes: A22, A23, A27, H51, H52, H53, or H55. Those patients who met both the aforementioned conditions were designated the study group. The group of reoperated patients was identified by the same ICD-10 and DRG codes, provided that they were reported not later than 365 days after the end of the primary hospitalisation.

Ethics statement

This study is part of the Maps of Health Needs project implemented by the Ministry of Health, co-financed by the European Union through the European Social Fund under the Operational Programme Knowledge Education Development

(EU grant number: POWR 05.02.00-00-0149/15-01). The study was conducted in accordance with the tenets of the Declaration of Helsinki with respect to research involving human subjects. The approval of the Bioethics Committee was not necessary. The study protocol was approved by the Polish Ministry of Health, which is authorised under the law of the Republic of Poland to process NHF data.

Study procedure

We defined any spinal surgery (instrumented or non-instrumented) as an index operation and a degenerative spinal disease as an index disease. Distinguishing between instrumented (with implants) *vs*. non-instrumented (without implant) surgery was possible owing to DRG codes reported to the National Health Fund. Reoperation was defined as a consequent spinal surgery performed within 365 days after the end of the primary hospitalisation for spinal surgery.

Our analysis used NHF data concerning the reported inpatient, outpatient, primary healthcare, psychiatric and addiction treatment services, i.e. services reported to the payer in 2017–2019 and relating to prescriptions purchased during the corresponding period. Information concerning patient deaths for the period 2018–2019 was released by the Ministry of Administration and Digitisation.

Several risk factors that have a potential impact on the risk of reoperation were defined based on a literature review and the knowledge and experience of a medical expert. Factors related to medical history and pertaining to the patient's demographic profile were included in the analysis, as was a profile of the facility where the patient was hospitalised. The former group of risk factors includes variables whose definitions were taken from the article by Elixhauser et al. [18]; they are also included in the Elixhauser Comorbidity Index. The latter group of risk factors, the facility profile, includes information concerning for example the range of services provided at the facility, the presence of specific departments, or the facility's classification as a teaching hospital.

Statistical analyses

The statistical analysis included constructing a logistic regression model in which a response variable concerned reoperation for DSD within 365 days of the discharge from hospitalisation associated with the primary surgery, according to explanatory variables. The qualitative variables used in the analysis were recoded for the correct model construction using one-hot encoding. To eliminate the problem of strong multicollinearity, the effect of VIF coefficients was verified and the Pearson's linear correlation coefficients were analysed, as well as the correlation values of any monotonic relationship (including non-linear relationship) by calculating the Spearman's rank correlation coefficients. The Akaike information criterion algorithm was used to identify the model that best fits the data and for extraction of explanatory variables that have the greatest impact on the response variable. The model parameters were estimated using the maximum likelihood estimation. Variables found to be very rare among the analysed cohort were excluded from the analysis. To ensure the evaluation of the quality of the model and to control its level of fit to the data, the considered set of observations was randomly divided into a learning (70%) part and a testing (30%) part. The quality of the resulting classifiers was evaluated using the Area Under ROC Curve (AUC) measure. Logistic regression analysis resulted in odds ratios (OR) that were calculated together with a 95% confidence interval (CI). P-values of less than 0.05 were considered statistically significant. The analysis was performed using Python (version 3.6.5) and R (version 3.6.1) programs.

Results

There were 38,953 surgical hospitalisations for DSD reported in 2018. After 3,942 hospitalisations (10.12%), reoperations within 365 days after hospital discharge were noted (Fig. 1). Figure 2 shows the differences in terms of age distribution compared to surgical hospitalisation for DSD. The mean patient age in the analysed group was 53.59 years. The mean age of patients who underwent reoperation up to one year after hospital discharge was 56.66 years, and the mean age of patients who did not need reoperation was 53.24 years. Figure 3 shows that women were more likely to undergo surgery for DSD than men (134 women compared to 100 men). The mean age of women who needed reoperation was 57.42 years and that of men was 55.62 years. The likelihood of no reoperation decreased evenly within consecutive days of the primary surgery (Fig. 4). The figures characterise the study group, the statistical significance of the differences was tested using logistic regression, and the results are given below.

Table 1 shows comorbidities in patients undergoing surgical hospitalisations for DSD. The most common comorbidities in the study group included spontaneous hypertension (12.58% of patients), diabetes mellitus (11.41% of diabetic patients treated with oral medications and 3.14% of diabetic patients treated with insulin), and chronic respiratory diseases (6.15%).

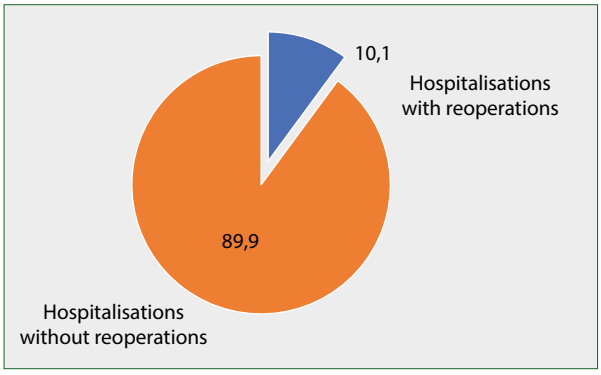

Figure 1. Distribution of hospitalisations compared to reoperations within 365 days of hospital discharge

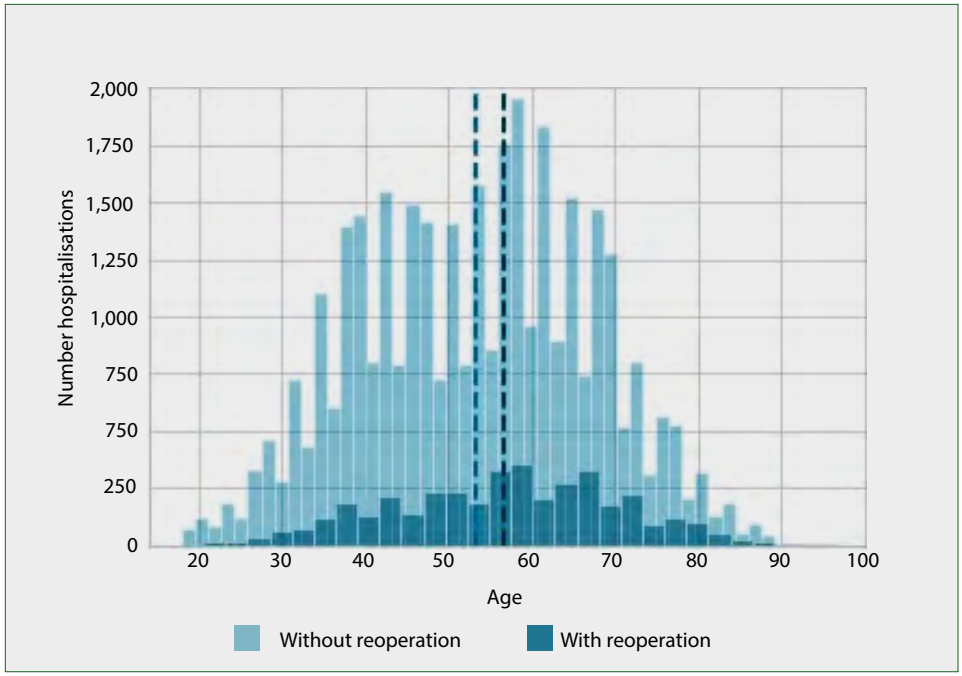

Figure 2. Distribution of hospitalisations with and without reoperation compared to patient age (dashed lines indicate mean age of patients)

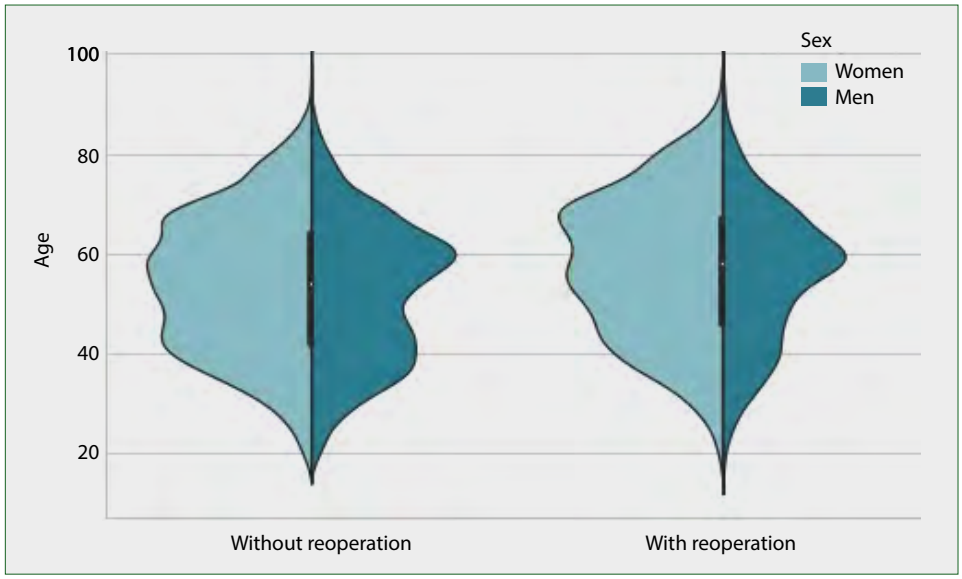

Figure 3. Violin plots showing number of reoperations for DSD according to patient's age and sex. Area under plot corresponds to number of performed reoperations. White dot in middle of plot indicates median age, whereas vertical thick lines indicate quartiles

The highest reoperation rate was reported for patients with severe malnutrition (24%), lymphomata and haematological cancers (21.13%), although the number of patients with these diseases was low and thus they were not included in the model. The highest reoperation rate among the variables included in the further analysis was for patients with diagnoses of metastatic cancer (18.11%), obesity (15.11%), depression (14.76%) and neurological diseases (14.71%). The lowest reoperation rate included patients with HIV infection (0%), iron-deficiency anaemia (5.26%), and psychotic disorders (3.16%). There was also an increasing reoperation rate according to the number of diagnosed comorbidities. In the group of patients without comorbidities, the reoperation rate was 8.81%. When patients suffered from one or two comorbidities, the reoperation rate increased to 11.33%, and when they suffered from three or more comorbidities, the rate was 15.31%.

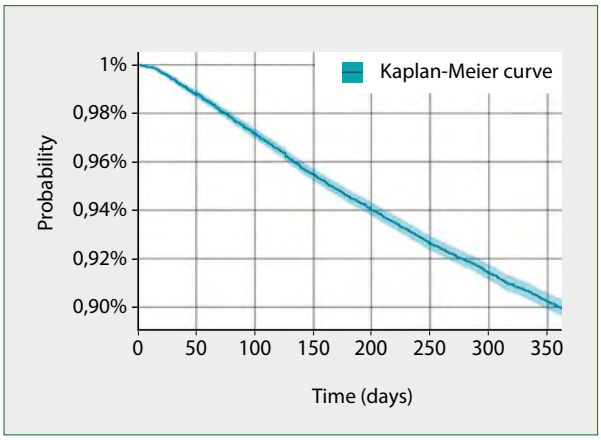

Figure 4. Kaplan-Meier curve showing a decrease in probability of no re-operation as number of days since primary hospital discharge increases

Table 2 shows 24 variables that were included in the logistic regression model. Other variables were eliminated during the initial stages of the analysis. The variables that most strongly increased the likelihood of reoperation included those reporting depression (OR = 1.507, Fig. 5), neurological diseases (OR = 1.426), obesity (OR = 1.401, Fig. 6), and hypertension associated with organ damage (OR = 1.253). Other significant variables that increased the likelihood of reoperation included age (highest likelihood of reoperation for patients aged 70–79 compared to those aged 18-49; OR = 1.225, Fig. 7) and the profile of the facility where the operation was performed (higher likelihood for clinical centres compared to non-clinical ones, OR = 1.101).

Variables that reduce the likelihood of reoperation included the place of residence (i.e. a lower likelihood of reoperation in patients living in rural areas compared to those living in

Table 1. Distribution of variables in study group

Variable	Number of patients	Percentage of patients in study group	Patients with a certain variable who underwent reoperation
Comorbidity variables			
Spontaneous hypertension	4,899	12.58%	606 (12.37%)
Diabetes treated with oral medications	4,443	11.41%	523 (11.77%)
Chronic respiratory diseases	2,397	6.15%	322 (13.43%)
Hypothyroidism	1,772	4.55%	209 (11.79%)
Depression	1,673	4.29%	247 (14.76%)
Arrhythmias	1,547	3.97%	221 (14.29%)
Hypertension associated with organ damage	1,304	3.35%	185 (14.19%)
Diabetes treated with insulin	1,225	3.14%	151 (12.33%)
Non-metastatic cancers	1,174	3.01%	150 (12.78%)
Arthropathies and connective tissue diseases	1,152	2.96%	163 (14.15%)
Peripheral vascular diseases	1,025	2.63%	149 (14.54%)
Neurological diseases	748	1.92%	110 (14.71%)
Heart failure	520	1.33%	72 (13.85%)
Obesity	483	1.24%	73 (15.11%)
Alcoholism	463	1.19%	39 (8.42%)
Liver diseases	441	1.13%	59 (13.38%)
Paralytic syndromes	433	1.11%	32 (7.39%)
Renal failure	340	0.87%	44 (12.94%)
Valvular heart defects	302	0.78%	40 (13.25%)
Drug use	177	0.45%	28 (15.82%)
Water-electrolyte imbalance	109	0.28%	16 (14.68%)
Coagulopathies	101	0.26%	16 (15.84%)
Nutritional-deficiency anaemia	96	0.25%	13 (13.54%)
Psychotic disorders	95	0.24%	3 (3.16%)
Lymphomata and haematological cancers	71	0.18%	15 (21.13%)
Peptic ulcers without bleeding or perforation	62	0.16%	5 (8.06%)
Pulmonary circulatory disorders	53	0.14%	5 (9.43%)
Metastatic cancers	43	0.11%	8 (18.6%)
Iron-deficiency anaemia due to blood loss	38	0.10%	2 (5.26%)
Smoking	31	0.08%	2 (6.45%)

→

Table 1. cont. Distribution of variables in study group

Variable	Number of patients	Percentage of patients in study group	Patients with a certain variable who underwent reoperation
Malnutrition and abnormal weight loss	25	0.06%	6 (24.00%)
Disease caused by HIV	3	0.01%	0 (0.00%)
Demographic variables			
Male	18,020	46.26%	1,679 (9.32%)
age: 50–59 years	9,329	23.95%	961 (10.3%)
age: 60–69 years	9,087	23.33%	1,014 (11.16%)
age: 70–79 years	4,139	10.63%	572 (13.82%)
age: 80–89 years	984	2.53%	161 (16.36%)
Place of residence: countryside	13,698	35.17%	1,197 (8.74%)
Facility profile			
Clinical centres	12,323	31.64%	1,049 (8.51%)
Operations performed in a neurosurgical department	27,921	71.68%	2,310 (8.27%)
Operations performed in an orthopaedic department	8,324	21.37%	970 (11.65%)
Other variables			
Surgeries with an implant	15,034	38.60%	992 (6.6%)
Emergency admission to hospital	6,492	16.67%	606 (9.33%)
Hospitalisation lasting 1–2 days	4,518	11.60%	559 (12.37%)
Hospitalisation lasting 3 days	7,071	18.15%	474 (6.7%)
Hospitalisation lasting 4–7 days	14,903	38.26%	931 (6.25%)
Hospitalisation lasting more than 7 days	8,079	20.74%	598 (7.4%)

Table 2. Results of logistic regression analysis (AUC for learning set = 0.687, AUC for test set = 0.69)

Variable	Coefficient	OR	2.5% OR	97.5% OR	P-value
Metastatic cancers	0.562	1.754	0.677	4.544	0.247
Depression	0.410	1.507	1.266	1.795	< 0.001*
Neurological diseases	0.355	1.426	1.105	1.841	0.006*
Obesity	0.337	1.401	1.019	1.926	0.038*
Hypertension associated with organ damage	0.225	1.253	1.019	1.541	0.033*
Patients aged 70–79	0.203	1.225	1.063	1.412	0.005*
Patients aged 60–69	0.180	1.197	1.070	1.339	0.002*
Patients aged 50–59	0.177	1.194	1.069	1.334	0.002*
Emergency admission to hospital	0.109	1.115	0.995	1.250	0.061
Liver diseases	0.107	1.113	0.777	1.595	0.558
Peripheral vascular diseases	0.105	1.111	0.880	1.403	0.378
Clinical centres	0.096	1.101	1.000	1.213	0.049*
Patients aged 80–89	0.019	1.020	0.805	1.291	0.872
Spontaneous hypertension	–0.048	0.953	0.842	1.079	0.445
Place of residence: countryside	–0.147	0.864	0.790	0.944	0.001*
Surgery with an implant	–0.202	0.817	0.738	0.903	< 0.001*
Operations performed in a neurosurgical department	–0.322	0.724	0.662	0.792	< 0.001*
Intercept*	–0.779	0.459	0.408	0.516	< 0.001*
Psychotic disorders	–0.880	0.415	0.125	1.380	0.151
Hospitalisation lasting 1–2 days	–1.071	0.343	0.298	0.394	< 0.001*
Iron-deficiency anaemia due to blood loss	–1.281	0.278	0.035	2.174	0.222
Hospitalisation lasting more than 7 days	–1.564	0.209	0.182	0.241	< 0.001*
Hospitalisation lasting 3 days	–1.661	0.190	0.164	0.220	< 0.001*
Hospitalisation lasting 4–7 days	–1.761	0.172	0.152	0.195	< 0.001*

*Constant parameter in logistic regression model, does not have a medical interpretation

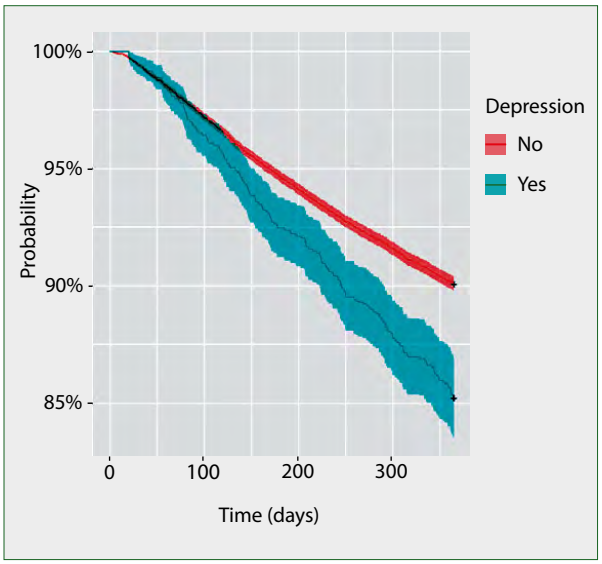

Figure 5. Kaplan-Meier curve showing changes in probability of no reoperation as number of days since hospital discharge increases, according to depression as a patient's comorbidity

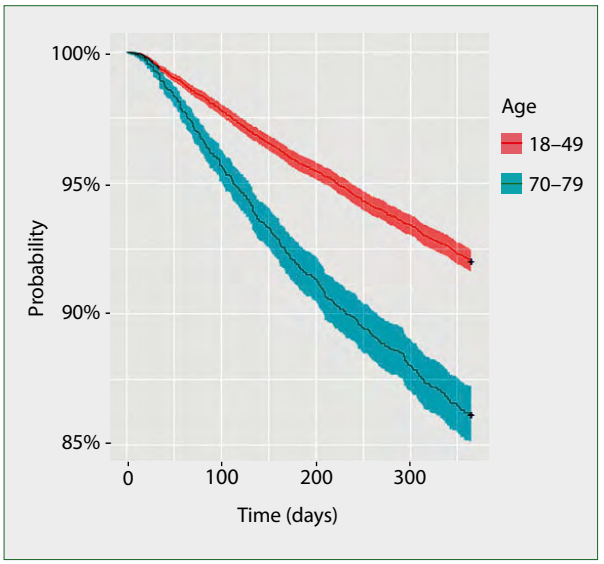

Figure 7. Kaplan-Meier curve shows changes in probability of no reoperation as number of days since hospital discharge increases, according to patient's age group at initial hospitalisation

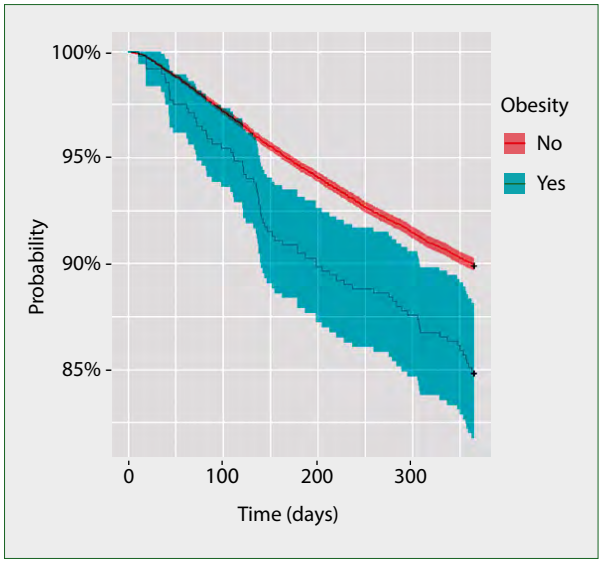

Figure 6. Kaplan-Meier curve showing changes in probability of no reoperation as number of days since hospital discharge increases, according to obesity as a patient's comorbidity

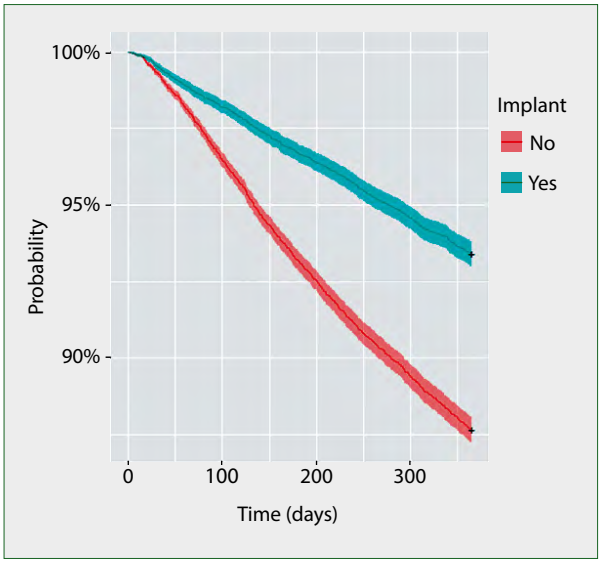

Figure 8. Kaplan-Meier curve showing changes in probability of no reoperation as number of days since hospital discharge increases, with and without use of implants

urban areas, OR = 0.864), surgery with an implant compared to surgery without an implant (OR = 0.817, Fig. 8), the performance of the primary surgery in a neurosurgical department (OR = 0.724) compared to other departments) and 1–2-day, 3-day, 4–7-day or > 7-day hospital stays compared to a one--day surgery (OR = 0.343, 0.19, 0.172, and 0.209, respectively). A detailed analysis of one-day surgeries, which is the reference group for the variables reporting other hospital stays, showed that out of 4,382 operations in this group, 4,324 (98.7%) were assessed according to DRG code H55 (arthroscopic and percutaneous spine procedures).

Discussion

Our results show there is a relationship between the demographic and clinical variables selected for the purposes of this study and the risk of reoperation within 365 days of hospital discharge after primary surgery for DSD. The reoperation rate

for all 38,953 observations was 10.12%. When analysing the distribution of comorbidity variables, it can be observed that the reoperation rate ranged from 3.16% to 21.13% (Tab. 1). Based on observations obtained from hospital discharges in Washington state (USA) for the period 1997–2007, Martin et al. estimated the reoperation rate for the period of one year after lumbar disc herniation surgery (one of the most common surgeries performed on the spine) to be 6.4% (range 2.8% to 12.5%). The risk of reoperation was higher in women and in patients with multimorbidity [19].

The logistic regression analysis provided several interesting and practically important observations. There were variables that increased, as well as others that decreased, the risk of reoperation. The variables that were associated with a statistically significant increase in the risk of reoperation included:

Demographic variables

Older age is one of the strongest predictors of reoperation; this is especially true for patients aged 70-79 (OR = 1.225). Park et al., in their study concerning the risk of reoperation for lumbar spondylosis after spinal decompression surgery using different methods of spinal instrumentation (implants), found an association between reoperation and older age / male sex [20]. In contrast, Pereira et al. [21], in their 24-month study, found no association between older age and the risk of reoperation in patients with lumbar DSD. However, the risk of reoperation increased significantly with the extent of surgery (the risk was higher for operations involving more than three spinal segments) [21]. With age, there is an increase in the number of health problems and in the sensitivity of the body to adverse effects of external factors, while there is at the same time a decrease in the adaptive capacity of the body and the capacity of individual organs and systems. In view of the increasing proportion of elderly patients receiving surgical treatment for DSD worldwide, we can expect to see an increasing number of adverse events, including reoperations in facilities providing healthcare for these patients. Surgical treatment for DSD in elderly patients provides an opportunity for many of them to relieve pain, return to daily activities and regain independence. Reduction of adverse events in elderly patients undergoing surgery is favoured by an optimal rebalancing of their health status before the planned operation — operating on patients classified as 1 or 2 on the ASA scale [21].

Clinical variables according to the Elixhauser classification

Depression was diagnosed in 1,673 patients in the study group, and 14.76% of them required reoperation within a year. This is a strong risk factor for reoperation, increasing its likelihood by more than 50%. Such a large increase in the risk of reoperation must be kept in mind when qualifying and preparing patients for surgery. Depression is one of the most important risk factors for persistent postoperative pain (PPS) in spinal surgery [22]. Studies have shown that preoperative depression is correlated with rates of complication, readmission and reoperation [23–26]. Boakye et al. distinguished not only confirmed depression, but also other groups of patients who use antidepressants for other reasons. In all groups, the reoperation rate was higher compared to patients without depression and not taking antidepressants (OR 1.4-2.03) [26]. Persistent pain, which negatively affects satisfaction with the outcome of the primary spinal surgery, may result in more frequent patient eligibility for reoperation. Studies demonstrate that independent of surgical effectiveness, baseline depression influences patient satisfaction after spinal surgery [27, 28]. The possibility of interplay between DSD and depression should be noted; it is thought that reduced physical fitness (frequently faced by DSD patients) can result in depression and other affective disorders [29]. Maintaining physical activity in older age can reduce the risk of depression and improve self-esteem [10]. Hence, proper treatment of depression can reduce its negative impact on the musculoskeletal system. On the other hand, effective treatment (including surgical) of DSD symptoms can reduce the incidence or severity of depression and improve quality of life. However, it should be underlined that it is not only an effective treatment which improves the mental condition of patients. Before the treatment itself, they should be properly prepared. The need for information about pain, disability and return to work are found to be factors associated with anxiety and depression in patients undergoing spinal surgery [30]. This group of patients requires a personalised approach and the utmost attention from medical personnel to obtain optimal results.

Obesity was found to be another strong risk factor for reoperation (OR = 1.401). It was diagnosed in 438 patients, and 15.11% of them were reoperated. The observed increase in risk has been confirmed in other studies [25, 30–32]. Goyal et al.'s meta-analysis of 32 studies involving 23,415 patients showed that in patients undergoing lumbar spine surgery, obesity increased the risk of complications (OR = 1.34) and reoperation (OR = 1.40). Minimally invasive surgery was not reported to have worse outcomes in obese patients [33]. The increased risk of postoperative complications, including surgical site infection and reoperation in obese patients, could be due to a higher level of surgical invasiveness, a longer duration of surgery, or higher intraoperative blood loss in obese patients [33, 34]. In the study by Gaudelli et al., the most common reason for reoperation of obese patients was surgical site infections [36]. In order to reduce the surgical risk, it is suggested to use minimally invasive techniques in obese patients [37]. In addition, these patients should be properly prepared for the procedure, and a multidisciplinary approach is essential in these cases.

An association between comorbidities (e.g. renal disease, severe liver disease, diabetes etc.) and recurrence rate after fusion surgery in DSD has been reported in studies based on Korean administrative data [37, 38].

Other variables

Patients operated on at a clinical centre had a higher likelihood of reoperation (OR = 1.101). This observation may be a result of both a higher degree of difficulty of primary surgeries performed at these centres and of the generally higher degree of 'complexity' of cases. It would be useful to compare the characteristics of patients treated in clinical centres to those treated in non-clinical ones, including the surgical techniques used.

The variables that were associated with a statistically significant decrease in the risk of reoperation included:

Demographic variables

The patient's place of residence was correlated with the risk of reoperation, which was lower for those living in rural areas (OR = 0.864). According to epidemiological data, there is no difference in terms of the prevalence of low back pain in urban and rural residents [3]. The variety of reoperation rates may be rooted in the availability of specialist services, and differences in terms of overall health status and socioeconomic conditions, including motivation to working life.

Other variables

Surgery with an implant was associated with a lower risk of reoperation compared to surgery without an implant (OR = 0.817). This result can be explained by the relatively short follow-up period of 365 days from the date of hospital discharge after the primary surgery. In long-term postoperative follow-up, the use of implants is generally associated with an increased rate of reoperation, contrary to the study presented here [39]. A systematic review conducted by Lang et al. showed similar reoperation rates for decompression alone or decompression plus fusion surgeries for degenerative lumbar diseases. The authors point out, however, that the most common cause of reoperation after spinal decompression surgery is disease of the same spinal segment, whereas reoperation after fusion surgery is most frequently caused by adjacent segment disease [40].

Surgical treatment performed in a neurosurgical department was associated with a lower risk of reoperation compared to surgical treatment performed in another department (OR = 0.724). The study by Seicean et al. found no differences in terms of postoperative complications and reoperation rate after spinal surgeries performed by neurosurgeons and orthopaedic surgeons; however, their follow-up period was only 30 days [41]. In this study, 27,921 (71.7%) patients were treated in the neurosurgical department and 8,324 (21.4%) in the orthopaedic department. It is difficult to clearly interpret the observed differences between the aforementioned departments. It is possible that the complexity of spinal disease, and thus the extent and scope of surgery for patients operated on in orthopaedic departments, is greater (coexisting scoliosis, multi-level spinal instability, etc.), which may be the reason for more frequent reoperations.

Length of hospital stay was a clear predictor of reoperation. The reference point for 1–2-day, 3-day, 4–7-day and > 7-day hospital stays was a one-day surgery, for which the reoperation rate was the highest. The high risk of reoperation in patients who underwent one-day surgery may be explained by the surgery profile. A detailed analysis of one-day surgery cases, which is the reference group for the variables reporting other hospital stays, showed that out of 4,382 operations in this group, 4,324 (98.7%) operations were assessed according to DRG code H55 (arthroscopic and percutaneous spine procedures). These include minimally invasive surgeries such as endoscopic discectomy, IDET, vertebroplasty and thermolesion of intervertebral joints. The reoperation rate in this group of patients may be linked to the limited or short-term effectiveness of surgical procedures. This is especially true in the case of thermolesion or IDET, the main purpose of which is symptomatic management of the pain associated with spinal disease, rather than treatment of the cause of the complaint. The risk of reoperation for > 24 h hospitalisations is lower, with the lowest values for 4–7-day hospital stays (OR = 0.172) and the highest values for 1–2-day hospital stays (OR = 0.343).

Two recently published studies based on Korean administrative data provide a comprehensive analysis of the variables associated with the reoperation rate after spinal surgeries for DSD [37, 38]. These studies focused on the association between reoperation rate and anatomical site [37], and on analysing the role of the surgical approach adopted[38]. However, the cited research included exclusively patients who underwent fusion procedures, who accounted for a mere 38.6% of cases in our study.

Strengths and limitations

The presented study is the first large-scale study concerning reoperation after surgery for DSD in Poland. This is a nationwide survey; the data was obtained from central sources, from the only public payer in Poland i.e. the NHF. The analysis included data concerning all publicly funded medical services of patients during the one-year period preceding the primary surgical treatment, which increases the likelihood of identifying comorbidities.

This study has limitations. This is a retrospective study based on reported data rather than a review of medical records. It is possible that many factors (smoking, alcohol, obesity, etc.) are underestimated compared to prospective studies. Also, data regarding the surgeon's experience and specialisation was not accessible. Subclassifications in terms of the anatomical site (cervical spine, lumbar spine, etc.), the surgical approach (anterior *vs.* posterior) and the underlying spine pathology (spinal stenosis, instability, spinal disc herniation, etc.) was not taken into consideration, and the postoperative follow-up period wass 12 months.

Conclusions

Reoperations within the first year after surgical treatment for DSD are common. Identifying risk factors for reoperation, including those related to the presence of comorbidities and the phenomenon of multimorbidity, can be an important tool in reducing the reoperation rate. This is particularly true for chronic diseases where appropriate medical management may enable the patient to be optimally prepared for surgery. In patients with several strong risk factors for reoperation, it may be prudent to forgo surgical treatment.

The practical implications of our results are linked to the awareness of the need for reoperation in quite a high percentage of patients subjected to spinal surgery. This applies mainly to general practitioners who refer patients to specialists such as neurosurgeons, spinal surgeons, and orthopaedic surgeons. In particular, elderly candidates for spinal surgery and those with multiple comorbidities should be thoroughly informed about the risks.

We recommend planning prospective studies concerning risk factors for reoperation after spinal surgery with a longer follow-up period. Optimally, this task could be realised within the framework of the national spine surgery registry.

Conflicts of interest: *None.*

Funding: *This research was funded by the European Union through the European Social Fund under the Operational Programme Knowledge Education Development (EU grant number: POWR 05.02.00-00-0149/15-01).*

References

1. Findings from the Global Burden of Disease Study 2017; Institute for Health Metrics and Evaluation, USA, Seattle. 2018.
2. Manchikanti L, Singh V, Datta S, et al. American Society of Interventional Pain Physicians. Comprehensive review of epidemiology, scope, and impact of spinal pain. Pain Physician. 2009; 12(4): E35–E70, indexed in Pubmed: 19668291.
3. Hoy D, Bain C, Williams G, et al. A systematic review of the global prevalence of low back pain. Arthritis Rheum. 2012; 64(6): 2028–2037, doi: 10.1002/art.34347, indexed in Pubmed: 22231424.
4. Kobayashi K, Ando K, Nishida Y, et al. Epidemiological trends in spine surgery over 10 years in a multicenter database. Eur Spine J. 2018; 27(8): 1698–1703, doi: 10.1007/s00586-018-5513-4, indexed in Pubmed: 29435653.
5. Spine Tango Annual Report 2020; EUROSPINE, the Spine Society of Europe. Uster-Zürich, Switzerland. 2020.
6. Ravindra VM, Senglaub SS, Rattani A, et al. Degenerative Lumbar Spine Disease: Estimating Global Incidence and Worldwide Volume. Global Spine J. 2018; 8(8): 784–794, doi: 10.1177/2192568218770769, indexed in Pubmed: 30560029.
7. Baranowska A, Baranowska J, Baranowski P. Analysis of Reasons for Failure of Surgery for Degenerative Disease of Lumbar Spine. Ortop Traumatol Rehabil. 2016; 18(2): 117–129, doi: 10.5604/15093492.1205004, indexed in Pubmed: 28155820.
8. The Encyclopedia of Surgery. https://www.surgeryencyclopedia.com (24 July 2021).
9. Zehnder P, Held U, Pigott T, et al. Development of a model to predict the probability of incurring a complication during spine surgery. Eur Spine J. 2021; 30(5): 1337–1354, doi: 10.1007/s00586-021-06777-5, indexed in Pubmed: 33686535.
10. World Health Organization: World report on ageing and health. 2015.
11. Katz JN, Stucki G, Lipson SJ, et al. Predictors of surgical outcome in degenerative lumbar spinal stenosis. Spine (Phila Pa 1976). 1999; 24(21): 2229–2233, doi: 10.1097/00007632-199911010-00010, indexed in Pubmed: 10562989.
12. Foulongne E, Derrey S, Ould Slimane M, et al. Lumbar spinal stenosis: which predictive factors of favorable functional results after decompressive laminectomy? Neurochirurgie. 2013; 59(1): 23–29, doi: 10.1016/j.neuchi.2012.09.005, indexed in Pubmed: 23246374.
13. Mannion AF, Fekete TF, Porchet F, et al. The influence of comorbidity on the risks and benefits of spine surgery for degenerative lumbar disorders. Eur Spine J. 2014; 23 Suppl 1(Suppl 1): S66–S71, doi: 10.1007/s00586-014-3189-y, indexed in Pubmed: 24458936.
14. Flakiewicz J, Wicentowicz Z, Sklepowicz A. Reoperations in lumbar discopathies. Neurol Neurochir Pol. 1992; Suppl 1: 156–160, indexed in Pubmed: 1407291.
15. Pala B, Kawalec P, Klepinowski T, et al. Causes of same-route reoperations in degenerative cervical spine disease after a primary anterior approach. Pomeranian J Life Sci. 2021; 67(1): 15–19.
16. Baranowska J, Baranowska A, Baranowski P, et al. Infections and antibiotic therapy in patients after spine surgery in a 5-year follow-up study. Archives of Medical Science. 2021, doi: 10.5114/aoms/139682.
17. Polish Society of Spine Surgery. Polspine - Polish registry for monitoring spinal surgical treatment. https://polspine.pl/ (14 February 2023).
18. Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. Med Care. 1998; 36(1): 8–27, doi: 10.1097/00005650-199801000-00004, indexed in Pubmed: 9431328.
19. Martin BI, Mirza SK, Flum DR, et al. Repeat surgery after lumbar decompression for herniated disc: the quality implications of hospital and surgeon variation. Spine J. 2012; 12(2): 89–97, doi: 10.1016/j.spinee.2011.11.010, indexed in Pubmed: 22193055.
20. Park MS, Ju YS, Moon SH, et al. Repeat decompression and fusions following posterolateral fusion versus posterior/transforaminal lumbar interbody fusion for lumbar spondylosis: a national database study. Sci Rep. 2019; 9(1): 4926, doi: 10.1038/s41598-019-41366-z, indexed in Pubmed: 30894618.
21. Pereira BJA, de Holanda CV, Ribeiro CAA, et al. Spinal surgery for degenerative lumbar spine disease: Predictors of outcome. Clin Neurol Neurosurg. 2016; 140: 1–5, doi: 10.1016/j.clineuro.2015.11.004, indexed in Pubmed: 26615462.
22. Costelloe C, Burns S, Yong RJ, et al. An Analysis of Predictors of Persistent Postoperative Pain in Spine Surgery. Curr Pain Headache Rep. 2020; 24(4): 11, doi: 10.1007/s11916-020-0842-5, indexed in Pubmed: 32072357.
23. Lee NJ, Lenke LG, Cerpa M, et al. The 90-Day Reoperations and Readmissions in Complex Adult Spinal Deformity Surgery. Global Spine J. 2022; 12(3): 415–422, doi: 10.1177/2192568220953391, indexed in Pubmed: 32878483.
24. Taliaferro K, Rao A, Theologis AA, et al. Rates and risk factors associated with 30- and 90-day readmissions and reoperations after spinal fusions for adult lumbar degenerative pathology and spinal deformity.

Spine Deform. 2022; 10(3): 625–637, doi: 10.1007/s43390-021-00446-9, indexed in Pubmed: 34846718.
25. Wadhwa RK, Ohya J, Vogel TD, et al. Risk factors for 30-day reoperation and 3-month readmission: analysis from the Quality and Outcomes Database lumbar spine registry. J Neurosurg Spine. 2017; 27(2): 131–136, doi: 10.3171/2016.12.SPINE16714, indexed in Pubmed: 28574331.
26. Boakye M, Sharma M, Adams S, et al. Patterns and Impact of Electronic Health Records-Defined Depression Phenotypes in Spine Surgery. Neurosurgery. 2021; 89(1): E19–E32, doi: 10.1093/neuros/nyab096, indexed in Pubmed: 33862621.
27. Adogwa O, Carr K, Fatemi P, et al. Psychosocial factors and surgical outcomes: are elderly depressed patients less satisfied with surgery? Spine (Phila Pa 1976). 2014; 39(19): 1614–1619, doi: 10.1097/BRS.0000000000000474, indexed in Pubmed: 24921847.
28. Adogwa O, Parker SL, Shau DN, et al. Preoperative Zung depression scale predicts patient satisfaction independent of the extent of improvement after revision lumbar surgery. Spine J. 2013; 13(5): 501–506, doi: 10.1016/j.spinee.2013.01.017, indexed in Pubmed: 23422730.
29. Navickas R, Petric VK, Feigl AB, et al. Multimorbidity: What do we know? What should we do? J Comorb. 2016; 6(1): 4–11, doi: 10.15256/joc.2016.6.72, indexed in Pubmed: 29090166.
30. Strøm J, Bjerrum MB, Nielsen CV, et al. Anxiety and depression in spine surgery-a systematic integrative review. Spine J. 2018; 18(7): 1272–1285, doi: 10.1016/j.spinee.2018.03.017, indexed in Pubmed: 29649613.
31. Marquez-Lara A, Nandyala SV, Sankaranarayanan S, et al. Body mass index as a predictor of complications and mortality after lumbar spine surgery. Spine (Phila Pa 1976). 2014; 39(10): 798–804, doi: 10.1097/BRS.0000000000000232, indexed in Pubmed: 24480950.
32. Sato S, Yagi M, Machida M, et al. Reoperation rate and risk factors of elective spinal surgery for degenerative spondylolisthesis: minimum 5-year follow-up. Spine J. 2015; 15(7): 1536–1544, doi: 10.1016/j.spinee.2015.02.009, indexed in Pubmed: 25681581.
33. Goyal A, Elminawy M, Kerezoudis P, et al. Impact of obesity on outcomes following lumbar spine surgery: A systematic review and meta-analysis. Clin Neurol Neurosurg. 2019; 177: 27–36, doi: 10.1016/j.clineuro.2018.12.012, indexed in Pubmed: 30583093.
34. Jiang J, Teng Y, Fan Z, et al. Does obesity affect the surgical outcome and complication rates of spinal surgery? A meta-analysis. Clin Orthop Relat Res. 2014; 472(3): 968–975, doi: 10.1007/s11999-013-3346-3, indexed in Pubmed: 24146361.
35. Gaudelli C, Thomas K. Obesity and early reoperation rate after elective lumbar spine surgery: a population-based study. Evid Based Spine Care J. 2012; 3(2): 11–16, doi: 10.1055/s-0031-1298613, indexed in Pubmed: 23230413.
36. Cofano F, Perna GDi, Bongiovanni D, et al. Obesity and spine surgery: a qualitative review about outcomes and complications. Is it time for new perspectives on future researches? Global Spine J. 2022; 12(6): 1214–1230, doi: 10.1177/21925682211022313, indexed in Pubmed: 34128419.
37. Park MS, Ju YS, Moon SH, et al. Reoperations after fusion surgeries for degenerative spinal diseases depending on cervical and lumbar regions: a national database study. BMC Musculoskelet Disord. 2021; 22(1): 617, doi: 10.1186/s12891-021-04491-3, indexed in Pubmed: 34246252.
38. Kim J, Ryu H, Kim TH. Early reoperation rates and its risk factors after instrumented spinal fusion surgery for degenerative spinal disease: a nationwide cohort study of 65,355 patients. J Clin Med. 2022; 11(12), doi: 10.3390/jcm11123338, indexed in Pubmed: 35743419.
39. Martin BI, Mirza SK, Comstock BA, et al. Reoperation rates following lumbar spine surgery and the influence of spinal fusion procedures. Spine (Phila Pa 1976). 2007; 32(3): 382–387, doi: 10.1097/01.brs.0000254104.55716.46, indexed in Pubmed: 17268274.
40. Lang Z, Li JS, Yang F, et al. Reoperation of decompression alone or decompression plus fusion surgeries for degenerative lumbar diseases: a systematic review. Eur Spine J. 2019; 28(6): 1371–1385, doi: 10.1007/s00586-018-5681-2, indexed in Pubmed: 29956000.
41. Seicean A, Alan N, Seicean S, et al. Surgeon specialty and outcomes after elective spine surgery. Spine (Phila Pa 1976). 2014; 39(19): 1605–1613, doi: 10.1097/BRS.0000000000000489, indexed in Pubmed: 24983930.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 4, pages: 363–370
DOI: 10.5603/PJNNS.a2023.0049

ISSN: 0028-3843, e-ISSN: 1897-4260

Experience of treatment of chronic migraine with botulinum toxin type A among aesthetic medicine professionals in Poland

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ABSTRACT

Introduction. This study aimed to evaluate the knowledge and standard of treatment of chronic migraine with botulinum toxin by Polish aesthetic medicine professionals.

Rationale for the study. Onabotulinum toxin A injections are used as a preventive treatment for chronic migraine. Besides neurologists, healthcare professionals of multiple specialisms can offer this treatment. Aesthetic medicine professionals commonly use the treatment to extend the scope of their practice. This may bring about a situation wherein physicians with different levels of experience and training are providing botulinum toxin injections for chronic migraine.

Material and methods. An online survey asking about patient qualification procedures, the level of adherence to the PREEMPT paradigm, product-, technique-, dosing-, and treatment intervals-related aspects of the treatment, efficacy evaluation practices and concerns about the use of botulinum toxin in chronic migraine was sent to 110 Polish physicians practicing aesthetic medicine.

Results. The response rate was 73.6%. The results of the survey revealed multiple deviations from the current paradigm of treatment of chronic migraine with botulinum toxin, from improper patient qualification through treatment procedure to the evaluation of the efficacy. Only around one-third of professionals evaluated the observed effectiveness of therapy as very good. Most respondents wanted to expand their knowledge and skills in chronic migraine treatment.

Conclusions. There is a considerable willingness among aesthetic medicine specialists to treat patients with chronic migraine with botulinum toxin. The current levels of knowledge and skills in this treatment are limited, and multiple physicians declared deviations from the diagnostic criteria and the therapeutic protocol. Transferring aesthetic medicine practices to neurology treatment is common and may result in a lack of effectiveness of treatment or even intensification of symptoms. An appropriate educational programme should be implemented for all physicians authorised to administer BoNT-A in Poland.

Key words: aesthetic medicine, chronic migraine, onabotulinum toxin type A, PREEMPT protocol

(*Neurol Neurochir Pol 2023; 57 (4): 363–370*)

Introduction

Onabotulinumtoxin A (OnaBoNT-A) was registered in Poland for the treatment of chronic migraine (CM) in 2010 [1]. Many randomised clinical trials have assessed its effectiveness and safety [2–7]. OnaBoNT-A is the only botulinum toxin type A (BoNT-A) registered for this indication. The drug has been reimbursed in Poland since July 2022 for patients with CM after previous failures of at least two oral prophylactic treatments [8, 9].

For 13 years, OnaBoNT-A therapy has been available to patients mainly in the private healthcare sector. Even so, many individuals who do not qualify for the reimbursed treatment due to lack of oral treatment failures, or those who prefer treatment in private clinics, receive OnaBoNT-A commercially as part of their out-of-pocket expenditure.

Both neurologists and aesthetic medicine professionals (AMPs) perform BoNT-A injections in CM. AMPs are involved in this treatment for several reasons. Firstly, the

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Received: 07.05.2023; Accepted: 27.06.2023; Early publication date: 24.07.2023

initial observations about the effectiveness of BoNT-A in the treatment of migraine came from the AMP. By treating glabellar and forehead wrinkles, they reduced migraine pain in their patients. This observation launched successful clinical trials of OnaBoNT-A in CM. Secondly, AMPs have extensive BoNT-A treatment experience and full access to this therapy. Thirdly, the aesthetic medicine sector is heavily commercialised, with extensive internet marketing, which means that patients quickly find a clinic offering BoNT-A migraine treatment and often go there first without waiting for an appointment with a neurologist.

After searching for a term, e.g. "treatment of migraine with botulinum toxin" in a browser, the patient is directed to the websites of aesthetic medicine clinics offering migraine treatment services with BoNT-A. Unfortunately, reading the information about this therapy available on the websites of some medical centres, one may suspect that these services have little to do with CM management according to the current standards and the PREEMPT protocol. This shows that BoNT-A treatment is offered to all migraine sufferers, not only those with CM, and the drug is administered mainly intramuscularly and at trigger points, which is supposed to cause muscle relaxation and thus relieve headache. Inadequate qualifications and treatment techniques result in a lack of therapeutic effect and discourage the patient from continuing.

The indication for the treatment of OnaBoNT-A is CM, which is defined as the presence of headache (tension and/or migraine type) for at least 15 days a month in the last three months, and which headache for at least eight days a month meets the criteria for the diagnosis of migraine with or without aura, and at the onset of the disease had a migraine character and responded to triptans or ergotamine derivatives [10].

The technique of OnaBoNT-A administration according to the PREEMPT protocol was described in detail in a document published in 2017 by Blumenfeld et al. [11, 12]. For years, Polish neurologists have had the opportunity to participate in practical workshops on treating CM with OnaBoNT-A, conducted by, among others, the author. AMPs do not have such a possibility and mainly explore how to administer BoNT-A in CM from the literature. Incorrect treatment may result in a lack of effectiveness of therapy [12]. An administration technique not following the PREEMPT protocol may also expose the patient to side effects. The effectiveness of therapy of CM is important also in the context of a high burden of disease and its undertreatment in Poland, which occurs despite relatively good access to physicians [13].

Objectives

This study's primary aim was to analyse the state of knowledge about CM and the technique of BoNT-A administration among Polish AMPs. The secondary objective was to analyse the educational needs of this group of physicians in CM treatment with BoNT-A.

Material and methods

This pilot study among AMPs was conducted between December 2022 and January 2023. A self-developed online questionnaire with 40 questions aimed to evaluate: the professional experience of practitioners; the level of knowledge about BoNT-A treatment in CM and its source; patient qualification procedures; the type of BoNT-A and dose used in CM treatment; the technique of drug administration with particular emphasis on injection sites, single dose, depth of BoNT-A administration and direction of needle insertion; evaluation of the effectiveness of BoNT-A treatment in CM; concerns related to BoNT-A treatment in CM; and interest in, and willingness to expand knowledge of, the field of BoNT-A treatment in the treatment of CM. The supplementary material contains the original survey and its translation.

The questionnaire was created in Google Forms, a survey software included in Google LLC's free, web-based Google Docs Editor. The author personally sent by e-mail the questionnaire to 110 AMPs with a detailed explanation of the purpose of the study and an assurance of data anonymity. Each physician was informed that the purpose of the analysis was not to indicate their possible errors in the procedure, but only to assess the state of knowledge and educational needs in this area. Personal contact with the author emphasised the problem's essence and ensured the survey's anonymity. This also served to eliminate the possibility of completing the questionnaire by unauthorised persons.

Respondents had the opportunity to omit questions that, in their opinion, did not apply to them (e.g. because they do not use BoNT-A in the treatment of CM) or which they did not want, or were unable, to answer. Therefore, a different number of answers were given to each question, which was considered in analysing the results. The results were presented as percentages of respondents.

Results

Participants

Eighty-one physicians completed the questionnaire; 67 women (82.7%) and 14 men (17.3%) aged from 26 to 60. None of the surveyed AMPs was a neurologist, and 21 (25.9%) of the respondents were dentists. The rest of the clinicians had a different medical specialism.

The respondents differed in terms of years of professional experience: 1–2 years or 3–5 years of work experience were declared by 11 respondents (13.6%) each, 6–10 years by 17 (21%), 11–15 years by 20 (24.7%), and over 15 years of work by 22 (27.2%).

Eligibility for botulinum toxin treatment of chronic migraine

Among all the doctors who completed the questionnaire, 37 (45.7%) confirmed that they perform BoNT-A injection procedures in treating CM.

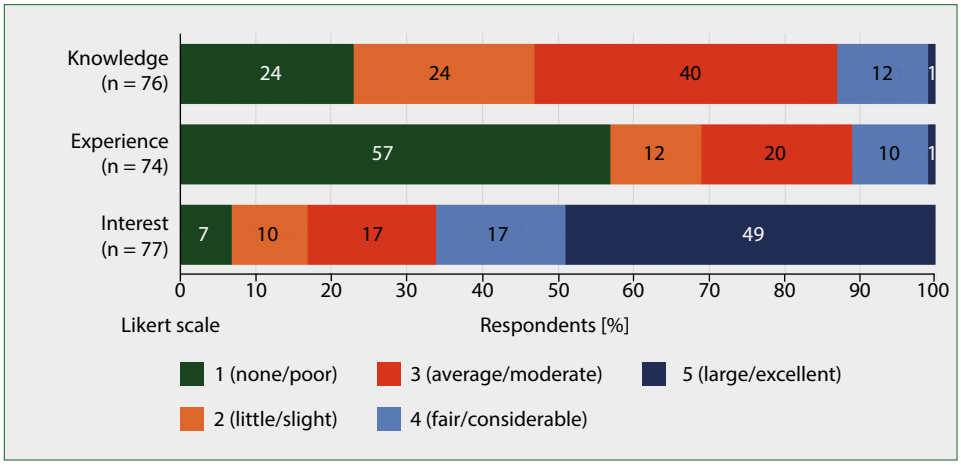

Figure 1. Level of knowledge, experience, and interest in botulinum toxin treatment for chronic migraine among aesthetic medicine professionals

Thirty-eight clinicians answered the question "For which patients do you use BoNT-A for migraine?" Most professionals (n = 30, 78.9%) confirmed that they use BoNT-A in patients diagnosed with CM, 12 (36.1%) declared that they used it in patients with many years' migraine, 13 (13.2%) indicated that they used it in patients with migraine regardless of whether they had been diagnosed with CM, and two (5.3%) indicated that they used it in all patients, regardless of the frequency of migraine attacks.

The question: "Do you verify the diagnosis of migraine before treatment with BoNT-A?" was answered by 56 physicians. Of them, 27 (48%) stated that they administered the drug based on the patient's medical history and declaration of being treated for migraine. Twelve clinicians (21.4%) stated that they did not verify the diagnosis because they knew nothing about migraine. Some physicians (n = 8, 14.3%) verified the diagnosis and independently confirmed the CM diagnosis. A few AMPs (n = 6, 10.7%) required a referral from a neurologist before the procedure, and one (1.8%) needed a referral from a pain medicine specialist. Only 17 of 74 surveyed AMPs (23%) cooperated with a neurologist in treating CM.

Most physicians use BoNT-A in migraine patients concomitantly with the same medication for wrinkles (22/40, 55%), bruxism (12/40, 30%), or other indications (11/40, 27%).

Knowledge of criteria for diagnosis of chronic migraine

Seventy-four respondents answered the question "Do you know the criteria for the diagnosis of CM?" Most clinicians confirmed they did (45/74, 60.8%). Only 17/31 respondents (54.8%) presented an accurate definition of CM.

Physicians' experience in botulinum toxin therapy for chronic migraine

In the last 12 months, 36 of 77 AMPs (46.8%) said they did not perform any procedure, 22 respondents (28.6%) treated ≤ 5 patients, and 10 (13%) treated 6-10 patients. The treatment of multiple patients (> 50 patients/year) was declared by only three physicians (3.9%). The question about their experience and knowledge about CM treatment with the use of BoNT-A was answered by 74 physicians, assessing them on a scale of 1 (poor) to 5 (very good) (Fig. 1). 68/78 of the surveyed physicians were interested in expanding their knowledge and skills in CM treatment using BoNT-A (Fig. 1).

Knowledge and experience of PREEMPT protocol

Of 47 physicians who answered the question about the type of BoNT-A used to treat CM, 42 (89.3%) indicated using OnaBoNT-A, but as many as 32 (68.0%) also used other BoNT-As. Only 16 of 55 respondents (29.1%) declared that they always used a toxin according to the PREEMPT protocol, and 17 (30.9%) of the respondents modified the paradigm depending on the patient's needs. Many physicians (16/55, 29.1%) admitted that they did not know the PREEMPT protocol, and six (10.9%) administered BoNT-A only in the forehead and temples. Knowledge of the PREEMPT protocol came mainly from the internet, e.g. Google and YouTube searches (27/47 and 44.7%), their peers or medical representatives, and a summary of product characteristics (9/47, 19.1% each).

Only 22 of 38 physicians (57.9%) indicated the correct dose of OnaBoNT-A, a fixed dose in line with the PREEMPT protocol. Sixteen specialists (42.1%) gave an incorrect dose of BoNT-A, including 10 (26.3%) selecting a fixed dose but different from the PREEMPT protocol, and six (15.8%) who adjusted the dose individually.

Most physicians (35/38, 94.6%) used an amount of 0.9% saline other than 2 mL to dilute BoNT-A, using 1–2.5 mL of solvent. Only three clinicians (8.1%) declared that they diluted the medication correctly using 2 mL of 0.9% saline. Two physicians (5.3%) mixed BoNT-A with lidocaine.

Out of 40 doctors who answered the question about the depth of drug administration, as many as 35 (87.5%) injected

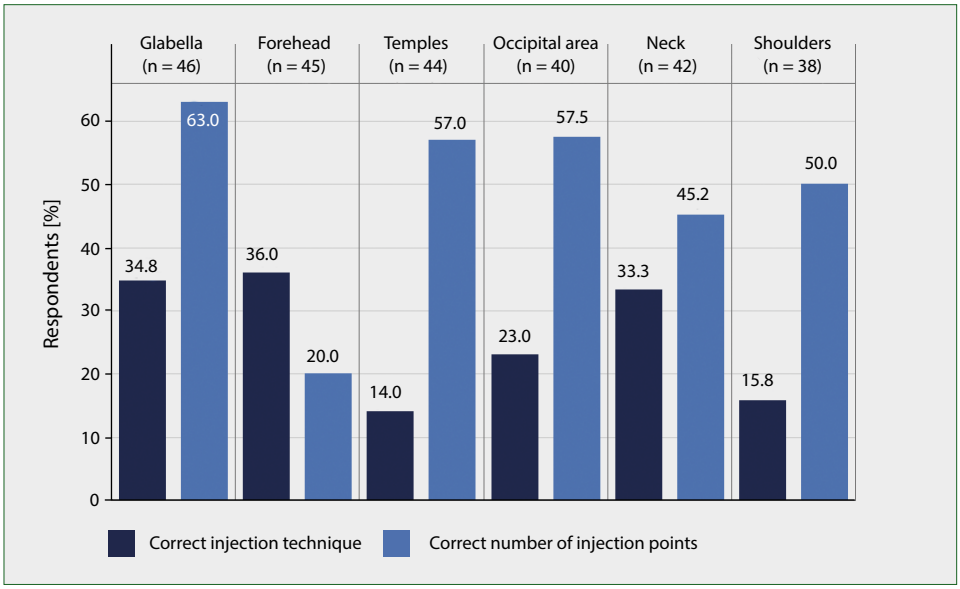

Figure 2. Compliance with PREEMPT paradigm during botulinum toxin injections for chronic migraine analysed from perspective of treatment in different areas of head and body

BoNT-A deep into the muscles. Others administered the drug subcutaneously (6/40, 15%) or intradermally (6/40, 15%), or deep into the periosteum (2/40, 5%). AMPs mainly injected BoNT-A into the temples (40/41, 97.6%), forehead (38/41, 92.7%), back of the head (35/41, 85.4%), glabella (34/41, 82.9%), neck (26/41, 63.4%) and shoulders (14/41, 34.1%). The great majority, 37 of 39 AMPs (94.9%), administered the drug bilaterally, and only two persons (5.1%) injected only half of the head.

The results relating to the detailed technique of OnaBoNT-A injection into particular areas of the head and face, following the PREEMPT protocol, e.g. the location and number of injection points as well as the depth and angle of drug administration, are presented in Figure 2.

Only 16 of 46 physicians (34.8%) administered BoNT-A correctly, i.e. at a 90-degree angle, in the glabella area. Others declared that they inserted the needle diagonally upwards (n = 14/46, 30.4%) or downwards (n = 2/46, 4.3%). In addition, as many as 13/46 (28.3%) specialists administered an additional dose of BoNT-A in this area laterally into the skin attachment of the frowning muscle. Only 12 of 45 respondents (26.7%) applied BoNT-A in the upper third of the forehead, with the other 33 doing so in other places. Most AMPs (33/47, 70.2%) did not aspire before injecting.

As per the PREEMPT paradigm, additional doses in the so-called Follow-the-Pain protocol were always used by 6/40 (15%) of respondents. 19/40 (47.5%) gave these doses correctly but not in every patient, and 15/40 (37.5%) were unfamiliar with this part of the PREEMPT protocol.

Only 18 of 43 (41.9%) physicians give the correct dose of BoNT-A at each injection point (5 units). The others use different drug doses, as shown in Figure 3.

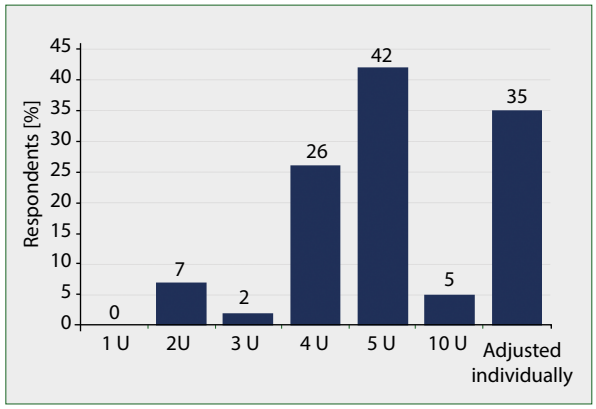

Figure 3. Specific doses of botulinum toxin used per injection point. U — units; N = 43

Evaluation of effectiveness of chronic migraine treatment with botulinum toxin

Evaluation of effectiveness of chronic migraine treatment with botulinum toxin 7/40 (17.5%) doctors, by the recommendations, administered BoNT-A at least three times at 3-month intervals, and 5/40 (12.5%) declared that they treat migraine with BoNT-A every three months and give it as many times as needed. The others repeated the procedure irregularly, usually when the migraine reoccurred (13/40, 32.5%).

The answer to the question "How do you assess the effectiveness of migraine treatment with BoNT-A?" was presented on the Likert scale [from poor (1) to very good (5)]. Of 43 respondents, 16 (37.2%) indicated a very good effect of BoNT-A. The others rated therapy effectiveness as 4 (n = 19/43, 44.2%) or 3 (n = 8/43, 18.6%).

Concerns of aesthetic medicine professionals about BoNT-A therapy for chronic migraine

Fifty-seven physicians shared their worries and anxieties about CM therapy with BoNT-A. As many as 32 of them (56.1%) were most afraid of patient qualification errors, 20 (35.1%) of performing the procedure incorrectly, 11 (19.3%) of damage to nervous structures and neurological complications, five (8.8%) of eyelid ptosis, eight (14.%) of the unsightly appearance of the patient, 24 (42.1%) of the patient's dissatisfaction with the procedure performed or the entire therapy, 24 (42.1%) of the ineffectiveness of BoNT-A, eight (14%) of a patient's negative opinions, and seven (12.3%) of patient's claims against them.

According to the majority of physicians (43/59, 72.9%), patients were discouraged from using BoNT-A by the high price of the therapy. Only 36 of 70 AMPs (51.4%) knew that some patients with CM could obtain reimbursement for BoNT-A treatment, and 28 physicians (40%) believed that BoNT-A was not reimbursed for patients with CM in Poland.

Almost half of the specialists (29/59, 49.2%) believed that patients did not receive information about this therapy, and 27 (45.8%) respondents believed that patients were afraid of BoNT-A toxicity, including eight physicians (13.6%) claiming that patients were afraid to have head injections, and 16 (27.1%) who believed that patients were discouraged from starting treatment for fear of the uncertain effect of the therapy. Over a third of AMPs (23/64) believed that the CM treatment procedure with BoNT-A was not economically feasible for them.

Discussion

This was a pilot study among AMPs in Poland concerning migraine treatment. It was challenging to identify all Polish AMPs because aesthetic medicine is a skill, not a specialisation. Every doctor, including dentists, can become AMPs, and they acquire skills during postgraduate studies and additional courses. There are no reliable data, but it is estimated that 2,500–3,000 doctors practice aesthetic medicine in Poland, but not every professional is registered in databases of scientific societies. Only a few representatives of the aesthetic medicine community participated in this pilot study, but the author believes that its results indicate the need for further analysis and education in CM treatment with BoNT-A.

The PREEMPT paradigm is the only valid protocol for CM treatment with OnaBoNT-A [2, 3, 11, 14]. According to it, BoNT-A should be administered in 31–39 sites within the head and neck area, inserting the needle shallowly under the skin and administering 5 units of OnaBoNT-A at each point. The minimum dose of BoNT-A is 155U, which corresponds to 31 injection points (registered in both the USA and Europe), and the maximum dose is 195U, which corresponds to 39 injection points (European registration) [15]. The initial administration technique has been improved, taking into account new scientific reports on the proposed mechanism of action of BoNT-A in neuropathic pain [16, 17]. Today, it is known that the goal of BoNT-A treatment in CM is not muscle relaxation but rather reaching the nerve endings of the trigeminal-occipital-cervical nerve complex. BoNT-A affects unmyelinated C fibres, inhibiting the secretion of pain neurotransmitters [16–19]. This molecule is supposed to be transported by axonal retrograde transport along peripheral nociceptive pathways and affects the central mechanisms of migraine pain generation, including reducing the duration of cortical spreading depression [18, 19]. BoNT-A could have a unique neuromodulatory effect, causing peripheral and central desensitisation of nerve pathways involved in the pathogenesis of migraine pain [2, 17]. Therefore, there is no reason to administer this medication deep intramuscularly but only shallowly under the skin innervated by the endings of the trigeminal nerve, occipital and supraclavicular nerves [11]. Performing at least three treatment cycles every 12 weeks is necessary to obtain a satisfactory clinical effect, and the continuation brings further clinical benefits [20]. Evidence from open-label real-world trials has proven the safety and effectiveness of treatment according to the PREEMPT protocol [21]. Recent observational studies indicate a clinical benefit even from several years of regular administration of OnaBoNT-A every 12 weeks [22].

BoNT-A for CM is one of the most important and effective treatment methods for this severe condition. The therapy's success depends on the patient's proper qualification for the procedure and on conducting it according to a strictly defined protocol, including a specific injection technique, drug dose, and intervals between treatments [12, 23]. In order to achieve a beneficial long-term effect, it is necessary to monitor and verify the patient's clinical condition systematically and to supervise the emergency medication used concomitantly.

In most cases, such treatment should be carried out by neurologists, although not all of them can administer injections of BoNT-A in CM. Given cooperation between a neurologist and another doctor, e.g. an AMP, who has injection skills, BoNT-A therapy can be appropriately conducted [23].

This study is the first attempt at an analysis of CM treatment with BoNT-A performed by AMPs to evaluate their state of knowledge, experience, and educational needs.

To the best of the author's knowledge, this is the first available analysis of CM procedures among AMPs performed by online questionnaires. Perhaps thanks to the individual contact and establishing a relationship between the author and the respondent, the response rate was as high as 73.6%. In the study by Begasse de Dhaem et al., who conducted a similar questionnaire analysis of modifying the PREEMPT protocol among headache specialists, only 20.7% of practitioners responded [24].

The anonymous survey revealed that half of AMPs perform BoNT-A injections in CM. Most do these procedures to accompany the treatment of wrinkles or bruxism. Unfortunately,

only a few AMPs can qualify the right patient for the procedure and treat migraine sufferers without considering the BoNT-A treatment.

OnaBoNT-A is registered for treating CM, and there is insufficient evidence for its effectiveness in episodic migraine (EM) or other types of headaches. Proper treatment of BoNT-A of CM starts with qualifying the right patient. Most respondents claim that they use BoNT-A only in patients with CM, but almost half of the respondents gave this medication "at the patient's request" without verifying and confirming the diagnosis of CM. Only a few of the respondents cooperated permanently with a neurologist or performed the procedure based on a referral from a neurologist. 20% of the surveyed AMPs admitted that they do not verify the diagnosis because they "know nothing about migraine". Qualification of inappropriate patients comes from ignoring the criteria for CM diagnosis.

More than half of the surveyed physicians claimed to know the criteria for diagnosing CM, but few could provide the correct definition of CM. The most common definition of CM given by the respondents was at least 15 days with a headache in a month. Few doctors knew that at least eight of these days should have migraine symptomatology, and the observation period must be at least three months. This raises suspicions that patients who do not meet the criteria for CM diagnosis and suffer from other types of headaches, such as tension-type headaches, may still qualify for BoNT-A treatment. However, ignorance of the full criteria for diagnosing CM is not only the domain of AMPs. Indeed, the great majority (90%) of Polish family physicians cannot list the full criteria for the diagnosis of migraine; only one in two of them claimed that they could distinguish between CM and EM, and only one in three could provide the correct definition of CM [25].

According to this study, AMPs do not often perform BoNT-A injections in CM. Only every second surveyed physician carried out at least one procedure last year; most performed it once every few months. Such a frequency of injections does not allow for developing and maintaining the experience in CM therapy with OnaBoNT-A.

Based on this survey's results, it can also be concluded that most AMPs perform the CM treatment procedure misusing BoNT-A. Many of them, apart from OnaBoNT-A, also use other types of BoNT-A for treatment, which are not registered and tested for CM treatment. Almost all dilute the drug incorrectly, usually using a larger amount of 0.9% saline, a typical dilution protocol for treating wrinkles. Some clinicians mix BoNT-A with lidocaine, perhaps trying to gain additional therapeutic effects.

Unfortunately, only a third of respondents perform injections as per the PREEMPT protocol, a third modify it at his/her discretion, and the last third do not even know the protocol. Only half of those familiar with the PREEMPT paradigm administer Follow-the-Pain injections. Half of the physicians administer the incorrect dose of OnaBoNT-A per injection point, and most give a lower dose, due to worrying about side effects.

The depth of drug administration is a strategic element of the technique in the procedure of BoNT-A injection in CM. Most AMPs inject BoNT-A deep into the muscles and perform injections at the wrong angle, adhering to aesthetic medicine treatment protocols. Most AMPs inject the drug into the frown muscle as recommended by the BoNT-A manufacturers, as they treat glabellar wrinkles and direct the needle upwards and laterally from the eye (towards the forehead). This corresponds to the original PREEMPT paradigm from 2010 [14]. According to this, the BoNT-A injection site in the PM is approximately 1.5 cm (i.e. one finger width) above the medial superior edge of the orbital ridge. The midpoint of puncture into the longitudinal muscle of the nose is located on the line connecting both injection points in the area of the frowning muscle, also about 1.5 cm above the edge of the eye socket, which in turn does not correspond to the location of the puncture in the longitudinal muscle of the nose in the treatment of lion's wrinkle. This one is shifted slightly downwards, even to the level of the bridge of the nose. Currently, according to the recommendations of Blumenfeld et al. from 2017, in the glabella area, BoNT-A should be administered at an angle of 90 degrees, not obliquely upwards [11].

Similarly to the study by Begasse de Dhaem et al. [24], most of the AMPs do not aspirate before injecting, which is recommended for CM treatment with BoNT-A in the temple and occipital area. The topic of aspiration during injections in aesthetic medicine still raises much controversy, and many experts have differing opinions [26]. Nonetheless, in areas with rich vascularity such as the temporal and occipital regions, it is worth aspirating during the injection so that the drug does not end up in the vessel. However, accidental injection of a small amount of drug into the vessel is not dangerous and is less important than losing the drug that is supposed to act on the nerve endings in this area.

The surveyed doctors did not know the principles of CM therapy using BoNT-A. OnaBoNT-A should be administered at least three times at 12-week intervals to evaluate the clinical effect. Only a few AMPs administer BoNT-A at least three times at 3-month intervals. Others repeat the treatments irregularly, usually when migraine recurs. In the case of such inconsistencies in therapy, the effectiveness of BoNT-A may be low, which was confirmed by the respondents; only 1/3 of them assess the effect of the treatment as very good.

AMPs are limited by worrying about incorrect procedures, from qualifying the wrong patient to the occurrence of side effects. Ignorance of the pathogenesis of migraine, neuroanatomy, and the mechanism of action of BoNT-A causes many AMPs to be worried about damage to the nervous structures and neurological complications. Ptosis, which is more common after wrinkle treatment than after CM treatment, is not as worrying as the presence of other neurological complications. On the other hand, some doctors are afraid of the unsightly

appearance of the patient, which may be related to the specificity of the PREEMPT protocol and the possibility of medial brow ptosis, full eyebrow ptosis, or the Mephisto phenomenon in anatomically predisposed patients. The anatomical differences should be considered in every case, but the general principles of the PREEMPT paradigm should be preserved.

Almost half of the respondents were afraid of patient dissatisfaction with the performed procedure or the entire therapy, the ineffectiveness of BoNT-A, and negative opinions or even claims made by the patient. Such worries are frequent among clinicians performing procedures in the commercial healthcare market, especially in aesthetic medicine.

Not all surveyed physicians knew the new possibilities of BoNT-A reimbursement in CM treatment in Poland [8, 9]. They also believed Polish migraine sufferers do not receive sufficient information about this therapy and that the high price and uncertainty of the therapeutic effect discouraged them from BoNT-A treatment.

Since July 2022, Polish neurologists and patients with CM migraine have been widely informed about free treatment programmes via the National Health Fund, the Polish Neurological Society, the Polish Headache Society, and social media websites. The truth is that the area of practical education in the field of BoNT-A in CM treatment in Poland is addressed mainly to neurologists. The Polish Headache Society and the manufacturer of OnaBoNT-A run free educational programmes, conferences, and workshops in which neurologists can participate. Doctors in other specialisms, including those with the skill of aesthetic medicine, have little opportunity to acquire knowledge and experience in this area. The only chance for them is to follow scientific reports or participate in commercially organised courses in aesthetic medicine, where the subject of CM is implemented. For most of the surveyed physicians, their source of information on CM treatment is the internet. For this purpose, they use the Google search browser or YouTube. The respondents confirmed they have little experience or knowledge in this area. They wanted to gain this knowledge and improve their skills in treating CM with BoNT-A. In additional comments at the end of the survey, several physicians asked for additional courses and training.

This study has several limitations; it relies on respondents' willingness to answer the survey, and despite a high responder rate it is not free of non-response bias. The sample size was relatively small compared to the number of AMPs in Poland; thus, the accurate representation of the respondents' population is limited. The cross-sectional design does not support determining cause and effect relationships; however, this first survey can create a baseline for a similar assessment to be conducted in the future, i.e. after implementing different educational initiatives. To make this possible, the original and translated questionnaire is published alongside this manuscript.

Conclusions

AMPs want to treat patients with CM with BoNT-A and strongly need education. Unfortunately, those doctors who have already conducted such treatment have mostly done it incorrectly, which is caused by ignorance of the CM diagnosis criteria and the current therapeutic protocol. This may result in the lack of effectiveness of BoNT-A treatment and even the intensification of symptoms due to the chronification of migraine in a patient not supervised by a neurologist.

To prevent such events, an appropriate educational programme should be implemented for all physicians authorised to administer BoNT-A in Poland. This would allow the broader therapeutic resources required to cope with the burden of CM in Poland [13].

Funding: *None.*
Conflicts of interest: *The author has served on advisory boards for, consulted for, and/or been a speaker or contributing author for Allergan/AbbVie, Teva, Novartis, Pfizer, and Polpharma.*
Acknowledgments: *The author thanks Marcin Balcerzak of Medink for editorial support for this manuscript.*

References

1. BOTOX® (onabotulinumtoxinA) for injection, for intramuscular, intradetrusor, or intradermal use. Purple Book Database of Licensed Biological Products. Internet: U.S. Food and Drug Administration; 1991.
2. Aurora SK, Dodick DW, Turkel CC, et al. PREEMPT 1 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia. 2010; 30(7): 793–803, doi: 10.1177/0333102410364676, indexed in Pubmed: 20647170.
3. Diener HC, Dodick DW, Aurora SK, et al. PREEMPT 2 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010; 30(7): 804–814, doi: 10.1177/0333102410364677, indexed in Pubmed: 20647171.
4. Dodick DW, Turkel CC, DeGryse RE, et al. PREEMPT Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache. 2010; 50(6): 921–936, doi: 10.1111/j.1526-4610.2010.01678.x, indexed in Pubmed: 20487038.
5. Blumenfeld AM, Stark RJ, Freeman MC, et al. Long-term study of the efficacy and safety of OnabotulinumtoxinA for the prevention of chronic migraine: COMPEL study. J Headache Pain. 2018; 19(1): 13, doi: 10.1186/s10194-018-0840-8, indexed in Pubmed: 29404713.
6. Rothrock JF, Adams AM, Lipton RB, et al. FORWARD Study investigative group. FORWARD study: evaluating the comparative effectiveness of onabotulinumtoxina and topiramate for headache prevention in adults with chronic migraine. Headache. 2019; 59(10): 1700–1713, doi: 10.1111/head.13653, indexed in Pubmed: 31559634.
7. Ahmed F, Gaul C, García-Moncó JC, et al. REPOSE Principal Investigators. An open-label prospective study of the real-life use of onabotulinumtoxinA for the treatment of chronic migraine: the REPOSE study.

J Headache Pain. 2019; 20(1): 26, doi: 10.1186/s10194-019-0976-1, indexed in Pubmed: 30845917.
8. Domitrz I, Kozubski W, Rożniecki JJ, et al. The Polish Headache Society and the Headache Section of the Polish Neurological Society Consensus Statement: update on new pharmacological therapies for migraine in clinical practice and public medication reimbursement program for chronic migraine. Arch Med Sci. 2022; 18(6): 1705–1707, doi: 10.5114/aoms/153955, indexed in Pubmed: 36457955.
9. Boczarska-Jedynak M, Domitrz I, Kozubski W, et al. Komentarz ekspertów Sekcji Bólu Głowy Polskiego Towarzystwa Neurologicznego oraz Polskiego Towarzystwa Bólów Głowy do programu leczenia migreny przewlekłej (B.133) Narodowego Funduszu Zdrowia. Pol Przegl Neurol. 2022, doi: 10.5603/ppn.a2022.0027.
10. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018; 38(1): 1–211, doi: 10.1177/0333102417738202, indexed in Pubmed: 29368949.
11. Blumenfeld AM, Silberstein SD, Dodick DW, et al. Insights into the Functional Anatomy Behind the PREEMPT Injection Paradigm: Guidance on Achieving Optimal Outcomes. Headache. 2017; 57(5): 766–777, doi: 10.1111/head.13074, indexed in Pubmed: 28387038.
12. Boczarska-Jedynak M, Sławek J. Praktyczne aspekty leczenia migreny przewlekłej toksyną botulinową typu A. Pol Przegl Neurol. 2017; 13: 189–98.
13. Waliszewska-Prosół M, Straburzyński M, Czapińska-Ciepiela EK, et al. Migraine symptoms, healthcare resources utilization and disease burden in a large Polish migraine cohort : Results from 'Migraine in Poland'-a nationwide cross-sectional survey. J Headache Pain. 2023; 24(1): 40, doi: 10.1186/s10194-023-01575-4, indexed in Pubmed: 3704149
14. Blumenfeld A, Silberstein SD, Dodick DW, et al. Method of injection of onabotulinumtoxinA for chronic migraine: a safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program. Headache. 2010; 50(9): 1406–1418, doi: 10.1111/j.1526-4610.2010.01766.x, indexed in Pubmed: 20958294.
15. Botox 100 Allergan Units, Powder for solution for injection Botulinum toxin type A. Public Assessment Report for a Medicinal Product for Human Use. Internet: Health Products Regulatory Authority. 2022.
16. Burstein R, Zhang X, Levy D, et al. Selective inhibition of meningeal nociceptors by botulinum neurotoxin type A: therapeutic implications for migraine and other pains. Cephalalgia. 2014; 34(11): 853–869, doi: 10.1177/0333102414527648, indexed in Pubmed: 24694964.
17. Zhang X, Strassman AM, Novack V, et al. Extracranial injections of botulinum neurotoxin type A inhibit intracranial meningeal nociceptors' responses to stimulation of TRPV1 and TRPA1 channels: Are we getting closer to solving this puzzle? Cephalalgia. 2016; 36(9): 875–886, doi: 10.1177/0333102416636843, indexed in Pubmed: 26984967.
18. Melo-Carrillo A, Strassman AM, Schain AJ, et al. OnabotulinumtoxinA affects cortical recovery period but not occurrence or propagation of cortical spreading depression in rats with compromised blood-brain barrier. Pain. 2021; 162(9): 2418–2427, doi: 10.1097/j.pain.0000000000002230, indexed in Pubmed: 34448754.
19. Gazerani P, Au S, Dong X, et al. Botulinum neurotoxin type A (BoNTA) decreases the mechanical sensitivity of nociceptors and inhibits neurogenic vasodilation in a craniofacial muscle targeted for migraine prophylaxis. Pain. 2010; 151(3): 606–616, doi: 10.1016/j.pain.2010.07.029, indexed in Pubmed: 20728992.
20. Silberstein SD, Dodick DW, Aurora SK, et al. Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT. J Neurol Neurosurg Psychiatry. 2015; 86(9): 996–1001, doi: 10.1136/jnnp-2013-307149, indexed in Pubmed: 25500317.
21. Frampton JE. OnabotulinumtoxinA in Chronic Migraine: A Profile of Its Use. CNS Drugs. 2020; 34(12): 1287–1298, doi: 10.1007/s40263-020-00776-8, indexed in Pubmed: 33314008.
22. Santoro A, Copetti M, Miscio AM, et al. Chronic migraine long-term regular treatment with onabotulinumtoxinA: a retrospective real-life observational study up to 4 years of therapy. Neurol Sci. 2020; 41(7): 1809–1820, doi: 10.1007/s10072-020-04283-y, indexed in Pubmed: 32052306.
23. Domitrz I, Sławek J, Słowik A, et al. Onabotulinumtoxin A (ONA-BoNT/A) in the treatment of chronic migraine. Neurol Neurochir Pol. 2022; 56(1): 39–47, doi: 10.5603/PJNNS.a2021.0061, indexed in Pubmed: 34477213.
24. Begasse de Dhaem O, Gharedaghi MH, Rizzoli P. Modifications to the PREEMPT Protocol for OnabotulinumtoxinA Injections for Chronic Migraine in Clinical Practice. Headache. 2020; 60(7): 1365–1375, doi: 10.1111/head.13823, indexed in Pubmed: 32335918.
25. Domitrz I, Lipa A, Rożniecki J, et al. Migraine diagnosis and treatment in Poland: survey of primary care practitioners. Neurol Neurochir Pol. 2021; 55(4): 380–386, doi: 10.5603/PJNNS.a2021.0045, indexed in Pubmed: 34132385.
26. Albornoz CA, Jhawar N, Durso TA, et al. Preinjection aspiration for injectable fillers in aesthetic dermatology: Trust or bust? J Cosmet Dermatol. 2020; 19(5): 1063–1064, doi: 10.1111/jocd.13377, indexed in Pubmed: 32181574.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 4, pages: 371–378
DOI: 10.5603/PJNNS.a2023.0050

ISSN: 0028-3843, e-ISSN: 1897-4260

Cladribine tablets for highly active relapsing-remitting multiple sclerosis in Poland: a real-world, multi-centre, retrospective, cohort study during the COVID-19 pandemic

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ABSTRACT

Introduction. Treatment with cladribine tablets is indicated in highly active relapsing-remitting multiple sclerosis (RRMS). Cladribine tablets proved safe and effective in the pivotal CLARITY trial, but that trial included primarily treatment-naïve patients. In clinical practice however, cladribine tablets are often given to patients who have failed other treatments. Therefore, this study investigated the real-world safety and efficacy of cladribine tablets.

Material and methods. We gathered data from nine MS clinical centres across Poland for patients with RRMS who started treatment with cladribine tablets from December 2019 to June 2022.

Results. We enrolled 140 patients, with follow-up data available for 136 in year 1 and for 66 in year 2. At baseline, the mean age was 35.6 years, mean disease duration was 7.3 years, median EDSS score was 2.5, and 94% of patients were treatment-experienced. Thirty-nine patients (27.9%) had undergone COVID-19, and 94 (67.1%) were vaccinated against COVID-19. The annualised relapse rate (ARR) decreased from 1.49 at baseline to 0.33 in year 1 ($p < 0.001$) and to 0.25 in year 2 ($p < 0.001$). The percentage of relapse-free patients increased from 11.5% at baseline to 70.2% in year 1 and 82.1% in year 2. The percentage of patients with active lesions decreased from 91.4% at baseline to 36.2% in year 1 and 18.2% in year 2. EDSS score remained stable or improved in 83.7% of patients in year 1 and 89.6% in year 2. No evidence of disease activity (NEDA-3) was achieved in 42.7% of patients in year 1 and 66.7% in year 2. Only one patient (0.72%) had grade 4 lymphopenia and 21 (15.1%) had grade 3 lymphopenia. *Varicella zoster* virus infections occurred in three patients. Eight patients discontinued treatment with cladribine: five due to inefficacy, one due to lymphopenia, and two due to a personal decision.

Conclusions. Cladribine tablets proved safe and effective in a real-world cohort of treatment-experienced patients. However, the efficacy measures improved to a lesser extent in our cohort than in the pivotal clinical trial, which is probably due to a higher proportion of treatment-experienced patients in our cohort.

Key words: cladribine, relapsing-remitting multiple sclerosis, safety, efficacy, COVID-19

(*Neurol Neurochir Pol 2023; 57 (4): 371–378*)

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Received: 01.03.2023 Accepted: 11.05.2023 Early publication date: 25.07.2023

Introduction

Multiple sclerosis (MS) is a chronic and progressive neurological disease characterised by recurrent episodes of inflammatory demyelination of the brain and spinal cord [1, 2]. Cladribine is a potent anti-inflammatory agent to treat relapsing-remitting MS (RRMS). The drug selectively targets lymphocytes, depleting primarily CD19+ B cells, with a small reduction in CD4+ or CD8+ T-cells and CD16+/CD56+ natural killer cells [3–5]. Cladribine depletes lymphocytes via apoptosis rather than cell lysis, which is associated with a favourable safety profile during dosing. Cladribine is given in two courses 12 months apart, and leads to long-lasting disease control without the need for chronic immunosuppression and with minimal monitoring requirements [6]. This treatment regimen with cladribine tablets was particularly advantageous during the COVID-19 pandemic, often requiring self-isolation at home.

In the pivotal phase III trial among primarily treatment-naïve patients, cladribine tablets significantly reduced the annualised relapse rate, risk of disability progression, lesion activity on neuroimaging, and brain atrophy [7]. In Poland, cladribine tablets were approved for highly active RRMS in 2017 when the drug was licensed in the European Union [6]. However, the reimbursement criteria in Poland require evidence of a more active disease than is specified in the drug's label [6, 8].

Six years after the marketing authorisation of cladribine tablets, the data on its safety and efficacy in a real-world setting is limited. Our study aimed to examine the real-world efficacy and safety of cladribine tablets given as part of the reimbursement scheme in Poland, mostly to patients who had failed other disease-modifying therapies (DMTs).

Clinical rationale for the study

Treatment with cladribine tablets proved safe and effective in the CLARITY trial. However, that trial was carried out when few DMTs were available to patients with RRMS. Consequently, the CLARITY trial enrolled primarily treatment-naïve patients. Recently, the treatment landscape has changed considerably, with more than a dozen DMTs now available. Cladribine tables are now often given to patients who have failed previous treatments, including other high-efficacy DMTs. Therefore, post-marketing studies are needed to investigate the real-world safety and efficacy of cladribine tablets.

Material and methods

This retrospective observational study was carried out in nine MS clinical centres across Poland in a cohort of all patients with RRMS who started treatment with cladribine tablets from December 2019 to June 2022. One treatment course consisted of two cycles. All diagnoses complied with the 2017 revisions of the McDonald criteria [9]. The study was approved by the ethics committee of the Polish Military Chamber of Physicians (approval no. 235/22).

We gathered the following data: demographics; disease duration; prior DMTs; the number of relapses in the 12 months before cladribine initiation and 12 and 24 months after treatment initiation; EDSS scores at cladribine initiation and 12 and 24 months later; the reason for discontinuing previous DMTs; adverse reactions; history of COVID-19 infection and SARS-CoV-2 vaccination; and lymphocyte counts before cladribine initiation and at two, six, 12, 14, and 18 months.

Active MRI lesions were defined as Gd(+) or new/enlarging T2 lesions. No evidence of disease activity (NEDA-3) was defined as the absence of clinical relapses, disability progression, and active MRI lesions [10]. The annualised relapse rates (ARRs) with 95% confidence intervals (CI) were calculated with a negative binomial regression model for the 12 months before the first course, 12 months between the two courses, and 12 months after the second course. In accordance with previous reports [11], changes in EDSS scores were classified as an improvement or worsening as follows: among patients with baseline EDSS of 0 — a change of at least 1.5 points; among patients with baseline EDSS of 0.5 to 4.5 — a change of at least 1 point; and among patients with baseline EDSS ≥ 5 — a change of at least 0.5 points. EDSS changes that did not meet the criteria for an improvement or worsening were classified as stable EDSS. Lymphopenia grades were defined as follows: grade I (< 1.0–0.8 × 10^9/L); grade II (< 0.8–0.5 × 10^9/L); grade III (< 0.5–0.2 × 10^9/L); and grade IV (< 0.2 × 10^9/L) [12]. We assessed the frequency of lymphopenia among patients who had lymphocyte counts measured two months after the first treatment cycle or later, taking into account the lowest value of the lymphocyte count for each patient.

Descriptive data was presented as means ± standard deviations (SD) or medians and interquartile ranges (IQR). A Wilcoxon test was used to compare the ARR and EDSS at year 1 and year 2 with the ARR at baseline. A p-value < 0.05 was considered statistically significant. All analyses were completed in the R software (version 4.1.3).

Results

Cohort description

In total, 140 patients who started treatment with cladribine tablets were enrolled in the study: four patients completed only one treatment week and were excluded from the efficacy analysis; 70 patients received one course (1.75 mg/kg), and 66 received two courses (3.5 mg/kg). Thus, follow-up data was available for 136 patients in year 1 and for 66 patients in year 2 (Fig. 1).

Of the 140 patients, 109 (77.9%) were women, the mean (SD) age was 35.6 (11.0) years, the mean disease duration was 7.3 (5.2) years, and the median (IQR) EDSS at baseline was 2.5 (1.5, 3.5).

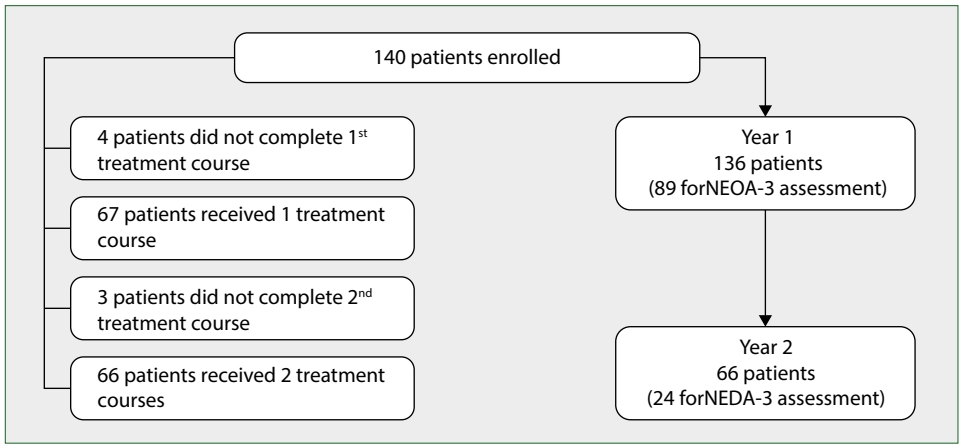

Figure 1. Flow diagram showing disposition of patients enrolled to study

Before cladribine tablets, 131 (93.6%) patients had previously received at least one DMT, whereas only eight patients were treatment-naïve (all had rapidly evolving severe MS). Most patients were switched from dimethyl fumarate (43.8%), fingolimod (17.7%), or natalizumab (10.8%). Inefficacy was the most frequent reason for discontinuing previous DMTs (86.3% of patients). Thirty-nine patients (27.9%) had undergone COVID-19, and 94 (67.1%) had been vaccinated against COVID-19 during the study. Table 1 sets out the baseline characteristics in detail.

Efficacy

The ARR decreased from 1.49 (95% CI: 1.30–1.70) at baseline to 0.33 (0.23–0.46) at year 1 ($p < 0.001$) and to 0.25 (0.11–0.48) at year 2 ($p < 0.001$, Fig. 2A). The percentage of relapse-free patients increased from 11.5% at baseline to 70.2% in year 1 and 82.1% in year 2 (Fig. 2B). The percentage of patients with active MRI lesions decreased from 91.4% at baseline to 36.2% in year 1 and 18.2% in year 2 (Fig. 2C). EDSS remained stable or improved in 83.7% of patients in year 1 and 89.6% in year 2 (Fig. 2D). Compared to baseline, the median EDSS score did not change significantly at year 1 [2.75 (1.50, 4.00), $p = 0.643$] and year 2 [3.00 (2.00, 4.00) $p = 0.135$]. Among patients with sufficient data (see Fig. 1), NEDA-3 was achieved in 42.7% of patients in year 1 and 66.7% in year 2 (percentages of patients with the full set of data needed for NEDA-3 assessment, Fig. 2E). Table 2 sets out the detailed characteristics by NEDA-3 status.

Safety

All patients had a lymphocyte count of at least 800/μL before the start of treatment with cladribine tablets [median 1.56 (1.25, 2.00)]. The median lymphocyte count was 0.88 (0.70, 1.00) at two months, 0.94 (0.80, 1.16) at six months, 1.11 (0.90, 1.45) at 12 months, 0.77 (0.56, 1.00) at 14 months, and 0.86 (0.68, 1.15) at 18 months (see Fig. 3). Only one patient (0.72%) had grade 4 lymphopenia, 21 (15.1%) had grade 3 lymphopenia, 52 (37.4%) had grade 2 lymphopenia,

Table 1. Baseline characteristics of study patients

Characteristic	
Sex (female); n (%)	109 (77.9)
Age (years); mean (SD)	35.6 (11.0)
Disease duration (years); mean (SD)	7.3 (5.2)
Time from last DMT to cladribine (months); mean (SD)	4.3 (9.5)
Number of previous DMTs; n (%)	
0*	8 (5.8)
1–2	94 (67.2)
≥ 3	37 (26.4)
EDSS; median (IQR)	2.5 (1.5, 3.5)
ARR; mean (SD)	1.49 (0.88)
Patients with active MRI changes; n (%**)	127 (91.4)
Lymphocyte count (cells/μL); median (IQR)	1,560 (1,250, 2,000)
Patients who underwent COVID-19; n (%)	39 (27.9)
Patients vaccinated against COVID-19; n (%)	94 (67.1)
DMT; n (%***)	
Dimethyl fumarate	57 (43.8)
Fingolimod	23 (17.7)
Natalizumab	14 (10.8)
Teriflunomide	12 (9.2)
Glatiramer acetate	10 (7.7)
IFNβ-1a	6 (4.6)
IFNβ-1b	5 (3.8)
Ocrelizumab	2 (1.5)
Alemtuzumab	1 (0.8)
Reason for last DMT discontinuation; n (%)	
switch from 1st line DMT for inefficacy****	89 (68.5)
switch from 2nd line DMT for inefficacy	23 (17.7)
switch from 2nd line DMT for adverse events	8 (6.1)
switch from 2nd line DMT for high titre of anti-JCV antibodies	8 (6.1)
planned pregnancy	2 (1.5)

*All naive patients (not previously treated with DMT) had rapidly evolving severe multiple sclerosis
**Percentage of patients with available MRI data (N = 139)
***Percentage of patients with available data on previous DMT (N = 130)
****Second-line treatments include fingolimod, natalizumab, ocrelizumab, and alemtuzumab. Other treatments are considered first-line
ARR — annualised relapse rate; COVID-19 — coronavirus disease 19; DMF — dimethyl fumarate; DMT — disease-modifying therapy; EDSS — Expanded Disability Status Scale; IFNβ — interferon β; IQR — interquartile range; JCV — John Cunningham virus; SD — standard deviation

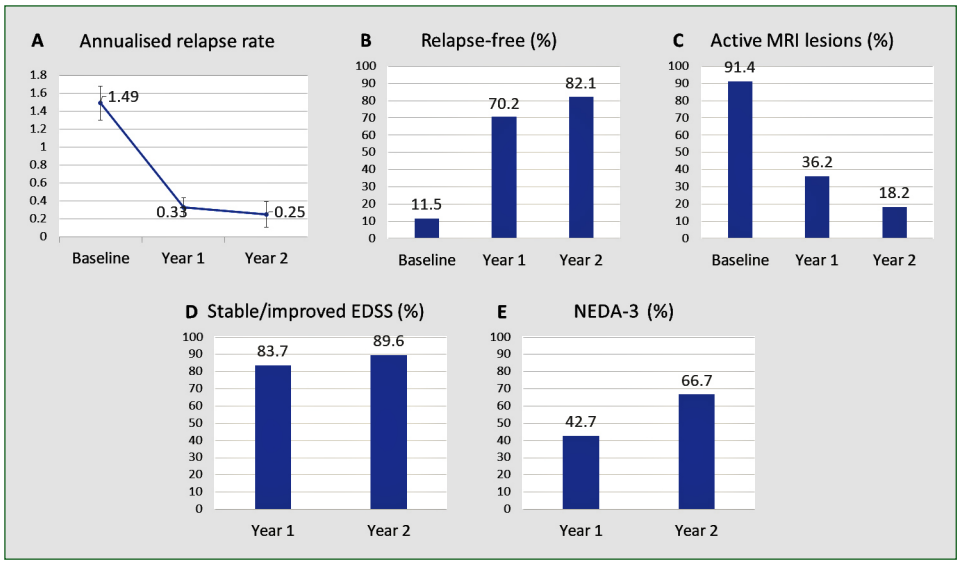

Figure 2. Efficacy outcomes after treatment with cladribine tablets. **A.** Annualised relapse rate — point estimates are means and error bars are standard deviations. **B.** Percentage of relapse-free patients. **C.** Percentage of patients with active MRI lesions. **D.** Percentage of patients with stable/improved EDSS. **E.** Percentage of patients with NEDA-3. Denominators at baseline, year 1, and year 2 were as follows: A and B (139, 94, 28); C (139, 80, 22); D (–, 86, 29); E (–, 89; 24). EDSS — Expanded Disability Status Scale; MRI — magnetic resonance imaging; NEDA-3 — No Evidence of Disease Activity 3

Table 2. Characteristics by NEDA-3 status at 1st and 2nd year of study

Characteristic	
Year 1	N = 89
NEDA-3; n (%)	
Achieved	38 (42.7)
Switchers from 1st line DMT	21 (23.6)
Switchers from 2nd line DMT	14 (15.7)
Not achieved	51 (57.3)
Year 2	N = 24
NEDA-3; n (%)	
Achieved	16 (66.7)
Switchers from 1st line DMT	8 (33.3)
Switchers from 2nd line DMT	7 (29.2)
Not achieved	8 (33.3)

ARR — annualised relapse rate; EDSS — Expanded Disability Status Scale; DMT — disease-modifying therapy; IQR — interquartile range; NEDA-3 — No Evidence of Disease Activity 3; SD — standard deviation

33 (23.7%) had grade 1 lymphopenia, and 32 (23.0%) had normal lymphocyte counts.

Other than lymphopenia, adverse events occurred in 19 patients (13.5% of the cohort). There were three cases of *Varicella zoster* virus infections, urinary tract infections, fatigue, and nausea and two patients reported headaches. There were single cases of Herpes simplex infection, elevated liver enzymes, an unspecified infection, and stomatitis.

Eight patients discontinued treatment with cladribine: five due to inefficacy (all later received ocrelizumab), one due to lymphopenia, and two due to a personal decision. After completing two cladribine courses, one patient developed secondary progressive MS and received mitoxantrone. Seven patients discontinued treatment after two cycles and one after three cycles.

Discussion

This retrospective study looked at clinical and neuroimaging outcomes for a real-world cohort of patients treated with cladribine tablets. The treatment was safe and effective among predominantly treatment-experienced patients, with nearly 95% of patients switching to cladribine tablets from other DMTs. In year 2, over 80% of patients were relapse-free, EDSS was stable or improved in over 80% of patients, and over 60% of patients achieved NEDA-3. There were no substantial safety issues in our study; the rates of adverse events were similar to or below those reported in phase III trials. Our cohort was of a similar age and had a similar baseline disability as in the pivotal CLARITY study, but the proportion of women was greater (78% *vs.* 68%) [7]. In a registry-based study from Finland, the proportion of women among patients who received cladribine tablets was even greater (86%) [13].

The baseline disease activity in our cohort was substantially higher than in the pivotal CLARITY study (ARR of 1.49 in our cohort, ARR of 0.33 in the placebo arm of the CLARITY study); consequently, the on-treatment ARR was also higher in our cohort (~ 0.25 *vs.* 0.15) [7]. This difference is probably because cladribine tablets in our cohort were mostly

given to treatment-experienced patients who had failed other treatments (owing to the reimbursement policy in Poland). Supporting this view, a post hoc analysis of the CLARITY study showed that patients with prior DMT had a significantly lower reduction in the risk of ARR (rate ratio *vs.* placebo, 0.55) than treatment-naïve patients (0.26, p = 0.032) [14]. Only 12% of patients in our cohort were switched to cladribine tablets because of safety concerns, and the rest because of inefficacy, including those who switched from other second-line DMTs. In contrast, only 26% of patients in the cladribine arm of the CLARITY study had previously received DMTs, predominantly low-efficacy drugs such as interferon beta and glatiramer acetate [7]. Post-marketing studies have reported that the ARR after treatment with cladribine tablets are greater among switchers from other DMTs than in treatment-naïve patients, and the ARR was particularly high in those who used many previous DMTs or were switched from second-line treatments [13–15].

Data from other real-world studies shows that cladribine tablets are used in patients with greater disease activity than in the pivotal CLARITY study. In a real-world study from Italy, among 1,236 patients (~80% treatment-experienced), the ARR within 12 months before starting cladribine tablets was ~1.1, decreasing to 0.2 after treatment [14]. Similarly, among nearly 300 patients from Germany (~75% treatment-experienced), the baseline ARR was 1.0, and it decreased to ~0.2 during treatment with cladribine tablets [16]. Similarly, a Finland-based real-world study reported ARR before (1.0) and after treatment (0.1) with cladribine tablets [13]. In a study from Australia where nearly all patients were treatment-experienced, the ARR decreased from 1.4 at baseline to 0.31 at follow-up [17]. The ARRs in our study were greater (1.49 at baseline, 0.25 in 2 years) than those from most previous real-world studies, which can be explained by the stringent reimbursement criteria in Poland.

We observed a similar proportion of patients who achieved NEDA-3 (67%) as in a real-world study from Italy: 64% of patients over a median follow-up of 22- months [15]. We found that cladribine tablets were associated with stabilisation or improvement of disability scores in over 80% of patients in year 1 and nearly 90% in year 2. These figures are similar to those reported in a post-hoc analysis of the CLARITY extension studies for the respective intervals (100%, 94%) [11]. Likewise, in a real-world study from Italy, 97% of patients were progression-free at 12 months after the last cladribine dose [18]. In particular, an early intensive treatment with high-efficacy agents, such as cladribine, as opposed to an escalation strategy, has been associated with favourable disability outcomes [19].

As mentioned above, the higher disease activity in our cohort than in the pivotal trial and other real-world cohorts is likely to be due to the Polish reimbursement policy. In Poland, treatment with cladribine tablets is reimbursed only for patients with disease activity greater than specified in the drug's label, which states that cladribine tablets are indicated in highly active diseases [6]. In treatment-naïve patients, highly active disease is defined as one relapse in the last year and evidence of MRI activity or two relapses in the last year without MRI activity [6, 20]. In contrast, the Polish reimbursement criteria require a treatment-naïve patient to have had two or more relapses and several active lesions in the preceding 12 months (two or more Gd+ lesions and three or more new T2 lesions) [8]. In treatment-experienced patients, a highly active disease might be considered even in patients without relapses, with at least one Gd+ lesion or at least two new T2 lesions [20]. In the Polish reimbursement scheme, treatment-experienced patients need to have two relapses within 12 months of first-line treatment or 1 "severe" relapse within 6 months of starting first-line treatment with two or more Gd+ lesions and three or more new T2 lesions [8]. A post-hoc analysis of the CLARITY study found that patients with two or more relapses in the year before enrollment had a greater relative risk reduction for the occurrence of relapse compared to other patients (relative risk *vs.* placebo, 0.32 *vs.* 0.49, p = 0.068); similarly, they had a greater reduction in the risk of 6-month confirmed disability (hazard ratio *vs.* placebo, 0.18 *vs.* 0.81, p = 0.004) [21].

Treatment with cladribine tablets is an immune reconstitution therapy characterised by the three phases of reduction, repopulation, and reconstitution [22, 23]. The lymphocyte count decreases in the reduction phase, which may be associated with transient immunosuppression, but it regenerates in the repopulation phase, resulting in immune competence that enables normal responses to infections and vaccinations [22–24]. For example, 38 patients treated with cladribine tablets (time from the last dose to vaccination 2–96 weeks) developed humoral responses after anti-COVID-19 vaccinations, and the responses did not depend on the lymphocyte count [25]. The reconstitution phase leads to long-term qualitative changes in the immune system, which results in sustained disease control in the long-term, as was shown in the CLASSIC-MS study with 9–15 years of follow-up [22, 23, 26].

Compared to other oral DMTs (fingolimod, teriflunomide, dimethyl fumarate), cladribine tables have been shown to be associated with a significantly longer time to treatment discontinuation and lower ARRs [27]. A recent network-metanalysis of high efficacy DMTs reported that treatment with cladribine tablets was associated with a greater likelihood of sustained disability improvement compared to all other DMTs assessed (fingolimod, natalizumab, alemtuzumab, and ocrelizumab) [28]. Immune reconstitution therapy with cladribine tablets is associated with a favourable safety profile because immune suppression is transient in the reduction phase, but the risk of adverse events decreases with the repopulation of lymphocytes. In contrast, maintenance DMTs are typically associated with chronic immunosuppression, and the risk accumulates with longer treatment periods. Treatment with cladribine tablets is well tolerated

by patients with MS, which is partly due to a convenient dosing scheme and low monitoring burden. We observed lower rates of adverse events compared to other studies. As a reflection of cladribine's mechanism of action, lymphopenia was the most frequent adverse event, with the lowest levels reached 3–4 months after the start of therapy, followed by a reconstitution of these cells [29]. Of note, reductions in the lymphocyte count following cladribine administration are more gradual compared to the rapid decrease after treatment with monoclonal antibodies [30]. In our cohort, only ~15% of patients had lymphopenia of grade 3 or greater (compared to ~25% in CLARITY). Treatment with cladribine tablets is associated with a long-term reduction of memory B cells that persists after overall lymphocyte counts have recovered from the initial reduction. The risk of infections outside the periods of lymphopenia seems unchanged, suggesting that the sustained clinical effect is not associated with the potential risks associated with immunosuppression [6].

The safety profile of cladribine tablets in our cohort was similar to that reported in the pivotal trial: we observed a similar frequency of *Varicella zoster* virus infections, nausea, and headache. Around 30% of patients had a documented SARS-CoV-2 infection, with no cases of severe disease course, which is in line with previous observations that treatment with cladribine tablets is not associated with a more serious disease course [31]. Similarly, Czarnowska et al. [32] reported that the course of COVID-19 among patients with MS receiving DMTs in Poland was favourable, with similar rates of hospitalisation and death as in the general population. Interestingly, some of the DMTs (interferon-beta, fingolimod) used to treat MS have been investigated as potential treatments for COVID-19 [33]. Cladribine tablets were discontinued in seven patients after two cycles and in one patient after three cycles; thus, these patients did not receive the full dose of 3.5 mg/kg. For patients who experience disease reactivation between doses, the updated ECTRIMS/EAN guidelines recommend giving the full dose of cladribine before switching to other drugs [34]. A higher proportion of patients in our cohort discontinued cladribine tablets (~6%) compared to the pivotal trial (3.5%); in a registry-based study from Finland, 5% of patients discontinued cladribine tablets [13]. The greater frequency of discontinuation in a real-world setting could be related to more active disease than in clinical trials: most patients in our cohort discontinued cladribine tablets due to inefficacy (5/8).

Our study was limited by a small sample size, with a substantial proportion of patients not having a full follow-up. Overall, our data shows that treatment with cladribine tablets reduces the risk of relapse and stabilises disability. These findings add to the growing real-world evidence of the safety and efficacy of cladribine. In conclusion, cladribine tablets proved safe and effective in a real-world setting among primarily treatment-experienced patients with very high disease activity.

Clinical implications/future directions

Cladribine tablets appear to be safe and effective in a real-world setting among primarily treatment-experienced patients with very high disease activity. Therefore, cladribine tablets may be given to patients who have failed previous treatments, including other highly effective DMTs. The safety profile of cladribine tablets in a real-world setting was similar to that observed in the pivotal CLARITY study. Thus, no additional precautions, except for those already included in the drug label, seem necessary.

Acknowledgements: *The authors would like to thank Urszula Skalska, PhD, of Proper Medical Writing Sp. z o. o. for her support in preparation of this manuscript (including text editing and graphical data presentation).*

Conflicts of interest: *A.S. — in relation to the content of the publication: served as a lecturer and an expert at advisory boards for Allergan, Amgen, Bayer, Novartis, Biogen, Merck, Polpharma, Roche, Teva, and Eli Lilly; A.P.-W. — declares no conflict of interest; E.T.-K. — received compensation for speaking services and support for congress participation from Biogen Poland, Bayer, Novartis Poland, Roche, Merck and Sanofi-Aventis; A.S. — received compensation for speaking services and support for congress participation from Biogen Poland, Bayer, Boehringer-Ingelheim, Novartis Poland, Roche, Merck and Sanofi-Aventis; P.P. — received funding to attend educational events and speaking honoraria from Biogen, Roche, Merck and Novartis; M.A.-S. — received compensation for speaking and consulting services from Biogen, Bayer, Novartis, Roche, Merck, Teva, Sanofi-Genzyme and BMS. None of the consulting agreements are relevant to the submitted work; I.K.-J. — is the principal investigator in clinical trials sponsored by Merck. She also received consultancy fees from Merck; A.K. — received compensation for speaking and consulting services from Biogen, Bayer, Novartis, Roche, Merck, Teva, and Sanofi-Genzyme; M.Ch. — declares no conflict of interest; K.P.-S. — declares no conflict of interest; A.J.-W. — received honoraria for advisory boards and travel grants from Merck, Roche, Teva, Biogen, Novartis, Sanofi and Bayer; H.B.-P. — received advisory board and/or speaker honoraria from Biogen, BMS, Novartis, Merck, Roche and Teva and support for congress participation from Roche and Biogen; K.R. — received honoraria for advisory boards and travel grants from Merck, Roche, Teva, Biogen, Novartis, Sanofi and Bayer.*

Funding: *This study did not receive any external funding. The medical writing service was supported by an independent medical writing grant from Merck Sp. z o.o., Warsaw, Poland, an affiliate of Merck KGaA (CrossRef Funder ID: 10.13039/100009945).*

References

1. Reich DS, Lucchinetti CF, Calabresi PA. Multiple Sclerosis. N Engl J Med. 2018; 378(2): 169–180, doi: 10.1056/NEJMra1401483, indexed in Pubmed: 29320652.

2. Kalinowska-Łyszczarz A, Guo Y, Lucchinetti CF. Update on pathology of central nervous system inflammatory demyelinating diseases. Neurol Neurochir Pol. 2022; 56(3): 201–209, doi: 10.5603/PJNNS.a2022.0046, indexed in Pubmed: 35758517.
3. Sipe JC, Romine JS, Zyroff J, et al. Treatment of Multiple Sclerosis with Cladribine. Multiple Sclerosis. 1996: 313–334, doi: 10.1007/978-1-4471-1271-6_14.
4. Stuve O, Soelberg Soerensen P, Leist T, et al. Effects of cladribine tablets on lymphocyte subsets in patients with multiple sclerosis: an extended analysis of surface markers. Ther Adv Neurol Disord. 2019; 12: 1756286419854986, doi: 10.1177/1756286419854986, indexed in Pubmed: 31244898.
5. Manouchehri N, Shirani A, Salinas VH, et al. Clinical trials in multiple sclerosis: past, present, and future. Neurol Neurochir Pol. 2022; 56(3): 228–235, doi: 10.5603/PJNNS.a2022.0041, indexed in Pubmed: 35712986.
6. Mavenclad - Summary Of Product Characteristics n.d. https://www.ema.europa.eu/en/documents/product-information/mavenclad-epar-product-information_en.pdf (20.02.2023).
7. Giovannoni G, Comi G, Cook S, et al. CLARITY Study Group. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010; 362(5): 416–426, doi: 10.1056/NEJMoa0902533, indexed in Pubmed: 20089960.
8. Brola W, Adamczyk-Sowa M, Kułakowska A, et al. Highly active disease and access to disease-modifying treatments in patients with relapsing-remitting multiple sclerosis in Poland. Neurol Neurochir Pol. 2022; 56(3): 256–260, doi: 10.5603/PJNNS.a2022.0047, indexed in Pubmed: 35766058.
9. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018; 17(2): 162–173, doi: 10.1016/S1474-4422(17)30470-2, indexed in Pubmed: 29275977.
10. Lu G, Beadnall HN, Barton J, et al. The evolution of "No Evidence of Disease Activity" in multiple sclerosis. Mult Scler Relat Disord. 2018; 20: 231–238, doi: 10.1016/j.msard.2017.12.016, indexed in Pubmed: 29579629.
11. Giovannoni G, Comi G, Rammohan K, et al. Long-term disease stability assessed by the expanded disability status scale in patients treated with cladribine tablets 3.5 mg/kg for relapsing multiple sclerosis: an exploratory post hoc analysis of the CLARITY and CLARITY extension studies. Adv Ther. 2021; 38(9): 4975–4985, doi: 10.1007/s12325-021-01865-w, indexed in Pubmed: 34370275.
12. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (23.02.2023).
13. Rauma I, Viitala M, Kuusisto H, et al. Finnish multiple sclerosis patients treated with cladribine tablets: a nationwide registry study. Mult Scler Relat Disord. 2022; 61: 103755, doi: 10.1016/j.msard.2022.103755, indexed in Pubmed: 35483129.
14. Annovazzi P, Prosperini L, Capuano R, et al. Relapse-free and NEDA status with Cladribine in a real life population: a multicentre study. ECTRIMS, 13–15 Oct. Poster Present P842. 2021.
15. Petracca M, Ruggieri S, Barbuti E, et al. Predictors of cladribine effectiveness and safety in multiple sclerosis: a real-world, multicenter, 2-year follow-up study. Neurol Ther. 2022; 11(3): 1193–1208, doi: 10.1007/s40120-022-00364-6, indexed in Pubmed: 35653061.
16. Pfeuffer S, Rolfes L, Hackert J, et al. Effectiveness and safety of cladribine in MS: Real-world experience from two tertiary centres. Mult Scler. 2022; 28(2): 257–268, doi: 10.1177/13524585211012227, indexed in Pubmed: 33975489.
17. Lizak N, Hodgkinson S, Butler E, et al. Real-world effectiveness of cladribine for Australian patients with multiple sclerosis: An MSBase registry substudy. Mult Scler. 2021; 27(3): 465–474, doi: 10.1177/1352458520921087, indexed in Pubmed: 32530363.
18. Patti F, Visconti A, Capacchione A, et al. CLARINET-MS Study Group. Long-term effectiveness in patients previously treated with cladribine tablets: a real-world analysis of the Italian multiple sclerosis registry (CLARINET-MS). Ther Adv Neurol Disord. 2020; 13: 1756286420922685, doi: 10.1177/1756286420922685, indexed in Pubmed: 32587633.
19. Iaffaldano P, Lucisano G, Caputo F, et al. Italian MS Register. Long-term disability trajectories in relapsing multiple sclerosis patients treated with early intensive or escalation treatment strategies. Ther Adv Neurol Disord. 2021; 14: 17562864211019574, doi: 10.1177/17562864211019574, indexed in Pubmed: 34104220.
20. Sørensen PS, Centonze D, Giovannoni G, et al. Expert opinion on the use of cladribine tablets in clinical practice. Ther Adv Neurol Disord. 2020; 13: 1756286420935019, doi: 10.1177/1756286420935019, indexed in Pubmed: 32636933.
21. Giovannoni G, Soelberg Sorensen P, Cook S, et al. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. Mult Scler. 2019; 25(6): 819–827, doi: 10.1177/1352458518771875, indexed in Pubmed: 29716436.
22. Giovannoni G, Mathews J. Cladribine tablets for relapsing-remitting multiple sclerosis: a clinician's review. Neurol Ther. 2022; 11(2): 571–595, doi: 10.1007/s40120-022-00339-7, indexed in Pubmed: 35318617.
23. Lünemann JD, Ruck T, Muraro PA, et al. Author Correction: Immune reconstitution therapies: concepts for durable remission in multiple sclerosis. Nat Rev Neurol. 2020; 16(2): 125, doi: 10.1038/s41582-020-0310-1, indexed in Pubmed: 31937911.
24. Nojszewska M, Kalinowska A, Adamczyk-Sowa M, et al. COVID-19 mRNA vaccines (Pfizer-BioNTech and Moderna) in patients with multiple sclerosis: a statement by a working group convened by the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society. Neurol Neurochir Pol. 2021; 55(1): 8–11, doi: 10.5603/PJNNS.a2021.0016, indexed in Pubmed: 33555604.
25. Grothe C, Steffen F, Bittner S. Humoral immune response and lymphocyte levels after complete vaccination against COVID-19 in a cohort of multiple sclerosis patients treated with cladribine tablets. J Cent Nerv Syst Dis. 2021; 13: 11795735211060118, doi: 10.1177/11795735211060118, indexed in Pubmed: 34880703.
26. Giovannoni G, Leist T, Aydemir A, et al. Long-Term efficacy for patients receiving cladribine tablets in CLARITY/CLARITY extension: primary results from 9–15 years of follow-up in the CLASSIC-MS study. Multiple Sclerosis and Related Disorders. 2022; 59: 103633, doi: 10.1016/j.msard.2022.103633.
27. Spelman T, Ozakbas S, Alroughani R, et al. Comparative effectiveness of cladribine tablets versus other oral disease-modifying treatments for multiple sclerosis: Results from MSBase registry. Mult Scler. 2023; 29(2): 221–235, doi: 10.1177/13524585221137502, indexed in Pubmed: 36433775.
28. Piasecka-Stryczyńska K, Kaczyński Ł, Rolka M, et al. Systematic review and network meta-analysis (NMA) for cladribine tablets in achieving sustained disability improvement (SDI) in multiple sclerosis. Neurol Neurochir Pol. 2022; 56(6): 480–489, doi: 10.5603/PJNNS.a2022.0068, indexed in Pubmed: 36421066.

29. Comi G, Cook S, Giovannoni G, et al. Effect of cladribine tablets on lymphocyte reduction and repopulation dynamics in patients with relapsing multiple sclerosis. Mult Scler Relat Disord. 2019; 29: 168–174, doi: 10.1016/j.msard.2019.01.038, indexed in Pubmed: 30885375.
30. Baker D, Herrod SS, Alvarez-Gonzalez C, et al. Both cladribine and alemtuzumab may effect MS via B-cell depletion. Neurol Neuroimmunol Neuroinflamm. 2017; 4(4): e360, doi: 10.1212/NXI.0000000000000360, indexed in Pubmed: 28626781.
31. Giovannoni G, Berger J, Leist T, et al. Post-approval safety of cladribine tablets with particular reference to COVID-19 outcomes: An update. Mult Scler J. 2021; 27(suppl. 2): 638–639.
32. Czarnowska A, Brola W, Zajkowska O, et al. Clinical course and outcome of SARS-CoV-2 infection in multiple sclerosis patients treated with disease-modifying therapies - the Polish experience. Neurol Neurochir Pol. 2021; 55(2): 212–222, doi: 10.5603/PJNNS.a2021.0031, indexed in Pubmed: 33856686.
33. Adamczyk B, Morawiec N, Arendarczyk M, et al. Multiple sclerosis immunomodulatory therapies tested for effectiveness in COVID-19. Neurol Neurochir Pol. 2021; 55(4): 357–368, doi: 10.5603/PJNNS.a2021.0051, indexed in Pubmed: 34346052.
34. Montalban X. ECTRIMS/EAN Clinical Guidelines on MS treatment: an update. ECTRIMS 2021, 2021.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 4, pages: 379–386
DOI: 10.5603/PJNNS.a2023.0053

ISSN: 0028-3843, e-ISSN: 1897-4260

Impact of treatment on blood–brain barrier impairment in Wilson's disease

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ABSTRACT

Introduction. Our study assessed changes in concentrations of serum markers for brain damage and blood–brain barrier (BBB) dysfunction in untreated and treated Wilson's disease (WD) patients, and examined correlations between these changes and neurological impairment.

Objective. These results hold the potential to determine BBB impairment and neurological advancement in WD to develop the most effective treatment for patients with severe neurological deterioration.

Material and methods. The study groups included 171 patients with WD (77 with hepatic and 94 with neurological manifestations), treated either for up to 5 or 15 years, and 88 healthy controls. Serum concentrations of intercellular adhesion molecule 1 (ICAM1), P-selectin, matrix metallopeptidase 9 (MMP9), glial fibrillary acidic protein (GFAP), and S100 calcium-binding protein B (S100B) were measured before and during anti-copper treatment. The Unified Wilson's disease Rating Scale (UWDRS) was used to assess neurological advancement.

Results. ICAM1 concentrations were elevated before and during anti-copper treatment compared to controls ($p < 0.01$), but therapy led to substantial decreases both in patients with hepatic ($p < 0.01$) and in patients with neurological manifestations ($p < 0.05$). P-selectin concentrations remained elevated before and during treatment ($p < 0.05$) regardless of the treatment duration and disease form. MMP9 concentrations before treatment were lower ($p < 0.05$), but reached control levels during treatment. GFAP concentrations were significantly elevated only in untreated patients with neurological symptoms in the longer-treated group compared to controls ($p < 0.05$). A significant reduction during treatment was observed only in the shorter-treated neurological group ($p < 0.05$). No substantial changes were observed in S100B. Only ICAM1 concentrations positively correlated ($r = 0.27$, $p < 0.001$) with the UWDRS.

Conclusions. Our results provide evidence of endothelial activation in WD. However, inconclusive GFAP results, and no increase in S100B, do not allow us to conclude whether the reactive gliosis is not prominent or alternatively whether the BBB is disrupted. Elevated ICAM1 concentrations and their correlation with neurological advancement indicate BBB impairment. A decrease in ICAM1 during treatment suggests that the inflammatory process is reduced, and the BBB partially repaired. Decreased MMP9 concentrations may be the result of active liver fibrosis and higher copper concentrations. Elevated P-selectin concentrations indicate a systemic inflammatory process.

Key words: blood–brain barrier, serum inflammatory markers, UWDRS, neurodegeneration, Wilson's disease

(*Neurol Neurochir Pol 2023; 57 (4): 379–386*)

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Received: 04.04.2023 Accepted: 02.06.2023 Early publication date: 1.08.2023

Introduction

Wilson's disease (WD) is a rare autosomal recessive disorder of the copper metabolism caused by mutations in the copper-transporting P-type adenosine triphosphate (*ATP7B*) gene, resulting in copper overload in hepatocytes with associated liver pathology [1]. Excess copper is also released into the circulation with secondary pathological accumulation in other tissues, particularly the brain, leading to neurological and psychiatric symptoms. In WD, concentrations of total serum copper may be decreased due to low ceruloplasmin formation, but concentrations of toxic non-ceruloplasmin-bound copper (NCC) are elevated.

The mechanisms by which copper crosses the blood–brain barrier (BBB) remain unclear. However, it has been demonstrated that copper transport into the brain is mainly achieved in the form of NCC [2]. Furthermore, copper importer Cu transporter 1 (CTR1), and exporters ATP7A and ATP7B, are essential in ensuring copper-requiring processes and preventing copper accumulation in the brain [3].

In WD patients, elevated NCC concentrations with a concomitant uptake of copper into the brain through CTR1, and an impaired copper re-export into the blood due to an ATP7B defect can result in brain copper accumulation [4]. Intracellular copper accumulation can induce mitochondrial stress, leading to brain cell death [5]. As a result, an inflammatory process may be triggered, which can aggravate the brain damage. This inflammatory process is characterised by endothelial cell activation, cytokines production, oxidative stress induction, the stimulation of microglia, astrocytes, and the further migration of inflammatory cells into the central nervous system (CNS) [6].

The BBB consists of a tightly connected monolayer of brain endothelial cells and pericytes separated by the basement membrane and unsheathed by astrocytic end-feet [7]. Entry of leukocytes from the blood into a tissue is a multi-step process that includes rolling adhesion, firm adhesion, and extravasation. This requires a series of different leukocyte adhesion molecules, including selectins for rolling adhesion, and immunoglobulin family members for firm adhesion [8]. Under normal conditions, the endothelial layer remains at rest and the expression of adhesive molecules, such as intercellular adhesion molecule 1 (ICAM1) [9–15] and P-selectin [16–19], increases under the influence of inflammatory processes. With the increase in expression, adhesive molecules may be shed from the surface of the activated endothelial cells and released into the circulation in soluble form.

The pathogenesis of diseases associated with BBB damage may involve metalloproteinases, enzymes involved in the degradation of basement membranes, and extracellular matrix proteins. One of the most widely investigated metalloproteinases is matrix metallopeptidase 9 (MMP9) [20].

WD is neuropathologically characterised by a dominant alteration of astrocytes. Therefore, it has been considered as a primary gliopathy, represented by progressive astrocytic changes, taking the form of generalised proliferation and hypertrophy concomitant with nonspecific degeneration of astrocytes [21].

Activated or damaged astrocytes can release specific substances into the cerebrospinal fluid (CSF) and blood, which can serve as biomarkers of CNS injury and BBB disruption. One of these proteins is glial fibrillary acidic protein (GFAP), an emerging biomarker in brain and spinal cord disorders [22–24].

Another marker of CNS injury is S100 calcium-binding protein B (S100B) [25–30], produced mainly by astrocytes, which is also a marker of early BBB disruption that may precede brain damage. At the same time, massive elevations in S100B are indicators of extensive brain damage [31].

The characteristics of the serum markers for brain damage and blood–brain barrier dysfunction, i.e. ICAM1, P-selectin, MMP9, GFAP and S100B, are summarised in Table 1.

In patients with WD, copper-reducing therapy with D-penicillamine, zinc sulfate, trientine or bis-choline tetrathiomolybdate may lower NCC concentrations with later redistribution from the brain into the blood and subsequent copper excretion [32]. The copper-related toxic effects on the brain and the BBB in neurological WD patients have been demonstrated by an increased albumin ratio (AR) in CSF versus serum which normalises during anti-copper therapy. In addition, an initial worsening of the neurological condition after starting chelator therapy has been linked to the disturbance of BBB function, measured as a transient increase in AR [32].

Thus, brain damage from NCC may start at the BBB, facilitating further unregulated copper entry into the brain [33], and inflammatory processes in the liver and brain may impair BBB function and contribute to CNS damage.

This study aimed to examine changes in concentrations of serum markers for brain damage and BBB dysfunction in untreated and treated WD patients, and assess correlations with the severity of neurological impairment.

Clinical rationale for the study

The aim of this study was to assess changes in serum concentrations of ICAM1, P-selectin, MMP9, GFAP and S100B in untreated and treated WD patients, and examine correlations between these changes and neurological advancement. Our goal was better determining BBB impairment and identifying possible improvements to treatment for WD.

Material and methods

This study was approved by the Committee for Ethics in Human Research at the Institute of Psychiatry and Neurology in Warsaw, Poland. Informed written consent was obtained from each participant. This publication was prepared without any external source of funding. All authors declare that they have no conflict of interest.

Table 1. Characteristics of serum markers for brain damage and blood–brain barrier dysfunction

Serum marker	Type	Location	Function	Clinical significance in neurogenerative and liver diseases
ICAM1	Intercellular adhesion molecule 1, glycoprotein of immunoglobulin family	Expressed constitutively on surface of various cell types, especially endothelial cells	Firm adhesion of leukocytes to endothelium and their transendothelial migration to sites of inflammation [9]	Increased in active multiple sclerosis [10, 11], viral encephalitis [11], acute ischaemic stroke [12], Alzheimer's disease [13], liver diseases and other inflammatory processes [14, 15]
P-selectin	Cell adhesion glycoprotein of selectin family	Stored within platelets and endothelial cells, exposed on surface after inflammatory stimulation	Initial recruitment of leukocytes, efficient leukocyte capturing [16]	Reports in neurodegenerative disorders reveal inconsistencies [17, 18], elevated in liver diseases [19]
MMP9	Matrix metallopeptidase 9	Produced by many cell types, including inflammatory cells	Degradation of basement membranes and extracellular matrix proteins [20]	Higher in WD patients with neurological than in hepatic forms and higher in hepatic presentations than in controls [20]
GFAP	Glial fibrillary acidic protein, intermediate filament	Produced mainly by astrocytes	Involved in structure and function of cell's cytoskeleton [22]	Emerging biomarker in brain and spinal cord disorders, elevated in mild traumatic brain injury, progressive multiple sclerosis [22], higher in WD patients with neurological manifestations [23], but in another study no significant differences between neurological, hepatic and control groups, and no association with severity of neurological impairment [24]
S100B	S100 calcium-binding protein B	Produced mainly by astrocytes	Involved in cell cycle progression, cell differentiation, and cytoskeletal-membrane interactions [25]	Potential parameter of glial activation in brain damage and neurodegeneration [26], studied in Parkinson's disease [27], Alzheimer's disease [28, 29] and Creutzfeldt–Jakob disease [30], but not yet in WD

WD — Wilson's disease

Study population

The study was performed in the Second Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland. Patients were diagnosed with WD based on a combination of clinical examination, abnormal copper results, the presence of a Kayser-Fleischer ring, typical abnormalities seen by brain magnetic resonance imaging (MRI), and genetic testing results. The form of the disease was determined based on the results of a clinical examination and additional tests (basic laboratory liver tests, ultrasound examination of the liver and brain MRI). Patients classified as hepatic manifestations did not present abnormalities in neurological assessment or brain MRI [34]. Patients were treated with either D-penicillamine or zinc sulfate in standard doses. The Unified Wilson's disease Rating Scale (UWDRS) was used to assess the neurological status advancement, including part II (disability, based on the Barthel Scale) and part III (detailed neurological examination) [35]. Patients with abnormalities in neurological assessment or brain MRI were scored according to the sum of parts II and III of the UWDRS.

The control group consisted of healthy volunteers with similar sex and age distributions and no history of liver disease, neurological or mental disease, chronic inflammatory disease, or infectious disease.

Blood collection

Blood was collected twice from the patients in the experimental group, before and during anti-copper treatment for periods of up to 5 or 15 years, and once from the patients in the control group. After collection, the venous whole blood samples (10 mL) were incubated at room temperature for c.30 minutes to form a clot. Then the blood was centrifuged for 10 minutes at 3,000 rpm at 4°C. After centrifugation, the obtained supernatant was decanted. Serum was pooled successively and stored at –80°C.

ICAM1, P-selectin, MMP9, GFAP and S100B measurements

ICAM1, P-selectin, MMP9, GFAP and S100B serum concentrations were measured with sandwich-type enzyme-linked immunosorbent assays in accordance with the manufacturers' instructions (R&D Systems, Minneapolis, MN, USA; ELK Biotechnology, Wuhan, China). Absorbance at 450 nm was measured with Multiskan Go (Thermo Fisher Scientific, Waltham, MA, USA).

Statistical analysis

Shapiro-Wilk test was used to estimate the normality of the studied groups for statistical analyses. Normal distribution

Table 2. Characteristics of Wilson's disease (WD) patients and controls

					WD form						
					Hepatic n = 77				Neurological n = 94		
		Controls (C) n = 88	All WD patients n = 171	p	5-year treated n = 47	p	15-year treated n = 30	p	5-year treated n = 53	p	15-year treated n = 41	p
Age	before	34 (30–43)	29 (22–38)	**< 0.001**	25 (21–31)	**< 0.001**	23.5 (19–41)	**< 0.001**	31 (24–38)	**0.0043**	33 (24–42)	0.18
	during		33 (25–43)	0.070	26 (23–33)	**< 0.001**	33 (26–47)	0.47	32 (27–39)	0.069	44 (33–50)	**0.015**
Sex (female)		46 (52%)	94 (55%)	0.68	29 (62%)	0.29	21 (70%)	0.091	24 (45%)	0.42	20 (49%)	0.71
Treatment												
D-penicillamine		–	72 (42%)	–	21 (45%)	–	10 (33%)	–	27 (51%)	–	14 (34%)	–
Zinc sulfate		–	99 (58%)	–	26 (55%)	–	20 (67%)	–	26 (49%)	–	27 (66%)	–

Results are shown as medians (interquartile range) or numbers (percentages). Statistically significant values are given in bold and $p < 0.05$ was considered a statistically significant difference; p-values refer to comparison of preceding group to controls

was not observed, and therefore results were presented as medians and interquartile ranges (IQR). Nonparametric tests such as Mann-Whitney U and Wilcoxon for matched pairs were used to compare groups. Correlation analysis was performed with the Spearman correlation test. All results for categorical variables were presented as numbers and percentages. Categorical data was analysed with the Chi-square test. Significance was assumed at $p < 0.05$. Statistica 13.3 software was used for data analysis.

Results

Patient characteristics

Detailed data is set out in Table 2. Of the 181 patients with WD, 10 were lost to follow-up. Of the 171, 100 were treated for up to 5 years (47 with hepatic and 53 with neurological forms) and 71 were treated for up to 15 years (30 with hepatic and 41 with neurological forms). The WD group consisted of 94 women (55%) and 77 men (45%), with a median age of 29 years (IQR, 22–38 years). Regarding treatment, 72 patients (42%) received D-penicillamine and 99 (58%) were treated with zinc sulfate. The group of 88 healthy controls comprised 46 women (52%) and 42 men (48%), with a median age of 34 years (IQR, 30–43 years).

ICAM1, P-selectin, MMP9, GFAP and S100B serum concentrations

Detailed data is set out in Table 3. ICAM1 serum concentrations were significantly elevated before anti-copper treatment in patients with hepatic or neurological forms compared to the control group ($p < 0.001$). Anti-copper therapy led to a substantial decrease both with hepatic ($p < 0.01$) and neurological manifestations ($p < 0.05$) compared to before treatment. In the 15-year treated group in patients with hepatic symptoms, ICAM1 concentrations were not significantly different from the control group. In patients with neurological forms, ICAM1 concentrations remained significantly elevated after 15 years compared to controls ($p < 0.01$).

P-selectin serum concentrations remained elevated before and during treatment compared to the control group ($p < 0.05$) and there were no significant differences between patients with hepatic and neurological manifestations. These values did not decrease regardless of the treatment duration or the disease form.

MMP9 serum concentrations before treatment were lower than in the control group ($p < 0.05$) but reached the level of the controls during the treatment. There were no significant differences in MMP9 concentrations between patients with hepatic and neurological symptoms.

There were no significant differences in GFAP in patients with the hepatic form compared to controls. GFAP serum concentrations were significantly elevated only in untreated patients with neurological symptoms in the longer-treated group compared to controls ($p < 0.05$). There was a significant reduction during treatment only in the shorter-treated group ($p < 0.05$).

No substantial changes were observed in S100B serum concentrations in patients with either form of WD compared to the control group or during treatment.

There were no significant differences in serum concentrations of the tested markers in patients treated with D-penicillamine or zinc sulfate (data not shown).

Table 3. Changes in concentrations of serum markers (ng/ml) for brain damage and blood–brain barrier dysfunction in patients with hepatic and neurological forms, treated for up to 5 or 15 years

		ICAM1	P-selectin	MMP9	GFAP	S100B
Controls (C) n = 88		180 (140–290)	130 (62–180)	560 (210–790)	0.3 (0.0–1.3)	0.78 (0.72–0.88)
Hepatic form, n = 77						
5-year treated group, n = 47	0 y	350 (270–490)	200 (120–330)	290 (170–500)	1.0 (0.0–4.1)	0.83 (0.72–1.0)
	5 y	270 (210–370)	170 (93–310)	470 (340–730)	0.5 (0.0–2.4)	0.77 (0.73–0.92)
	p-value 0 y *vs.* C	**< 0.001**	**0.0012**	**0.0074**	0.052	0.12
	p-value 5 y *vs.* C	**< 0.001**	**0.034**	0.99	0.22	0.55
	p-value 0 y *vs.* 5 y	**0.0016**	0.43	**< 0.001**	0.051	0.061
15-year treated group, n = 30	0 y	340 (250–450)	270 (120–410)	370 (150–750)	0.8 (0.0–3.5)	0.85 (0.74–0.95)
	15 y	220 (170–300)	250 (110–470)	510 (320–760)	0.0 (0.0–2.5)	0.82 (0.75–0.91)
	p-value 0 y *vs.* C	**< 0.001**	**0.0010**	0.41	0.17	0.17
	p-value 15 y *vs.* C	0.16	< 0.001	0.87	1.0	0.17
	p-value 0 y *vs.* 15 y	**0.0011**	0.057	0.29	0.17	0.20
Neurological form, n = 94						
5-year treated group, n = 53	0 y	350 (250–490)	160 (63–250)	320 (140–620)	0.1 (0.0–3.5)	0.82 (0.73–0.97)
	5 y	290 (190–400)	180 (97–300)	420 (230–810)	0.0 (0.0–1.5)	0.84 (0.73–1.0)
	p-value 0 y *vs.* C	**< 0.001**	0.12	**0.021**	0.58	0.23
	p-value 5 y *vs.* C	**0.0020**	**0.0055**	0.87	0.27	0.20
	p-value 0 y *vs.* 5 y	0.027	0.24	**0.016**	**0.014**	0.59
15-year treated group, n = 41	0 y	330 (260–430)	180 (120–300)	320 (210–550)	1.9 (0.0–4.7)	0.86 (0.73–0.96)
	15 y	260 (210–360)	220 (140–410)	550 (340–710)	1.3 (0.0–4.3)	0.80 (0.73–0.97)
	p-value 0 y *vs.* C	**< 0.001**	**0.010**	0.085	**0.021**	0.082
	p-value 15 y *vs.* C	**0.0027**	**< 0.001**	0.81	0.057	0.23
	p-value 0 y *vs.* 15 y	**0.0061**	0.15	**0.0018**	0.68	0.12

Results are shown as medians (interquartile range). Statistically significant values are given in bold and $p < 0.05$ was considered a statistically significant difference; GFAP — glial fibrillary acidic protein; ICAM1 — intercellular adhesion molecule 1; MMP9 — matrix metallopeptidase 9; S100B — S100 calcium-binding protein B

Correlations between serum concentrations of brain damage, BBB dysfunction markers, and severity of neurological impairment

The serum concentration of ICAM1 positively correlated ($r = 0.27$, $p < 0.001$) with the advancement of the neurological status assessed according to the sum of parts II and III of the UWDRS (Fig. 1). In contrast, the concentration of MMP9 showed a negative correlation ($r = -0.25$, $p < 0.01$) with the advancement of the neurological status (Fig. 2). The concentrations of the other markers tested did not show significant correlations with the severity of the neurological status.

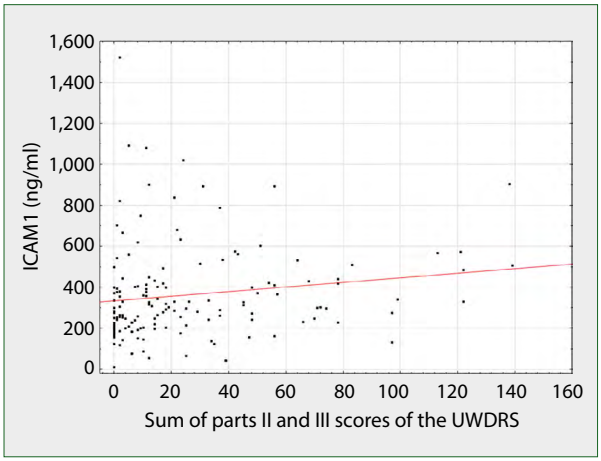

Figure 1. Positive correlation between serum concentration of ICAM1 and advancement of neurological status assessed according to UWDRS parts II and III ($r = 0.27$, $p < 0.001$)

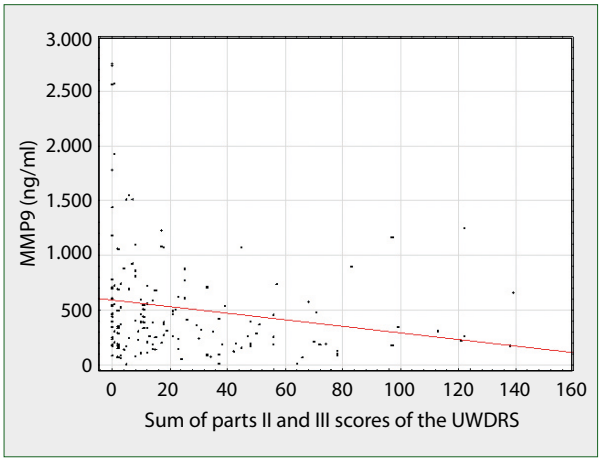

Figure 2. Negative correlation between serum concentration of MMP9 and advancement of neurological status assessed according to UWDRS parts II and III ($r = -0.25$, $p < 0.01$)

Correlations between serum concentrations of brain damage, BBB dysfunction markers, and age

MMP9 concentrations were positively correlated ($r = 0.3$, $p < 0.01$) with age in the control group, but this effect was not observed in the WD group (data not shown). Concentrations of the other BBB dysfunction markers tested showed no correlation with age in the control or WD groups.

Discussion

These results provide evidence of endothelial activation in WD patients, probably due to a toxic copper effect. The most promising result concerns ICAM1. Elevated concentrations of endothelial activation markers have previously been observed not only in neurological disorders but also in chronic liver diseases and other inflammatory processes [14, 15, 19]. Therefore, increased serum values may not necessarily indicate damage to the BBB, but rather a systemic inflammatory process due to liver disease.

However, the positive correlation between serum ICAM1 concentrations and the severity of the neurological status found in our study suggests that the BBB in WD patients is impaired. Thus, ICAM1 may become a potential biomarker of neurological impairment severity. A decrease in ICAM1 concentrations during treatment suggests that the inflammatory process is reduced and the BBB partially repaired. This is also confirmed by ICAM1 returning to control concentrations only in long-treated patients with hepatic symptoms. It might be helpful to determine the concentrations of markers such as ICAM1 in the CSF, but this is not done routinely, and we did not collect CSF samples during our study. It would be interesting to correlate concentrations of these markers with AR in CSF versus serum to minimise the effect of systemic inflammatory response and to confirm the BBB interruption.

In our study, P-selectin concentrations remained elevated with treatment, which may indicate an ongoing inflammatory process in WD patients. P-selectin concentrations did not allow a distinction to be made between hepatic and neurological manifestations and to assess the severity of CNS damage.

Unexpectedly, MMP9 serum concentrations before treatment were lower in WD patients than in the control group, but reached the level of the controls during the treatment. This is inconsistent with previous results [20], in which serum MMP9 concentrations were higher in patients with neurological WD than in patients with hepatic WD, which in turn were higher than in the control group. Nevertheless, our study examined patients regarding their treatment duration, and included larger WD and control groups. The positive correlation between MMP9 concentrations and age could impact upon the results of patients studied after several years, but this correlation was observed only in the control group, and not in the WD group. However, the process of liver fibrosis may be essential. It has been shown that fibrotic matrix stiffness downregulates MMP9 expression and secretion in hepatic stellate cells, thus promoting fibrosis perpetuation [36]. Increased copper concentrations may also downregulate MMP9 expression, as has been demonstrated in rat livers [37]. Thus, untreated patients with higher copper concentrations and liver fibrosis should have lower MMP9 concentrations. Also, MMP9 concentrations increase after anti-copper treatment, which improves liver and brain function and reduces the inflammatory process [38]. Therefore, MMP9 is not a suitable marker for assessing BBB disruption in WD.

Elevated serum GFAP concentrations in untreated WD patients with neurological manifestations can serve as a biomarker for different subtypes of WD. This was previously reported [23], although not confirmed in another study [24]. In our study, GFAP concentrations were significantly elevated

only in untreated patients with neurological symptoms in the longer-treated group compared to controls. This may indicate astrocytic damage in WD patients with neurological manifestation. No substantial changes were observed with serum S100B in our study. Therefore, we cannot definitely determine whether the reactive gliosis is not prominent, or if the BBB is disrupted in WD.

Our study investigated commonly used markers of brain damage and BBB impairment, broadly reviewed in various neurological disorders. Unfortunately, most of them are unspecific for BBB vasculature and depend on their peripheral production. Therefore, it is essential to investigate other promising indicators of BBB disruption, including vascular endothelial cadherin, claudin-5, ocludine, vascular endothelial growth factor, as well as anti-aquaporin 1 antibodies, which have been studied in primary BBB permeability diseases such as neuromyelitis optica spectrum disorders and multiple sclerosis [39].

Further studies involving other inflammatory molecules and brain-specific proteins in serum, but also in CSF, are necessary to get a fuller picture of BBB involvement in WD. It may also be valuable to investigate the concentrations of markers at additional timepoints. Moreover, adherence to therapy is crucial, which should have been considered in this study.

Confirmation of BBB damage in WD patients with severe neurological deterioration may prompt the consideration of temporary immunosuppressive therapy to silence the inflammatory response and rebuild the BBB to reduce further CNS damage, as proposed in some neurological diseases such as refractory status epilepticus [40]. In addition, it might be beneficial to investigate the correlations between BBB dysfunction markers and copper metabolism parameters to determine optimal anti-copper treatment.

Conclusions and clinical implications

Elevated serum concentrations of ICAM1, and their correlation with the advancement of neurological status, suggest that the BBB in WD patients is impaired, especially in patients with neurological symptoms. Furthermore, these results hold the potential to assess neurological impairment and indicate the role of endothelial dysfunction in this process. However, unclear GFAP results and no increase in S100B do not allow us to conclude whether the reactive gliosis is not prominent, or alternatively if the BBB is disrupted in WD. In addition to copper toxicity, impaired immune functions might influence neurological advancement. Therefore, characterising inflammatory molecules and their relationship to neurological deterioration warrants further investigations to determine the most effective treatment for patients with WD.

Conflicts of interest: *None.*
Funding: *None.*

References

1. Członkowska A, Litwin T, Dusek P, et al. Wilson disease. Nat Rev Dis Primers. 2018; 4(1): 21, doi: 10.1038/s41572-018-0018-3, indexed in Pubmed: 30190489.
2. Choi BS, Zheng W. Copper transport to the brain by the blood–brain barrier and blood-CSF barrier. Brain Res. 2009; 1248: 14–21, doi: 10.1016/j.brainres.2008.10.056, indexed in Pubmed: 19014916.
3. Wang Y, Hodgkinson V, Zhu S, et al. Advances in the understanding of mammalian copper transporters. Adv Nutr. 2011; 2(2): 129–137, doi: 10.3945/an.110.000273, indexed in Pubmed: 22332042.
4. Telianidis J, Hung YaH, Materia S, et al. Role of the P-Type ATPases, ATP7A and ATP7B in brain copper homeostasis. Front Aging Neurosci. 2013; 5: 44, doi: 10.3389/fnagi.2013.00044, indexed in Pubmed: 23986700.
5. Tang D, Chen X, Kroemer G. Cuproptosis: a copper-triggered modality of mitochondrial cell death. Cell Res. 2022; 32(5): 417–418, doi: 10.1038/s41422-022-00653-7, indexed in Pubmed: 35354936.
6. Clark LF, Kodadek T. The Immune System and Neuroinflammation as Potential Sources of Blood-Based Biomarkers for Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease. ACS Chem Neurosci. 2016; 7(5): 520–527, doi: 10.1021/acschemneuro.6b00042, indexed in Pubmed: 27046268.
7. Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron. 2008; 57(2): 178–201, doi: 10.1016/j.neuron.2008.01.003, indexed in Pubmed: 18215617.
8. Daneman R, Prat A. The blood-brain barrier. Cold Spring Harb Perspect Biol. 2015; 7(1): a020412, doi: 10.1101/cshperspect.a020412, indexed in Pubmed: 25561720.
9. Dietrich JB. The adhesion molecule ICAM-1 and its regulation in relation with the blood-brain barrier. J Neuroimmunol. 2002; 128(1-2): 58–68, doi: 10.1016/s0165-5728(02)00114-5, indexed in Pubmed: 12098511.
10. Sharief MK, Noori MA, Ciardi M, et al. Increased levels of circulating ICAM-1 in serum and cerebrospinal fluid of patients with active multiple sclerosis. Correlation with TNF-alpha and blood-brain barrier damage. J Neuroimmunol. 1993; 43(1-2): 15–21, doi: 10.1016/0165-5728(93)90070-f, indexed in Pubmed: 8096220.
11. Hartung HP, Michels M, Reiners K, et al. Soluble ICAM-1 serum levels in multiple sclerosis and viral encephalitis. Neurology. 1993; 43(11): 2331–2335, doi: 10.1212/wnl.43.11.2331, indexed in Pubmed: 7901809.
12. Shyu KG, Chang H, Lin CC. Serum levels of intercellular adhesion molecule-1 and E-selectin in patients with acute ischaemic stroke. J Neurol. 1997; 244(2): 90–93, doi: 10.1007/s004150050055, indexed in Pubmed: 9120502.
13. Rentzos M, Michalopoulou M, Nikolaou C, et al. Serum levels of soluble intercellular adhesion molecule-1 and soluble endothelial leukocyte adhesion molecule-1 in Alzheimer's disease. J Geriatr Psychiatry Neurol. 2004; 17(4): 225–231, doi: 10.1177/0891988704269822, indexed in Pubmed: 15533994.
14. Thomson AW, Satoh S, Nüssler AK, et al. Circulating intercellular adhesion molecule-1 (ICAM-1) in autoimmune liver disease and evidence for the production of ICAM-1 by cytokine-stimulated human hepatocytes. Clin Exp Immunol. 1994; 95(1): 83–90, doi: 10.1111/j.1365-2249.1994.tb06019.x, indexed in Pubmed: 7904546.

15. Sookoian S, Castaño GO, Burgueño AL, et al. Circulating levels and hepatic expression of molecular mediators of atherosclerosis in nonalcoholic fatty liver disease. Atherosclerosis. 2010; 209(2): 585–591, doi: 10.1016/j.atherosclerosis.2009.10.011, indexed in Pubmed: 19896127.
16. Timmerman I, Daniel AE, Kroon J, et al. Leukocytes crossing the endothelium: a matter of communication. Int Rev Cell Mol Biol. 2016; 322: 281–329, doi: 10.1016/bs.ircmb.2015.10.005, indexed in Pubmed: 26940521.
17. Järemo P, Milovanovic M, Buller C, et al. P-selectin paradox and dementia of the Alzheimer type: circulating P-selectin is increased but platelet-bound P-selectin after agonist provocation is compromised. Scand J Clin Lab Invest. 2013; 73(2): 170–174, doi: 10.3109/00365513.2013.764572, indexed in Pubmed: 23421771.
18. Corsi MM, Licastro F, Porcellini E, et al. Reduced plasma levels of P-selectin and L-selectin in a pilot study from Alzheimer disease: relationship with neuro-degeneration. Biogerontology. 2011; 12(5): 451–454, doi: 10.1007/s10522-011-9335-6, indexed in Pubmed: 21484243.
19. Tacke F, Schöffski P, Trautwein C, et al. Plasma P-selectin levels are elevated in patients with chronic liver disease. Blood Coagul Fibrinolysis. 2003; 14(4): 319–325, doi: 10.1097/00001721-200306000-00001, indexed in Pubmed: 12945872.
20. Cheng N, Wang H, Dong J, et al. Elevated serum brain natriuretic peptide and matrix metalloproteinases 2 and 9 in Wilson's disease. Metab Brain Dis. 2015; 30(4): 1087–1091, doi: 10.1007/s11011-015-9685-x, indexed in Pubmed: 26077744.
21. Mossakowski MJ, Weinrauder H. Glial fibrillary acidic protein and S100 protein in abnormal astrocytes in Wilson's disease. Neuropatol Pol. 1986; 24(3): 365–376, indexed in Pubmed: 3561797.
22. Abdelhak A, Foschi M, Abu-Rumeileh S, et al. Blood GFAP as an emerging biomarker in brain and spinal cord disorders. Nat Rev Neurol. 2022; 18(3): 158–172, doi: 10.1038/s41582-021-00616-3, indexed in Pubmed: 35115728.
23. Lin J, Zheng Y, Liu Y, et al. Higher concentration of plasma glial fibrillary acidic protein in Wilson disease patients with neurological manifestations. Mov Disord. 2021; 36(6): 1446–1450, doi: 10.1002/mds.28509, indexed in Pubmed: 33502774.
24. Shribman S, Heller C, Burrows M, et al. Plasma neurofilament light as a biomarker of neurological involvement in Wilson's disease. Mov Disord. 2021; 36(2): 503–508, doi: 10.1002/mds.28333, indexed in Pubmed: 33078859.
25. Kligman D, Hilt DC. The S100 protein family. Trends Biochem Sci. 1988; 13(11): 437–443, doi: 10.1016/0968-0004(88)90218-6, indexed in Pubmed: 3075365.
26. Rothermundt M, Peters M, Prehn JHM, et al. S100B in brain damage and neurodegeneration. Microsc Res Tech. 2003; 60(6): 614–632, doi: 10.1002/jemt.10303, indexed in Pubmed: 12645009.
27. Schaf DV, Tort ABL, Fricke D, et al. S100B and NSE serum levels in patients with Parkinson's disease. Parkinsonism Relat Disord. 2005; 11(1): 39–43, doi: 10.1016/j.parkreldis.2004.07.002, indexed in Pubmed: 15619461.
28. Chaves ML, Camozzato AL, Ferreira ED, et al. Serum levels of S100B and NSE proteins in Alzheimer's disease patients. J Neuroinflammation. 2010; 7: 6, doi: 10.1186/1742-2094-7-6, indexed in Pubmed: 20105309.
29. Chaudhuri JR, Mridula KR, Rathnakishore C, et al. Association serum S100B protein in Alzheimer's disease: a case control study from south india. Curr Alzheimer Res. 2020; 17(12): 1095–1101, doi: 10.2174/1567205018666210119145104, indexed in Pubmed: 33463467.
30. Otto M, Wiltfang J, Schütz E, et al. Diagnosis of Creutzfeldt-Jakob disease by measurement of S100 protein in serum: prospective case-control study. BMJ. 1998; 316(7131): 577–582, doi: 10.1136/bmj.316.7131.577, indexed in Pubmed: 9518907.
31. Marchi N, Rasmussen P, Kapural M, et al. Peripheral markers of brain damage and blood-brain barrier dysfunction. Restor Neurol Neurosci. 2003; 21(3-4): 109–121, indexed in Pubmed: 14530574.
32. Stuerenburg HJ. CSF copper concentrations, blood-brain barrier function, and coeruloplasmin synthesis during the treatment of Wilson's disease. J Neural Transm (Vienna). 2000; 107(3): 321–329, doi: 10.1007/s007020050026, indexed in Pubmed: 10821440.
33. Borchard S, Raschke S, Zak KM, et al. Bis-choline tetrathiomolybdate prevents copper-induced blood-brain barrier damage. Life Sci Alliance. 2022; 5(3), doi: 10.26508/lsa.202101164, indexed in Pubmed: 34857647.
34. Członkowska A, Litwin T, Dzieżyc K, et al. Characteristics of a newly diagnosed Polish cohort of patients with neurological manifestations of Wilson disease evaluated with the Unified Wilson's Disease Rating Scale. BMC Neurol. 2018; 18(1): 34, doi: 10.1186/s12883-018-1039-y, indexed in Pubmed: 29621974.
35. Członkowska A, Tarnacka B, Möller JC, et al. Unified Wilson's Disease Rating Scale - a proposal for the neurological scoring of Wilson's disease patients. Neurol Neurochir Pol. 2007; 41(1): 1–12, indexed in Pubmed: 17330175.
36. Lachowski D, Cortes E, Rice A, et al. Matrix stiffness modulates the activity of MMP-9 and TIMP-1 in hepatic stellate cells to perpetuate fibrosis. Sci Rep. 2019; 9(1): 7299, doi: 10.1038/s41598-019-43759-6, indexed in Pubmed: 31086224.
37. Alexandrova A, Bandžuchová E, Kebis A, et al. Copper decreases gene expression of TNF-α, IL-10, and of matrix metalloproteinases MMP-2 and MMP-9 in isolated perfused rat livers. Biologia. 2007; 62(3): 365–369, doi: 10.2478/s11756-007-0061-0.
38. Czlonkowska A. The influence of prolonged treatment with D-penicillamine on the immune response in Wilson's disease. Eur J Clin Pharmacol. 1977; 12(4): 265–271, doi: 10.1007/BF00607425, indexed in Pubmed: 590312.
39. Jasiak-Zatońska M, Michalak S, Osztynowicz K, et al. Relationship between blood-brain permeability and antibodies against aquaporins in neuromyelitis optica spectrum disorders and multiple sclerosis patients. Neurol Neurochir Pol. 2022; 56(4): 308–317, doi: 10.5603/PJNNS.a2022.0007, indexed in Pubmed: 35029294.
40. Hanin A, Cespedes J, Dorgham K, et al. Cytokines in new-onset refractory status epilepticus predict outcomes. Ann Neurol. 2023; 94(1): 75–90, doi: 10.1002/ana.26627, indexed in Pubmed: 36871188.

SHORT COMMUNICATION

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 4, pages: 387–391
DOI: 10.5603/PJNNS.a2023.0039

ISSN: 0028-3843, e-ISSN: 1897-4260

Glomangioma in the hand: diagnosis, treatment, and challenges

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ABSTRACT

Introduction. In this paper, we have analysed all hand glomangioma cases referred to our clinic in the context of symptoms, time to diagnosis, and the role of surgical resection of the lesion.

Material and methods. We have collected the following data: the presence of risk factors, manifestation, time to diagnosis, the treatment applied, and follow-up of patients.

Results. We have collected medical records from six patients, three males and three females. The median age was 45 (IQR: 29.5–65.75). The main symptom in all patients was severe pain and tenderness. The first-choice physician(s) were: general practitioners, general surgeons, and neurologists. The median time to diagnosis was 7 (IQR: 5–10) years. The main complaint of our patients was severe pain — 9 (IQR: 9–10) on the VAS scale, which was significantly alleviated after surgical treatment — 0 (IQR: 0–0; p = 0.043).

Conclusions. Extremely long times to final diagnosis, and excellent outcomes of surgical treatment, highlight the necessity of raising awareness of glomangiomas among clinicians.

Key words: subungual glomangioma, glomangioma, glomuvenous malformation, glomangiosarcoma, risk factors, treatment

(*Neurol Neurochir Pol 2023; 57 (4): 387–391*)

Introduction

Glomangioma is a rare, typically benign, lesion accounting for up to 2% of soft tissue tumours. According to the World Health Organisation guidelines, it is defined as "a mesenchymal neoplasm composed of cells resembling the perivascular modified smooth muscle cells of the normal glomus body" [1]. The small (< 1 cm) visible and/or palpable mass (Fig. 1A, Supp. Fig. 1), with a pinkish-red or bluish macule and/or spot, is usually located in the distal extremities - especially in the subungual region, but also in the hand, wrist, and foot [1, 2]. Other localisations have been observed especially in males e.g. nerves, bones, muscles, mediastinum, lung, gastrointestinal tract (preferably stomach), genitourinary system, and others [3–9].

Our patients reported the typical triad of symptoms: paroxysmal pain, cold sensitivity, and exquisite point tenderness in the region of the tumour. Not all of these symptoms were present consistently, and pain was the most common [1, 2]. The diagnosis was based on clinical presentation and clinical signs/tests, especially the Hildreth sign, cold-sensitivity test, and transillumination test [2]. The final verification was made by a pathologist.

In this paper, we analyse all hand glomangioma cases referred to the Department of Neurosurgery, Spine and Peripheral Nerves Surgery of the Medical University of Lodz,

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Received: 22.12.2022 Accepted: 11.05.2023 Early publication date: 21.06.2023

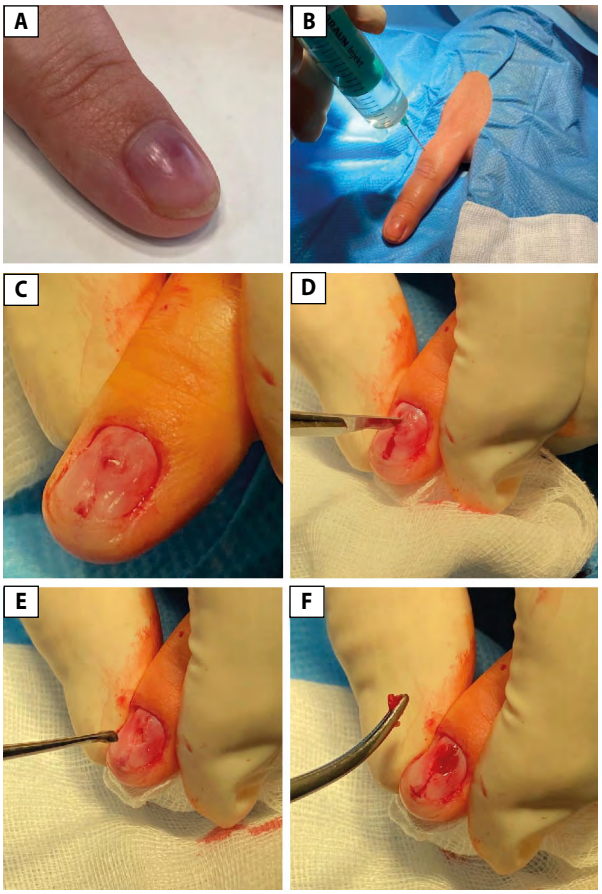

Figure 1. Intraoperative images show dissection of glomangioma: (**A**) presurgical photography of lesion, (**B**) usage of infiltration anaesthesia with lignocaine just after standard preparation of operating field, (**C**) visualisation of subungual glomangioma, (**D**) incision of aforementioned lesion, (**E**) removal of lesion, (**F**) state after subungual glomangioma removal

Poland in the context of symptoms, time to diagnosis, and the role of surgical resection of the lesion.

Material and methods

Patient selection and collected data

We analysed the medical records of six patients treated for glomangioma in the Department of Neurosurgery, Spine and Peripheral Nerves Surgery of the Medical University of Lodz between 1 January, 2017 and 31 October, 2022. From all of these patients, we attempted to collect the following data: preoperative [age, sex, occupation, lesion location, initial symptoms, photographic documentation, duration of symptoms, first-choice physician, time to diagnosis, presurgical pain severity according to the Visual Analogue Scale (VAS)], intraoperative (photographic documentation, surgery description), and postoperative [histopathological verification result, appearance of new similar lesions in patient or patient's family, pain severity in VAS (Supp. Tab. 1)]. Moreover, the data was juxtaposed with the presence/absence of selected risk factors including positive familial history, multiple lesions, mutations in the glomulin gene (GLMN), and neurofibromatosis type 1.

Surgical technique

The patients underwent Oberst anaesthesia just after the standard preparation of the operating field. Then the nail was removed if needed. In the case of nonvisible, nonpalpable lesions, they were further visualised using transillumination. The lesions were further totally dissected (Fig. 1B–F) and sent for histopathological verification (Supp. Fig. 2). The control of haemostasis was performed. A sterile dressing was used. These steps are shown in Supp. Video 1.

Results

We collected medical records from six patients, three males and three females. The median age was 45 (IQR: 29.5–65.75). One patient (16.67%) (Tab. 2) missed the follow-up. A lesion was found in the following localisations: (1) subungual in the first finger of the right hand, (2) fingertip of the third finger of the right hand, (3) subungual in the fifth finger of the left hand, (4) subungual in the first finger of the left hand, (5) subungual in the second finger of the left hand, and (6) fingertip of the first finger of the left hand. The lesion was visible in just one case (Fig. 1A). The lesion was palpable in three patients (50%).

The main symptoms in all patients were severe pain with the presence of point tenderness in the region of the tumour. Patients were diagnosed by general practitioners (n = 3), general surgeons (n = 2), and neurologists (n = 2). Two of them were diagnosed by more than one physician. The median time to diagnosis was 7 (IQR: 5–10) years.

Preoperative pain and its relief

The main complaint of our patients was initially severe pain — 9 (IQR: 9–10) on the VAS scale. The specificity differed between patients (Tab. 1). Three months after surgery, median pain severity was 0 (IQR: 0–0; p = 0.043).

Risk factor presence

There was no case of positive familial history of glomangioma, multiple lesions, detected mutations in the glomulin gene (*GLMN*), or neurofibromatosis type 1 symptoms (diagnosed NF1, six or more café-au-lait spots over 5 mm in greatest diameter in pre-pubertal individuals and over 15 mm in greatest diameter in post-pubertal individuals, two or more neurofibromas of any type or one plexiform neurofibroma, optic nerve glioma, two or more Lisch nodules (pigmented iris hamartomas), a distinctive osseous lesion such as sphenoid dysplasia, or thinning of the long bone cortex with or without pseudarthrosis, or a first-degree relative (i.e. parent, sibling, or offspring) with NF1 by the above criteria).

Table 1. Results of pre-, intra-, and postoperative examinations juxtaposed with presence of selected risk factors

No.	Sex	Age	Symptoms	Lesion	First-choice physician(s)	Time to diagnosis [years]	Pain severity in VAS scale pre- and postoperative	Risk factors
1.	M	74	Pain radiating to elbow, especially at night, tenderness	Nonvisible, palpable	Neurologist	5	7 > 1	No
2.	M	34	Dull pain, tenderness	Nonvisible, nonpalpable	General surgeon	10	9 > 0	No
3.	M	28	Pulsating pain, tenderness	Nonvisible, nonpalpable	GP, general surgeon	4	9 > 0	No
4.	F	69	Pain, tenderness	Nonvisible, nonpalpable	N.D.	N.D.	N.D.	No
5.	F	24	Paroxysmal pain, and tenderness, aggravated by temperature changes	Visible (Fig. 1), palpable	GP, neurologist	7	10 > 0	No
6.	F	56	Tenderness	Nonvisible, palpable	GP	10	10 > 0	No

GP — general practitioner; N.D. — no data; VAS — visual analogue scale

Discussion

Glomangioma remains a rare entity that significantly affects patients' quality of life. These six patients reported the typical triad of symptoms: paroxysmal pain, cold sensitivity, and point tenderness in the region of the tumour. Not all of the symptoms were present consistently, and pain was the most common [2]. This statement is supported by our data. All patients reported severe pain and the presence of point tenderness in the region of the tumour. Interestingly, sensitivity to temperature changes was observed in just 1/6 cases. Glomangioma may be visible as a small pinkish-red or bluish macule and/or spot, as was seen in the case presented in Figure 1 [1].

Glomangioma is mostly localised on distal extremities — especially in the subungual region but also in the hand, wrist, and foot. In the current study, we have focused on glomangioma localised in the hand: 5/6 (83.33%) presented with a subungual lesion, and only 1/6 (16.67%) presented glomangioma in the fingertip of the third finger of the right hand. Other localizations are rarely observed but can include: nerves, bones, muscles, the mediastinum, lungs, the gastrointestinal tract, and the genitourinary system [4–9].

Diagnostic problems

Falcone has stated that hand glomangiomas are characterised by a high rate of misdiagnosis, due to "the very ignorance of their existence by the medical corpus" [10]. The extremely long time to diagnosis among our patients — 7 (IQR: 5–10) years — reveals a good deal of justification for this thesis. As patients were first diagnosed by general practitioners, general surgeons, and neurologists, there is a need to raise awareness of glomangiomas among clinicians.

In the case of uncertain diagnosis, the following entities should be taken into consideration in differential diagnosis, especially during histopathological verification: exostosis, enchondroma, leiomyoma, ganglion spiradenoma, and hemangioma [2]. Fortunately, in all of our cases, the initial diagnosis was confirmed.

Surgical treatment

Complete surgical resection remains the best treatment for subungual/finger glomangioma [10]. There are two main surgical approaches: trans-ungual with the removal of the nail, and lateral. The first of these is recommended for lesions localised in the central subungual region, while the second approach should be used in the case of glomangioma observed in the lateral subungual region and/or on the finger pad [2].

2–4 weeks after surgery, most of the patients reported significant relief, although pain can last longer in some cases [2]. In 4/6 (66.67%) cases we observed relief within the first month. One patient (16.67%) had pain lasting for two months, with complete recovery subsequently.

Histopathological diagnosis

Glomus tumours are composed of cells that resemble the modified smooth muscle cells of the normal glomus body. These glomus cells are round, monomorphic, and have indistinct borders, but no atypia. In most cases, they form dense nests that surround small vessels in hyalinised stroma. Oncocytic or epithelioid changes are occasionally present in glomus tumours [11, 12]. Features indicating malignant transformation include marked cellular (nuclear) atypia and atypical mitotic figures adjacent to the normal (benign) component.

According to the WHO 2020 Classification of Soft Tissue Tumours, an accurate diagnosis of glomus tumours should include the following immunohistochemical stainings: Smooth Muscle Actin (SMA) and CD34, to confirm the glomus body's origin; desmin, to exclude other tumours of

myogenic differentiation; chromogranin, to exclude neuroendocrine differentiation; pan-cytokeratin (CKAE1/AE3), to exclude epithelial differentiation; melan-A, to exclude melanocytic differentiation; and Ki-67, to confirm a low proliferation index [1].

Risk factors

The established risk factors are a positive familial history of glomangioma, multiple lesions, detected mutations in the glomulin gene (*GLMN*), or neurofibromatosis type 1 [1]. Small studies have shown that pathogenic variants in *BRAF, NOTCH, PDGFRB, KRAS*, and *SMARCB1* can predispose to glomangiomas. In our group of patients, there were no clinical indications for further genetic counselling, and therefore it was waived.

Prognosis and recurrence risk

The largest series of glomangioma patients in the last 15 years have been presented by Lin et al. (n = 75) and Chou et al. (n = 50) [13, 14]. Although all of these patients underwent surgical removal of the lesion with good therapeutic effect, the outcome was not event-free in all cases. Chou et al. observed recurrence in three (6%) and nail deformity in three (6%) patients, while Lin et al. noted 13 (17%) recurrences [13, 14]. Recurrences can be divided into early (caused by incomplete excision or undiagnosed secondary tumours) or delayed (caused by the development of a new tumour) [15]. Recurrence risk factors encompass being skin-coloured (OR = 31.67; 95% CI = 2.68–373.74), being located within the nail matrix (OR = 5.79, 95% CI = 1.03–32.49), and a genetic condition predisposing to glomangiomas [13].

Conclusions

Glomangioma remains a rarely observed lesion that strongly affects the patient's quality of life, mainly due to severe pain. Unfortunately, knowledge regarding this entity seems to be relatively scarce among physicians, which results in an extremely long time until the final diagnosis. The excellent outcomes of surgical treatment highlight the necessity to raise awareness of glomangiomas among clinicians.

Clinical implications/future directions

We observed a high necessity to raise awareness of glomangiomas among clinicians, especially general practitioners, neurologists, and general surgeons. This may result in a reduction of the time to diagnosis and prompt treatment.

Strengths and limitations

The main advantage of this study was the relatively large group of patients with subungual glomangioma from the Department of Neurosurgery, Spine and Peripheral Nerves Surgery. All the questions were consulted with an experienced dermatologist, a neurologist, a general practitioner, and a neurosurgeon. All data was collected by medical doctors experienced in scientific work.

Nevertheless, the study also has visible limitations, especially its retrospective character and the fact that the research was performed in a single centre.

Conflicts of interests: *None*

Funding: *The APC was funded by the Department of Neurosurgery, Spine and Peripheral Nerves Surgery of the Medical University of Lodz, 90–549 Lodz, Poland.*

Acknowledgments: *We would like to thank Prof. Andrzej Radek for raising awareness of glomangioma in our Department. Moreover, we would like to thank all of our patients for their trust and motivation to let us become better and more experienced clinicians.*

References

1. Specht K, Antonescu C. Glomus tumour. Soft Tissue Bone Tumours WHO Classif. Tumours, vol. 3. 5th ed. International Agency for Research on Cancer, Lyon 2020: 179–181.
2. Samaniego E, Crespo A, Sanz A. [Key diagnostic features and treatment of subungual glomus tumor]. Actas Dermosifiliogr. 2009; 100(10): 875–882, indexed in Pubmed: 20038364.
3. Gombos Z, Zhang PJ. Glomus tumor. Arch Pathol Lab Med. 2008; 132(9): 1448–1452, doi: 10.5858/2008-132-1448-GT, indexed in Pubmed: 18788860.
4. Miettinen M, Paal E, Lasota J, et al. Gastrointestinal glomus tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 32 cases. Am J Surg Pathol. 2002; 26(3): 301–311, doi: 10.1097/00000478-200203000-00003, indexed in Pubmed: 11859201.
5. Rössle M, Bayerle W, Löhrs U. Glomangioma of the lungs: a rare differential diagnosis of a pulmonary tumour. J Clin Pathol. 2006; 59(9): 1000, doi: 10.1136/jcp.2005.031237, indexed in Pubmed: 16935981.
6. Scheithauer BW, Rodriguez FJ, Spinner RJ, et al. Glomus tumor and glomangioma of the nerve. Report of two cases. J Neurosurg. 2008; 108(2): 348–356, doi: 10.3171/JNS/2008/108/2/0348, indexed in Pubmed: 18240933.
7. Wang Y, Xiang Y, Bian Y, et al. Glomus tumors associated with the bone and joints: a review of 91 cases. Ann Transl Med. 2020; 8(21): 1460, doi: 10.21037/atm-20-6998, indexed in Pubmed: 33313205.
8. Bistazzoni S, Polosa M, Bellocchi SD. Unusual location of glomus tumors. Case Reports and Images in Surgery. 2020; 3(2), doi: 10.15761/cris.1000144.
9. Lee TJ, Reddy GP, Leung JWT, et al. Mediastinal glomangioma: CT and octreotide scintigraphy appearance, and review of the literature. J Thorac Imaging. 2008; 23(4): 289–291, doi: 10.1097/RTI.0b013e31817eee70, indexed in Pubmed: 19204477.
10. Falcone MO. Glomus tumors of the fingers. Rev Prat. 2022; 72(3): 313–316, indexed in Pubmed: 35638965.
11. Slater DN, Cotton DW, Azzopardi JG. Oncocytic glomus tumour: a new variant. Histopathology. 1987; 11(5): 523–531, doi: 10.1111/j.1365-2559.1987.tb02660.x, indexed in Pubmed: 3038728.

12. Pulitzer D, Martin P, Reed R. Epithelioid glomus tumor. Human Pathology. 1995; 26(9): 1022–1027, doi: 10.1016/0046-8177(95)90093-4.
13. Lin YC, Hsiao PF, Wu YH, et al. Recurrent digital glomus tumor: analysis of 75 cases. Dermatol Surg. 2010; 36(9): 1396–1400, doi: 10.1111/j.1524-4725.2010.01647.x, indexed in Pubmed: 20629689.
14. Chou T, Pan SC, Shieh SJ, et al. Glomus tumor: twenty-year experience and literature review. Ann Plast Surg. 2016; 76 Suppl 1: S35–S40, doi: 10.1097/SAP.0000000000000684, indexed in Pubmed: 26808758.
15. Lee IJ, Park DH, Park MC, et al. Subungual glomus tumours of the hand: diagnosis and outcome of the transungual approach. J Hand Surg Eur Vol. 2009; 34(5): 685–688, doi: 10.1177/1753193408104799, indexed in Pubmed: 19959449.

SHORT COMMUNICATION

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 4, pages: 392–396
DOI: 10.5603/PJNNS.a2023.0048

ISSN: 0028-3843, e-ISSN: 1897-4260

Visual disturbances in patients with Parkinson's disease treated with oral medications or deep brain stimulation

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ABSTRACT

Aim of the study. Ophthalmological symptoms are common in patients with Parkinson's disease (PD) and can be evaluated by the Visual Impairment in Parkinson's Disease Questionnaire (VIPD-Q). This study aimed to assess the prevalence of ophthalmological symptoms in PD depending on the type of treatment used i.e. pharmacological or subthalamic nucleus deep brain stimulation (STN-DBS).

Material and methods. We performed a cross-sectional study. The data was gathered from a VIPD-Q and from medical records. Patients with PD were divided into two groups based on the type of treatment – pharmacological (control group, CG) (39 patients) or STN-DBS (40 patients).

Results. The great majority of patients — 72 (91.1%) — experienced an ophthalmological symptom. The prevalence of three symptoms differed significantly between the groups. A burning sensation or a gritty feeling in the eyes occurred more often in patients in the STN-DBS group (40.0% *vs.* 15.4%; p = 0.015). On the other hand, the inability to read plain text on a coloured or grey background and problems with rapid changes of light intensity were more common in the CG group (38.5% *vs.* 15.0%, p = 0.018 and 28.2% *vs.* 10.0%, p = 0.039, respectively).

Conclusions and clinical implications. The prevalence of ophthalmological symptoms in PD is high. Despite significant differences in the three symptoms, the overall prevalence of ophthalmological clinical features was similar in the evaluated groups.

Key words: Parkinson's disease, deep brain stimulation, ophthalmological symptoms, levodopa

(*Neurol Neurochir Pol 2023; 57 (4): 392–396*)

Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder, and, at the same time, the most frequent movement disorder [1]. Non-motor symptoms in PD are common and can contribute to reduced quality of life [2, 3]. Among non-motor symptoms, ophthalmological symptoms are of significant importance [4, 5]. The most common of these symptoms include defects in visual acuity, eye movements, pupil abnormalities, lens opacity, and diplopia [6, 7]. Visual impairment, together with postural and gait impairment, increases the risk of falls and fall-related injuries [8].

Recently, a new PD-specific questionnaire, the Visual Impairment in Parkinson's Disease Questionnaire (VIPD-Q), has been developed to assess ophthalmological symptoms [8]. This instrument facilitates the assessment of both the prevalence of specific symptoms and the domains in which those symptoms manifest themselves. There is a paucity of

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Received: 24.04.2023; Accepted: 12.07.2023; Early publication date: 28.07.2023

data on the impact on ophthalmological symptoms of treatment modalities used to treat PD. The aim of this study was to assess the prevalence of visual impairment in patients with PD treated only pharmacologically, i.e. with l-dopa, or by a combination of oral treatment with subthalamic nucleus deep brain stimulation (STN-DBS).

Material and methods

Study design

This cross-sectional study was conducted in one academic centre between June 2020 and June 2021. Ethical approval was granted by the institutional review board (opinion number: 1072.6120.104.2020). Participants provided written informed consent.

Consecutive patients meeting the following inclusion criteria were recruited: a PD diagnosis based on the UK Brain Bank Criteria [9]; first symptoms of the disease having occurred after the age of 30; stable doses of PD medications (for at least four weeks); age at least 60; and ability to give informed consent for participation in the study. Exclusion criteria were as follows: a score of ≥ 4 on the Hoehn and Yahr scale [10]; secondary parkinsonism (drug-induced, vascular, tumour, infectious, immunological); dementia according to DSM-IV (not allowing questions to be understood); a major depressive disorder according to DSM-IV; a psychotic disorder according to DSM-IV; previous brain surgery (except for DBS); previous ophthalmological surgery (except for cataract surgery); blindness in one eye; medication that influences normal visual function other than PD medication (detailed information see ref. [8]); systemic diseases which may influence visual function; a history of lesions near the optic chiasm or occipital cortex; and migraine.

Additional data was obtained from medical records. Patients were divided into two groups based on their type of PD treatment. Patients in the control group (CG) were treated with oral medications, while patients in the other group were treated with STN-DBS in combination with oral treatment. The Polish version of the VIPD-Q was administered to patients during a visit to the outpatient clinic. Detailed information on the VIPD-Q was presented in a previous study [8].

The main outcome of our study was the prevalence of ophthalmological symptoms in the two groups depending on the type of PD treatment.

Questionnaire and analysis

VIPD-Q consists of 17 questions divided into four domains: ocular surface, intraocular, oculomotor, and optic nerve [8]. The answers "every week" or "every day" were defined as the presence of all symptoms except for hallucinations, the presence of which was defined as the answer "every month" or higher [8]. The total score of the VIPD-Q and the score in each domain were calculated.

Statistical analysis

The analysis was conducted with IBM SPSS Statistics 28. Descriptive variables were presented as mean and standard deviations (SD) or median and first and third quartiles (Q1–Q3) depending on the distribution. The distribution was explored with Shapiro-Wilk's test. The differences between non-normally distributed variables were assessed with the Mann-Whitney *U* test and Spearman's rho was used for correlation analysis. Categorical variables were presented as number (n) and percentage (%). The differences between qualitative data were analysed with the Chi-square test. P-value < 0.05 was considered significant.

Results

Seventy-nine patients were included in the study. The demographic and clinical features of patients are set out in Table 1.

Almost all of the patients (72; 91.1%) experienced at least one ophthalmological symptom that occurred at least once a week; 37 (94.9%) patients in the CG group and 35 (87.5%) in the STN-DBS group (p = 0.432). The median total VIPD-Q score (Q1–Q3) in both groups was 9.0 (5.0–14.0); 9.0 (6.0–16.0) in the CG group and 9.0 (4.0–14.0) in STN-DBS group (p = 0.312). The median score in the ocular surface was 4.0 (2.0–5.0); in CG it was 3.0 (2.0–5.0), and in STN-DBS it was 4.0 (2.0–6.0) (p = 0.933). In the intraocular domain, median score overall and in both groups separately was 2.0 (0.0–4.0) (p = 0.536). The median score in the oculomotor domain was 1.0 (0.0–3.0); in CG it was 1.0 (0.0–3.0) and in STN-DBS it was 1.0 (0.0–2.0) (p = 0.551). In the optic nerve domain, the median score was 1.0 (0.0–4.0); in CG it was 2.0 (0.0–4.0) and in STN-DBS it was 1.0 (0.0–3.0) (p = 0.096) (Tab. 2). The prevalence of the three symptoms differed significantly between the groups. Burning sensation or gritty feelings in the eyes occurred in six (15.4%) patients in the CG group and in 16 (40.0%) patients in the STN-DBS group (p = 0.015; 95% confidence interval (CI) for proportions difference: 5.7%–43.5%). The inability to read plain text on a coloured or grey background was present in 15 (38.5%) patients in the CG group and in six (15.0%) in the STN-DBS group (p = 0.018; 95%CI for proportions difference: –42.4% to –4.6%). Problems with rapid changes of light intensity occurred in 11 (28.2%) patients in the CG group and in four (10.0%) patients in the STN-DBS group (p = 0.039; 95%CI for proportions difference: –35.1% to –1.3%) (Fig. 1).

Considering both groups together, there was a significant positive correlation between VIPD-Q total score and UPDRS III (rho = 0.278, p = 0.013). In a separate analysis, a moderate correlation between VIPD-Q total score and UPDRS III was found only in the STN-DBS group (rho = 0.392, p = 0.012). Time from STN-DBS implantation moderately correlated with 'intra-ocular' and 'oculomotor' domains (rho = 0.327, p = 0.040, rho = 0.331, p = 0.037; respectively).

Table 1. Characteristics of study group

Parameter		All patients (n = 79)	CG (n = 39)	STN-DBS (n = 40)	P-value
Male, n (%)		46 (58.2%)	26 (66.7%)	20 (50.0%)	0.203
Age (years), median (Q1-Q3)		69.0 (60.0–73.0)	70.0 (60.0–73.0)	65.5 (60.0–71.8)	0.211
Disease duration (years), median (Q1-Q3)*		11.0 (7.0–16.0)	7.0 (5.0–11.0)	14.0 (11.5–19.5)	< 0.001
Subtype of PD**	Tremor dominant, n (%)	11 (14.7%)	7 (18.4%)	4 (10.8%)	0.703
	PIGD, n (%)	34 (45.3%)	16 (42.1%)	18 (48.6%)	
	Mixed, n (%)	30 (40.0%)	15 (39.5%)	15 (40.5%)	
LEDD (mg), median (Q1–Q3)		580.0 (410.0–760.0)	705.0 (535.0–1,360.0)	480.0 (380.0–618.8)	< 0.001
UPDRS part III, median (Q1-Q3)		16.0 (8.0–26.0)	18.0 (8.0–28.0)	14.0 (7.0–22.8)	0.247
Comorbidity, n (%)		70 (88.6%)	37 (94.9%)	33 (82.5%)	0.154
Dementia, n (%)		21 (26.6%)	15 (38.5%)	6 (15.0%)	0.023
Diabetes mellitus type 2, n (%)		11 (13.9%)	9 (23.1%)	2 (5.0%)	0.025
Coronary artery disease, n (%)		11 (13.9%)	6 (15.4%)	5 (12.5%)	0.711
Hypertension, n (%)		36 (45.6%)	22 (56.4%)	14 (35.0%)	0.056
Atrial fibrillation, n (%)		11 (13.9%)	5 (12.8%)	6 (15.0%)	0.780
Any medication for disease other than PD, n (%)		68 (86.1%)	36 (92.3%)	32 (80.0%)	0.210
Time from STN-DBS implantation (years), median (Q1-Q3)		–	–	3.5 (2.0-6.8)	–

*data available for 37 patients in CG group and 37 patients in DBS group;
**data available for 38 patients in CG group and 37 patients in DBS group
CG — control group; STN-DBS — subthalamic nucleus deep brain stimulation; PIGD — postural instability and gait disturbance; LEDD — levodopa equivalent daily dose; UPDRS III — Unified Parkinson's disease Rating Scale III

Table. 2. Overall and 4-domains VIPD-Q results

Domain	All patients (n = 79)	Controls (n = 39)	STN-DBS (n = 40)	P-value
Ocular surface, median (Q1–Q3) (95% CI)	4.0 (2.0–5.0) (4.0–5.0)	3.0 (2.0–5.0) (3.0–5.0)	4.0 (2.0–6.0) (3.0–5.0)	0.933
Intra-ocular, median (Q1–Q3) (95% CI)	2.0 (0.0–4.0) (2.0–3.0)	2.0 (0.0–4.0) (2.0–3.0)	2.0 (0.0–4.0) (2.0–5.0)	0.536
Oculomotor, median (Q1–Q3) (95% CI)	(0.0–3.0) (0.0–2.0)	1.0 (0.0–3.0) (0.0–2.0)	1.0 (0.0–2.0) (0.0–2.0)	0.551
Optic nerve, median (Q1–Q3) (95% CI)	(0.0–4.0) (1.0–2.0)	2.0 (0.0–4.0) (2.0–4.0)	1.0 (0.0–3.0) (1.0–3.0)	0.096
Total VIPD-Q score, median (Q1–Q3) (95% CI)	9.0 (5.0–14.0) (7.0–12.0)	9.0 (6.0–16.0) (7.0–13.0)	9.0 (4.0–14.0) (7.0–12.0)	0.312

Discussion

Our study is one of the first to compare ophthalmological symptoms in patients with PD treated with medications and STN-DBS. Patients treated with oral medication more often complained about two symptoms from the optic nerve domain, while one symptom from the ocular surface domain was more frequent in patients with STN-DBS.

Ophthalmological symptoms are common in patients with PD as has been shown by previous studies [5]. In our study, their prevalence reached over 91% without significant differences in the treatment type groups. This is higher than in the existing literature where the prevalence has ranged between 10% and 78% [6]. However, it is in line with the previously published studies using the VIPD-Q, which took into consideration a greater number of ophthalmological symptoms — there the prevalence reached 82% and 92% [8, 11].

There is only our previous study comparing ophthalmological symptoms in patients treated with DBS or with l-dopa [12]. However, only saccadic eye movements were analysed, showing better results in patients with DBS. The current study took into consideration a broad spectrum of ophthalmological symptoms.

Patients with STN-DBS experienced a burning sensation in the eyes more often than those in CG. Nevertheless, those

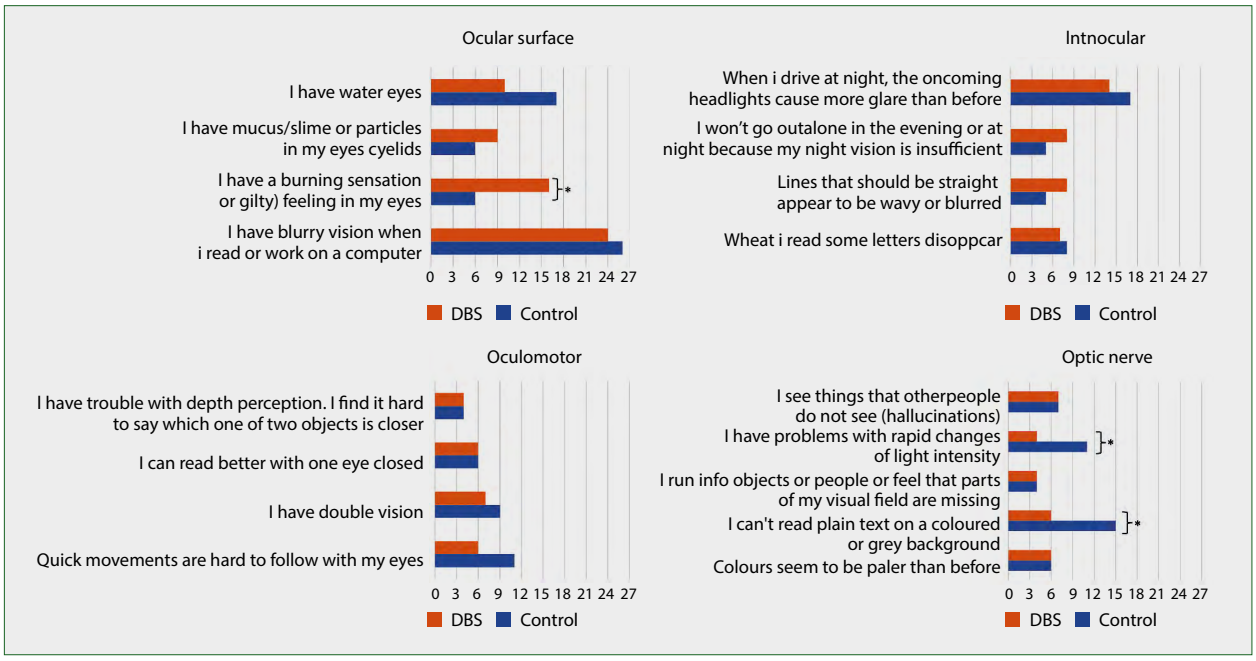

Figure 1. Prevalence of symptoms with division into domains. DBS — deep brain stimulation; *p < 0.05

results did not influence the median score of VIPD-Q domains, which showed no significant differences between groups. Dry eyes in PD are thought to result from a decreased blink rate, but they may also result from decreased tear production caused by autonomic dysfunction, based on the partial parasympathetic innervation of the lacrimal gland [5]. Bologna et al. revealed that the spontaneous blink rate increases after either STN-DBS or l-dopa [13]. Thus, we speculate that autonomic dysfunction and STN-DBS may have a pivotal role in decreased tears production in such patients. Moreover, a "burning sensation in the eye" may be considered, among others, an ocular adverse effect after STN-DBS in PD patients [14, 15].

Reduced contrast sensitivity, which is a common symptom in PD, is not yet fully understood [6]. A deficiency of retinal dopamine and impaired primary visual cortex function is thought to be involved [8]. Treating retinal and optic nerve pathology involves the optimisation of the l-dopa therapy [16]. The results of our study are contradictory. CG patients experienced an inability to read plain text on a coloured or grey background and difficulties with adaptation to rapid light changes significantly more often than STN-DBS patients. We suggest that this might be due to the impact of l-dopa or other antiparkinsonian medication (e.g. amantadine), especially since the CG group had a significantly higher LEDD. According to the literature, PD medications cause several adverse effects concerning the vision, such as mydriasis, miosis, and reduced accommodation [5]. Thus, antiparkinsonian medication may lead to adaptation difficulties [5]. In addition, the inability to read plain text on a coloured or grey background and difficulties with adaptation to rapid light changes had a lower prevalence in the STN-DBS group. That led us to speculate that STN-DBS positively impacted upon their prevalence. Moreover, this would be in line with the existing literature that shows that STN-DBS improves saccades as well as other more complex eye movements such as gaze holding or fixation [17].

Moreover, CG patients experienced fluctuations in ON and OFF states, commonly unpredictable in advanced condition. The evaluation of VIPD-Q was performed regardless of the ON or OFF condition, introducing a bias toward a more severe outcome. Symptoms may also result from PD itself, as has been shown in a previous study [18].

We demonstrated that the severity of ophthalmological symptoms weakly correlated with motor disability. Visual impairment in PD may be caused by the neurodegenerative process underlying PD itself [19, 20]. Considering the groups separately, a positive correlation between motor disability and VIPD-Q score was found in the STN-DBS group. Although patients suffered from motor symptoms of a similar severity (there was no significant difference in UPDRS part III between the groups), patients in the STN-DBS group had a significantly longer disease duration. This leads us to speculate that the degenerative changes in the brain were more severe in those patients. The literature shows that brain volume decreases with the duration of PD, and that the visual tract — especially the occipital lobe — is also affected [21].

We acknowledge that this study has several limitations, such as a small sample size. Patients completed the questionnaires on their own. Thus, even though they were given precise instructions, they could have made some mistakes.

Furthermore, patients might have overinterpreted their symptoms while reading them in the questionnaire.

Conclusions

We have confirmed that the prevalence of ophthalmological symptoms in PD is high. Although we found some significant differences regarding single symptoms between the methods, there were no significant differences in the overall prevalence of symptoms between the group treated pharmacologically and the group treated with STN-DBS. However, there was a significant correlation between UPDRS III and VIPD-Q total score, showing that motor severity is positively correlated with ophthalmological symptoms prevalence.

Clinical implications/future directions

Patients with PD should be regularly assessed ophthalmologically, especially in the advanced state as the symptoms might progress with disease duration. The detailed influence of STN-DBS on the optic tract should be further studied in order to establish the precise interaction.

References

1. Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008; 79(4): 368–376, doi: 10.1136/jnnp.2007.131045, indexed in Pubmed: 18344392.
2. Siuda J. Importance of non-motor symptoms in PD and atypical parkinsonism. Neurol Neurochir Pol. 2021; 55(6): 503–507, doi: 10.5603/PJNNS.a2021.0085, indexed in Pubmed: 34939662.
3. Figura M, Koziorowski D, Sławek J. Cannabis in Parkinson's disease - the patient's perspective versus clinical trials: a systematic literature review. Neurol Neurochir Pol. 2022; 56(1): 21–27, doi: 10.5603/PJNNS.a2022.0004, indexed in Pubmed: 34985112.
4. Biousse V, Skibell BC, Watts RL, et al. Ophthalmologic features of Parkinson's disease. Neurology. 2004; 62(2): 177–180, doi: 10.1212/01.wnl.0000103444.45882.d8, indexed in Pubmed: 14745050.
5. Ekker MS, Janssen S, Seppi K, et al. Ocular and visual disorders in Parkinson's disease: Common but frequently overlooked. Parkinsonism Relat Disord. 2017; 40: 1–10, doi: 10.1016/j.parkreldis.2017.02.014, indexed in Pubmed: 28284903.
6. Guo Li, Normando EM, Shah PA, et al. Oculo-visual abnormalities in Parkinson's disease: Possible value as biomarkers. Mov Disord. 2018; 33(9): 1390–1406, doi: 10.1002/mds.27454, indexed in Pubmed: 30311977.
7. Śmiłowska K, Wowra B, Sławek J. Double vision in Parkinson›s Disease: a systematic review. Neurol Neurochir Pol. 2020; 54(6): 502–507, doi: 10.5603/PJNNS.a2020.0092, indexed in Pubmed: 33300115.
8. Borm CD, Visser F, Werkmann M, et al. Seeing ophthalmologic problems in Parkinson disease: Results of a visual impairment questionnaire. Neurology. 2020; 94(14): e1539–e1547, doi: 10.1212/WNL.0000000000009214, indexed in Pubmed: 32161030.
9. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015; 30(12): 1591–1601, doi: 10.1002/mds.26424, indexed in Pubmed: 26474316.
10. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967; 17(5): 427–442, doi: 10.1212/wnl.17.5.427, indexed in Pubmed: 6067254.
11. Borm CD, Werkmann M, de Graaf D, et al. Undetected ophthalmological disorders in Parkinson's disease. J Neurol. 2022; 269(7): 3821–3832, doi: 10.1007/s00415-022-11014-0, indexed in Pubmed: 35262759.
12. Dec-Ćwiek M, Tutaj M, Gracies JM, et al. Opposite effects of l-dopa and DBS-STN on saccadic eye movements in advanced Parkinson's disease. Neurol Neurochir Pol. 2017; 51(5): 354–360, doi: 10.1016/j.pjnns.2017.06.002, indexed in Pubmed: 28669542.
13. Bologna M, Fasano A, Modugno N, et al. Effects of subthalamic nucleus deep brain stimulation and L-DOPA on blinking in Parkinson's disease. Exp Neurol. 2012; 235(1): 265–272, doi: 10.1016/j.expneurol.2012.02.004, indexed in Pubmed: 22366535.
14. Samborska-Ćwik J, Szlufik S, Migda B, et al. Carbohydrate metabolism and lipid profile in patients with Parkinson's disease with subthalamic deep brain stimulation. Neurol Neurochir Pol. 2022; 56(5): 441–450, doi: 10.5603/PJNNS.a2022.0060, indexed in Pubmed: 36102235.
15. Malek N. Deep brain stimulation in Parkinson's disease. Neurol India. 2019; 67(4): 968–978, doi: 10.4103/0028-3886.266268, indexed in Pubmed: 31512617.
16. Savitt J, Aouchiche R. Management of Visual Dysfunction in Patients with Parkinson's Disease. J Parkinsons Dis. 2020; 10(s1): S49–S56, doi: 10.3233/JPD-202103, indexed in Pubmed: 32741840.
17. Klarendic M, Kaski D. Deep brain stimulation and eye movements. Eur J Neurosci. 2021; 53(7): 2344–2361, doi: 10.1111/ejn.14898, indexed in Pubmed: 32643303.
18. Armstrong RA, Armstrong RA, Armstrong RA. Visual symptoms in Parkinson's disease. Parkinsons Dis. 2011; 2011(4): 908306–726, doi: 10.4061/2011/908306, indexed in Pubmed: 21687773.
19. Kuribara T, Enatsu R, Kitagawa M, et al. Neuroimaging and neurophysiological evaluation of severity of Parkinson's disease. J Clin Neurosci. 2020; 74: 135–140, doi: 10.1016/j.jocn.2020.02.006, indexed in Pubmed: 32070672.
20. Archibald NK, Clarke MP, Mosimann UP, et al. The retina in Parkinson's disease. Brain. 2009; 132(Pt 5): 1128–1145, doi: 10.1093/brain/awp068, indexed in Pubmed: 19336464.
21. Pieperhoff P, Südmeyer M, Dinkelbach L, et al. Regional changes of brain structure during progression of idiopathic Parkinson's disease - A longitudinal study using deformation based morphometry. Cortex. 2022; 151: 188–210, doi: 10.1016/j.cortex.2022.03.009, indexed in Pubmed: 35439717.

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 4, pages: 397–400
DOI: 10.5603/PJNNS.a2023.0003

ISSN: 0028-3843, e-ISSN: 1897-4260

Poor prognosis in paediatric haemorrhagic stroke

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Key words: haemorrhagic stroke, child, prognosis

(*Neurol Neurochir Pol 2023; 57 (4): 397–400*)

To the Editors

Stroke, increasingly recognised in children in recent years, is an important cause of long-term morbidity and disability. A wide range of conditions associated with paediatric stroke has been identified, which differ significantly from those in adults. Paediatric stroke can also present with a variety of symptoms and signs, both specific and non-specific [1, 2]. Paediatric haemorrhagic stroke (HS) is a rare but severe condition, with lifelong multifaceted adverse functional, psychosocial, and economic consequences [3].

In this study, we have evaluated the clinical, laboratory and neuroimaging findings in children with HS in order to draw attention to the high morbidity and mortality rates of paediatric HS.

Our study included 12 children with HS admitted to the Department of Paediatric Neurology, Necmettin Erbakan University, Turkey between January 2010 and January 2019. Paediatric HS has been defined as intracerebral haemorrhage, which is brain parenchymal bleeding with or without intraventricular extension, occurring between the ages of 29 days and 18 years [3]. For cerebral palsy, the insult to the brain is believed to occur between the time of conception and the age of two years, at which time a significant amount of motor development has already occurred. A similar injury to the brain after the age of two can have a similar effect however, and this is often also called cerebral palsy. By the age of eight, most of the development of the immature brain is complete, as is gait development, and an insult to the brain now will result in a more adult-type clinical picture and outcome [4]. Patient data for our study was obtained from a chart review of hospital records. Children who had a history of head trauma, a haemorrhage that was restricted to epidural, subdural, intraventricular or subarachnoid compartments, and children with both cerebral sinovenous thrombosis and haemorrhagic transformation were excluded from our study. The patients were evaluated for demographic characteristics, risk factors, and clinical, laboratory and neuroimaging findings including cranial computerised tomography and cranial magnetic resonance imaging, retrospectively.

Demographic, clinical and laboratory characteristics of the children with HS are set out in Table 1. The most common symptoms and the most common abnormal physical examination finding were headache and altered mental status, respectively. All patients except for one child had at least one risk factor. The most common risk factors were sepsis and thrombocytopenia. Haemorrhage on a single lobe was more common than haemorrhage on multiple lobes (Fig. 1). None of the patients except for one child had vascular imaging. Digital subtraction angiography showed an arteriovenous malformation (AVM) feeding from the left anterior cerebral artery in this child. HS recurred in two patients (15%). Four patients (33.3%) required evacuation of haematoma, and one patient (8.3%) underwent ventriculoperitoneal shunt because of hydrocephalus. Embolisation for cerebral AVM was performed in one patient. HS recurred in two patients (15%) with factor VII deficiency during their follow-up. Three and five HS attacks occurred in these patients, respectively. Three patients

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Received: 9.11.2022 Accepted: 22.12.2022 Early publication date: 20.01.2023

Table 1. Demographic, clinical and laboratory characteristics of children with haemorrhagic stroke

Characteristics*	N = 12 n (%)	Characteristics*	N = 12 n (%)
Age (months) [median (Q1–Q3)]	74 (3–128.5)	**Imaging methods**	
Gender		Computerised tomography	5 (41.6)
Female	7 (58.3)	Computerised tomography + magnetic resonance imaging	4 (33.3)
Male	5 (41.6)	Magnetic resonance imaging	2 (16.6)
Symptoms		Computerised tomography + digital subtraction angiography	1 (8.3)
Headache	6 (50.0)	**Lateralisation of haemorrhage**	
Nausea/vomiting	5 (41.6)	Right	5 (41.6)
Prone to sleep	4 (33.3)	Left	4 (33.3)
Restlessness	4 (33.3)	Both sides	3 (25.0)
Impaired consciousness	3 (25.0)	**Location of haemorrhage**	
Decrease in feeding	3 (25.0)	Single	
Convulsion	2 (16.6)	Parietal lobe	2 (16.6)
Focal numbness	1 (8.3)	Temporal lobe	2 (16.6)
Fainting	1 (8.3)	Frontal lobe	3 (25.0)
Physical examination findings		Subependymal	1 (8.3)
Altered mental status	8 (66.6)	Multiple	
Agitation/irritability	4 (33.3)	Frontal + parietal lobes	1 (8.3)
Left hemiparesis	1 (8.3)	Frontal lobe + temporal + parietal lobes	1 (8.3)
Risk factors/underlying diseases		Frontal lobe + subarachnoid	1 (8.3)
Thrombocytopenia	3 (25.0)	Temporal + occipital lobes	1 (8.3)
Sepsis	3 (25.0)	**Hospitalisation in paediatric intensive care unit**	
Factor VII deficiency	2 (16.6)	Yes	8 (66.6)
Vitamin K deficiency	2 (16.6)	No	4 (33.3)
Arteriovenous malformation	1 (8.3)	**Duration of hospitalisation (days) [median (Q1–Q3)]**	27 (10–66)
Afibrinogenemia	1 (8.3)	**Prognosis**	
Acute lymphoblastic leukaemia	1 (8.3)	Died	3 (25.0)
Disseminated intravascular coagulation	1 (8.3)	Survived without sequelae	1 (8.3)
Immune thrombocytopenic purpura	1 (8.3)	Survived with sequelae	8 (66.6)
Fanconi aplastic anaemia	1 (8.3)	Cerebral palsy	3 (37.5)
Renal tubular acidosis	1 (8.3)	Cerebral palsy + epilepsy	2 (25.0)
		Hemiparesis + epilepsy	1 (12.5)
		Hemiparesis	1 (12.5)
		Paraparesis	1 (12.5)

*One patient had more than one clinical and imaging characteristic

died from sepsis, disseminated intravascular coagulation, and severe haemorrhage, respectively. Nine patients were followed up for 37.6 ± 36.6 months (0.5–120 months). All of these patients, except for one, demonstrated at least one sequel, of which cerebral palsy was the most common. The ages of the patients with cerebral palsy at the time of stroke were 21.6 ± 17.8 months (2–33 months).

It has been reported that the most common symptoms in many series of childhood HS are headache, vomiting, and altered mental status [5–9]. Cerebral AVM has been reported as the most common cause of HS [7–9]. Yock-Corrales et al. [5] reported that seven patients (20.5%) had an AVM and five patients (14.7%) had a cavernous venous malformation, subarachnoid haemorrhage, and bleeding diathesis. The cause was not established in one third of the patients. In another series, haematological causes were identified in 26 (52%) patients and vascular malformations in seven (14%). No cause could be identified in 13 (26%) patients [6]. Gerstl et al. [7] reported that HS was caused by vascular malformations in more than half of patients. Other risk factors were brain tumour, coagulopathy, and miscellaneous severe underlying diseases. A known aetiology was identified in 121 (86.4%) patients and the leading cause of HS was AVM in 72 (51.4%) patients in another series [8]. In a systematic review, haemorrhages comprised 43% of all

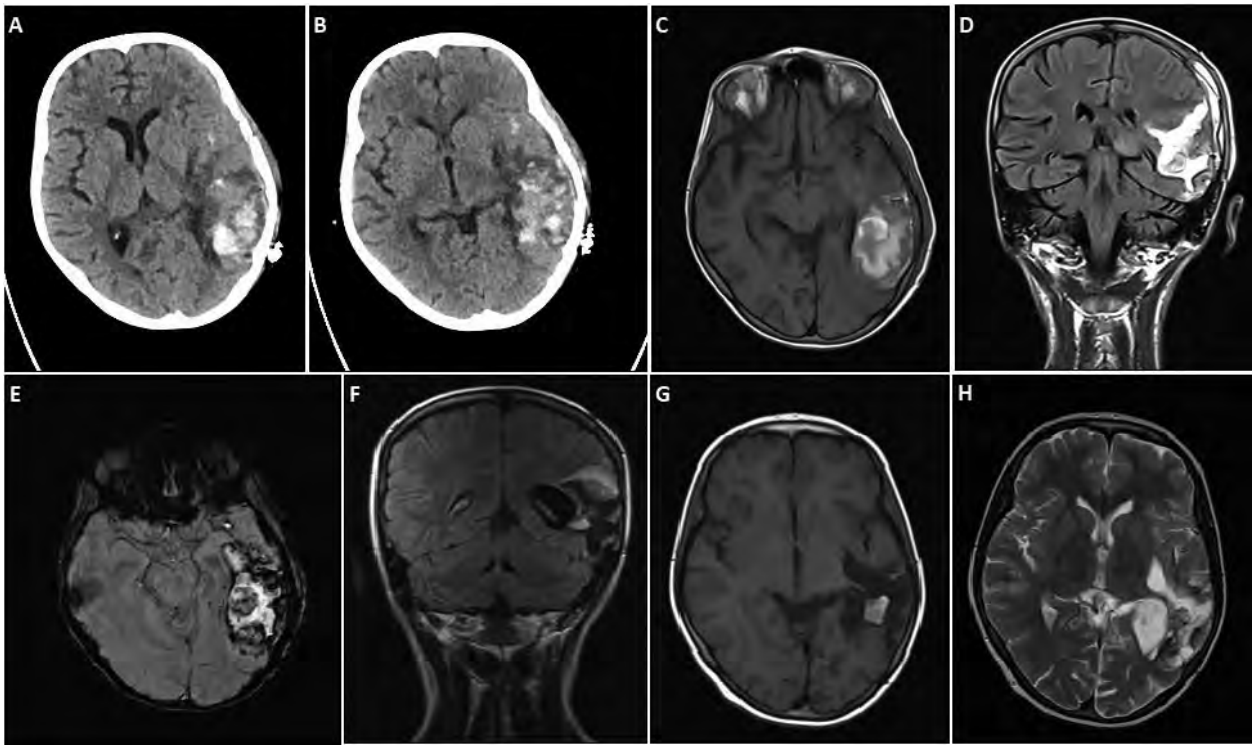

Figure 1. In a 12-year-old girl, cranial computerised tomography demonstrates acute haemorrhage in left temporal lobe (**A**, **B**). Fifteen days after evacuation of haematoma, axial T1-weighted and coronal fluid attenuated inversion recovery images show haemorrhage and haematoma (**C**, **D**). Axial susceptibility-weighted imaging shows haemorrhage in acute-subacute period (**E**). After 8 months, coronal fluid attenuated inversion recovery, axial T1-weighted, and axial T2-weighted, images show enlarged occipital horn of left lateral ventricle, porencephaly, and gliotic changes in cerebral parenchyma (**F**–**H**)

identified aetiologies or risk factors, with AVMs being the most common vascular cause (70.9% of all vascular causes). Haematological and systemic causes, brain tumours, intracranial infections, and cardiac causes were the less commonly encountered risk factors and aetiologies [10].

In line with the literature, the most common symptoms in our series were headache, nausea/vomiting, and altered mental status. All patients except for one had one or more risk factor. Sepsis and thrombocytopenia were the most common risk factors. However, in contrast to the literature, we found vascular malformation in one patient (8.3%) only. This low ratio is related to the fact that not all patients underwent vascular imaging.

HS is a serious condition that may require early surgical intervention in many patients. Of 50 patients with HS, 18 (36%) and three (6%) underwent neurosurgical intervention and vascular interventional radiology, respectively [6]. In another series including 25 children with HS, 17 (68%) required neurosurgical therapy. Neurological deficits were noted in 12 (48%) patients: hemiparesis ± facial palsy (n = 8), ataxia (n = 1), speech disturbance (n = 1), impaired short-term memory (n = 1), and multiple severe neurological sequelae (n = 1). No data was provided about the long-term outcome in this series [7]. Deng et al. [8] reported that neurological deficits occurred in 72.8% of patients with HS on discharge. The most common complications were epilepsy (17.1%) and hydrocephalus (12.1%). Early post-stroke rehabilitation strategies using, in addition to the daily rehabilitation programme, virtual reality therapy with visual biofeedback is more effective on upper extremity motor performance than is conventional physiotherapy, and their effectiveness does not diminish with patient age. This may represent a promising addition to conventional physiotherapy in older stroke patients, as well as in younger [11]. Although no death was noted in the series of Uzunhan et al. [12], mortality rates of up to 33.8% have been reported in paediatric HS [5–7, 13]. In our series, four (33.3%) children required evacuation of haematoma and one (7.5%) child underwent ventriculoperitoneal shunt due to hydrocephalus. Three patients (25%) died. During follow-up, neurological sequelae, mostly cerebral palsy, were diagnosed in eight (88.8%) of the nine patients who survived. Conventional physiotherapy was applied to the children with neurological sequelae.

In conclusion, our study showed that sepsis and thrombocytopenia were the most common risk factors in children with HS, and that paediatric HS had a poor prognosis with high morbidity (66.6%) and mortality (25%) rates. Therefore, we suggest that HS can be prevented by early diagnosis and treatment of the risk factors that lead to HS in a group of patients, and thus the prognosis of HS can be improved.

Conflicts of interest: *None.*
Funding: *None.*

References

1. Oborska Z, Urban P, Wychowaniec K, et al. Paediatric stroke - a review of current guidelines for diagnosis and treatment. Neurol Neurochir Pol. 2020; 54(2): 116–124, doi: 10.5603/PJNNS.a2020.0010, indexed in Pubmed: 31985031.
2. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the american heart association/american stroke association. Stroke. 2019; 50(12): e344–e418, doi: 10.1161/STR.0000000000000211, indexed in Pubmed: 31662037.
3. Boulouis G, Blauwblomme T, Hak JF, et al. Nontraumatic pediatric intracerebral hemorrhage. Stroke. 2019; 50(12): 3654–3661, doi: 10.1161/STROKEAHA.119.025783, indexed in Pubmed: 31637968.
4. Spence DD, Sheffer BW. Cerebral palsy. In: Azar F, Canale STW, Beaty J. ed. Campbell's Operative Orthopaedics. 14th ed. Elsevier, Amsterdam 2020: 1316–1368.
5. Yock-Corrales A, Varela-Bulgarelli F, Barboza C, et al. Presentation of acute childhood stroke in a tertiary pediatric emergency department. Pediatr Emerg Care. 2018; 34(8): 552–557, doi: 10.1097/PEC.0000000000000918, indexed in Pubmed: 27749807.
6. Abbas Q, Merchant QU, Nasir B, et al. Spectrum of intracerebral hemorrhage in children: a report from PICU of a resource limited country. Crit Care Res Pract. 2016; 2016: 9124245, doi: 10.1155/2016/9124245, indexed in Pubmed: 26881068.
7. Gerstl L, Badura K, Heinen F, et al. Childhood haemorrhagic stroke: a 7-year single-centre experience. Arch Dis Child. 2019; 104(12): 1198–1202, doi: 10.1136/archdischild-2018-316749, indexed in Pubmed: 31221624.
8. Deng Y, Liu G, Zhang G, et al. Childhood strokes in China describing clinical characteristics, risk factors and performance indicators: a case-series study. Stroke Vasc Neurol. 2022; 7(2): 140–148, doi: 10.1136/svn-2021-001062, indexed in Pubmed: 34862326.
9. Pangprasertkul S, Borisoot W, Buawangpong N, et al. Comparison of arterial ischemic and hemorrhagic pediatric stroke in etiology, risk factors, clinical manifestations, and prognosis. Pediatr Emerg Care. 2022; 38(9): e1569–e1573, doi: 10.1097/PEC.0000000000002614, indexed in Pubmed: 35113509.
10. Ciochon UM, Bindslev JB, Hoei-Hansen CE, et al. Causes and risk factors of pediatric spontaneous intracranial hemorrhage — a systematic review. Diagnostics (Basel). 2022; 12(6), doi: 10.3390/diagnostics12061459, indexed in Pubmed: 35741269.
11. Gueye T, Dedkova M, Rogalewicz V, et al. Early post-stroke rehabilitation for upper limb motor function using virtual reality and exoskeleton: equally efficient in older patients. Neurol Neurochir Pol. 2021; 55(1): 91–96, doi: 10.5603/PJNNS.a2020.0096, indexed in Pubmed: 33314016.
12. Uzunhan TA, Aydinli N, Çalişkan M, et al. Short-term neurological outcomes in ischemic and hemorrhagic pediatric stroke. Pediatr Int. 2019; 61(2): 166–174, doi: 10.1111/ped.13737, indexed in Pubmed: 30449056.
13. Lo WD, Hajek C, Pappa C, et al. Outcomes in children with hemorrhagic stroke. JAMA Neurol. 2013; 70(1): 66–71, doi: 10.1001/jamaneurol.2013.577, indexed in Pubmed: 23108798.

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 4, pages: 401–402
DOI: 10.5603/PJNNS.a2023.0043

ISSN: 0028-3843, e-ISSN: 1897-4260

Before blaming levodopa/carbidopa intestinal gel for demyelinating polyneuropathy, all differential aetiologies must be ruled out

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Key words: polyneuropathy, Parkinson, nerve conduction studies, demyelination, side effect

(*Neurol Neurochir Pol 2023; 57 (2): 401–402*)

To the Editors

We read with interest the article by Piekarski et al. featuring a 55-year-old male with Parkinson's disease (PD) of 16 years' duration who developed demyelinating polyneuropathy (dPNP) 12 weeks after the initiation of levodopa/carbidopa intestinal gel (LCIG) therapy, which was published alongside a review of 15 cases with LCIG-associated dPNP [1]. It was found that LCIG therapy was discontinued in all 15 cases with LCIG therapy-associated dPNP, and that only in the index patient was LCIG therapy maintained, and that he additionally received intravenous immunoglobulins (IVIGs) [1].

It was concluded that all PD patients scheduled for LCIG therapy should have nerve conduction studies (NCSs) performed prior to initiating LCIG, and that LCIG therapy should not be discontinued if dPNP develops, but should rather be combined with immunosuppressive treatment [1]. This study is compelling, but has limitations that should be discussed.

The main limitation of the case report and review is that alternative aetiologies of dPNP were not adequately ruled out in each of the included cases. Demyelinating large fibre neuropathy is generally due to an immunological disease, such as Guillain–Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), anti-myelin associated protein (MAG) associated neuropathy, nodopathies due to antibodies against neurofascin, POEMS syndrome, connective tissue disease, vasculitis, a hereditary disease such as Charcot-Marie-Tooth (CMT) disease, paraneoplastic conditions (e.g. gammopathies), or neoplastic conditions [2]. To diagnose these conditions, a comprehensive and costly work-up is necessary. However, to remain scientifically sound, all of these differentials must be 'off the table' before a toxic aetiology of dPNP in the enrolled patients can be considered.

A second limitation of the study is that GBS/CIDP following an infection with, or vaccination against, SARS-CoV-2 was not adequately ruled out. Since there is evidence that the virus and the vaccination against it can be complicated by polyradiculitis, and since this patient was reported during the pandemic and had dissociation cyto-albuminique on cerebrospinal fluid (CSF) examination, as did 10 of the 15 patients from the literature, it is crucial that this infectious or immunological cause of dPNP is ruled out.

A strong argument against LCIG therapy as the cause of dPNP in the index patient is that NCSs prior to the onset of LCIG therapy showed a moderate decrease of nerve conduction velocities in sural nerves, severe axonal neuropathy in both peroneal nerves, and mild reduction of conduction velocity and amplitude in both tibial nerves [1]. These results indicate that there was a combined demyelinating and axonal lesion already prior to the initiation of LCIG therapy. Thus, at best, LCIG therapy could have enhanced dPNP, but did not cause it.

We disagree with the statement that nerve conduction velocity in the tibial nerve was "previously intact" [1]. The NCS of the tibial nerves prior to the onset of LCIG therapy

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Received: 30.04.2023 Accepted: 10.05.2023 Early publication date: 19.07.2023

was described as mildly reduced [1]. This discrepancy needs to be resolved.

Another limitation of the study is that the current medication, in addition to LCIG, of the index patient and of the 15 patients from the literature was not provided.

Overall, this interesting study has limitations that put the results and their interpretation into perspective. Addressing these issues would strengthen the conclusions and could improve the status of the study.

Before blaming levodopa/carbidopa intestinal gel for dPNP, alternative aetiologies must be adequately ruled out.

Conflicts of interest: *None.*
Funding: *None.*

References

1. Piekarski R, Roszmann A, Dulski J, et al. Acute/subacute demyelinating polyneuropathy in Parkinson's disease patients on levodopa-carbidopa intestinal gel therapy: systematic review with new case report. Neurol Neurochir Pol. 2023; 57(2): 169–176, doi: 10.5603/PJNNS.a2023.0001, indexed in Pubmed: 36628506.
2. Finsterer J, Löscher WN, Wanschitz J, et al. Orphan Peripheral Neuropathies. J Neuromuscul Dis. 2021; 8(1): 1–23, doi: 10.3233/JND-200518, indexed in Pubmed: 32986679.

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 4, pages: 403–404
DOI: 10.5603/PJNNS.a2023.0045

ISSN: 0028-3843, e-ISSN: 1897-4260

Response to 'Before blaming levodopa/carbidopa intestinal gel for demyelinating polyneuropathy, all differential aetiologies must be ruled out'

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To the Editors

We thank the author of the Letter to the Editors entitled 'Before blaming levodopa/carbidopa intestinal gel for demyelinating polyneuropathy, all differential aetiologies must be ruled out' [1] concerning our article [2]. The author points out the need for thorough differential diagnosis in all Parkinson's disease (PD) patients treated with LCIG (levodopa/carbidopa intestinal gel), before identifying this medication as causing polyneuropathy (PNP).

We do agree that before making the diagnosis of Guillain–Barré syndrome (GBS)/chronic inflammatory demyelinating polyneuropathy (CIDP), all the differential diagnoses listed in this Letter to the Editors [1] should be excluded. This is crucial especially when considering the introduction of intravenous immunoglobulins (IVIG) treatment. Such a decision should always be made with great caution because the treatment itself is indicated only in a limited number of illnesses, is limited in its access, and generates high therapy costs. The authors of the referred papers on single cases usually make the diagnosis of GBS/CIDP-like neuropathies, which might suggest that the differential diagnostic was in fact performed. However, data from referred papers on the performed differential diagnosis is scarce and — as mentioned in this Letter to the Editors [1] — may be a limitation of this review. Nevertheless, we have made only a review of the existing literature and we have presented already published data.

The problem of GBS or CIDP following an infection or vaccination against SARS-CoV-2 might also be another limitation of the discussed review. However, despite the article being published in the SARS-CoV-2 pandemic period, all of the patients (including our patient) were diagnosed several years before the pandemic began.

Regarding our case report presented in the 'clinical vignette' with the pre-existing nerve damage, we were aware of this condition. However it was asymptomatic. Our patient did not suffer from any other illnesses except for PD and PD-related mild dementia, and only rivastygmine treatment was introduced shortly before the PNP diagnosis. Furthermore, no unequivocal conclusion on whether the LCIG caused the PNP was made in this particular case.

Patients with long-lasting Parkinson's disease (PD) are usually treated with high levodopa (LD) doses. It has been proven in previous papers [3] that PNP in PD may be related to high homocysteine levels and its neural toxicity may be triggered by LD therapy. This is usually of the axonal type, but in this paper [2] we discussed the far less common demyelinating type. As PNP due to LCIG therapy is common, it is easy to miss such a potentially treatable cause. We advise physicians to look carefully at the type of neuropathy and not to exclude patients from something that is usually a 'last chance' treatment of choice in advanced PD.

Our aim was to emphasise the possible demyelinating form on neuropathy; however, we agree that there was uncertainty as to whether this was LCIG-related or just a coincidence.

Again, the fact of limited access to detailed clinical data, i.e. that our paper was based on the available historical cases, was discussed at length in our paper. No unequivocal conclusions should be made upon such data, and no such conclusions were presented by us. We concluded that all patients starting LCIG therapy should be carefully examined (both clinically and electrophysiologically) to detect those at risk (with initially mild symptoms) of developing any type of neuropathy. Those patients should be thoroughly monitored during therapy. Indeed, this is routine procedure at our centre.

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Received: 05.07.2023 Accepted: 05.07.2023 Early publication date: 19.07.2023

Conflicts of interest: None.
Funding: None.

References

1. Finsterer J. Before blaming levodopa/carbidopa intestinal gel for demyelinating polyneuropathy, all differential aetiologies must be ruled out. Neurol Neurochir Pol. 2023 [Ahead of print], doi: 10.5603/PJNNS.a2023.0043.
2. Piekarski R, Roszmann A, Dulski J, et al. Acute/subacutae demyelinating polyneuropathy in Parkinson's disease patients on levodopa-carbidopa intestinal gel therapy: systematic review with new case report. Neurol Neurochir Pol. 2023; 57(2): 169–176, doi: 10.5603/PJNNS.a2023.0001, indexed in Pubmed: 36628506.
3. Szadejko K, Dziewiatowski K, Szabat K, et al. Polyneuropathy in levodopa-treated Parkinson's patients. J Neurol Sci. 2016; 371: 36–41, doi: 10.1016/j.jns.2016.09.061, indexed in Pubmed: 27871444.