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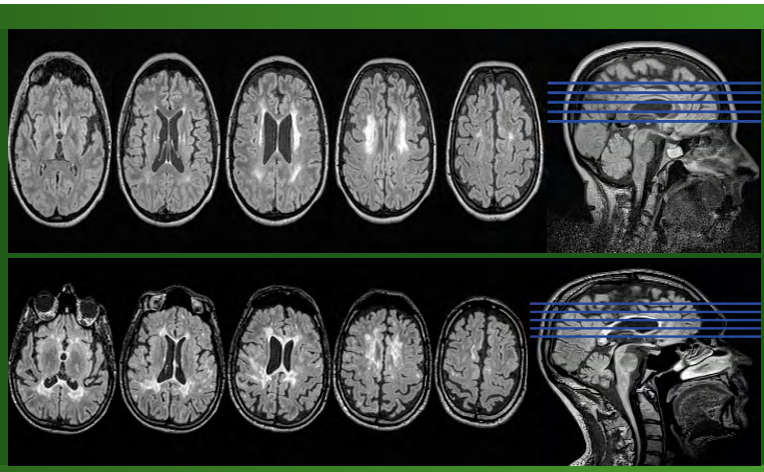

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Polyneuropathy and levodopa therapy in Parkinson's Disease: an evolving clinical challenge

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Parkinson's Disease (PD) is a progressive neurodegenerative disorder characterized by a combination of motor and non-motor symptoms that significantly impact the quality of life of patients [1–5]. Levodopa formulations with peripheral dopa decarboxylase inhibitors, such as benserazide or carbidopa, remain the gold standard treatment due to their effectiveness in replenishing striatal dopamine levels [6].

Traditionally administered orally, levodopa therapy has evolved to include intrajejunal and, more recently, subcutaneous delivery methods to better manage motor fluctuations and dyskinesias in advanced stages of PD [7].

An association between levodopa therapy and polyneuropathy was first observed in patients receiving high doses of oral levodopa [8]. The metabolism of levodopa and dopamine through catechol-O-methyltransferase leads to the production of homocysteine, a neurotoxic amino acid.

Remethylation of homocysteine back to methionine requires vitamin B12 and folate as essential cofactors. Alternatively, homocysteine can be converted to cystathionine through the transsulfuration pathway, which requires vitamin B6. In PD patients, increased levodopa intake elevates homocysteine levels, potentially depleting these vitamins and leading to deficiencies in folic acid, and vitamins B6 and B12 [8]. Elevated homocysteine levels and vitamin deficiencies have been implicated in the development of polyneuropathy. However, it remains unclear whether these factors alone or other mechanisms are primarily responsible for the neuropathy, suggesting a multifactorial etiology [9].

With the advent of levodopa-carbidopa intestinal gel (LCIG), concerns about polyneuropathy have resurfaced [10, 11]. Unlike the predominantly chronic and sensory polyneuropathy observed with oral levodopa intake [12], patients receiving LCIG can develop acute, subacute, and chronic neuropathic symptoms. The acute form is particularly concerning, as it is often disabling and leads to discontinuation of therapy. In the original paper by Havránková et al. [13] published in this issue, the authors report findings from a multicentre study examining the association between LCIG and acute polyneuropathy. They retrospectively evaluated 183 patients treated with LCIG across seven Czech and Slovak movement disorder centers and identified acute polyneuropathy in six patients. Discontinuation of LCIG in all six patients resulted in stabilization or improvement of their neuropathic symptoms.

Havránková et al. suspected two mechanisms involved in the pathophysiology of acute polyneuropathy in LCIG-treated patients: inherited (genetic) and acquired (e.g. autoimmune factors post-infection) predispositions, and the potential toxic effects of high doses of LCIG on the jejunum or directly on the peripheral nervous system [13].

The genetic landscape of both familial and sporadic PD is continuously evolving, and it is likely that certain genetic variants may influence an individual's susceptibility to developing polyneuropathy [14]. Genetic factors could modulate individual responses to levodopa and its metabolites, influencing the risk of neuropathy development. For example, polymorphisms in genes involved in homocysteine metabolism could predispose patients to higher homocysteine levels [15].

Furthermore, neuropathy could be related to autoimmune mechanisms, as seen in other autoimmune diseases that manifest with neuropathic symptoms [16]. Immune activation following infections could lead to an autoimmune response targeting peripheral nerves, resulting in neuropathy. Recently, attention has been given to atrophy of the vagus nerve in PD patients; however, whether this is part of the

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neurodegenerative process or secondary to other insults is still unclear [17]. Some authors have argued that other causes have not been adequately ruled out, suggesting that sporadic diseases such as Guillain–Barré syndrome or chronic inflammatory demyelinating polyneuropathy could be contributing to the observed phenomena [18]. Lastly, the medication formulations for LCIG include additional ingredients, such as methylcellulose, which may have an impact on the gut microbiota and could potentially induce inflammatory bowel disease, thus indirectly affecting the nervous system [19].

It is important to note that in most patients, therapies with oral, intrajejunal, and subcutaneous levodopa formulations are well tolerated, and adverse effects are generally manageable. Supplementation with folic acid, vitamin B6 (not exceeding 25 mg per day), and vitamin B12 (avoiding cyanocobalamin in cases of renal impairment) is relatively safe in most cases, and can help mitigate neuropathy associated with hyperhomocysteinemia [8]. However, more information is needed to fully understand the mechanisms underlying acute polyneuropathy in patients treated with LCIG and to develop effective strategies for prevention and management. The introduction of subcutaneous foslevodopa/foscarbidopa as a novel treatment option adds another layer of complexity, as the frequency and risk of polyneuropathy associated with this therapy remain to be estimated.

Prospective studies involving larger cohorts and systematic monitoring of nutritional status, genetic factors, and immune markers are needed. Such research could provide valuable insights into the pathophysiology of neuropathy in PD patients and inform clinical practice to enhance patient outcomes. Addressing these gaps will be essential for optimising levodopa intrajejunal and subcutanous therapies and minimising their potential adverse effects.

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INVITED EDITORIAL

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Sinus headache — migraine or sinusitis?

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A sinus headache as a symptom of sinusitis is quite commonly diagnosed, despite the fact that specialists, especially otolaryngologists, consider this pain to be relatively rare [1]. It seems, therefore, that migraine, and perhaps other types of headache, are sometimes confused with headache of sinus origin. Why is this the case?

Nasal symptoms often accompany migraine, although these symptoms are not part of the International Headache Society (IHS) diagnostic criteria for migraine [2]. Parasympathetic activation, as well as neurogenic and immunogenic inflammatory mechanisms, to some extent explain the frequent occurrence of nasal symptoms in migraine. On the other hand, acute sinusitis itself can be a trigger for migraine headache in migraine patients. It should therefore be emphasised that the presence of nasal symptoms as well as the localisation of pain in the sinus cast should neither *a priori* result in the diagnosis of sinusitis nor exclude the diagnosis of migraine.

In fact, it should lead to the consideration of the diagnosis of both conditions. In the American Migraine Study II, it was shown that many people diagnosed with migraine had previously thought that they were suffering from a sinus headache. Out of the nearly 30,000 participants in the study, only roughly half who were eventually diagnosed with migraine knew they were suffering from it before the study. And the most common misdiagnosis for them was sinus headache [3].

Headache and rhinosinusitis are the two most common reasons why patients visit doctors. Rhinosinusitis affects more than 30 million adults in the United States each year for example [4]. As already mentioned, pain of sinus origin is over-diagnosed, yet on the other hand, pain resulting from sinusitis (especially sphenoid) is frequently not diagnosed promptly, leading to poor treatment outcomes because it has been delayed [5]. Understanding the appropriate management of suspected rhinosinusitis, and the diagnostic criteria for headache attributed to rhinosinusitis, is essential for diagnosis and treatment.

The International Classification of Headaches (ICHD-3) lists secondary headaches in the course of acute, chronic or recurrent sinusitis as causes of sinus pain. This classification does not mention migraine pain as a cause of sinus pain [2]. Meanwhile, according to some studies, primary migraine pain should be considered as an alternative diagnosis. One study showed that among patients with sinus headache and no sinusitis on imaging, more than 80% of them had a significant reduction in headache after the use of triptans [6]. In another study, patients with headache in the sinus were treated with a 'migraine' dose of amitriptyline, which had an effect in half of them [7]. A large study by Schreiber et al. found that of patients complaining of pain and a spreading sensation in the sinus cast (without fever) and a blocked nose, 88% met the criteria for migraine [8].

Studies conducted following the outbreak of the SARS-Cov2-19 pandemic show that the migraine phenotype was far more common than facial (sinus) pain among people with SARS-Cov2 infection, and was associated with a more severe course of infection. There is also evidence that migraine-like headache in COVID-19 is associated with pre-existing migraine [9].

A lack of understanding of how migraine can mimic sinusitis, the lack of a distinct name for migraine pain in the sinus location, and finally the absence of diagnostic criteria and a standard of treatment can together lead to inadequate patient care, and especially the overuse of antibiotics. It should also be underlined that the efficacy of antibiotics in the treatment of sinusitis is generally low [10].

Very simple tools, e.g. the ID Migraine Questionnaire, are useful and effective in this type of differential diagnosis [11]. A good collaboration between the neurologist and the otolaryngologist is also helpful.

In the current issue of 'Polish Journal of Neurology and Neurosurgery', you will find a very interesting article in which the authors present the most common headache phenotypes

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occurring during upper respiratory tract infections [12]. They point out that the differences in the incidence of sinus pain (facial pain) and migraine-like or tension headache depend on the viral aetiological agent, as well as on the immunocompetence status (i.e. the protective role of vaccination). The authors also discuss the need for criteria for headaches dependent on viral aetiological agents. Does this make sense? So far, the answer to this question is 'not entirely'.

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REVIEW ARTICLE

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Facts and myths about aggressive relapsing-remitting multiple sclerosis — current state of knowledge and future perspectives

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ABSTRACT

Multiple sclerosis is a demyelinating disease of the central nervous system (CNS), and the most common cause of neurological disability in young adults. Thanks to years of intensive research, the disease can now be largely controlled by disease-modifying treatment (DMT), of which the mode of action is mostly immunomodulatory and/or immunosuppressive. For years, balancing the benefits and risks of DMT by escalating only after a suboptimal response has been the recommended course of action. However, this approach may be insufficient, especially in a subset of patients with aggressive disease course and rapid accrual of disability. Currently, highly effective therapies (HET) are often recommended as first-line treatment, even for patients with relatively good prognostic factors. This is debatable given the relatively higher risks, and costs, associated with HET. Therefore, establishing the true risk of aggressive MS course would aid clinicians in balancing the benefit-risk ratio for individual patients. The aim of this narrative review was to summarise and evaluate research on aggressive multiple sclerosis, with a special focus on the most relevant findings and identifying gaps in our knowledge in this field.

Keywords: multiple sclerosis, aggressive multiple sclerosis, disease-modifying treatment

(*Neurol Neurochir Pol 2024; 58 (6): 548–556*)

Introduction

Multiple sclerosis (MS) is a common cause of neurological disability in young adults. Even though years of research have brought us closer to understanding the aetiology of MS-related central nervous system (CNS) damage, there are still unanswered questions [1]. The pathology behind the process consists of both inflammatory autoimmune-mediated demyelination, and neurodegeneration [2, 3]. Whether degeneration starts from the beginning of the disease or if it is rather a direct result of neuroinflammation remains uncertain. This uncertainty is of great importance regarding the design of an effective therapeutic regimen [4].

Relapsing-remitting multiple sclerosis (RRMS), which is the most common MS course, is treated with disease-modifying therapies (DMTs), the mode of action of which is mostly immunomodulatory and/or immunosuppressive. DMTs can be divided into two groups depending on their efficacy and safety profile, namely into moderate efficacy (typically with a better safety profile) or high efficacy treatment (HET, typically with a more challenging safety profile) [5]. The traditional approach was to start newly diagnosed (usually termed treatment-'naive') MS patients on moderate efficacy DMTs as a first-line treatment and, in cases of its insufficiency in controlling the disease (such as breakthrough relapses or new magnetic resonance imaging, MRI, activity), escalating to second-line, high efficacy DMTs [6]. Although this approach seems to balance the benefits and risks well for some patients, in a proportion of patients it may be suboptimal, especially those with an aggressive disease course resistant to standard treatment protocol, and who are accumulating disability faster [7, 8].

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In patients with aggressive MS (aMS), the window of opportunity for efficiently modifying the course of the disease is narrower than in standard MS patients. After a certain period of immune-mediated damage, the threshold is crossed. Beyond that point, the progression of neurological disability accumulates in spite of treatment [9]. This has sparked a debate on our understanding of the pathology of sustained disability in multiple sclerosis, the prediction of long-term outcomes, and of therapeutic strategies.

Currently, two large, prospective, randomised clinical trials, namely TREAT-MS (Traditional versus Early Aggressive Therapy for MS, NCT03500328) and DELIVER-MS (Determining the Effectiveness of Early Intensive versus Escalation Approaches for the Treatment of Relapsing–Remitting MS, NCT03535298) are in progress. They are designed to verify whether HET from the beginning (an early intensive/aggressive approach) would be more useful than the traditional/escalatory approach. However, in recent years, growing evidence has been suggesting that MS should be treated with a high-efficacy regimen from the beginning, unless there are contraindications to such an intensive treatment approach [9–12].

While we await definitive results of clinical trials, it is very important to be able to identify patients who are at risk of aMS course, as this population requires highly individualised and highly effective treatment, with careful monitoring and zero tolerance for any disease activity [13].

In this review article we examine some of the facts and myths regarding aMS that should be useful for both MS clinicians and researchers in designing their therapeutic and scientific strategies, respectively.

MYTH 1: *The definition of aggressive multiple sclerosis course is unified, and means rapidly evolving, severe MS.*

The lack of consensus regarding the definition of aggressive multiple sclerosis stems from ambiguous nomenclature in the literature over the years. Aggressive multiple sclerosis should not be confused with fulminant multiple sclerosis, which is a subtype of the disease characterised by rapid progression, often fatal within a short period, or tumefactive MS, in which large, tumour-like lesions occur in the CNS [14].

The term 'aggressive multiple sclerosis' was first used by Menon et al., who divided it into three groups: 'Patient who reached an EDSS of 6.0 within five years from onset' (AMS1); 'Patient who reached an EDSS ⩾ 6.0 at age 40' (AMS2); and 'Patients who entered SPMS phase within three years after rMS onset' (AMS3) [15]. The same definition as for AMS1 was previously used by Gholipor et al. in 2011 in describing 'ever-malignant MS' [16].

The term 'malignant multiple sclerosis' was coined in 1996 in a work by Lublin et al. describing „a disease with a rapid progressive course, leading to significant disability in multiple neurologic systems or death in a relatively short time after disease onset" [17].

A term close to aMS is "highly active multiple sclerosis": this was first used by Saccardi et al. in 2012, who defined it as a „failure of conventional treatment and ⩾1 severe relapses and/or incomplete recovery from clinically significant relapses and ⩾1 Gd+ lesion of diameter ⩾ 3mm or accumulation of ⩾ 0.3 T2 lesions/month in two consecutive MRIs 6–12 months apart" [18]. The term 'aggressive MS' would appear to be a broader one than 'highly active MS', since patients may experience progression independent of relapse activity (PIRA) [19].

PIRA is one of the two mechanisms explaining disability accumulation in patients with MS. While relapse-associated worsening (RAW) was already well established, so-called 'silent progression' was first studied as recently as 2019 by Cree et al., who concluded that long-term disability worsening is independent of relapses and associated with brain atrophy [20, 21].

The 2018 ECTRIMS Workshop Group focused on aMS and the urgent need to create a universal definition of this course of multiple sclerosis, but unfortunately was unable to provide one. The Working Group highlighted the significance of further research and creating a unified, evidence-based definition for early recognition [22]. Since then, Malpas et al. and Tintore et al. have defined aMS as "reaching an EDSS ⩾ 6.0 within 10 years of disease onset" [23, 24].

The definitions proposed to date require long-term observations that allow the retrospective recognition of aggressive multiple sclerosis, perhaps after crossing the threshold point for disability accrual. That puts the pressure on researching factors that contribute to developing aMS, predict long-term disability and, in the clinical setting, on careful screening for potential aMS patients.

It is important to keep as low as possible the threshold for qualifying MS as aggressive, and, in cases of patients suspected of aMS, to start a watchful observation.

MYTH 2: *Aggressive MS course is defined by ambulation.*

One of the misconceptions of aMS is that it only includes patients who need ambulation aids due to severe walking disability. The milestone EDSS set for aMS definition being ⩾ 6.0 actually narrows the diagnosis to patients who reach it in a predefined, and relatively short, period of time [23]. Aggressive multiple sclerosis should be also considered in cases of rapidly progressing disease, even before reaching EDSS 6.0. Indeed, it has been proven that an at least 2.0-point increase in EDSS resulting in EDSS ≥ 4.0 is a risk factor for reaching severe disability [25].

An aggressive MS course may also be marked by a failure to respond to treatment, especially multiple treatments, and by rapid accumulation of new T2 lesions and/or gadolinium-enhancing lesions in consecutive MRIs [26]. Another marker of aMS is a high brain atrophy rate, both global and regional, especially thalamic and cortical [27].

MYTH 3: *All patients with relapsing-remitting multiple sclerosis have the same risk of irreversible disability.*

Certain clinical features suggest that MS patients are at risk for an aggressive disease course. According to research, aMS can be identified in 4–14% of RRMS patients [16]. Most of our knowledge in this matter is based on retrospective studies evaluating progression in MS over the long term.

Male sex and older age at disease onset (i.e. > 35 or > 40 years) have been shown to correlate with both more advanced disability in the future and earlier conversion to secondary progressive MS (SPMS) [28]. Similar observations were previously reported in studies regarding the natural history of MS [29]. In an Argentinian study focused on patients with an aggressive form of the disease, the authors identified the following risk factors at the initial clinical presentation of MS: male sex, older age at symptom onset, multifocal presentation, primary progressive (PPMS) phenotype, and spinal cord and brainstem lesions on MRI [30].

Analysing early disease course is also beneficial in recognising patients who may develop aMS: multifocal attacks with incomplete recovery, and attacks affecting motor, cerebellar and sphincter functions, all suggest the risk of aMS [31, 32].

In a study analysing prodromal symptoms in MS, Kania et al. found that urinary and cognitive disturbances in the years preceding an MS diagnosis were significantly more common in patients with the highest annual EDSS increase, which further confirms that an early disease course profile can be predictive of further worsening [33, 34].

Frequent relapses in the first 2–5 years, with short inter-attack intervals, are also associated with poor outcomes and reaching disability faster [35, 36].

The pivotal study by Scalfari et al. confirmed that the risk of entering the secondary progressive phase is not related to the total number of attacks during the RR phase of MS, but rather that rapid disability accrual is associated with early relapse frequency in the first two years [37]. This observation makes early recognition of such patients vital in preventing future disability.

FACT 1: *There are a number of radiological findings that are considered negative prognostic factors, and could indicate a high risk of an aggressive MS course.*

The investigation of characteristics typical for patients with poor MS outcomes goes further than the clinical features and neurological examination. In recent years, studies have focused on searching for tell-tale signs on MRI. Tintore et al. found that in a cohort of patients with clinically isolated syndrome (CIS), a higher number of T2 lesions at baseline was associated with the risk of earlier irreversible disability and fulfilling the criteria for aggressive multiple sclerosis in the future in a follow-up study (defined as reaching an EDSS of 6 within 10 years) [24]. In a 15-year observational study, baseline spinal cord lesions and gadolinium-enhancing lesions were associated with RRMS conversion to secondary progressive MS (SPMS) [38].

In T1 images in MRI, the presence of hypointense lesions, sometimes called 'black holes', correlates with disability in MS, and furthermore in SPMS patients the rate of progression is related to the rate of accumulation of T1 black holes [39].

The latest research has presented brain volume atrophy as an important factor driving accumulation of disability [40]. Loss of brain volume seems to be connected with expanding chronic lesions, which are called smouldering or slow-burning lesions. Early atrophy, smouldering lesions, deep grey matter, and cortical and spinal cord atrophy are all factors correlated with worse outcomes in multiple sclerosis [41, 42].

Spinal cord atrophy is one of the earliest signs of brain atrophy, as its annual rates are greater, and its magnitude correlates with disability in MS [43].

Importantly, brain volume loss not only predicts EDSS worsening, but is a negative predictive factor of future cognitive performance [44, 45].

Paramagnetic rim lesions (PRLs) are MRI findings specific to MS that indicate chronic inflammation [46]. Their characteristic paramagnetic rims visualised on susceptibility-weighted imaging sequences are evidence of accumulation of iron in microglia/macrophages at the edges of the lesion [47]. Research by Borrelli et al. shows that PRLs at baseline correlate with PIRA at 2-year follow up [48]. The presence of both PRLs and cortical lesions are also predictive of higher disability and more severe MS [49–51].

FACT 2: *Blood and cerebrospinal fluid (CSF) biomarkers could help identify patients at risk for aMS.*

The most commonly applied and typical findings in cerebrospinal fluid in MS patients are IgG oligoclonal bands, which are detected in 80–90% of patients, and confirm intrathecal synthesis of antibodies within the CNS [52]. They are a strong predictor of developing clinically definite MS in patients with radiologically isolated syndrome (RIS) [53].

However, they are not correlated with patient prognosis regarding the future disease course. Type IgM oligoclonal bands have been shown to correlate with both short-term (occurrence of the next relapse) and long term outcomes in MS (severe disability in the first years of MS) [54, 55]. Another closely related factor involves lipid specific IgM oligoclonal bands – a subset that has been shown to predict MS prognosis even more precisely and to correlate with brain atrophy and lesion load [56–58]. A number of innovative blood and serum markers of CNS destruction, including NfL, GFAP, CHI3L, have emerged in recent years. They show great potential in predicting disease course, especially when used in combination, even earlier than when judged by clinical findings.

Neurofilament (Nfl) protein is a structural protein of neurons that, in cases of neuronal and axonal damage, is released into extracellular space. It has thus been used as a marker of axonal damage. Its subunit neurofilament light chain can be detected in cerebrospinal fluid (CSF) and serum of patients with MS [59, 60]. Cantó et al. proposed serum Nfl

Table 1. Characteristics of aggressive relapsing-remitting multiple sclerosis

Clinical	Radiological	Laboratory
Male sex	Higher number of T2 lesions at baseline	IgM oligoclonal bands
Older age at disease onset (> 35 or > 40 years)	Baseline spinal cord lesions	LS OCB
Multifocal presentation	Baseline gadolinium-enhancing lesions	NfL increase
Incomplete recovery after relapses	T1 black holes	GFAP increase
Attacks affecting motor, cerebellar and sphincter functions	Deep grey matter, cortical and spinal cord atrophy	CHI3L increase
Early relapse frequency in the first two years	Cortical lesions	
	PRLs	

LS OCB — lipid specific oligoclonal bands; NfL — neurofilament light; GFAP — glial fibrillary acidic protein; CHI3L — chitinase-3-like protein 1; PRLs — paramagnetic rim lesions

(sNfl) as a biomarker of disease activity in multiple sclerosis, because in a 12-year observation, serum neurofilament light chain levels were associated with brain atrophy and disability worsening [61]. Barro et al. recently confirmed that sNfl levels were a predictor of future brain atrophy [62]. Increased sNfl concentration also correlates with contrast enhancing, with new or enlarging lesions, and with clinical relapses, and is predictive of future EDSS worsening [63–65].

Chitinase 3-like 1 (CHI3L1), also known as YKL-40, is a protein produced mainly by macrophages and astrocytes and has recently been proposed as a promising marker of disease progression in MS. Higher levels of CHI3L1 in the CSF correlate with EDSS in PPMS [66]. Canto et al. analysed CSF levels of CHI3L in patients with CIS, and concluded that elevated levels of this protein are useful in predicting MS development in patients with CIS — the levels correlated with shorter time to MS and more rapid development of disability, which confirmed a previous report by Comabella et al. [67, 68].

A study taking into consideration all three of the abovementioned markers was conducted by Fissolo et al. to determine the use of sGFAP, sNfL and sCHI3L1 as biomarkers in PPMS. They found that the levels of the three proteins were associated with EDSS changes, but in patients with no clinical or radiological signs of disease activity, only sCHI3L1 levels predicted EDSS increase [69].

Glial fibrillary acid protein (GFAP) is a cytoskeletal protein highly expressed in astrocytes, the serum levels of which are used as a biomarker in MS. GFAP, unlike NfL, does not increase during relapses, but has been shown to be a prognostic factor of worse outcomes [70]. Abdelhak et al. found elevated serum GFAP levels in patients with higher disease severity scores and higher counts of MRI lesions [71]. GFAP also correlates with the count of slowly expanding lesions (SEL) [72]. Meier et al. reported that increased GFAP is prognostic of progression independent of relapse activity (PIRA) [73]. This confirms that elevated GFAP could be a marker of chronic smouldering inflammation causing PIRA.

PIRA was investigated by the MAGNIMS Group to see if it could explain the accumulation of disability in the absence of relapses. The Group concluded that increasing disability status within a relapse-free timeframe may be due to chronic inflammation, pathologically defined by: chronic active lesions (slowly expanding lesions, smouldering and paramagnetic rim lesions), persistent leptomeningeal enhancement and neurodegeneration, cortical lesions, atrophy of the grey matter in the brain and spinal cord, and damaged white matter tracts. They also concluded that PIRA could be associated with microglial activation [74]. Importantly, microglia are not directly targeted by any DMTs approved for MS, which could explain the fact that even HET are not especially effective with regards to PIRA.

Further research regarding this newly described phenomenon might help the understanding of the biology behind disability accumulation in aMS and the design of treatment focused on chronic inflammation. Several studies including Bruton's tyrosine kinase inhibitors (BTKis), which have an impact on macrophage population, are already in progress [75].

High-dimensional flow cytometry and serum proteomics have been used by Gross et al. to distinguish between different phenotypes of MS and their relationship with the response to treatment, proving that patients who fall into distinct endophenotypes respond differently; in particular, endophenotype 3 patients treated with interferon-β had higher MRI activity and disease progression than those treated with other agents [76].

Immunopathological subtyping has also been done in biopsy-confirmed MS lesions and although Tobin et al. confirmed the presence of three distinct immunopatterns, no differences in long-term outcomes were found. In patients with pathologically-confirmed multiple sclerosis, an early aggressive course, even with tumefactive lesions, does not alter the long-term prognosis [77].

Genetic determinants behind multiple sclerosis severity have also been analysed — The International Multiple Sclerosis Genetics Consortium and MultipleMS Consortium found an association between rs10191329 (DYSF-ZNF638) variant and age-related MS severity, although this finding is yet to be replicated in further studies [78].

FACT 3: *Early intensive disease modifying therapy is crucial for patients with aggressive multiple sclerosis.*

Implementing effective treatment from the beginning of the disease seems extremely important, especially in patients with aMS, since disability accumulation through frequent

relapses with incomplete recovery in the first years is predictive of higher long term disability.

Since the critical timeframe identified by Scalfari is the first two years of the disease, and since the relapses within them are responsible for long-term disability accrual, shifting to high efficacy medication later might not save patients from reaching a higher disability status [37]. This information is especially important in those most vulnerable to aMS, and the focus should be on implementing effective treatment to lower the odds of reaching substantial disability.

The benefits of early aggressive therapy have been assessed by Brown et al., who compared the risk of conversion to SPMS in patients on different medications. They found that initial treatment with HET, namely fingolimod, alemtuzumab, or natalizumab, was associated with a lower risk of conversion to secondary progressive MS vs. initial treatment with platform therapies, namely glatiramer acetate or interferon beta [79].

To assess whether early HET is more beneficial in reducing disability, He et al. conducted an observational, retrospective analysis of patients who started high-efficacy therapies within two years of disease onset and of patients who started 4–6 years after disease onset. Based on their EDSS scores after 6–10 years, the authors concluded that patients who started high efficacy treatment earlier had better outcomes than the matched cohort [80]. This confirmed previous findings by Harding et al., who researched 5-year EDSS changes and time to sustained accumulation of disability in patients on early intensive therapy versus escalation therapy [81].

The outcomes of long term treatment with a high-efficacy anti-CD20 antibody, namely ocrelizumab, as a first-line medication were recently presented as part of the OPERA trial, which has shown that patients treated with ocrelizumab early after the onset of the disease compared to those who switched from IFN beta 1A have a better chance of achieving no evidence of disease activity (NEDA) and of reduced disability outcomes [82]. Similarly, in the ASCLEPIOS clinical trials, treatment with another anti-CD20 antibody, ofatumumab, was associated with a lower relapse rate than treatment with teriflunomide [83]. Other high efficacy agents include cladribine, the efficacy of which in highly active multiple sclerosis was recently tested in the MAGNIFY-MS study, wherein de Stefano et al. found cladribine use reduced active MRI lesions counts [84]. A selective S1PR1 and S1P5 modulator more recently approved for treatment in MS, ozanimod, was compared to interferon β-1a during the SUNBEAM and RADIANCE clinical trials, where it reduced annualised relapse rates. Gadolinium-enhancing and new and enlarging T2 lesions counts were also significantly lower in ozanimod-treated patients [85, 86].

In recent years, clinical trials have been launched comparing high efficacy medication to moderate efficacy DMT. TREAT-MS is an ongoing, randomised controlled trial evaluating the effect of early aggressive therapy in patients with a high risk of disability accumulation compared to the traditional approach [87]. DELIVER-MS is a study designed to assess the efficacy of starting on highly effective treatment in slowing brain volume loss compared to an escalation approach and its safety and tolerability [88].

Future perspectives

With ever-growing insights into the underpinning biology of multiple sclerosis, we have learned that patients with aggressive RRMS might be an internally diverse group — in some of them, the disability accrual might be related to relapses and sequelae of residual deficits, but in some others it may progress independently of the attacks. It was recently suggested that progression in multiple sclerosis is mostly driven by PIRA [89–91].

There is a substantial need for research into the mechanisms behind chronic inflammation and neurodegeneration and their relationship with disability accumulation, especially in cases of patients with aggressive RRMS, who tend to reach this outcome more quickly and who need appropriate treatment to be implemented as early as possible.

Conclusions

Aggressive multiple sclerosis remains a challenge for both clinicians and researchers dealing with demyelinating disorders of the CNS. In clinical practice, it is important to focus on recognising patients at risk of severe disability and remain watchful when treating patients with rapidly increasing disability.

We suggest that researchers should focus on assessing the effect of specific clinical, radiological and laboratory factors on disability accrual (Tab. 1), while clinicians should implement use of the term 'aggressive multiple sclerosis' in their practice.

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Clinical, immunological and neuroimaging spectrum of CNS lupus: can we reliably differentiate it from MS?

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ABSTRACT

Introduction and state of the art. Systemic lupus erythematosus (SLE) is an autoimmune disease that affects many organs throughout its course, most frequently the joints, skin and kidneys. Both the central (CNS) and peripheral (PNS) nervous systems are also often affected. The involvement of the CNS has a negative prognosis in lupus patients. Neurological symptoms are diverse, from headaches and cognitive dysfunction to life-threatening seizures or stroke. Due to the great diversity of neurological presentations, diagnosing neuropsychiatric SLE (NPSLE, neurolupus) can be challenging and necessitates a careful differential diagnostic work-up. Furthermore, neurological symptoms can be one of the first signs of the disease, making the correct diagnosis even more challenging. White matter lesions in NPSLE may closely resemble lesions formed during multiple sclerosis (MS), which is a chronic autoimmune disease of the CNS resulting in neuroinflammatory damage to the myelin sheath, axonal impairment, and neurodegeneration. Based on imaging only, it is challenging to differentiate between the two diseases.

Clinical implications. While both diseases have characteristic features, in their early stages they may mimic each other. The purpose of this literature review was to emphasise the differences in clinical, immunological and neuroimaging features between the two diseases in order to facilitate diagnosis, highlighting the most useful diagnostic tools.

Future directions. Prompt and accurate diagnosis is crucial for implementing appropriate, disease-specific treatment and thereby improving the prognosis for the patient. Therefore, there is a need for novel imaging and laboratory biomarkers, possibly used as a multifactorial profile, to differentiate NPSLE from MS.

Keywords: multiple sclerosis, systemic lupus erythematosus, neurolupus, neuropsychiatric SLE, MRI, autoantibodies, cerebrospinal fluid, CSF

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Introduction

Multiple sclerosis (MS) and systemic lupus erythematosus (SLE) are both chronic autoimmune diseases, but they affect different systems, leading to distinct sets of clinical symptoms. However, there can be some overlap, making diagnosis difficult in certain cases, especially at the onset of symptoms or in atypical presentations. Early in the disease course, symptoms such as fatigue, cognitive complaints, and neurological disturbances can resemble one another, complicating initial diagnosis. In such cases, a detailed clinical evaluation and the use of specialised tests, including neuroimaging and laboratory tests, are crucial for distinguishing between the two conditions and reaching an accurate diagnosis. A summary of key epidemiological, clinical, laboratory and imaging findings in both disorders is set out in Table 1.

Key facts about SLE

Systemic lupus erythematosus is a long-term autoimmune disorder that presents with diverse clinical symptoms and follows a pattern of relapses and remissions [1]. It is distinguished by inflammation and immune-driven injury affecting

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Table 1. Key facts about multiple sclerosis and neuropsychiatric systemic lupus erythematosus

	MS	SLE	References
Global incidence	~2–10 per 100,000 per year More common in Northern Europe and North America, and less frequent near the equator	~1–10 per 100,000 per year Higher incidence in African-American, Hispanic, and Asian populations 20–60% of SLE patients may experience NPSLE	[3, 90–93]
Female:male ratio	2:1	9:1	[92–96]
Age at onset	20 to 40	15 to 45	[97–98]
Disease course (MS – relapsing-remitting or progressive)	MS – relapsing-remitting or progressive	Chronic with flare-ups	
Most frequent clinical presentation	Optic neuritis Motor dysfunction (paresis), spasticity Sensory involvement: numbness, tingling, or burning sensations (paresthesia, hypoesthesia) Coordination and balance problems Fatigue Cognitive dysfunction Bladder and bowel dysfunction Lhermitte's sign pain	Arthralgia and arthritis Malar rash (butterfly rash) Discoid rash Photosensitivity Skin rashes triggered by exposure to sunlight Alopecia Fatigue Fever Renal involvement (*Lupus nephritis*) Serositis Neurological symptoms Haematological abnormalities (anaemia, leukopenia, thrombocytopenia) Cardiovascular issues	[99, 100]
Laboratory tests	— Normal routine labs: Blood tests are generally unremarkable in MS — Vitamin D deficiency: Common in MS patients and associated with disease severity — Inflammatory markers [CRP, ESR]: Usually within normal range. — Positive ANA may occur in 2.5-81% of MS patients	Positive ANA: present in > 95% of SLE patients, a hallmark of lupus Anti-dsDNA and anti-Sm antibodies: specific to SLE, seen in active disease, especially with renal involvement Anti-Sm could be linked to neuropsychiatric manifestations Anti-dsDNA antibodies are considered specific for SLE, but they are not reliable markers of NPSLE Anti-RNP: present in ~25–30% of SLE cases, also seen in mixed connective tissue disease (MCTD); associated with joint and muscular symptoms Anti-Ro/SSA: found in ~30–40% of SLE patients; linked to photosensitivity, rashes, and congenital heart block in neonates. Linked to cognitive dysfunction and mood disorders in some patients aPL, including anti-cardiolipin, anti-β2 glycoprotein, and lupus anticoagulant] — present in ~30–40%, associated with antiphospholipid syndrome, increased clotting risk Anti-ribosomal P protein antibodies — linked specifically to neuropsychiatric manifestations Low complement levels (C3, C4): common in active SLE, indicating immune complex consumption Elevated ESR and CRP during flares or active disease Thrombocytopenia, leukopenia, anaemia: often present due to autoimmune activity or medication effects	[7, 8, 21, 101, 102]

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Table 1 cont. Key facts about multiple sclerosis and neuropsychiatric systemic lupus erythematosus

	MS	SLE	References
CSF findings	— OCBs: present in ~85–95% of patients, indicating CNS-restricted IgG production — Elevated IgG Index: increased in ~70–90%, reflecting immune activity in CNS — Mild pleocytosis: low lymphocyte count increase (5–50 cells/μL) in some cases — Normal glucose levels: glucose is typically within normal range	Mild pleocytosis: slight increase in lymphocytes, generally < 50 cells/μL — Elevated protein: common in active CNS lupus, reflecting inflammation — Rare OCBs: oligoclonal bands are uncommon, appearing only in certain cases with active CNS involvement in SLE but can be found in up to 60% of NPSLE cases	[22, 40, 41]
Neurological presentation	— No PNS involvement — Sensory symptoms (paresthesia, numbness): 40–80%, often early symptom — Motor weakness: 40–70%, leading to difficulty in movement — Visual disturbances [optic neuritis]: 20–50%, blurred vision or vision loss — Gait/balance issues [ataxia]: ~50%, impacts mobility — Spasticity: 40–60%, muscle stiffness, often in legs	— CNS and PNS — Headache [(39–61%) — Mood disorder (69–74%) — Cognitive dysfunction (75–80%) — Cerebrovascular disease (stroke, TIA) (5–20%) — Epilepsy (14–25%) — Psychosis (3–5%) — Myelopathy (1–5%) — Acute confusional state — Aseptic meningitis — Movement disorder (chorea) 1% — Anxiety disorder — Demyelinating syndrome (0.5–1%)	[7, 8 96–98, 100]
Typical MRI findings	— T2 Hyperintense lesions: common in periventricular, juxtacortical, infratentorial, and spinal cord regions (Dawson's Fingers pattern) — T1 Hypointense lesions (black holes): seen in chronic disease stages, indicating permanent damage — Gadolinium enhancement: active lesions show enhancement, indicating ongoing inflammation	— T2/FLAIR Hyperintense lesions: Usually nonspecific, in cortical or subcortical areas; less organsed than MS — Cerebral atrophy: more common in chronic cases or neuropsychiatric lupus — Gadolinium enhancement: rare, usually mild if present; indicates active inflammation	[7, 22, 42–79]
Treatment	Disease-modifying Therapies (DMTs): e.g. interferon-beta, glatiramer acetate, dimethyl fumarate, teriflunomide, S1PR modulators (fingolimod, ozanimod, ponesimod, siponimod), anti-CD20 antibodies (ocrelizumab, ofatumumab, ublituximab), natalizumab, alemtuzumab, oral cladribine Relapse management: high-dose corticosteroids (e.g. methylprednisolone) for acute relapses Symptom management: myorelaxants, baclofen pump, botulinum toxin injections for spasticity, amantadine for fatigue, gabapentin/pregabaline for neuropathic pain	— Immunosuppressants: hydroxychloroquine (standard), azathioprine, mycophenolate, leflunomide, cyclophosphamide, TNF-alpha inhibitors (i.e. infliximab), anti-CD20 antibodies. — Corticosteroids: prednisone for flares and severe organ involvement — Symptom management: NSAIDs for joint pain, anticoagulants if antiphospholipid antibodies are present	[104–106]

MS — multiple sclerosis; SLE — systemic lupus erythematosus; ANA — antinuclear antibodies; Anti-dsDNA — anti-double stranded DNA antibodies; Anti-Sm — anti-Smith antibodies; Anti-RNP — anti-Ribonucleoprotein antibodies; Anti-Ro/SSA — anti-Ro/Sjögren's syndrome antigen A antibodies; aPL — antiphospholipid antibodies; ESR — erythrocyte sedimentation rate; CRP — C-reactive protein; CSF — cerebrospinal fluid; OCBs — oligoclonal bands

multiple organs, such as the skin and mucous membranes, the musculoskeletal system, the blood, the kidneys, and the cardiovascular system [2], which makes its clinical manifestation very diverse. It affects c.3.4 million individuals globally [3]. Each year, 400,000 new cases of SLE are diagnosed worldwide [2]. A systemic review and modelling study from 2023 of 112 studies found that Poland, the US, China and Barbados reported the highest incidence of SLE [2]. Like other autoimmune diseases, women are much more frequently affected than men, with a ratio of 9-10:1, and typically at childbearing age [4, 5]. However, similarly to MS, male gender has been linked to a more severe presentation of SLE in terms of symptoms and prognosis [4]. On the other hand, in females, early SLE symptoms can cause severe complications during pregnancy, including lupus flare, diabetes, pre-eclampsia, miscarriage, preterm birth, intrauterine growth restriction, and congenital heart block [6]. The nervous system (both central and peripheral) is often affected during the disease. An estimated 25–75% of SLE patients have neuropsychiatric symptoms [7]. Neuropsychiatric SLE (NPSLE, neurolupus) can present as either focal or diffuse syndrome, with symptoms ranging from mild cognitive impairment, headache or anxiety to an acute confusional state, seizure disorders, stroke and psychosis [8].

In the Polish population, NPSLE most commonly presents as cerebrovascular disease, seizures, psychosis, or cognitive dysfunction [9]. Involvement of the CNS is linked to a more severe disease course and a poor prognosis [10]. The aetiology of lupus is complex and associated with environmental, genetic, and immunological factors. Complex interactions between the immune system and various tissues lead to widespread inflammation and multi-organ damage. The key mechanisms include autoantibody production [antinuclear antibodies (ANA), anti-dsDNA and anti-Smith (Sm)], immune complex formation, complement activation, apoptosis and clearance defects, inflammation and tissue damage cytokine imbalance [11, 12].

Key facts about multiple sclerosis

The exact cause of MS is still unknown, but similarly to SLE it is believed to arise from a complex interaction of genetic, environmental, and immunological factors that trigger autoimmune response, leading to the autoimmune demyelination of CNS nerve fibres. The key pathophysiological events in MS are autoreactive T cells (particularly CD4+) migration across the disrupted blood-brain barrier (BBB), macrophage-mediated myelin phagocytosis (demyelination), B cells production of autoantibodies against myelin components, and consequently axonal damage, gliosis and neurodegeneration [13–15], with partial remyelination. MS ranks as the most prevalent autoimmune condition affecting the CNS [7]. In its most frequent (up to 85%) relapsing-remitting course, the typical symptomatology includes acute relapses of motor, sensory, visual (optic neuritis), and cerebellar dysfunction [16]. Patients with the progressive course (10–15% of cases) present most commonly with paraparesis or ataxia. In both disease courses, cognitive dysfunction is common, and quality of life may be reduced [17]. The first symptoms usually occur in young adults (between the ages of 20 and 40), with a female predominance (2:1) [16, 18]. An estimated 2.8 million individuals around the globe are living with MS [18]. As of the end of 2021, data from the National Health Fund in Poland indicated that MS had been diagnosed in 54,887 individuals. This translates to a prevalence rate of 144 cases per 100,000 residents [19]. In its most aggressive form, MS can reduce life expectancy, but on the other hand up to 25% of cases never develop significant disability [20].

Overlap between MS and SLE

There is a considerable clinical and biological overlap between MS and SLE. In both, first symptoms often manifest in young adults, with a higher prevalence in women than men. MS and SLE are characterised by a relapsing-remitting course. Although the diseases affect different systems, the overlapping symptoms, such as fatigue, spinal cord involvement or the presence of disseminated white matter lesions on brain magnetic resonance imaging (MRI), can make distinguishing between them difficult. While MS targets the CNS directly, neuropsychiatric lupus can also cause neurological symptoms, e.g. seizures, headaches, cognitive dysfunction, cerebrovascular events, and psychosis. Importantly, cognitive impairment is also seen in both diseases and has a significant negative impact on quality of life. Both MS (via optic neuritis) and SLE (via vasculitis or inflammation) can cause visual disturbances, or paresthesia/hypoesthesia (in MS via CNS, and in lupus via central or peripheral neuropathy). Pain can also occur in both, although it is more common and more severe in lupus.

Differentiating SLE from MS remains a clinical challenge. Diagnosis of both conditions relies on specific diagnostic criteria [21, 22], but it is essential to rule out other diseases in order to ensure an accurate diagnosis. Both diseases can begin with non-specific symptoms. Furthermore, the initial symptoms of lupus can be solely neurological in up to 39–50% of patients [23], while MS can present with a variety of symptoms that are caused by CNS damage, but they can give the impression of a multisystem disease. What makes diagnosis even more challenging is the fact that SLE can co-occur with CNS demyelination [24] and Neuromyelitis Optica Spectrum Disorders (NMOSD) [25].

In this review article, we aimed to demonstrate how similar MS and SLE can be, especially at disease onset. We sought to highlight the differences between the two conditions, while also pointing out their common features, to raise awareness among doctors about the need for careful differentiation, particularly in cases with atypical presentations and 'red flags' (Tab. 2).

Table 2. Red flags suggesting lupus in cases with suspected MS [103]

In a patient presenting with CNS involvement plus one red flag, lupus diagnosis should be considered	
Renal involvement	Cerebrovascular disease
Livedo reticularis	Recurrent spontaneous abortion
Rash	Thrombotic events
Arthritis/arthralgia/myalgia	PNS involvement
Headache	Seizures
Meningismus	Photosensitivity
Psychiatric disease	Raynaud's phenomenon

CNS — central nervous system

Material and methods

We performed a systematic review of the PubMed database as of October 2024 to find applicable English language articles concerning SLE and MS. The key words used were: '(neuropsychiatric) systemic lupus erythematosus', 'neurolupus' and 'multiple sclerosis'. Since our work required a thorough analysis and more detailed data, searches were also conducted for the following phrases: 'antibodies AND MS AND SLE', 'cerebrospinal fluid (CSF) AND MS AND SLE', and 'MRI AND SLE AND MS'. After careful analysis, we included 106 studies into our review. Since knowledge about both diseases is constantly expanding, we restricted our search to articles from the last decade (2014–24). However, since SLE and NPSLE is less frequently studied, and some important data was found in articles published before 2014, we also included them in our study (a total of 16 papers published between 2003 and 2013). The aim of this study was to present the distinguishing features of MS and NPSLE from the clinical, immunological and neuroimaging standpoint, which we believe could be particularly useful in NPSLE cases presenting as a demyelinating syndrome on MRI.

Immunological testing in SLE vs. MS differentiation

Laboratory findings can be helpful in classical cases of SLE. Based on the literature search, we concluded that the most important, widely available and easily applicable laboratory tests are antinuclear antibodies (ANA), anti-double stranded DNA (anti-dsDNA), Sm nucleoprotein antibodies, anti-ribosomal P protein antibodies [anti-Rib-P], and antiphospholipid antibodies (aPL), alongside anti-aquaporin-4 antibodies (AQP4) in cases with spinal cord and/or optic nerves involvement.

Antinuclear antibodies are generalised antibodies that target components within the cell nucleus. Their levels can be determined through serum testing [26]. Serum ANA antibodies are associated with a number of connective tissue diseases and are typically found in lupus patients. However, they can also be found in multiple MS (2.5–81% of cases) [7]. Moreover, non-specific low titres of ANA can be found in healthy individuals in c.10–30% of the population [27], and their specificity decreases with age [7].

Anti-dsDNA antibodies are considered specific markers for SLE [7]. However, they are not reliable markers of NPSLE [7]. Both anti-dsDNA and anti-Sm nucleoprotein are regarded as specific to lupus, and contribute to the classification criteria for SLE established by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) [21]. Interestingly though, a case of anti-dsDNA antibody production was described in MS subjects on interferon beta treatment [28]. It has been suggested that lupus could be induced in MS patients treated with beta-interferons [29, 30].

Anti-ribosomal P protein antibodies target three (P0, P1, P2) similar proteins found on the ribosomal subunit 60 [31]. Anti-ribosomal P0 antibodies are typically associated with SLE. While it is theoretically possible for these antibodies to occur in MS, it has not been reported often. Their presence has been associated with the occurrence of neuropsychiatric symptoms in SLE [32], and is considered a risk factor for a generally unfavourable prognosis in NPSLE patients, potentially leading to life-threatening complications [33].

Antiphospholipid antibodies target phospholipids and phospholipid-binding proteins. While they can be identified in low titres in healthy individuals without pathological significance [2–5%], higher titres are often indicative of autoimmune diseases [34]. These antibodies can increase the risk of thromboembolic complications and recurrent miscarriages. Their presence in the serum points towards a diagnosis of SLE rather than MS [35]. However, a co-incidence of aPL antibodies in MS is possible [36]. It is worth noting that, in SLE subjects, aPL have been associated with neuropsychiatric symptoms and cognitive impartment [36]. Testing for aPL can be useful in patients with non-typical presentation of MS, alongside disseminated white matter lesions (WML) and lack of oligoclonal bands (OCBs) in CSF [34].

Anti-aquaporin 4 antibodies (AQP4-abs, NMO-IgG) specifically target aquaporin 4, a water channel protein predominantly found in the brain and spinal cord. Aquaporin 4 facilitates water transport across cell membranes, playing a crucial role in maintaining water homeostasis in the central nervous system. AQP4 antibody is a highly specific marker of NMOSD [37], and is not present in MS. However, the co-existence of connective tissue autoimmune disease, such as SLE or Sjogren's syndrome, has been described in NMOSD [30]. In SLE patients who develop optic neuritis or myelitis, testing for AQP4 antibodies should be mandatory and can aid in differential diagnosis and treatment strategies, as SLE patients with superimposed NMOsd would require therapy that preferably targets both conditions [38, 39], i.e. anti-CD20 monoclonal antibodies.

Cerebrospinal fluid analysis

In suspected MS, CSF examination is a key laboratory test, but lumbar puncture is not routinely performed in SLE patients unless they present with neurological symptoms. CNS-specific oligoclonal bands (OCBs) are non-specific plasma cells-derived immunoglobulins that are heterogenic

among MS patients [40]. In the context of MS, the presence of intrathecal production of OCBs, along with other clinical and radiological findings, supports the diagnosis of MS. They are detectable in 85–90% of cases [41] and are considered a laboratory equivalent of the dissemination in time criterion as an integral part of the McDonald criteria used for MS diagnosis [40, 22].

In systemic immune-mediated conditions affecting the CNS, the presence of OCBs is less frequent than in patients with MS, yet in NPSLE 43% of cases are linked with intrathecal OCBs production [40]. The presence of OCBs in the CSF of these patients can indicate underlying inflammation and immune activity within the CNS. OCBs are not specific to MS; however, the pattern and number of OCBs can provide additional diagnostic information when evaluating patients with suspected demyelinating diseases. Their presence may support the diagnosis of MS or NPSLE in conjunction with other clinical and laboratory findings.

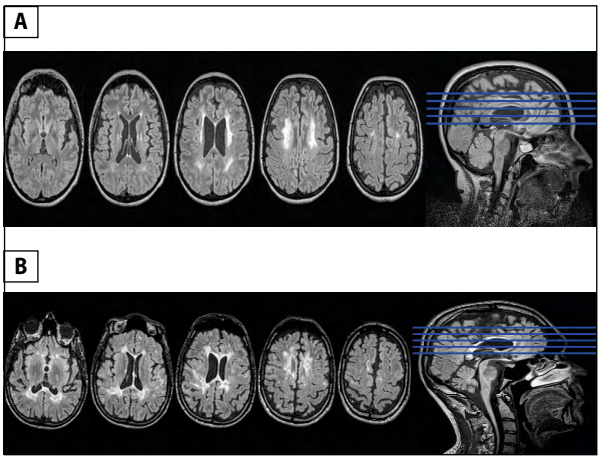

Figure 1. Examples of disseminated white matter lesions on MRI--FLAIR images in patients with clinically established systemic lupus erythematosus (**A**) and multiple sclerosis (**B**)

Magnetic resonance imaging findings

MRI is a key tool in diagnosing and monitoring MS, as it detects characteristic lesions within the CNS. MRI of the brain is not as commonly performed in SLE as in MS, and is usually not critical for a diagnosis of SLE, but it can provide important information regarding CNS involvement, such as cerebral infarcts, haemorrhages, and disseminated WML.

MS plaques are typically located in the white matter (WM) of the CNS and are larger than 3 mm in diameter. The most typical locations include the periventricular, juxtacortical, infratentorial and spinal cord regions [22, 42]. They are visualised best as hyperintense areas on T2-weighted and FLAIR images. Cortical lesions are also typical in MS, but are more difficult to see using standard MRI sequences. Specific sequences, such as double inversion recovery (DIR), may be needed to identify cortical lesions in MS [43]. One of the classic MS findings are Dawson's Fingers (ovoid, finger-like projections of demyelination that radiate perpendicular to the lateral ventricles) [44]. Gadolinium-enhanced T1-weighted images may show active, inflammatory lesions as areas of enhancement, which indicates a breakdown of the BBB and ongoing inflammation. Chronic lesions may appear hypointense on T1-weighted images often referred to as 'black holes'), indicating axonal loss and permanent damage [45]. Generalised or regional brain atrophy occurs as a result of extensive demyelination and neurodegeneration and can be seen as widened sulci, enlarged ventricles, and reduced brain parenchymal volume [46, 47].

It is atrophy, rather than total lesion volume, that correlates best with long-term physical disability and cognitive impairment in MS patients [48]. Lesions in the spinal cord are often seen in the cervical and thoracic regions, typically in the dorsolateral aspects of the cord, and do not extend for more than two vertebral segments in length [42]. In contrast, NPSLE lacks a characteristic pattern of MRI changes. Moreover, a significant proportion of patients with SLE do not exhibit abnormalities on brain MRI [49,50]. While MRI can detect CNS involvement such as cerebral infarcts, haemorrhages, and white matter lesions, these findings are not specific to SLE and can overlap with other neurological disorders. Also, brain involvement on MRI can vary greatly between SLE patients [50–53].

However, MRI plays a supportive role in diagnosing NPSLE, aiding in the exclusion of other conditions such as MS and guiding appropriate management. WML in SLE patients are often found in the subcortical and periventricular white matter, similar to MS, but are less specific in pattern and distribution [54]. See examples in Figure 1.

Both grey and white matter regions can be affected in SLE [54, 55]. The pattern of atrophy in SLE has not been precisely defined. Some studies have shown that, in patients with SLE, hippocampal atrophy, as well as grey matter and corpus callosum atrophy, occurs to a greater extent than in healthy controls (HC) [56]. Significant differences between MS and SLE have been identified, specifically in the fourth ventricle, posterior section of corpus callosum, and third ventricle to thalamus ratio [7]. Based on our findings, we have suggested that distinct correlation patterns between volumetric and clinical data may be due to the fact that while in MS atrophy is driven mainly by disease activity, in SLE it is mostly associated with age [7]. Areas of focal ischaemia or stroke can occur in various brain regions, often related to vasculitis or thrombotic events [57]. Finally, the enlargement of the choroid plexus [CP], which is a network of cells in the ventricles of the brain responsible for producing CSF, is also worth mentioning. In recent years, it has been observed that the CP expands in autoimmune diseases of the CNS. While changes in the choroid plexus are not specific to MS or SLE, their presence and pattern can provide useful information about the extent of CNS involvement in these autoimmune diseases [58–67]. The CP is a structure within the brain responsible for producing cerebrospinal fluid (CSF)

and maintaining the BBB. MRI studies in MS often reveal an enlargement of the CP, especially in patients with active inflammatory lesions. This enlargement may result from inflammation and associated oedema in the surrounding tissue, reflecting an active disease process. CP enlargement is especially evident in contrast-enhanced MRI, where post-contrast enhancement often reflects increased permeability and BBB dysfunction in areas with active inflammation. The extent of CP enlargement in MS has been shown to correlate with disease activity, including the presence of gadolinium-enhancing lesions, which are markers of active inflammation in MS. Moreover, CP enlargement has been observed not only in patients with relapsing-remitting MS (RRMS) but also in progressive forms of the disease, although the extent and pattern of CP changes may vary depending on the MS subtype.

In progressive MS, CP enlargement might be associated with chronic, low-grade inflammation rather than acute inflammatory episodes typical of RRMS. This could reflect the ongoing immune dysregulation and subtle neurodegeneration that characterises progressive MS stages. In addition to its role in neuroinflammation, emerging evidence suggests that the CP may also play a part in neurorepair mechanisms. The CP produces a variety of growth factors and neurotrophic factors that could promote remyelination and repair of damaged neural tissue. However, the inflammatory environment in MS may impair the CP's ability to effectively secrete these factors, or the factors may be outpaced by the ongoing inflammatory processes. Understanding how to modulate CP activity to promote repair without enhancing immune cell entry could open up new therapeutic avenues for MS [68–77]. While research on CP changes in MS is well-established, investigations into CP involvement in SLE are more recent.

Despite SLE being a multi-organ autoimmune disease with primary effects outside the CNS, emerging studies indicate that the CP also undergoes changes in SLE. Particularly in NPSLE, MRIs frequently show CP enlargement and post-contrast enhancement, which can be indicative of active disease and increased BBB permeability. This finding mirrors observations in MS, where CP enlargement and BBB disruption are often associated with active inflammatory lesions. However, while in MS, CP changes are typically linked to localised inflammatory responses within focal lesions, NPSLE appears to reflect a more widespread inflammatory involvement in the CNS. Structural and functional changes in the CP in NPSLE may play a role in modulating immune cell migration into the CNS, potentially contributing to neurological symptoms.

NPSLE is often characterised by increased permeability of the CP and more pronounced BBB dysfunction. In NPSLE, the CP may facilitate the entry of specific autoantibodies such as anti-neuronal and anti-ribosomal P antibodies into the CNS. These autoantibodies are crucial in NPSLE pathogenesis, and are thought to contribute to the neurological manifestations by promoting immune-mediated damage within the brain [78, 79].

Conclusions

Both MS and SLE typically manifest in early to mid-adulthood, are autoimmune in nature, and exhibit a higher prevalence among women. The differences in the laboratory findings, especially autoantibodies (ANA, anti-dsDNA antibodies, anti-ribosomal antibodies, anti-cardiolipin antibodies, all typical for lupus) detected in blood and the presence of oligoclonal bands in CSF, paired with distinct MRI patterns, may be enough to distinguish the two disease entities in classical cases. However, one should be mindful of the potential overlap between SLE and demyelinating diseases, such as MS or NMOSD [80].

For a neurologist, it is crucial to consider whether an atypical clinical presentation of MS could indicate SLE or NPSLE, especially if the atypical presentation of MS is associated with negative common markers for MS (like OCB). It may suggest the need to consider alternative diagnoses, including lupus. A suggested algorithm for MS and NPSLE differentiation is set out in Figure 2. It is worth remembering that in patients with already established MS who are on beta-interferon therapy, there is a potential risk of inducing or exacerbating SLE [28–30].

Interferons, particularly type I interferons (e.g. IFN-α), play an important role in the pathogenesis of SLE. A hallmark feature of SLE is the type I interferon signature, characterised by an increased expression of interferon-stimulated genes (ISGs) in peripheral blood cells and tissues, observed in a significant proportion of SLE patients. Type I interferons, particularly IFN-α, are central to the pathogenesis of SLE, amplifying autoimmune responses, driving chronic inflammation, and contributing to tissue damage. IFN-α promotes autoreactive B cells by facilitating the differentiation and survival of autoreactive B cells, enhancing the production of pathogenic autoantibodies, including anti-dsDNA and anti-Smith (anti-Sm) antibodies. IFN-α also contributes to the activation of T cells and antigen-presenting cells, perpetuating the autoimmune cascade. Type I interferons exacerbate inflammation by recruiting and activating immune cells in affected tissues, driving organ damage such as lupus nephritis. Type I interferons can also modify the epigenetic landscape of immune cells, making them hyperresponsive to stimulation and reinforcing the type I interferon signature [81–84].

It is important for clinicians to monitor MS patients on interferon therapy for any new or unusual symptoms that might suggest the development of SLE, and to conduct appropriate diagnostic evaluations. Early detection and management of SLE are essential to address any potential complications related to interferon treatment.

Future directions

In the future, a combined approach using radiological and laboratory biomarkers may be crucial in the differential diagnosis of MS and SLE.

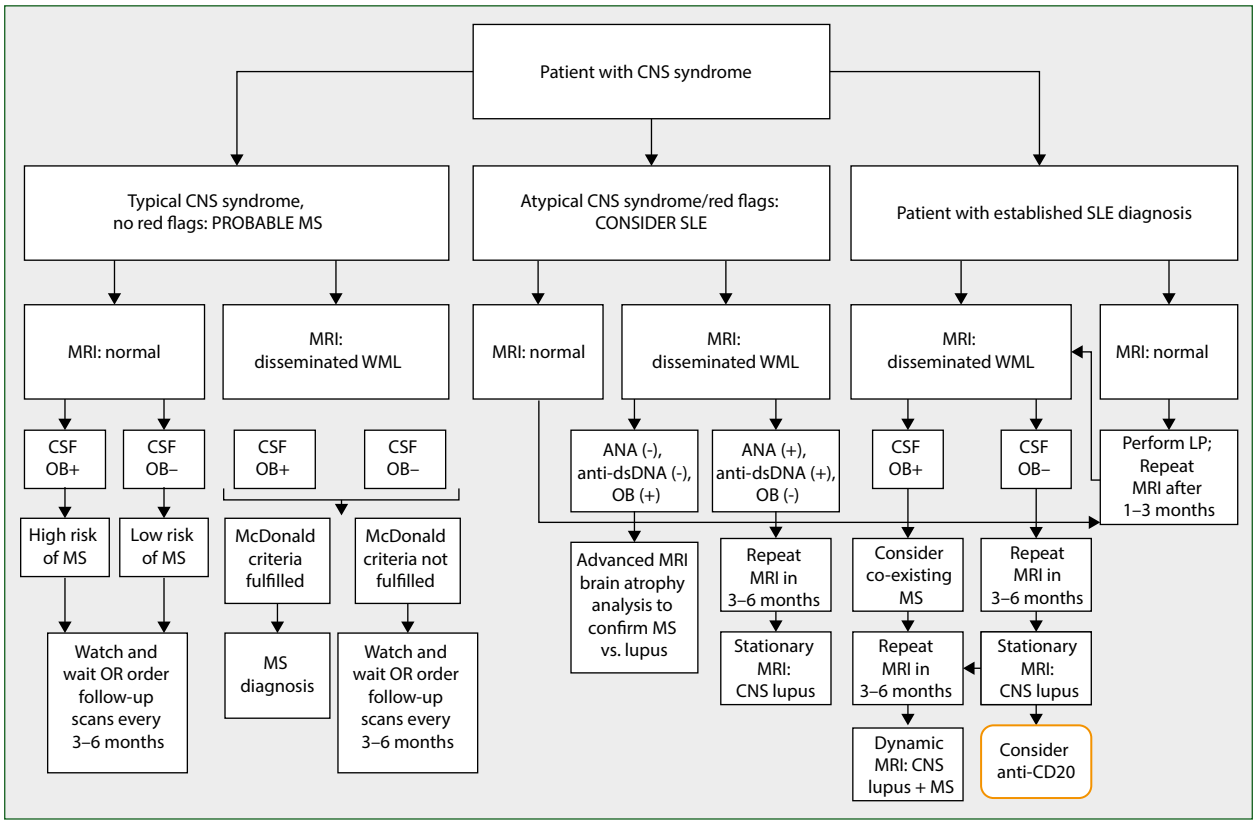

Figure 2. Suggested algorithm for MS vs. NPSLE differentiation. MS — multiple sclerosis; SLE — systemic lupus erythematosus; CNS — central nervous system; MRI — magnetic resonance imaging; OB — oligoclonal bands; WML — white matter lesions; LP — lumbar puncture; ANA — antinuclear antibodies; anti-dsDNA — anti-double stranded DNA antibodies; CSF —cerebrospinal fluid

In the context of MS, there are already highly specific imaging biomarkers, such as the central vein sign (CVS) and paramagnetic rim lesions (PRLs), which show a high specificity for this disease [85]. CVS is an imaging marker detected on MRI that appears as small, round, or oval demyelinating lesions with a clearly visible central vein [85]. Studies have shown that CVS is particularly common in MS patients, making it useful in differentiating MS from other conditions such as ischaemic WML. PRLs are demyelinating lesions with a distinctive, peripheral paramagnetic rim due to the accumulation of macrophages and microglia at the edge of the lesion [86]. PRLs often indicate chronically active lesions and are considered a marker of a more aggressive MS course. Including PRLs in standard imaging diagnostics could help in identifying patients at higher risk of rapid disease progression [86–89].

Unlike MS, SLE lacks similarly specific markers, particularly for its neuropsychiatric manifestations. Identifying biomarkers specific to SLE is essential, as this would greatly improve diagnostic accuracy, disease monitoring, and personalised treatment approaches. By integrating specific radiological and clinical biomarkers, clinicians may gain a more reliable basis for distinguishing MS from SLE, improving diagnostic accuracy, and ensuring that patients receive the most appropriate therapy.

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Disease-modifying therapy in multiple sclerosis: recommendations of Multiple Sclerosis and Neuroimmunology Section of Polish Neurological Society

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ABSTRACT

The treatment of multiple sclerosis (MS) has undergone significant changes since the first disease-modifying therapy (DMT) drug was introduced. Currently, 19 original DMT drugs are registered in the European Union. The choice of optimal therapy is becoming increasingly challenging in the absence of reliable biomarkers on the basis of which disease progression and prognosis can be determined. In addition, longer availability and a growing number of drugs used in MS mean that doctors and patients may have to change therapy when the treatment is ineffective or is associated with the occurrence of adverse effects. The ageing of the MS population, comorbidities, and administration of other drugs during DMT should also be considered. This paper presents recommendations for initiating, monitoring, changing and possibly discontinuing DMT.

Keywords: multiple sclerosis, relapsing-remitting multiple sclerosis, primary progressive multiple sclerosis, secondary progressive multiple sclerosis, disease-modifying therapy, clinically isolated syndrome, radiologically isolated syndrome, recommendations

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Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) of unclear aetiology. It is mostly diagnosed in adults aged 20–40. The disease is autoimmune-mediated [1, 2]. Observations of its natural course indicate that it is a severe and chronic disease which can lead to significant disability and shorten life expectancy in untreated patients. Recent advances in the treatment of MS have significantly improved the prognosis and offered the chance to substantially reduce disease activity, thus slowing disability progression in patients undergoing treatment [3].

Currently, there are therapies that favourably modify the relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS) phenotypes. The increasing number of DMTs, the lack of reliable biomarkers that would allow the selection of the optimal drug for a particular patient, and the need for long-term therapy with drugs associated with the risk of adverse effects, mean that the use of DMT in practice is becoming increasingly difficult and complicated.

These recommendations are based on available scientific data and the clinical experience of the experts of the Multiple Sclerosis and Neuroimmunology Section of the Polish Neurological Society. They are not the same as the current drug programme for the treatment of MS in Poland [1]. For the purposes of this paper, we used the most recent updates of the McDonald criteria [4] and the diagnostic criteria for Radiologically Isolated Syndrome (RIS) [5]. Our recommendations were established between May 2022 and March 2023. Seven co-authors (AKuł., DM-G, HB-P, AKal., WB, MS and MA-S) prepared a draft of the recommendations, which was discussed with other co-authors. Finally, the unanimously approved version was determined. These recommendations should be treated as guidelines to be implemented depending on clinical data, the results of additional tests, and the individual patient profile. This paper shows innovative DMTs according to their mechanism of action and the order of registration in European Union (EU) countries unless there were other important reasons for positioning the drugs.

Management of clinically isolated syndrome

Clinically isolated syndrome (CIS) is the first monophasic clinical episode that may suggest MS. During CIS, neurological symptoms are observed, which can be a monofocal or a multifocal inflammatory demyelinating process in the CNS [4, 6–8]. This can be acute or subacute, with symptoms lasting at least 24 hours, without fever or other signs of infection. CIS is usually characterised by a complete remission of symptoms [4–9].

In appropriate cases, the initiation of DMT may be considered as early as possible to inhibit disease activity and prevent brain volume loss [10] in patients with CIS who do not meet the criteria for the diagnosis of MS [11, 12]. Treatment with interferon beta or glatiramer acetate may be proposed for patients with CIS and CNS lesions on magnetic resonance imaging (MRI) suggestive of MS but not meeting the diagnostic criteria [13].

However, in such cases a careful differential diagnostic work-up is crucial, excluding other antibody-mediated CNS demyelinating diseases, such as aquaporin-4 antibody seropositive neuromyelitis optica spectrum disorders (NMOSD), where beta-interferons could be potentially harmful [14].

Patients with CIS who meet the McDonald 2017 diagnostic criteria for RRMS should immediately start DMT [13]. Currently, DMT is not reimbursed in Poland for patients with CIS without a diagnosis of MS.

Recommendations

- The initiation of DMT with interferon beta or glatiramer acetate may be considered in appropriate cases in patients with CIS who do not meet the criteria for the diagnosis of MS. This is particularly relevant for patients with CIS and CNS changes on MRI suggestive of MS.

Management of radiologically isolated syndrome

Radiologically isolated syndrome (RIS) was defined in 2009 by Okuda et al. [15]. It can be diagnosed if MRI shows lesions typical of MS. However, patients will not have presented with any neurological symptoms suggestive of the disease. Other causes of lesions mimicking MS should be excluded. The diagnostic management in patients with RIS is discussed in the diagnostic guidelines of the Multiple Sclerosis and Neuroimmunology Section of the Polish Neurological Society [9]. Until now, RIS has not been considered a separate MS phenotype [16]. However, this is likely to change considering the recently proposed novel McDonald criteria [17], where RIS would fulfill diagnostic criteria for MS provided that: (i) dissemination in space and time are fulfilled; or (ii) dissemination in space is fulfilled and the presence of intrathecal oligoclonal bands is confirmed; or (iii) dissemination in space is fulfilled and at least six central vein sign (CVS) lesions are present on MRI. The proposed update stems from the fact that about two thirds of patients with RIS show radiological progression [18], and c.50% of patients develop neurological symptoms during a 10-year follow-up [19]. Moreover, it has been shown that two DMTs approved for MS, namely dimethyl fumarate and teriflunomide, reduce the risk of the first demyelinating event in RIS patients by 82% and 63%, respectively [20, 21]. The decision to initiate DMT in patients with RIS at high risk of developing MS should be made on a case-by-case basis [16, 22]. In Poland, DMT is not reimbursed for patients with RIS.

Recommendations

- Currently, there is no data that clearly warrants the initiation of DMT in patients with RIS. More data is needed to be able to select patients with a higher risk of conversion to clinically definite MS, who would benefit most from DMTs.

Treatment of relapsing-remitting multiple sclerosis

Relapsing-remitting multiple sclerosis (RRMS) is the most common phenotype of MS [23]. Scientific evidence indicates that the earlier the DMT starts, the more effective it is [24, 25]. It should be implemented immediately after the diagnosis of RRMS and used in patients with active RRMS. Disease activity is defined as the occurrence of clinical relapses and/or radiological activity (active Gadolinium-enhancing [Gd (+)] lesions on MRI, new or enlarging T2 lesions) assessed during one year [13, 22].

DMT should be managed by a neurologist with knowledge and clinical experience related to MS. The team should also include a nurse and a coordinator of care for patients with MS. Only well-organised MS comprehensive care units with a multidisciplinary team providing constant communication with patients can meet the requirements of comprehensive MS therapy. The concept of establishing such units was developed by ECTRIMS/EAN experts [13, 26], and is supported by the Multiple Sclerosis and Neuroimmunology Section of the Polish Neurological Society.

Disease-modifying therapy drugs in RRMS

Disease-modifying therapy (DMT) drugs differ in their mechanisms of action, dosage and routes of administration, as well as a detailed description of indications and contraindications included in the Summary of Product Characteristics (SmPC) (Tab. 1) [27–42].

There have been very few head-to-head studies on the efficacy and safety of particular DMTs. However, data obtained indirectly from comparing different clinical trials using the propensity score matching method (which is always associated with the risk of error), real world data (RWD), and expert experience indicate that monoclonal antibodies (natalizumab, alemtuzumab, ocrelizumab, ofatumumab), sphingosine-1-phosphate (S1P) receptor modulators (fingolimod, ozanimod, ponesimod) and cladribine tablets are highly effective therapies, while beta interferons, glatiramer acetate, dimethyl fumarate, diroximel fumarate and teriflunomide are considered to be moderately effective [43–47]. It should be noted that even a drug with potentially high effectiveness may prove ineffective in some patients, while another with theoretically lower potency may show long-term effectiveness in specific cases. The use of drugs with higher efficacy may be associated with a higher risk of severe adverse effects. Therefore, DMT can be classified as:

— moderately effective therapy with a low risk of severe adverse effects
— highly effective therapy (HET) with a higher risk of severe adverse effects.

In the course of the disease, the benefit-risk ratio of DMT may change with age or due to the occurrence of new comorbidities.

Due to the mechanism of action determining the maintenance of the therapeutic effect and dosing mode, DMTs can be administered continuously (maintenance therapy) or intermittently (reconstitution, induction therapy) [48]. Maintenance therapy drugs must be administered continuously at regular intervals because their effect is short-lasting and occurs only during regular administration of the drug. Immune reconstitution therapies in the form of several repeated cycles induce long-term remission, which persists after drug discontinuation. There are non-selective reconstitution therapies, such as autologous hematopoietic stem cell transplantation (AHSCT), mitoxantrone and alemtuzumab and more selective therapies (cladribine).

Treatment strategies for RRMS

Two therapeutic strategies are applied for RRMS treatment, i.e. a strategy to intensify treatment if necessary (escalation therapy) and early intense therapy (early HET). The basis of the concept of escalation consists of starting treatment with drugs of lower efficacy and changing to a higher efficacy drug if this is ineffective. The concept of early intense therapy is associated with the administration of a highly effective drug at an early stage of the disease, which may be warranted by high clinical and radiological activity during this period [49, 50].

Currently, there is no clear scientific data that shows which therapeutic strategy is more beneficial. However, more reports indicate that using HET as the first-line treatment of RRMS allows a rapid clinical effect and offers better long-term effects [51–53]. However, further research is warranted in this respect.

Escalation therapy is based on continuous drug administration (maintenance therapy) at least in the initial period. In turn, the early HET strategy may involve the use of drugs included in maintenance therapy (natalizumab, fingolimod, ozanimod, ponesimod, ocrelizumab, ofatumumab) and reconstitution therapy (cladribine tablets, alemtuzumab).

Selection of first DMT

Currently, there are no biomarkers that would allow fully personalised treatment in clinical practice i.e. the choice of the optimal drug in terms of efficacy and safety for a specific patient. When RRMS therapy is started, the choice of DMT is based mainly on disease activity and the prognostic profile of its further course.

Table 1. Disease-modifying therapy drugs — basic information and selected common or significant adverse effects

International nonproprietary name	Trade names*	Dosage	Selected common/significant adverse effects
Beta-Interferons • Interferon beta-1b • Interferon beta-1a • Interferon beta-1a • Peginterferon-beta-1a	 Betaferon® Rebif® Avonex® Plegridy®	Depending on the drug: 250 µg *s.c.* every other day 44 µg *s.c.* three times a week 30 µg *i.m.* once a week 125 µg *s.c.* every 2 weeks	injection site reactions, flu-like symptoms, leukopenia, lymphopenia, elevated liver enzymes, depressed mood (depression)
Glatiramer acetate	Copaxone®	20 mg *s.c.* once daily or 40 mg *s.c.* three times a week	injection site reactions and rarely lipoatrophy and skin necrosis, transient systemic reaction to the drug immediately after administration: vasodilatation (flushing), dyspnea, chest pain, palpitations or tachycardia
Natalizumab	Tysabri®	300 mg *i.v.* every 4 weeks** or 300 mg *s.c.* every 4 weeks	infusion-related reactions during i.v. administration, pain at the injection site during s.c. administration, for both ways of administration: hypersensitivity reactions, rhinopharyngitis, urinary tract infection, opportunistic infections (e.g. PML)
Fingolimod	Gilenya®	0.5 mg *p.o.* daily	lymphopenia, bradyarrhythmia, hypertension, bronchospasm, infections, including opportunistic infections (e.g. *Herpes zoster*, PML, cryptococcosis), macular edema, basal cell carcinoma, elevated liver enzymes, liver damage and PRES
Siponimod	Mayzent®	CYP2C9 genotyping should be performed prior to initiation of the treatment; dose depending on CYP2C9 genotype; during the first 5 days of treatment, the dose is increased from 0.25 mg/d to 1.25 mg/d; from Day 6, a main-tenance dose of 2 mg/d or 1 mg/d, depending on the genotype	lymphopenia, bradyarrhythmia, hypertension, bronchospasm, infections, including opportunistic infections (e.g. Herpes zoster, cryptococcosis), macular edema, basal cell carcinoma, elevated liver enzymes Observation for PML and PRES
Ozanimod	Zeposia®	dose gradually increased from 0.23 mg *p.o.* once daily (days 1 to 4), then 0.46 mg *p.o.* once daily (days 5 to 7) to the target dose of 0.92 mg *p.o.* once daily	lymphopenia, bradyarrhythmia, hypertension, bronchospasm, infections, including opportunistic infections (e.g. Herpes zoster, PML, cryptococcosis), hypertension, macular edema, basal cell carcinoma, elevated liver enzymes, PRES
Ponesimod	Ponvory®	dose gradually increased from 2 mg *p.o.* once daily (Days 1 and 2), 3 mg *p.o.* once daily (days 3 and 4), 4 mg *p.o.* once daily (days 5 and 6), then increase by 1 mg *p.o.* every day to 10 mg *p.o.* once daily (days 12, 13 and 14), from day 15 the target the of dose 20 mg *p.o.* once daily	lymphopenia, bradyarrhythmia, hypertension, bronchospasm, infections, including opportunistic infections (e.g. Herpes zoster, cryptococcosis), hypertension, macular edema, basal cell carcinoma, elevated liver enzymes Observation for PML and PRES
Dimethyl fumarate	Tecfidera®	initially 120 mg *p.o.* twice daily, then 240 mg *p.o.* twice daily	immediately after drug administration: transient redness of the skin, burning sensation, flushing, gastrointestinal symptoms; long-term adverse effects: gastroenteritis, lymphopenia, leukopenia, opportunistic infections (e.g. PML), elevated liver enzymes, drug-induced liver injury
Diroximel Fumarate	Vumerity®	initially 231 mg *p.o.* twice daily, then 462 mg *p.o.* twice daily	immediately after drug administration: transient redness of the skin, burning sensation, flushing, gastrointestinal symptoms; long-term adverse effects: gastroenteritis, lymphopenia, leukopenia, opportunistic infections (e.g. PML), elevated liver enzymes, liver injury Observation for opportunistic infections (e.g. PML)
Teriflunomide	Aubagio®	14 mg *p.o.* once daily	leukopenia, infections, elevated liver enzymes, acute hepatitis, drug-induced liver injury, hair loss, hypertension, polyneuropathy
Alemtuzumab	Lemtrada®	12 mg *i.v.* for 5 days in year 1 and 12 mg *i.v.* for 3 days in year 2 of therapy	infusion-related reactions, infections (including opportunistic infections), leukopenia, immune reactions, including late autoimmune reactions (thyroiditis, hepatitis, ITP, MGN, Anti-GBM disease), vascular complications (e.g. myocardial ischemia, myocardial infarction, stroke, cervicocephalic arterial dissections)

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Table 1 cont. Disease-modifying therapy drugs — basic information and selected common or significant adverse effects

International nonproprietary name	Trade names*	Dosage	Selected common/significant adverse effects
Cladribine tablets	Mavenclad®	10 mg tablets; cumulative dose of 3.5 mg/kg body weight over 2 years. The drug is administered for 4–5 days in the first and second month in the first year and 4–5 days in the first and second month in the second year of the treatment	lymphopenia, infections (including opportunistic infections), elevated liver enzymes, symptomatic hepatitis, liver damage
Ocrelizumab	Ocrevus®	the dose is administered as two separate *i.v.* infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion; then a single 600 mg *i.v.* infusion every 6 months	(systemic) infusion-related reactions, decreased IgM and IgG levels, infections (including opportunistic infections); observation for reactivation of hepatitis B infection
Ofatumumab	Kesimpta®	20 mg administered by *s.c.* injection at weeks 0, 1 and 2, followed by subsequent monthly dosing, starting at week 4 (20 mg *s.c.*)	injection-related reactions (systemic, e.g. flu-like) and injection site reactions, infections, decreased IgM Note: Attention should be paid to opportunistic infections and hepatitis B reactivation
Mitoxantrone	Mitoxantron Sandoz®	12 mg/m^2 of body surface area, given as an *i.v.* dose every 3 months; the maximum lifetime cumulative dose should not exceed 72 mg/m^2 of body surface area	anemia, leukopenia, granulocytopenia, acute leukemia, infections, cardiac arrhythmias, cardiomyopathy, circulatory failure, amenorrhea, hair loss

s.c. — subcutaneous(ly); i.m. — intramuscular(ly); *i.v.* — intravenous(ly); *p.o.* — orally; PML — progressive multifocal leukoencephalopathy; PRES — posterior reversible encephalopathy syndrome; ITP - immune thrombocytopenia; MGN — membranous glomerulonephritis; anti-GBM — goodpasture syndrome
*Preparations of innovative medicinal products registered in Poland.
In the coming years, further generic preparations and new biosimilars equivalent to biological medicinal products should be expected to be introduced to the market. Although it may raise uncertainty about the effectiveness and safety of treatment, it is worth noting that the registrations of generics and biosimilars are carried out under strictly defined rules, in accordance with the requirements of national and European regulatory authorities (the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products in Poland and the European Medicines Agency in Europe) and adequate legal regulations. Verification in real clinical practice requires confirmation of maintaining the effectiveness and safety of therapy when biological and biosimilar drugs are interchanged, including multiple replacements. For this purpose, further research and follow-up are warranted also within the framework of appropriate registries [94].
#Selection based on the Summary of Product Characteristics (SmPC) and expert experience. When making therapeutic decisions, it is necessary to follow current SmPCs and safety information.
**Possible regimen with an extended dosing interval (approximately 6 weeks on average) to reduce the risk of PML, as initially demonstrated in a retrospective analysis (TOUCH program). At the same time, the effect of such a change in the dosing regimen on the efficacy of treatment has not been established. Therefore, the definitive benefit-risk ratio of therapy with the modified dosing regimen remains unknown. Statistical modelling results indicate that the risk of relapse of MS in patients who switched to a dose regimen with an extended dosing interval may be higher if their body weight is > 80 kg or the dosing interval is ≥ 7 weeks

The following show unfavourable prognostic significance [54–56]:

- clinical factors, including a high annualised relapse rate (≥ 2 relapses/year), a short interval between the first and the second relapse, incomplete resolution of symptoms after relapse, and multifocal signs and symptoms at the onset of the disease, especially the occurrence of cerebellar, pyramidal and sphincter disorders
- radiological factors: at least 2 Gd(+) or ≥ 9 hyperintense lesions on T2 MRI, the presence of demyelinating lesions in the spinal cord or brainstem
- demographic and other factors: male sex, older age of patient (> 40), obesity, smoking.

Other patient-dependent factors also play an important role in the choice of DMT. These include reproductive plans, comorbidities and their treatment, seropositivity for John Cunninghan (JC) virus or hepatitis B virus (HBV), the need/necessity for preventive vaccinations, the patient's lifestyle, and their reluctance to take the risk of therapy (a strong fear of adverse drug effects) and the patient's preferences for the route and frequency of drug administration. In practice, the availability of DMT is also crucial, which can result from the rules of therapy reimbursement (the provisions of the drug programme in Poland).

The decision to start therapy and the choice of drug should be discussed with the patient during another appointment, specially planned for this purpose, which should take place at the right time (preferably 1–4 weeks after the patient is informed about the diagnosis). The patient's participation in therapeutic decisions determines further effective cooperation, including compliance with the therapy. The patient should be informed that DMT will not cure MS and may not bring about a significant clinical improvement. However, it is aimed at inhibiting disease progression. The patient should also know that DMT is associated with a risk of adverse effects and requires regular monitoring of the clinical condition, laboratory parameters and MRI examinations. Before starting each DMT, additional tests should be performed as indicated in the SmPC (Tab. 2). To achieve adequate immunity after vaccination, immunisation should be conducted before starting immunosuppressive DMT.

Proposed algorithm for initiating RRMS treatment with DMT

Patients with low/moderate disease activity (1 clinical relapse or 1 active (Gd+) lesion or 1–2 new T2 lesions on MRI in the last 12 months) can start treatment with any of the following: interferon beta, glatiramer acetate, dimethyl fumarate, diroximel fumarate, teriflunomide, ocrelizumab, ofatumumab, ozanimod or ponesimod. The important factor when choosing the first drug from among those listed above is as follows:

— a prognostic profile of the disease course

If unfavorable prognostic factors are present (see above), initiation of HET should be considered with consideration given to comorbidities and their treatment.

— reproductive plans

They should always be discussed with the patient at the time of starting DMT. Women of childbearing age who plan pregnancy or do not want to use contraception should be offered treatment with interferon beta or glatiramer acetate, which can be used until conception and even during pregnancy and breastfeeding, after considering the benefit-risk ratio.

— the route of administration and dosing regimen preferred by the patient.

Patients with high disease activity

There is no universally recognised definition of highly active disease in the case of RRMS. Even so, there is a consensus among experts that it is a broader concept than 'rapidly evolving severe RRMS' (RES-RRMS).

According to most experts [57–59], high disease activity is evidenced by:

— ≥ 2 relapses/year, especially with pyramidal and/or cerebellar signs and symptoms
— incomplete resolution of relapse symptoms
— > 9 T2 lesions on MRI, especially located in the spinal cord and/or brainstem
— several active (Gd+) lesions on MRI.

Patients with high disease activity should initiate therapy with highly effective drugs, i.e. natalizumab, fingolimod, ozanimod, ponesimod, ocrelizumab, ofatumumab, cladribine tablets or alemtuzumab in accordance with the indications and in the absence of contraindications to their use included in the SmPC. The choice of drug should be based on the patient's individual profile in each case. When considering the choice among HETs, a test for (latent) infections should be performed.

In patients with high disease activity, moderate-efficacy drugs may be introduced (interferon beta preferably in a high dose, glatiramer acetate, teriflunomide, dimethyl fumarate, diroximel fumarate) if indicated by clinical findings (e.g. contraindications to the use of HET, pregnancy, breastfeeding). As in the case of patients with low/moderate disease activity, the choice of drug is also influenced by other factors, including reproductive plans, comorbidities and their treatment, the safety profile of the DMT, and patient preferences.

Recommendations

- DMT should be initiated in patients with active RRMS immediately after the diagnosis. RRMS activity is defined clinically and/or radiologically
- The decision to start DMT and the choice of drug should be discussed with the patient during another appointment. The patient should be informed that DMT will not cure MS, and may not even bring about a significant clinical improvement. The patient should also be informed about the risk of adverse effects and the necessity of regular monitoring of therapy
- When starting DMT for RRMS, choice of the drug should be mainly based on disease activity and the prognostic profile of its further course. The following should be considered: reproductive plans, comorbidities and their treatment, drug safety profile, and patient preferences
- Patients with RRMS and low/moderate disease activity (1 clinical relapse or 1 active (Gd+) lesion or 1–2 new T2 lesion(s) on MRI within the last 12 months) may start therapy with interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, diroximel fumarate, ocrelizumab, ofatumumab, ozanimod, or ponesimod. The choice of drug should be based on the patient's individual profile
- Patients with RRMS with high disease activity should start therapy with highly effective drugs such as natalizumab, ocrelizumab, ofatumumab, fingolimod, ozanimod, ponesimod, cladribine tablets or alemtuzumab. The choice of drug should be based on the individual profile of the patient
- Females of childbearing age who are not using contraception or who are breastfeeding are encouraged to initiate treatment with interferon beta or glatiramer acetate. More safety data is needed with regards to other DMTs. However, this should be discussed on an individual basis, especially in cases with high disease activity
- In patients with high risk of disease reactivation post-partum who decide to breastfeed, the use of highly effective monoclonal antibodies, the amount of which that pass into breastmilk is expected to be low, should be discussed on an individual basis. More safety data is needed in this area
- Continuation of treatment with interferon beta or glatiramer acetate may be considered in pregnant patients after evaluating the benefit-risk ratio. If natalizumab is used, continuation of therapy until the end of the 34th week of gestation may be taken into account
- In patients with RRMS with high disease activity who plan pregnancy, reconstitution therapies (cladribine tablets, alemtuzumab) may be considered to stabilise the disease before pregnancy

Table 2. Principles of monitoring adverse effects of disease–modifying therapies in multiple sclerosis#

	Laboratory parameters	Clinical parameters	Radiological parameters
Beta interferons	1 Before starting the therapy and then at regular intervals (more often in the case of abnormalities in laboratory findings or individual clinical indications): 1. complete blood count with differential; 2. biochemical parameters of liver function; parameters of kidney function: urinalysis 3. TSH	1. Before starting the therapy and then at regular intervals: a. medical interview to check for current symptoms of severe depression and/or suicidal ideation; b. medical interview to check for and observation for possible signs symptoms of decompensated liver failure* 2. Regular observation of injection sites 3. Regular medical interview to check for flu-like symptoms	No need to monitor from the perspective of the safety of the therapy
Glatiramer acetate	Periodic monitoring of liver and kidney function tests is required	Points 1b and 2 as above	No need to monitor from the perspective of the safety of the therapy
Dimethyl fumarate and diroximel fumarate	1. Complete blood count with differential before starting the treatment and then every 3 months **NOTE:** In the case of lymphopenia, more frequent monitoring of blood count with differential is recommended, especially if lymphocyte count < 800/mm^3; if lymphopenia is present below this level for > 6 months — the benefit—risk ratio of the therapy should be reconsidered (eg determination of anti–JCV antibodies) Dimethyl fumarate should be discontinued if lymphopenia persists < 500/mm^3 for > 6 months 2. Biochemical parameters of renal function and urinalysis before the therapy, after 3 and 6 months, and then every 6—12 months, depending on clinical indications 3. Biochemical parameters of liver function: before starting treatment and then depending on clinical indications 4. If PML is suspected, JCV DNA should be determined by PCR in the cerebrospinal fluid	1. Medical interview to check for gastrointestinal symptoms before starting the therapy and then at regular intervals 2. Medical interview to check for flushing symptoms (at each visit) 3. In the case of persistent lymphopenia, medical interview to check for and observation for infection, including the symptoms of varicella–zoster virus infection and PML**	1. Usually no need to monitor from the perspective of the safety of the therapy 2. In appropriate cases with persistent lymphopenia between 500 and 800/mm^3 and a high anti–JCV antibody index and/or previous immunosuppression, increased frequency of MRI scans examinations (every 3–6 months) should be considered using a short protocol (ie FLAIR, T2, DWI) for the preclinical stage of PML
Teriflunomide	1. Before starting the therapy and then at regular intervals (as clinically indicated; more often in the case of abnormalities in findings): — complete blood count with differential — liver function tests: • for the first 6 months of therapy — ALT assessment every 4 weeks, and then at regular intervals; • in patients on other drugs with hepatotoxic potential OR who have concomitant liver disease OR clinical signs and symptoms of liver failure — ALT assessment every 2 weeks for 6 months, then at least once every 8 weeks for at least 2 years from the start of therapy; • if ALT > 2–3x the upper limit of normal (ULN), ALT should be assessed weekly; • if ALT > 3x ULN, therapy should be discontinued	1. Before starting the therapy and then at regular intervals: — medical interview to check for hypertension and periodic blood pressure monitoring, at least once every 3 months; — medical interview to check for and observation for possible symptoms of decompensated liver failure* 2. Medical interview to check for pregnancy and contraception before starting the therapy and at each visit	No need to monitor from the perspective of the safety of the therapy
Natalizumab	1. Before starting therapy: • test for anti–JCV antibodies (anti–JCV antibody index); • complete blood count with differential; • biochemical parameters of liver function; parameters of renal function: at least urinalysis 2. During the therapy: • determination of the anti–JCV antibody index every 6 months; • complete blood count with differential and liver function test and urinalysis with microscopic examination of sediment — at regular intervals, depending on clinical indications 3. If PML or JCV GCN is suspected, JCV DNA should be determined by PCR in the cerebrospinal fluid	1. Medical interview to check for and observation for PML symptoms** 2. Medical interview to check for decreased visual acuity, redness and eye pain (retinal examination should be performed for ARN)	More frequent MRI scans (every 3–6 months) using a short protocol (ie FLAIR, T2, DWI) should be performed in patients at a higher risk of PML Such patients include: a) those with all three risk factors for PML (ie the presence of anti–JCV antibodies and on natalizumab for > 18 months and previously on immunosuppressive drugs) OR b) those with a high anti–JCV antibody index treated with natalizumab > 24 months and with no history of immunosuppressive treatment Available data suggest that the risk of PML is low at ≤ 09 and increases significantly at > 15 in patients treated with natalizumab > 24 months MRI should also include a T1 sequence before and after contrast administration in the case of suspected PML

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Table 2. cont. Principles of monitoring adverse effects of disease–modifying therapies in multiple sclerosis[#]

	Laboratory parameters	Clinical parameters	Radiological parameters
Fingolimod — information also applies to other S1P receptor modulators (ozanimod/ /ponesimod/ /siponimod) unless indicated otherwise	1. Before starting the therapy: • complete blood count with differential; • liver function tests: at least ALT, AST and bilirubin; • kidney function tests: at least creatinine and urinalysis; • determination of antibodies against varicella zoster virus (VZV) In the absence of the antibodies, vaccination is mandatory at least one month before the therapy; • CYP2C9 genotyping (in the case of siponimod) 2. During the therapy: • complete blood count at Month 3, then periodically and in the case of symptoms of infection (for fingolimod at least once a year) — confirmed absolute lymphocyte count < 200/mm^3 x109/l should result in treatment discontinuation until recovery to baseline values (fingolimod, ozanimod — recovery to 500/mm^3 is sufficient to restart therapy, ponesimod — required level > 800/mm^3); • ALT, AST and bilirubin tests at 1, 3, 6, 9 and 12 months of treatment, and then at least every 6 months and up to 2 months after the discontinuation of therapy or as clinically indicated (in the case of siponimod — periodically or if the symptoms of hepatic impairment occur): — if transaminases are > 3x ULN but < 5x ULN without clinical symptoms and without an increase in bilirubin, more frequent monitoring is recommended, including determination of bilirubin and alkaline phosphatase levels; in the case of an increase in transaminases ≥ 5x ULN or > 3x with the increase in bilirubin, the drug should be discontinued (fingolimod); — treatment should be discontinued if significant liver injury is reported, eg, increase in ALT > 3x ULN or total bilirubin 2x ULN (ponesimod); — treatment should be discontinued if transaminases > 5x ULN (ozanimod); — in patients who develop symptoms of hepatic impairment during treatment, liver enzymes should be tested and treatment should be discontinued if significant liver impairment is confirmed (siponimod); • Periodic urinalysis; • Regular cervical smear according to the standards of practice (in the case of fingolimod)	1. Before starting the therapy: • ECG and blood pressure measurement; • cardiology consultation in patients on drugs that may slow the heart rate and in patients with a history of arrhythmias and conduction disorders, heart failure, cardiogenic syncope, or other significant heart disease and sleep apnea; • ophthalmology consultation — in the case of ponesimod — in all patients in whom the drug is planned; — in the case of ozanimod – in patients with a history of diabetes, uveitis or retinal disease; — in the case of fingolimod and siponimod — in patients with a history of diabetes or uveitis; • Dermatology consultation within 6 months before treatment (fingolimod and siponimod) 2. In connection with the first drug administration: For fingolimod: • ECG monitoring for 6 hours after the drug intake, additionally blood pressure and heart rate measurement every hour; additional 2–hour ECG monitoring is recommended if the heart rate reached the lowest levels 6 hours after the drug intake; • ECG monitoring should be prolonged if the heart rate decreases < 45/min in adults OR if QTc is prolonged > 500 ms OR the at least second–degree atrioventricular block is present; • the patient should be hospitalized at least until the next day and until the symptoms have resolved FOR ozanimod, ponesimod and siponimod: — ECG monitoring is recommended only in patients with a history of cardiac disease 3. During the therapy: • Medical interview to check for cardiac arrhythmias and blood pressure disorders (at each visit) and periodic blood pressure monitoring; • Medical interview to check for vision disorders (at each visit) and ophthalmology consultation: — in the case of fingolimod and siponimod: ophthalmology consultation is necessary 3–4 months after the start of treatment to exclude macular edema, and then at least once a year, depending on the ophthalmologist's opinion; ophthalmology consultation is also necessary if any visual disturbances occur during the treatment; — in the case of ozanimod — ophthalmology consultation during treatment is recommended in patients with a positive history of uveitis or retinal disease and in patients with diabetes AND in those with the symptoms of macular edema (therapy should be discontinued if the diagnosis is confirmed); — in the case of ponesimod – regular ophthalmology consultations in patients with a history of uveitis or diabetes AND if the patient reports any visual disturbances during the therapy; • Medical interview to check for new/enlarging skin nevi (at each visit) and dermatology consultation during therapy: — in the case of fingolimod and siponimod — every 6–12 months; — in the case of ponesimod — patients with pre–existing skin diseases and with new or changing skin nevi should be referred to a dermatologist for monitoring of the lesions; — in the case of ozanimod — patients should be warned against unprotected exposure to sunlight and against the use of phototherapy • If clinically indicated, spirometric assessment of respiratory function should be performed during treatment (ponesimod) • Medical interview to check for and observation for symptoms of infection, including opportunistic infections and neuroinfections (at each visit) • Medical interview to check for and observation for possible symptoms of decompensated liver failure*	No need to monitor from the perspective of the safety of the therapy unless the patient develops symptoms of opportunistic infections with possible CNS involvement (eg, cryptococcal meningitis, PML, meningitis and/or encephalitis caused by Herpes simplex virus or VZV)

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Table 2. cont. Principles of monitoring adverse effects of disease–modifying therapies in multiple sclerosis[#]

	Laboratory parameters	Clinical parameters	Radiological parameters
Alemtuzumab	1. Before starting the therapy: • Biochemical tests, including liver, kidney and thyroid function tests; • Complete blood count with differential; • Urinalysis with microscopic examination of sediment; • Screening tests for HIV infection (HIV Ag/Ab) and HBV (HBsAg, anti–HBc), HCV (anti–HCV), TBC (Quantiferon TB Gold Plus, IGRA test and chest X–ray) — if necessary, consultation with an infectious disease specialist or lung specialist 2. During the first cycle of treatment with infusions: — Platelet count should be determined immediately after the infusion on Days 3 and 5 of the first cycle, and immediately after the infusion on Day 3 of each subsequent cycle Clinically significant thrombocytopenia should be monitored until resolution Consultation with a hematologist should be considered 3. During the therapy between the infusion cycles: • complete blood count with differential, serum creatinine, urinalysis with microscopic assessment of sediment, liver function tests (transaminases) every month; • serum TSH every 3 months; • annual screening for HPV infection in female patients Tests should be continued up to 48 months after the last course of alemtuzumab 4. Assessment before the next infusion cycle: — HIV test, qualitative determination of HBV and HCV viral load, and chest X–ray should be repeated	Before starting the therapy: 1. ECG monitoring; 2. Measurement of heart rate and blood pressure; 3. Medical interview to check for autoimmune diseases, cardiovascular disease and immunodeficiencies; Premedication (before the infusion): — patients should be premedicated with glucocorticoids (1000 mg methylprednisolone for the first 3 days of each treatment cycle) during the first 3 days of each treatment cycle, immediately before the infusion; — premedication with antihistamines and/or antipyretics may also be considered; — all patients should be treated with oral prophylaxis of herpes virus infection from the first day of each treatment cycle and it should be continued for at least 1 month after the discontinuation of treatment (acyclovir 200 mg twice daily or equivalent); — patients should avoid ingestion of uncooked or undercooked meats, blue cheese and unpasteurized dairy products two weeks prior to, during, and for at least one month after LEMTRADA infusion to reduce the risk of infection caused by Listeria During the intravenous infusion: — monitoring of heart rate, blood pressure and general clinical status of patients at least every hour; — if severe infusion reactions occur, the intravenous infusion should be discontinued immediately (if the patient develops clinical signs and symptoms suggestive of myocardial ischemia, hemorrhagic stroke, cervicocephalic arterial dissections or pulmonary alveolar hemorrhage) Assessment immediately after the intravenous infusion: — observation for infusion reactions is recommended for at least 2 hours after the infusion; — patients with clinical signs and symptoms suggestive of a serious adverse event temporarily associated with the infusion (myocardial ischemia, hemorrhagic stroke, cervicocephalic arterial dissection and alveolar hemorrhage) should be closely monitored until the symptoms are completely resolved (hospitalization) During the therapy: 1. Medical interview to check for signs and symptoms of myocardial infarction, stroke, intracerebral artery dissection, pulmonary hemorrhage (may occur up to one month after alemtuzumab infusion) 2. Medical interview to check for signs and symptoms of hyperthyroidism or hypothyroidism (at each visit) 3. Medical interview to check for and observation for symptoms of infection, including opportunistic infections and neuroinfections (at each visit)	No need to monitor from the perspective of the safety of the therapy unless patients develop signs and symptoms of opportunistic infection with possible CNS involvement (eg, cryptococcal meningitis, PML)
Ocrelizumab and ofatumumab	1. Before starting the therapy: • complete blood count with differential; • liver function tests: at least ALT and AST; • kidney function tests: at least creatinine and urinalysis; • screening tests for HBV (anti–HBc, HBsAg) and, if necessary, consultation with an infectious disease specialist/hepatologist; • screening for immunodeficiency (eg HIV Ag/Ab); • standard breast cancer screening based on local guidelines (in the case of ocrelizumab) 2. During the therapy, before each administration of ocrelizumab: • blood count before each drug administration; • urinalysis before each administration of the drug; • kidney and liver function tests before each administration of the drug; • HBsAg and anti–HBc before each administration of the drug 1. During ofatumumab therapy — complete blood count with differential, assessment of liver and kidney function tests and urinalysis after 3 months, and then at least twice a year, depending on the patient's clinical condition	1. Medical interview to check for and observation for symptoms of infection, including opportunistic infections and neuroinfections (at each visit) 2. Medical interview to check for and observation for possible symptoms of decompensated liver failure * in patients with a history of hepatitis B or C 3. Regular observation of injection sites and medical interview to check for injection–related reactions (in the case of ofatumumab) Premedication for ocrelizumab infusion–related reactions: The following premedication must be administered prior to each ocrelizumab infusion: • 100 mg intravenous methylprednisolone (or an equivalent) approximately 30 minutes prior to each infusion; • antihistamine approximately 30–60 minutes prior to each infusion In addition, premedication with an antipyretic (eg, paracetamol) may also be considered approximately 30–60 minutes prior to each infusion	No need to monitor from the perspective of the safety profile of the therapy unless patients develop signs and symptoms of opportunistic infection with possible CNS involvement (eg PML)

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Table 2. cont. Principles of monitoring adverse effects of disease–modifying therapies in multiple sclerosis[#]

	Laboratory parameters	Clinical parameters	Radiological parameters
Cladribine tablets	1. Before starting the therapy: • complete blood count with differential; • biochemical parameters of liver function: ALT, AST, alkaline phosphatase and total bilirubin; • biochemical parameters of kidney function and urinalysis; • determination of antibodies against varicella zoster virus (VZV) In the absence of the antibodies, vaccination is mandatory at least one month before the therapy; • Screening tests for HIV infection (HIV Ag/Ab) and HBV (HBsAg, anti–HBc), HCV (anti–HCV), TBC (Quantiferon TB Gold Plus, IGRA test and chest X–ray); if necessary, consultation with an infectious disease specialist or lung specialist 2. During the therapy: • complete blood count with differential 2 months and 6 months after initiation of the treatment in each year of the therapy; • If the lymphocyte count decreased < 500/mm^3, it should be actively monitored until it increases to at least 800/mm^3; • regular monitoring of liver enzymes and bilirubin based on clinical signs and symptoms Before the next treatment course: • complete blood count with differential; • ALT, AST, alkaline phosphatase and total bilirubin before the next treatment course; • serum creatinine level; • screening tests for HIV (HIV Ag/Ab) and HBV (anti–HBc, HBsAg), HCV (anti–HCV), TBC (Quantiferon TB Gold Plus, IGRA test and chest X–ray)	1. Medical interview to check for and observation for symptoms of infection, including opportunistic infections (especially varicella zoster virus) and neuroinfections (at each visit)	No need to monitor from the perspective of the safety profile of the therapy unless patients develop signs and symptoms of opportunistic infection with possible CNS involvement (eg PML)

PML — progressive multifocal leukoencephalopathy, JCV — JC virus, SmPC — summary of product characteristics, MRI — magnetic resonance imaging, PCR — polymerase chain reaction, ALT — alanine aminotransferase, AST — aspartate aminotransferase, GGTP — gamma–glutamyl–transpeptidase, TSH — thyroid–stimulating hormone, ARN — acute retinal necrosis, GCN – JC virus granule cell neuronopathy, FLAIR — fluid attenuated inversion recovery, DWI — diffusion weighted imaging, CNS — central nervous system

#In each case, attention should be paid to the detailed recommendations in the current SmPC of a given medicinal product

*The signs and symptoms of decompensated liver failure include palmar erythema, yellowing of the sclera, ascites, Medusa's head sign, hepatosplenomegaly, pruritus, stellate angiomas (telangiectasia) on the abdomen and chest

**Signs and symptoms suggestive of PML: cognitive and behavioral disorders as well as other new neurological symptoms to be differentiated in the case of a suspected MS relapse

- Tests for (latent) infections should be performed to select the optimal drug before initiating a highly effective and immunosuppressive DMT. Particular attention should be paid to the JC virus, HBV, HIV, *Mycobacterium tuberculosis* and varicella zoster virus (VZV). If necessary, an infectious disease specialist should be consulted
- Before initiating treatment with natalizumab, the anti-JCV antibody index should be determined and the risk of progressive multifocal leukoencephalopathy (PML) should be stratified. During treatment with natalizumab, monitoring the anti-JCV antibody index is recommended. Extending the interval between the doses to six weeks may be considered after stabilisation of the disease to reduce the risk of PML development
- Preventive vaccinations should be performed before starting immunosuppressive DMT
- Drug dosing and additional tests before starting DMT and during treatment monitoring should be determined based on the current version of drug characteristics (SmPC).

Treatment of secondary progressive multiple sclerosis

Secondary progressive multiple sclerosis (SPMS) is characterised by gradual, relapse-independent disability progression after an initial relapsing-remitting course. In the early phase of SPMS, relapses and/or radiological activity (active SPMS) may occur. Currently, there are no unified diagnostic criteria for SPMS [9]. Siponimod, IFN-beta 1b, or mitoxantrone are recommended in active SPMS [13]. The choice of DMT should be individual and based on disease activity and progression, the adverse effect profile, and patient preferences.

Recommendations

- Siponimod or INF-beta 1b should be offered to patients with SPMS with signs and symptoms of inflammatory activity (relapses and/or radiological activity).

- Mitoxantrone may be considered in patients with active SPMS when there is no other therapy available. However, potential adverse effects should be taken into account.

Treatment of primary progressive multiple sclerosis

Primary progressive multiple sclerosis (PPMS) is characterised by the progression of disability from the onset of the disease without evident relapses [9]. Ocrelizumab has been approved for the treatment of PPMS based on clinical trials [60]. Its efficacy and safety have been confirmed in a clinical trial in patients at age < 55 years with disease duration < 15 years and a lower level of disability (EDSS < 6.5). Ocrelizumab is used in the treatment of adult patients with early PPMS assessed based on disease duration and the level of disability, as well as radiological features characteristic of inflammatory activity [35].

Initiation of treatment must be preceded by a thorough analysis of the benefit-risk ratio associated with the use of ocrelizumab [61, 62], which is particularly relevant in the case of older patients with PPMS without disease activity, in whom symptomatic treatment alone may be most appropriate.

Recommendations

- Ocrelizumab is recommended for patients with early and (clinically and/or radiologically) active PPMS
- Treatment effectiveness should be evaluated every 12 months. Treatment discontinuation should be discussed with the patient if there is significant disease progression.

Monitoring and change of DMT

Monitoring of MS treatment has two aims:

1. ensuring the safety of the therapy (monitoring clinical, laboratory and radiological parameters that may indicate adverse effects)
2. rapid detection of the ineffectiveness of therapy to modify it (monitoring of clinical and radiological disease activity).

Monitoring DMT safety

Monitoring of MS therapy for safety is mainly defined for individual drugs based on their SmPCs [27–42, 63]. Table 2 sets out clinical, laboratory and radiological parameters that must be regularly monitored to avoid, or early detect, possible adverse effects of individual DMTs. They are developed based on the provisions of the SmPCs and international recommendations [13, 22]. It should be noted that the monitoring of therapy in women also includes performing a pregnancy test each time pregnancy is suspected and in accordance with the SmPC.

The occurrence of adverse effects may be the basis for changing the therapy to a drug with a different safety profile. Severe adverse reactions require discontinuation of therapy, regardless of its duration, followed by a decision to reintroduce DMT. Serious adverse reactions of DMT include:

- anaphylactic reaction requiring immediate discontinuation of treatment
- liver failure or alanine transaminase (ALT) and aspartate transaminase (AST) > 3–5 x the upper limit of normal (ULN)
- leukopenia, particularly grade 3 and 4 neutropenia (< 1,000/mm^3 and < 500/mm^3, respectively) [64] and grade 3 (< 500/mm^3) and grade 4 lymphopenia (< 200/mm^3) (except for therapy with sphingosine receptor modulators, during which lymphocyte count may decrease to 200/mm^3, but not below this level) [65]
- thrombocytopenia, especially < 50,000/mm^3 [66]
- progressive multifocal leukoencephalopathy (PML) requiring immediate discontinuation of treatment
- severe skin complications due to injection therapy (abscess, necrosis).
- Highly effective therapies (HETs) may need to be discontinued and switched to a therapy with no immunosuppressive potential when the patient presents with:
- malignant neoplasm
- hepatitis B or C
- tuberculosis
- HIV
- another severe infection.

If pregnancy is confirmed, immediate discontinuation of DMT is usually recommended. Treatment with glatiramer acetate, beta-interferons, and natalizumab (until the 34th week of gestation) may be continued during pregnancy provided that the maternal benefit outweighs the potential risk to the foetus [67].

If teriflunomide is discontinued and switched to another therapy, regardless of the reason for treatment modification, the patient should undergo the standard procedure, i.e. accelerated drug elimination using oral cholestyramine (8 g 3 x day, or in the case of poor tolerance of the dose, 4 g 3 x day for 11 days) or oral activated charcoal (50 g every 12 hours for 11 days) before initiating a new therapy. If teriflunomide is discontinued due to planned pregnancy, the efficacy of drug elimination should be confirmed by the assessment of blood drug levels twice, with an interval of at least 14 days. The target concentration of the drug should be less than 0.02 mg/l [34, 67].

Monitoring effectiveness of DMT

Monitoring the effectiveness of MS therapy does not differ for individual drugs and should include [68]:

- regular neurological examination with assessment of the EDSS score at least once a year

– assessment of the radiological activity of the disease using brain MRI (new and/or enlarging T2 lesions and/or Gd(+) lesions) should be performed at least once a year. In the first year of treatment (3–6 months after the start of therapy), a contrast MRI (the so-called re-baseline MRI) may be considered to which subsequent MRI scans can be compared. In the absence of relapsing activity and new radiological lesions, another MRI without contrast administration may be considered.

If a relapse occurs, the following should be performed:

– a neurological follow-up examination during the relapse and c.90 days after the onset of relapse symptoms
– (if possible) a follow-up/comparative MRI examination before and after contrast administration (preferably before administration of high doses of glucocorticoids)
– a follow-up MRI examination of the relevant section of the spinal cord and a comparison of this examination with the baseline MRI in the case of spinal cord relapse.

The lack of effectiveness of the therapy can be found at least 6-9 months after its initiation and usually after 12 months. Change of treatment due to its ineffectiveness may occur earlier in exceptional cases i.e. due to high disease activity/aggressive course of the disease, and especially disease activity higher than before the start of therapy [9, 69, 70].

Definition of DMT ineffectiveness

There is no uniform definition of DMT ineffectiveness [13, 22, 68]. There is currently no therapy for complete recovery from MS. Therefore, residual clinical and/or radiological activity during DMT is highly possible.

Therapy is usually considered ineffective if one of the following conditions is met mostly after 12 months of therapy:

– at least 1 relapse
– at least 1 MRI lesion enhancing after contrast administration
– at least 2 new/enlarging T2 lesions on MRI
– a significant increase in disability (EDSS) lasting for 3–6 months (an increase of 0.5 or 1 point, depending on the baseline EDSS score).

DMT switching

A change in treatment can be related to an escalation strategy (escalating from moderate efficacy to higher efficacy) or a lateral switch (within the same category of DMT efficacy). If a DMT is ineffective, it should be escalated or changed to any other highly effective drug (lateral switch) if the patient is already treated with a highly effective DMT. However, lateral switching is usually recommended when adevrse reactions occur (see above and Tab. 2).

Regardless of the reason for changing treatment, the choice of another DMT should depend on similar factors as in the choice of the first therapy (see above) [22]. When switching DMTs, the duration of action of individual drugs should be considered to avoid the potential consequences of combining different therapies. Recommendations on time intervals to be maintained between therapies (wash-out) are given in Table 3.

Recommendations

- During DMT use, clinical and radiological parameters should be monitored by assessing the patient's neurological status and performing an MRI examination at least once a year
- MRI examination without contrast administration may be considered in the absence of relapse activity and new radiological lesions
- A more effective DMT should be used if disease activity occurs during therapy with a moderately effective drug
- Switching to a highly effective drug with a different mechanism of action should be made if disease activity occurs during highly effective DMT
- Therapy with another highly effective drug should be considered immediately if it is necessary to discontinue DMT affecting lymphocyte migration (natalizumab, S1P receptor modulators) due to the high risk of disease reactivation
- Scheduled administration of the next treatment cycle should be primarily considered based on the approved regimen if disease activity occurs before administration of the full therapeutic dose (before the second treatment cycle) of reconstitution therapies (cladribine tablets, alemtuzumab)
- In patients on reconstitution therapies (cladribine tablets, alemtuzumab), additional treatment cycles should be considered after assessing the benefit-risk ratio if disease activity recurs after a stabilisation period induced by the standard dose of the drug (two cycles)
- De-escalation of treatment should be considered: a highly effective DMT should be replaced with a moderately effective DMT in some cases – e.g. during pregnancy or due to patient safety
- If adverse reactions occur during DMT, another drug should be administered based on its safety profile, or, if the adverse reaction is due to the route of administration, the route should be changed if possible.

Completion of disease-modifying therapy

With the long-term course of MS, age-related changes to the immune system are observed (immunosenescence). The consequence of this process is associated with a change in the nature and severity of inflammatory reactions underlying the

Table 3. Recommended time intervals between the use of disease-modifying drugs in multiple sclerosis [95]

Switching from to	Beta-interferons	Glatiramer acetate	Dimethyl Fumarate, Diroximel Fumarate	Teriflunomide	S1P receptor modulators	Natalizumab	Alemtuzumab	Anti-CD20 (ocrelizumab, ofatumumab, rituximab*)	Cladribine tablets
Beta-interferons		Not required	Not required	Not required	Not required	Not required	Not required	Not required	Not required (provided that the lymphocyte count is normal prior to the first administration of cladribine)
Glatiramer acetate	Not required		Not required	Not required	Not required	Not required	Not required	Not required	Not required (provided that the lymphocyte count is normal prior to the first administration of cladribine)
Dimethyl fumarate°, Diroximel fumarate °	Not required	Not required		Not required	Not required	Not required	Not required	Not required	Not required (provided that the lymphocyte count is normal prior to the first administration of cladribine)
Teriflunomide	Accelerated elimination procedure	Accelerated elimination procedure	Accelerated elimination procedure		Accelerated elimination procedure	Accelerated elimination procedure	Accelerated elimination procedure	Accelerated elimination procedure	Accelerated elimination procedure (provided that the lymphocyte count is normal prior to the first administration of cladribine)
S1P receptor modulators° *	Optimally #^ ≥ 4 weeks	Optimally#^ ≥ 4 weeks	Optimally #^ ≥ 4 weeks	Optimally #^ ≥ 4 weeks		Optimally #^ ≥ 4 weeks	Optimally #^ ≥ 4 weeks	Optimally #^ ≥ 4 weeks	Optimally # ≥ 4 weeks provided that the lymphocyte count is normal prior to the first administration of cladribine
Natalizumab *&	Optimally # ≥ 6 weeks	Optimally # ≥ 6 weeks	Optimally # ≥ 6 weeks	Optimally # ≥ 6 weeks	Optimally # ≥ 6 weeks		Optimally # ≥ 6 weeks	Optimally # ≥ 6 weeks	Optimally # ≥ 6 weeks provided that the lymphocyte count is normal prior to the first administration of cladribine
Alemtuzumab°	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months		Optimally # ≥ 6 months	Optimally # ≥ 6 months provided that the lymphocyte count is normal prior to the first administration of cladribine
Anti-CD20 - ocrelizumab - ofatumumab	Optimally # ≥ 6 months Optimally # ≥ 1–3 months	Optimally # ≥ 6 months Optimally # ≥ 1–3 months	Optimally # ≥ 6 months Optimally # ≥ 1–3 months	Optimally # ≥ 6 months Optimally # ≥1–3 months	Optimally # ≥ 6 months Optimally # ≥ 1–3 months	Optimally # ≥ 6 months Optimally # ≥1–3 months	Optimally # ≥ 6 months Optimally # ≥ 1–3 months		Optimally # ≥ 6 months provided that the lymphocyte count is normal prior to the first administration of cladribine Optimally # ≥1-3 months provided that the lymphocyte count is normal prior to the first administration of cladribine
Cladribine tablets °	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	Optimally # ≥ 6 months	

*the possibility of a severe rebound after treatment discontinuation; °before starting another DMT drug, it should be verified whether the lymphocyte count meets the criteria for the inclusion of another DMT (complete blood count with differential should be performed); &before starting another DMT drug, the possibility of carry-over PML should be considered; #related to individual decision making, depending on the clinical and immunological status of the patient; ^related to individual decision making, depending on the S1P receptor modulator due to significant differences in pharmacokinetic parameters

disease, as well as higher susceptibility to infections and cancer [71–73]. Clinically, a reduction in the frequency of relapses and a reduction in disease activity on imaging studies are observed. However, an accelerated accumulation of neurological disability independent of relapses is found [71, 74, 75].

Most of the data obtained in clinical trials is related to patients up to 55–60. The amount of information on the drug action, including efficacy and safety, for people over 60 is limited [76]. The potential decrease in the efficacy of DMT with age, combined with increasing susceptibility to infections/cancer and comorbidities, means that some patients may experience an unfavorable change in the benefit-risk ratio of DMT, which may result in decision on therapy discontinuation [77].

Currently, there are no methods that could reliably predict disease progression and the risk of disease reactivation after DMT is discontinued. Available studies were concentrated mainly on discontinuation of moderately effective DMT. The results suggest that older age (most often defined as > 50–60 years), a longer period of clinical stabilisation, and the absence of signs of disease activity on imaging studies are associated with a lower risk of recurrence of MS activity [78–88]. There is no consensus on the progression of neurological disability after stopping of moderately effective DMT [11, 13, 22, 23]. Completion of a highly effective DMT, especially as regards drugs that affect lymphocyte migration (natalizumab, S1P receptor modulators) is associated with a high risk of disease reactivation [89,90]. Currently, there is insufficient data to reliably assess the risk [82, 91].

The DISCO-MS trial to assess the effect of discontinuation of DMTs on MS course did not yield conclusive results [92]. Further clinical trials in this respect are being conducted in patients with RRMS (DOT-MS) and SPMS (STOP-I-SEP). Different studies have also been performed on the development of adequate prognostic tools [93].

Recommendations

- DMT should be continued in patients during clinical and radiological stabilisation of the disease if there are no contraindications related to the safety of therapy or treatment tolerance.
- If DMT is discontinued, the patient should be informed of all aspects of the situation, including the need to remain under the constant care of a neurologist and regular follow-up for early detection of possible disease reactivation.

Author's comment:

During the publication process additional monoclonal antibody – ublituximab (Briumvi®) was registered in European Union countries, including Poland.

Article information

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RESEARCH PAPER

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Acute polyneuropathy: a serious complication of levodopa/carbidopa intestinal gel treatment for Parkinson's Disease

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ABSTRACT

Aim of study. To determine whether a high dose of levodopa-carbidopa intestinal gel (LCIG), expressed as levodopa equivalent daily dose (LE daily dose), is a risk factor for acute polyneuropathy in patients treated with LCIG.

Clinical rationale for study. Treatment with LCIG is an effective device-assisted therapy in the advanced stages of Parkinson's Disease (PD). Polyneuropathy is a well-known complication of PD treatment. Patients treated with oral levodopa usually suffer from sub-clinical or mild chronic sensory polyneuropathy. However, severe acute polyneuropathy occurs in patients treated with LCIG, which is causally related to the treatment and leads to its immediate discontinuation. The etiology is not yet clear, but some patients with acute polyneuropathy have been given high doses of LCIG.

Material and methods. A retrospective multicentre study of patients treated with LCIG was performed. Patients with acute polyneuropathy were subjected to a detailed analysis including statistical processing.

Results. Of 183 patients treated with LCIG in seven centres, six patients (five females, median age 63 years) developed acute polyneuropathy with LCIG discontinuation. The median (interquartile range) initial and final LE daily dose in patients with and without acute polyneuropathy was 3,015 (2,695–3,184) and 1,898 (1,484–2,167) mg, respectively. The final LE daily dose of 2,605 mg cut-off had 83% sensitivity and 93% specificity for the prediction of acute polyneuropathy.

Conclusions and clinical implications. The risk of acute polyneuropathy in LCIG-treated patients was associated with a daily LE dose of greater than 2,605 mg or with more than a 62% increase in the daily LE dose during LCIG treatment.

Keywords: acute polyneuropathy, Parkinson's Disease, levodopa/carbidopa intestinal gel, levodopa equivalent daily dose

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Introduction

Treatment with levodopa/carbidopa intestinal gel (LCIG) is an effective device-assisted therapy in the advanced stages of Parkinson's Disease (PD).

Polyneuropathy is a well-known complication of PD treatment. Patients treated with oral levodopa usually suffer from sub-clinical or mild chronic sensory polyneuropathy associated with elevated homocysteine levels and cobalamin or folate deficiency [1]. The prevalence of polyneuropathy is higher in patients with LCIG (up to 75%), and polyneuropathy is divided into chronic, subacute, and acute cases. Acute polyneuropathy in LCIG can occur especially during the first two years of LCIG treatment, and its prevalence is up to 11% [2, 3]. Some patients have experienced a rapid progression of severe acute polyneuropathy, leading to discontinuation of the LCIG treatment [3–5]. The etiology is not completely understood, but it seems certain that this is an acute and serious complication of LCIG treatment and that the condition improves or stabilizes after treatment is stopped. Some research has suggested that this could result from the high doses of LCIG [3, 6]. Other causes of acute polyneuropathy have been repeatedly ruled out.

Clinical rationale for study

Acute polyneuropathy is a serious and disabling complication of LCIG treatment. In this retrospective study, we focused on the association between the development of acute polyneuropathy and the dose of LCIG (expressed by levodopa equivalent (LE) daily dose [7]). If a statistically significant correlation were to be demonstrated, the results would be important for setting rules when starting LCIG treatment to minimize the risk of developing acute polyneuropathy.

Material and methods

Specialists from seven movement disorders centres in the Czech Republic and Slovakia were invited to complete a multicentre retrospective survey of all patients treated with LCIG therapy. All patients met the clinical criteria for advanced Parkinson's Disease [8]. The survey included basic demographic information including sex, age, clinical data, the incidence of polyneuropathy, the LE daily dose immediately before starting LCIG therapy (the initial LE daily dose), and the dose after three months on LCIG or before LCIG discontinuation due to acute polyneuropathy (the final LE daily dose).

In all patients with polyneuropathy, we were interested in its clinical manifestation and management: symptomatic therapy, LCIG dose reduction, or discontinuation. The diagnosis of polyneuropathy was based on a clinical examination and electrophysiological studies. Special attention was paid to cases of acute severe polyneuropathy which led to the discontinuation of LCIG. Acute polyneuropathy was defined as the development of polyneuropathic symptoms from within a few days to maximally a few weeks, leading to a rapid deterioration of the condition. Polyneuropathic symptoms were defined as dysesthesia/paraesthesia, hypesthesia, pain, or weakness in the extremities beginning in a typical distribution distally in the lower extremities and spreading proximally to the upper extremities. A clinical diagnosis was made according to the clinical criteria of polyneuropathy [9]. In these patients, more detailed information was further requested: clinical symptoms, concomitant diseases, and medication, electrophysiological studies, information about cobalamin or folate substitution, plasma levels of cobalamin and folate, lumbar puncture results, the interval between LCIG titration and polyneuropathy onset, the clinical outcome after LCIG withdrawal, and the actual LE daily dose at the time of polyneuropathy diagnosis.

When appropriate, continuous data was expressed as median and interquartile range (IQR). Differences in the primary outcomes between sexes were compared using the Fisher exact test. For univariate and multivariate prediction models, logistic regression was used, and the odds ratio was computed. The differences between the centres were subject to the Kruskal-Wallis test. P-values of less than 0.05 were considered statistically significant. Analyses were conducted using the R statistical package version 4.0.3.

Results

A total of 183 patients in the advanced stage of PD (80 females and 103 males, median age 69 (IQR 63–74)) years treated with LCIG were reported. Clinically relevant polyneuropathy occurred in 27 (15%) patients (10 *de novo* and 17 pre-existing cases), the majority of whom had mild chronic axonal polyneuropathy.

However, six of the 183 patients (3.3%), 5/6 women, median age 63 (IQR 57–68) years, developed acute severe polyneuropathy, which led to an immediate discontinuation of LCIG treatment. All patients with acute polyneuropathy met the clinical criteria for advanced stage Parkinson's Disease, and no red flags indicating another cause of Parkinson's syndrome were observed. Two patients developed acute polyneuropathy as a *de novo* polyneuropathy, and one patient had mild axonal polyneuropathy before LCIG initiation. In the remaining three patients, no electrophysiological studies were performed before LCIG treatment, but the patients did not have any pre-existing subjective or clinical signs of polyneuropathy. Polyneuropathic symptoms arose and worsened within a matter of days. Patients 1 and 2 suffered from paresthesia and dysesthesia, and patient 6 from dysesthesia only. Other patients developed flaccid paraparesis that progressed to tetraparesis. Patients 1, 2, 3, and 5 experienced a loss of dyskinesias and a gradual deterioration of Parkinsonian symptoms despite LCIG dose escalation. All patients with acute polyneuropathy were on LCIG monotherapy.

Table 1. Characteristics of six patients with acute polyneuropathy and LCIG discontinuation

Patient no.	1	2	3	4	5	6
Sex	F	F	F	F	F	M
Age [years]	66	56	68	60	69	54
PD duration [years]	16	13	6	16	5	14
Initial LE daily dose [mg]	2,238.75	1,950	1,845	2,671	1,363.25	923
Final LE daily dose [mg]	3,139	2,890	3,199	4,033	2,630	1,825
LCIG duration [days]	132	121	346	27	227	223
Cobalamin plasma level [normal 191–663 ng/L]	221	191	921	209	177	325.3
Folate plasma level [normal 3.1–17.5 ug/L]	5	2.2	3.1	6.4	1.7	3.74
The main clinical symptoms of polyneuropathy	Paresthesia, dysesthesia	Paresthesia, pain, dysesthesia	Paraparesis, fatigue	Paresthesia	Paraparesis	Dysesthesia
Initial electrophysiological studies	Normal	NK	NK	Axon Sens	Normal	NK
Final electrophysiological studies	Axon Dem Sens Mot	Axon Sens	Axon Dem Sens Mot	Axon Dem Sens Mot	Axon Sens Mot	Axon Sens
Outcome	Improved	Improved	Improved	Stabilized	Stabilized	NK
Initial BMI	16.7	NK	25.5	25	26.2	NK
Final BMI	17.7	NK	23.6	25	NK	NK

Age (years): age at the time of polyneuropathy onset; PD duration (years): duration of Parkinson's Disease; Initial LE daily dose (mg): LE daily dose before initiation of LCIG treatment; final LE daily dose (mg): LE daily dose at discontinuation of LCIG treatment due to acute polyneuropathy; LCIG duration (days): duration of LCIG treatment; Cobalamin plasma level after acute polyneuropathy onset; Folate plasma level after acute polyneuropathy onset; Initial electrophysiological studies: electromyography before LCIG treatment; Final electrophysiological studies: electromyography after acute polyneuropathy onset; Polyneuropathy specification (Axon = axonal, Dem = demyelinated, Mot = motor, Sens = sensory); Outcome after LCIG discontinuation (improved/stabilized/worsened); initial BMI (BMI before LCIG treatment); final BMI (BMI after polyneuropathy onset). M — male; F — female; NK — not known; BMI — body mass index

No significant weight changes were observed in patients with acute polyneuropathy during LCIG treatment. None of these patients took a cobalamin and folate substitution before the onset of symptoms. Cobalamin levels were low in patients 2 and 5 and high in patient 3. Folate depletion was shown in patients 2, 3, and 5. The other patients had these parameters within the normal range. However, after the development of polyneuropathy, a B-vitamin substitution was initiated. Acute polyneuropathy began 1-11 months after LCIG initiation. LCIG discontinuation and B-vitamin substitution led to stabilization or improvement of the polyneuropathy symptoms in five patients, while the outcome of patient 6 remains unknown. For more details, see Table 1.

Other causes of polyneuropathy were also considered. A basic screening was performed, where normocytic anemia was detected in patients 2 and 4. Patients 2, 3, and 4 also underwent a lumbar puncture, where the number of elements and protein levels were normal, and the serological examination did not show any pathological findings. Patients 1, 2, and 6 had no comorbidities and received dopaminergic treatment only. Patient 3 suffered from hypothyroidism for a long time but reacted well to substitution therapy. Patients 4 and 5 suffered from depressive syndrome and were chronically treated with selective serotonin reuptake inhibitors (SSRI).

The median initial LE daily dose in patients without acute polyneuropathy was 1,350 (IQR 1,118–1,713) mg, which did not differ across the centres ($p = 0.97$). The median final LE daily dose in patients without acute polyneuropathy was 1,543 (IQR 1,200–2,045) mg (Tab. 2). Nevertheless, the final LE daily dose significantly differed among the centres ($p < 0.01$). The LE daily doses were mostly increasing [median 14% (IQR -8–47%)], (Fig. 1).

The median LE daily dose of patients with acute polyneuropathy increased from an initial 1,898 (IQR 1,484–2,167) mg to a final 3,015 (IQR 2,695–3,184) mg, $p < 0.01$. Compared to patients without severe polyneuropathy, a higher dose change percentage was reported in acute polyneuropathy patients (median of 62% increase, IQR 49–88%, $p = 0.05$). In contrast to the LE daily doses, univariate analysis did not show that female sex *per se* was a predictor of acute polyneuropathy ($p = 0.09$).

A multivariate logistic regression model (Model 1 considering sex and the final LE daily dose) confirmed that acute polyneuropathy was predicted by female sex (OR = 17.4006, 95% CI: 1.3601–222.6088, $p = 0.0281$) together with final LE daily dose (OR = 1.0028, 95% CI: 1.0012–1.0044, $p = 0.0006$). A different model (Model 2 considering sex, initial LE daily dose, and dose change) showed that female sex (OR = 21.3809, 95%

Table 2. Epidemiological data of patients treated with LCIG with and without development of acute polyneuropathy

	Patients with acute polyneuropathy (n = 6)	Patients without acute polyneuropathy (n = 177)	P-value
Male/female	1/5	102/75	0.09
Median age [years] (Interquartile range IQR)	63 (57–67.5)	69 (63–74)	0.07
Median initial LE daily dose [mg] (IQR)	1,898 (1,484–2,167)	1,350 (1,118–1,713)	0.08
Median final LE daily dose [mg] (IQR)	3,015 (2,695–3,184)	1,543 (1,200–2,045)	< 0.01
Median LE daily dose change [%] (IQR)	62 (49–88)	14 (–8–47)	0.05

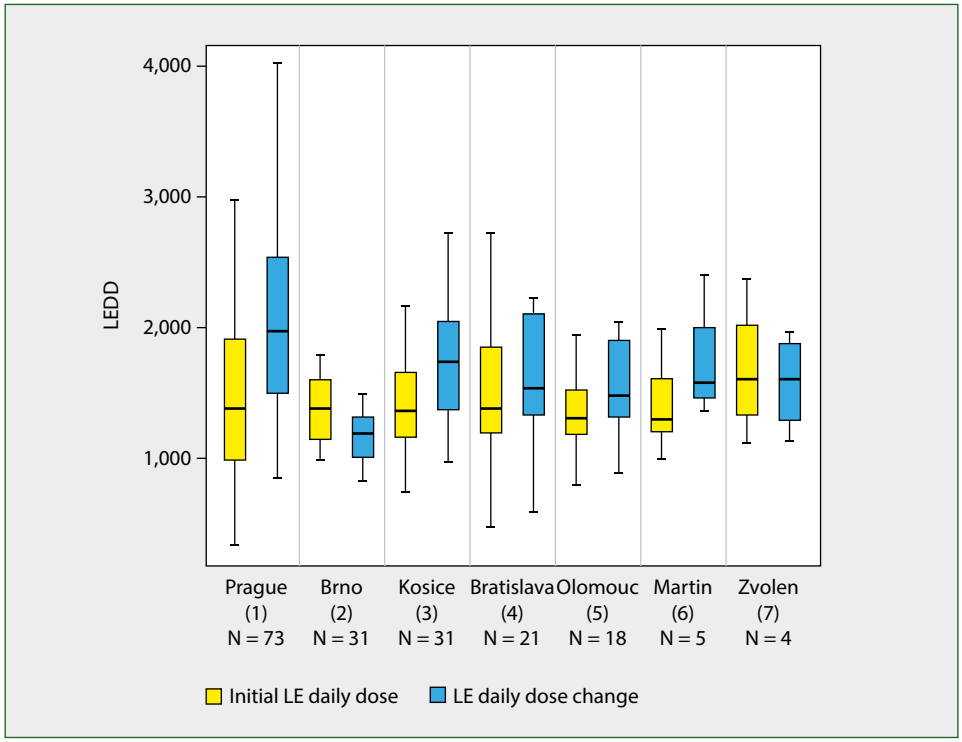

Figure 1. Comparison of initial LE daily dose and final LE daily dose among seven centres in the Czech Republic and Slovakia

CI: 1.2638–361.7058, p = 0.0338) together with initial LE daily dose (OR = 1.0032, 95% CI: 1.0012–1.0052, p = 0.0020) and dose change (OR = 1.0245, 95% CI: 1.0072–1.0420, p = 0.0052) also predicted acute polyneuropathy.

ROC (receiver operating characteristic) analysis (Fig. 2) showed high sensitivity and specificity for the LE daily dose as a predictor of acute polyneuropathy. The final LE daily dose was more strongly associated (area under ROC curve (AUC) 92%, threshold 2,605 mg, sensitivity 83% and specificity 93%) with the risk of acute polyneuropathy than the initial LE daily dose (AUC 70%, threshold 1,823 mg, sensitivity 67% and specificity 80%) or dose change (AUC 83%, threshold 40%, sensitivity 100% and specificity 71%).

Discussion

Our study aimed to report a retrospective evaluation of the development of polyneuropathy in patients treated with LCIG.

The total prevalence of polyneuropathy, regardless of origin and progression rate, was 15% for all LCIG patients from the seven Czech and Slovak centres, which roughly corresponds to the incidence of polyneuropathy estimated in previous studies [2, 5, 10]. The cause, duration, and association with LCIG treatment in all forms of polyneuropathy were difficult to determine. Subjective symptoms can be minimal in many patients, and electromyography is not yet a routine examination in all patients treated with LCIG.

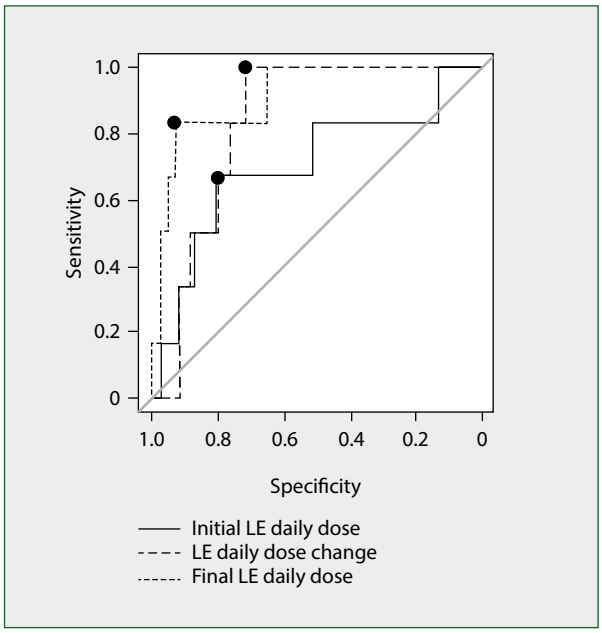

Figure 2. ROC analysis: sensitivity and specificity of factors associated with acute polyneuropathy. Depicted points indicate the level of sensitivity and specificity of each factor: initial LE daily dose (sensitivity 67% and specificity 80%); dose change (sensitivity 100% and specificity 71%); and final LE daily dose (sensitivity 83% and specificity 93%)

We focused on patients with acute polyneuropathy because this form is severe, often disabling, and repeatedly linked directly to the initiation of LCIG. It led to the immediate discontinuation of LCIG. The prevalence of acute polyneuropathy with the need for LCIG discontinuation in our group was relatively low (3.3%) and mostly linked to the female sex.

A causal relationship between the development of acute polyneuropathy and LCIG therapy appears to be unquestionable [3, 11–13] despite isolated objections [14]. The stabilization or even improvement of acute polyneuropathy after LCIG discontinuation, which we observed in our group of patients, also confirms a causal connection [4, 5, 12, 15]. A high LE daily dose as a risk factor for the development of acute polyneuropathy has been previously suspected; however, no detailed statistical analyses of patient cohorts were available [3–5, 12]. Therefore, we performed a comparison between patients with and without acute polyneuropathy.

The initial LE daily dose was not statistically different between patients with and without acute polyneuropathy. However, the final LE daily dose was significantly higher in the group of patients with acute polyneuropathy than in patients without. Also, the LE daily dose change was significantly higher in patients with acute polyneuropathy.

In addition, we demonstrated that a final LE daily dose over the threshold of 2,605 mg was a high-risk factor for acute polyneuropathy development in patients treated with LCIG. Since all patients with acute polyneuropathy were on LCIG monotherapy, the LE daily dose is equivalent to the LCIG dose. This result prompts a reconsideration of the appropriateness of such high doses.

We found only one safety study [10] in LCIG patients using doses higher than 2,000 mg, which reported more patients with acute polyneuropathy compared to patients with lower doses. However, no statistical analysis was performed. Thus, a dose of LCIG corresponding to the equivalent of 2,605 mg was considered the upper safe limit of LCIG treatment for the development of acute polyneuropathy in our study.

Two main mechanisms are probably involved in the development of acute polyneuropathy in LCIG patients: (i) intrinsic predisposition and (ii) the 'adverse' effects of high doses of LCIG on the jejunal membrane or directly on the peripheral nerves in predisposed patients. Predisposition could be a genetic factor, such as a low-activity catechol–O–methyltransferase (COMT) genotype, which is associated with a greater risk of polyneuropathy in PD patients [16]. Acquired predispositions include dysimmune or post-infective factors affecting the peripheral nerves. The 'adverse' effect could be direct damage caused by levodopa/carbidopa and/or gel to the peripheral nerves or the jejunal wall.

Adverse effects of levodopa/carbidopa *per se* are less likely because patients treated with oral levodopa/carbidopa may also suffer from polyneuropathy, but most commonly suffer from chronic axonal polyneuropathy at a mild to moderate intensity which is associated with higher levels of homocysteine and methylmalonate [1]. Acute polyneuropathy associated with oral levodopa/carbidopa has not been described in the literature but can develop accidentally due to another cause.

The gel in LCIG is composed of methylcellulose and water. For various reasons, methylcellulose is commonly used as a cheap and safe food additive. However, in studies using animal models, an association of methylcellulose administration with a change in microbiota and a higher incidence of inflammatory bowel disease has been described [17]. Prospective studies with a jejunal membrane biopsy in patients with acute polyneuropathy are needed. In contrast, no study has yet demonstrated methylcellulose's direct toxic effect on the peripheral nerves.

Considering malabsorption, we looked for cachexia development in patients with acute polyneuropathy. According to the BMI, only patient 1 showed evidence of cachexia, and, in contrast, there was a slight weight gain after the initiation of LCIG. Other available data (Tab. 1) showed normal BMI values in half of the patients. Cachexia was not detected even in the patient who developed acute polyneuropathy after 11 months of treatment. Thus, we did not demonstrate a clear association between low weight and the development of acute polyneuropathy.

The insufficient effectiveness of LCIG treatment with the necessity to further increase doses and the loss of dyskinesias (even with higher dosing) could support the theory of damage to the jejunal wall when levodopa is not properly absorbed. Low levels of cobalamin and/or folate in some patients can also indicate some malabsorption. Unfortunately, no previous

studies have discussed the need for dose escalation and the presence or absence of dyskinesia in patients with subsequent acute polyneuropathies.

Five of our six patients with acute polyneuropathy were menopausal women. However, female sex alone is not a predictor of acute polyneuropathy, as it requires additional factors the final LE daily dose or the initial LE daily dose together with dose change. Several reports mention the preponderance of female sex in LCIG patients with acute polyneuropathy [4, 12], although statistical analyses are lacking. The reason for this is unknown, but dysimmune or endocrine mechanisms should be considered.

We are aware that the retrospective nature of this study and the small number of patients with acute polyneuropathy represent limitations. Fortunately for patients, acute polyneuropathy is a rare complication of LCIG treatment and therefore the number of patients with this diagnosis is not high.

Nevertheless, we still consider it important to publish these results even given these limitations, because they can help improve understanding of the risk factors, and by extension the causes, of acute polyneuropathy.

Clinical implications/future directions

Our retrospective study found that patients with acute polyneuropathy received significantly higher LCIG doses than those without. We identified a threshold of 2,605 mg or a substantial dose increase (median 62%) as strong predictors for developing this condition. Additionally, we observed that the absence of dyskinesias and worsening akinesia, despite increasing LCIG doses, were warning signs for potential acute polyneuropathy. Considering these factors at the start of LCIG treatment can help minimize the risk of this complication.

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Comparison of headache and facial pain prevalence and phenotype in upper respiratory tract infections of differing origins — a cross-sectional study

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ABSTRACT

Aim of study. This study aimed to compare headache and facial pain prevalence and headache phenotype among people with common upper respiratory tract infections (URTIs).

Clinical rationale for study. Headache is a common symptom in viral URTI, but its phenotyping has so far been limited to coronavirus disease 2019 (COVID-19) and influenza. Additionally, the prevalence of facial pain in URTIs has only rarely been discussed in scientific publications.

Material and methods. Patients with acute URTI symptoms were evaluated for headache phenotype using a semi-structured questionnaire. Antigen swab tests were performed in all participants.

Results. The analysis included 276 URTI/APVRS (acute post-viral rhinosinusitis) episodes in 223 patients (136 women, 60.1%) aged 18–73 [mean 41.3 / median (25th, 75th) 40 / standard deviation 15.1]. Participants were diagnosed with: COVID-19 — 107/276 (38.8%); 'common cold' — 103/276 (37.3%); influenza — 36/276 (13.0%); or APVRS — 30/276 (10.9%). Headache was present in 183/276 (66.3%) and URTIs and facial pain in 107/276 (38.8%). Predictors of headache in URTIs included sinonasal symptoms (odds ratio (OR) 10.70, $p < 0.001$) and fever (OR 2.9, $p = 0.004$). Headache more often ($p = 0.030$) had a migraine-like phenotype in COVID-19 (27.4% (20/73) vs. 9.1% (10/110) and tension-type headache (TTH)-like phenotype in 'common cold' (75.4%, 49/64 vs. 61.3%, 73/119). Previous COVID-19 immunisation (vaccination or infection) was associated ($p = 0.004$) with a lower prevalence of migraine-like headache [6.3% (1/16) vs. 32.8% (19/58)].

Conclusions and clinical implications. Headache and facial pain are prevalent during URTIs, and are associated with general and sinonasal immune response rather than virus type. Headache phenotype may depend on the causative microorganism, but it can evolve in response to previous immunisation. Our study supports vaccination against COVID-19, as people with prior immunisation are probably less likely to experience migraine-like headache.

Keywords: migraine, tension-type headache, COVID-19, SARS-CoV-2, influenza, common cold

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Introduction

Headache and facial pain are highly prevalent in neurological practice. However, they are not specific to one disorder, and require differentiating between primary and secondary aetiologies. For that purpose, the phenotypes of headache attributed to different disorders should be clearly defined. The current literature provides limited data on the phenotype of headache or facial pain in upper respiratory tract infections (URTI) — one of the most prevalent secondary causes of pain

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in the head [1, 2]. Scientific interest in this complaint was renewed when the coronavirus 2019 (COVID-19) pandemic broke out [3]. Many publications in this area have led to the conclusion that headache is common during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [4–6]. Moreover, the available research allowed a typical headache phenotype to be described, and new classification criteria were proposed [4].

However, it should be remembered that SARS-CoV-2 is but one of many infective agents responsible for URTIs often classified under the umbrella diagnosis of 'common cold' [7]. The microorganisms that cause this disease include most often rhinoviruses, respiratory syncytial viruses (RSV), parainfluenza viruses, metapneumovirus, and other types of coronavirus [8–11]. Additionally, several infective agents cause infections with more severe disease, warranting a specific clinical approach. The most prevalent among these are influenza A and B viruses [12].

All of the above-mentioned microorganisms have been confirmed as causing headache during the acute infection phase [1]. This observation prompts the question as to whether headache in URTIs is specific to a particular virus, or is a result of pathomechanisms shared by these viral infections. Furthermore, it should be noted that both the migraine and the tension type-resembling headache phenotype have been described in COVID-19 and influenza [13, 14]. This in turn once again indicates that particular headache features might not be related to causative microorganisms, but rather to other factors modulating common pathways.

It should also be noted that COVID-19 can cause headaches that last longer than the active viral infection, especially when accompanied by post-COVID (sometimes called 'long COVID') conditions [15–17]. However, prolonged post-viral complaints have also been reported in literature predating the SARS-CoV-2 pandemic. One such prolonged syndrome after acute viral infection, proposed by European experts, is acute post-viral rhinosinusitis (APVRS) [18, 19]. Facial pain and headache are common in this condition. Once again however, the literature contains little data allowing a comparison between this disorder and acute viral symptoms.

Clinical rationale for study

The purpose of this study was to compare headache and facial pain phenotype in COVID-19, 'common cold', influenza, and APVRS. We hypothesised that headache is a symptom caused by an inflammatory response rather than a causative organism. Consequently, in acute infections with more pronounced inflammatory response (e.g. COVID-19, influenza), a headache should have a different prevalence or phenotype to a headache caused by 'common cold' or APVRS. To further evaluate this concept, this study also aimed to assess whether factors indicative of a stronger innate immune response (e.g. fever) or a local response (i.e. rhinitis) are associated with a different headache phenotype. Additionally, we looked for evidence that prior SARS-CoV-2 immunisation may lead to a different headache phenotype.

Material and methods

This was a cross-sectional study set in a primary care clinic serving a population of c.10,000 people. This study recruited consecutive adult patients who attended a physician consultation for recent (< 12 weeks) onset of acute URTI symptoms (anterior/posterior nasal discharge and/or nasal congestion and/or sore throat and/or fever and/or myalgia). Consultations in the same patient for different URTIs were allowed if the patient had reported a period of at least three weeks without any symptoms from the upper respiratory tract between infections. The study was approved by the Ethical Committee of Warmia and Mazury Medical Chamber (17/2023/VIII). The trial was registered in Clinical Trials (NCT06127186). Written informed consent was obtained from all participants before inclusion.

Patients were excluded from the study if they met any of the following criteria:

- Isolated general symptoms (i.e. fever and/or myalgia) without signs of URTI on physical examination
- Recurrent URTI (> 3 episodes of URTI in 6 months prior to visit)
- Chronic or recurrent upper respiratory tract disorders (i.e. allergic and nonallergic rhinitis, chronic rhinosinusitis, neoplasms)
- Immunodeficiency disorders
- Situations that prevented the performance of an examination (i.e. neurological or psychiatric disorders which made it impossible to obtain informed consent or a reliable medical history)
- Any chronic headache or facial pain (i.e. occurring on more than 14 days per month for more than three months prior to consultation). Patients with episodic headache (e.g. episodic migraine or tension-type headache) were not excluded
- Acute bacterial URTI
- No resolution of symptoms four weeks after URTI onset or 12 weeks in APVRS.

A practice nurse assessed the patients for URTI symptoms. If any symptom was present, then on the same day the patient was examined by a general practitioner with a special interest in headache (MS). History and physical examination were collected by the investigator with the help of a semi-structured questionnaire to decrease the risk of omitting data. Patient responses were noted if a particular symptom was present in any form on the day of consultation to avoid recall bias. Questions addressed:

- URT symptoms (time from onset, nasal discharge and congestion, hyposmia/anosmia, facial pressure, cough, fever)

- Headache and facial pain (location, intensity, character, duration)
- Accompanying symptoms (nausea, vomiting, cranial autonomic symptoms (CAS) according to trigeminal autonomic cephalalgias criteria in International Classification of Headache Disorders 3 — ICHD-3 [20])
- Physical examination (body temperature, oxygen saturation, heart rate, arterial pressure, anterior rhinoscopic examination, throat inspection).

Headache phenotype was classified using the ICHD-3 criteria for migraine without aura (B+C+D) or infrequent TTH (B+C+D) [20]. Cases that could not be classified as either of these were labelled 'unclassifiable' even if 2/3 criteria were met. An acute viral URTI diagnosis was confirmed if the inclusion criteria were met in combination with signs of URTI on physical examination (i.e. nasal discharge anterior/posterior, nasal mucosa oedema, nasal/throat mucosa reddening) and/or a positive antigen swab test result for COVID-19, influenza A/B virus or RSV (CorDx Test COMBO: COVID-19 positive predictive value (PPV) 89.09%, negative predictive value (NPV) 100.00%, Influenza A: PPV 100.00%, NPV 99.34%, Influenza B: PPV 96.00%, NPV 99.60%, RSV: PPV 98.98%, NPV 99.21%). APVRS was diagnosed according to the European Position Paper on Rhinosinusitis (EPOS 2020) in subjects with symptoms duration of 10 or more days. Currently no validation study in Polish for EPOS criteria is available. However, English language studies have confirmed the excellent sensitivity and specificity of EPOS 2012 [19]. Previous COVID-19 immunisation (vaccination and/or infection confirmed by a polymerase chain reaction or antigen test) was verified in the national electronic database in subjects with a positive swab test result for SARS-CoV-2 infection. A follow-up telephone consultation was performed to ensure symptom remission according to the exclusion criteria (after four weeks in URTI or 12 weeks in APVRS).

The recruitment target was based on the following premises: 1. Study duration of one infective season (November 2023 to March 2024) with c.1,000 URTI cases having been seen in participating primary care practices in previous seasons; and 2. Differences in incidence of migraine-like headache phenotype based on previous observations from this research group — 29% in COVID vs. 10% in 'common cold' (the latter value was an educated guess based on the authors' experience) [5]. The sample size calculation was performed with an online tool with $p < 0.05$ and 80% power [21]. The sample size was estimated at $n \geq 67$ in COVID-19 and $n \geq 67$ in 'common cold'. The calculated sample size was considered a minimal value which could be larger if more subjects were recruited, considering that the study was to last a whole infective season.

Statistical analysis was performed in the R statistical environment ver. 3.6.0, the PSPP program and MS Office 2019. $p < 0.05$ was adopted as the level of significant relationships between analysed values. Tests based on chi-square distribution were used for data expressed at the ordinal or nominal levels. In the case of 2x2 tables, a continuity correction was used, and when the conditions for the chi-square test were not met, Fisher's exact test with expansion was used for tables larger than 2x2. Non-parametric tests (e.g. Kruskal-Wallis test) were used to analyse quantitative values presented by groups. The tests were selected based on the distribution of variables, which was verified with the Shapiro-Wilk test. The existence of a relationship between the groups was verified using logistic regression analysis.

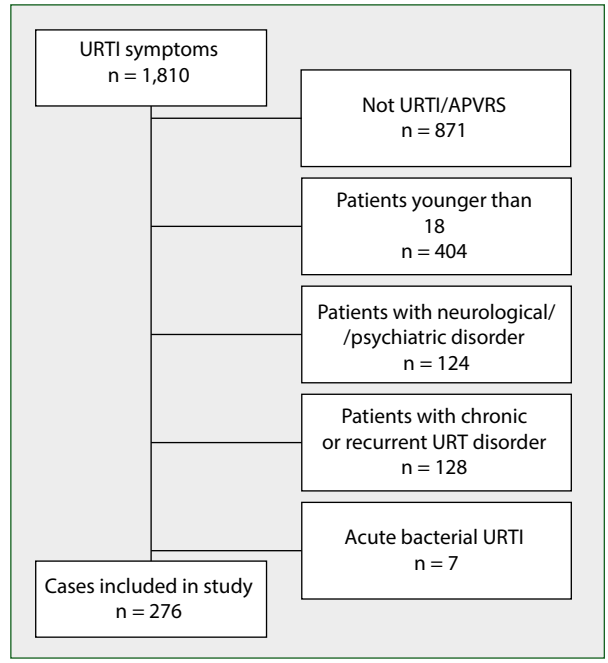

Figure 1. Selection process of patients fulfilling inclusion criteria (i.e. consultation in primary care for acute onset anterior/posterior nasal discharge and/or nasal congestion and/or sore throat and/or fever and/or myalgia). URTI — upper respiratory tract infection; APVRS — acute post-viral rhinosinusitis

Results

1,810 consultations were initially considered for inclusion in this study. The exclusion process is presented in Figure 1. The most prevalent neurological/psychiatric causes for exclusion (self-exclusion in terms of being prevented from obtaining informed consent and/or a reliable medical history) were: Alzheimer's Disease and other forms of dementia (35); the consequences of a stroke (27); an autism spectrum disorder (23); and a neurodevelopmental disorder (13). There was no missing data. In total, the analysis included 276 URTI/APVRS episodes due to the fact that consultations in the same patient for different URTIs were allowed: 26 patients were included for two separate diagnoses and 10 for three diagnoses. In accordance with the exclusion criteria, patients reporting for more than three different reasons were excluded from the study due to a recurrent URT disorder.

Table 1. Upper respiratory tract infections diagnosed in participants

Diagnosis	N = 276 [%]	Days from onset [median/SD]	
COVID-19	107 (38.8)	2–7 (3/1.8)	$\chi2$= 3.71
'Common cold'	103 (37.3)	2–7 (3/1.5)	*df* = 2
Influenza	36 (13.0)	2–7 (4/1.2)	p = 0.157
APVRS	30 (10.9)	10–60 (11/11.1)	NA

APVRS — acute post-viral rhinosinusitis; COVID-19 — coronavirus disease 2019; SD — standard deviation; $\chi2$ — statistical test used; *df* — degrees of freedom; p — statistical significance; NA — not applicable

Table 2. Prevalence of headache and facial pain in upper respiratory tract infections

			Diagnosis				Test result
			'Common cold' n = 103	COVID-19 n = 107	Influenza n = 36	APVRS n = 30	
Headache	NO	N	38	10	34	11	$\chi2 = 1.331$ *df* = 3 p = *0.722*
		%	36.9%	27.8%	31.8%	36.7%	
	YES	N	65	26	73	19	
		%	63.1%	72.2%	68.2%	63.3%	
Forehead pain	NO	N	12	7	18	5	$\chi2 = 1.191$ *df* = 3 p = *0.755*
		%	18.5%	26.9%	25.0%	25.0%	
	YES	N	53	19	54	15	
		%	81.5%	73.1%	75.0%	75.0%	
Facial pain	NO	N	24	14	32	6	$\chi2 = 3.539$ *df* = 3 p = *0.316*
		%	36.9%	53.8%	44.4%	30.0%	
	YES	N	41	12	40	14	
		%	63.1%	46.2%	55.6%	70.0%	
Other pain location	NO	N	39	11	40	11	$\chi2 = 2.357$ *df* = 3 p = *0.502*
		%	60.0%	42.3%	55.6%	55.0%	
	YES	N	26	15	32	9	
		%	40.0%	57.7%	44.4%	45.0%	
Isolated facial pain	NO	N	64	26	68	18	$\chi2 = 4.617$ *df* = 3 p = *0.202*
		%	98.5%	100.0%	94.4%	90.0%	
	YES	N	1	0	4	2	
		%	1.5%	0.0%	5.6%	10.0%	

COVID-19 — coronavirus disease 2019; APVRS — acute post-viral rhinosinusitis; $\chi2$ — statistical test used; df — degrees of freedom; n — number of participants; p — statistical significance

The study included 223 patients (136 women, 60.1%) aged 18-73 (mean 41.3, median [25th, 75th] 40 (standard deviation (SD) 15.1). The first patient was recruited in November 2023 and the last one in March 2024. Preexisting episodic migraine was confirmed in 45 participants (20.2%) and tension-type headache (TTH) in 56 (25.1%).

Table 1 sets out the number of consultations included for each URTI diagnosis. Days from disease onset to initial consultation did not differ between groups, although APVRS was excluded from this analysis due to the fact that it is, by definition, a disorder diagnosed after at least 10 days of symptoms.

Headache accompanied URTI in 66.3% of cases and isolated facial pain in 2.5% (Tab. 2). No significant differences in the prevalence of headache or pain location were found between different diagnoses. However, headache more often had a migraine-like phenotype in COVID-19 and a TTH-like phenotype in 'common cold' (Suppl. Tab. 1). Moreover, headache was accompanied by nausea/vomiting significantly more often in COVID-19. Previous COVID immunisation (vaccination or infection) was associated with a lower chance of migraine-like headache (Suppl. Tab. 2). However, immunisation was not associated with decreased incidence of any headache. Patients with APVRS had higher prevalence of headache phenotype that could not be classified as either migraine or TTH-like. Migraine-like headache was not associated with fever ($\chi2 = 0.950$, p = 0.330) or cough ($\chi2 = 0.895$, p = 0.639). However, patients with sinonasal symptoms during URTI had a lower chance of having a migraine-like headache

phenotype and a higher incidence of complaints that could not be classified as either migraine or TTH-like (Suppl. Tab. 3).

Patients included in the study reported sinonasal symptoms that fulfilled diagnostic criteria for acute rhinosinusitis in 212 (76.8%) cases. General symptoms included fever (n = 113, 40.9%) and cough (n = 208, 75.4%). Non-nasal CAS were reported by 53 (19.2%) participants (mostly lacrimation n = 51 or conjunctival injection n = 9). During facial palpation, 44 (15.9%) participants reported pain exacerbation. Logistic regression analysis revealed that predictors of headache in URTIs included (in order of statistical strength): sinonasal symptoms; non-nasal CAS; fever; and pain exacerbation by pressure applied over the paranasal sinuses (Suppl. Tab. 4).

Discussion

This study presents a direct comparison of headache phenotypes across URTIs of differing origins. Our results indicate that headache is common in URTIs, irrespective of the particular virus type. Also isolated facial pain may in rare cases accompany these infections. However, the phenotype of headache depends on additional factors such as the infective agent, previous immunisation, and sinonasal involvement. Overall, these results provide an insight into headache phenotype and facial pain prevalence in some of the most prevalent diseases worldwide.

Only a few studies have so far phenotyped headache in patients with SARS-CoV-2 infection and influenza [5, 13, 14]. Additionally, several other authors have provided evidence for headache-related complaints in COVID-19 [3, 5, 22, 23]. Most of this data indicates that migraine-like phenotype can occur not only in SARS-CoV-2, but also in influenza infections, in 25% and 43% of cases respectively [13, 14]. The results presented in these two studies were comparable to our research in regard to COVID-19 (27.4%), but differed in terms of influenza (15.4%). This latter variation may be due to differing study designs or to the small number of influenza patients in our current research. However, as the present study shows, headache phenotype may have been conditioned by other factors.

We hypothesised that patients with COVID-19 or influenza may have a different headache phenotype than do those with a 'common cold'. This hypothesis would appear to be at least partly correct, as migraine-like phenotype has been found to be more prevalent in COVID-19. It should be noted that both COVID-19 and influenza are considered to have a worse prognosis and more pronounced general symptoms (i.e. fever, myalgia) than 'common cold' [8, 24]. It has been previously proposed that this might be the result of stronger innate immune response activation manifesting with general symptoms (i.e. fever, myalgia) [1, 25]. The current study does not confirm that migraine-like headache phenotype is associated with fever independently of the infective agent. However, factors associated with a milder disease course (e.g. previous immunisation) reduce the odds of this headache phenotype appearing. Previous immunisation might have also contributed to the lower prevalence of migraine-like headache phenotype among influenza participants in this study, although the data that would confirm this was unavailable to us.

It should also be noted that fever, sinonasal symptoms or facial hypersensitivity to touch are predictors of any headache, independently of a potential causative virus. These observations further support the notion that headache during URTIs is secondary to immune response, especially when trigeminal afferents are directly exposed to inflammation (i.e. during sinonasal inflammation). Similar observations were made in a previous study by our group [5]. The association between sinonasal inflammation and headache might be explained by direct trigeminal C and A-δ fibre exposure to inflammatory mediators during local response to virus [1]. Moreover, a systemic inflammatory response accompanies URTIs. In this situation, the trigeminal ganglion or dura mater may be reached by the biochemical components of immune reaction (e.g. interferons, chemokines, prostaglandins), which in turn can contribute to headache [1]. Finally, a direct effect of viruses on the central nervous system has been postulated as a possible cause of headache during URTIs [4].

Despite these hypotheses, the authors of a recent systematic review on headache in COVID-19 stated that "there is no good documentation for any pathogenesis for headache in the context of COVID-19" [4]. A recent review by experts from the European Academy of Neurology and the European Headache Federation did not find evidence that facial pain accompanies COVID-19 [4], although some data from the past had suggested that this might be the case [5, 26]. The current study suggests that facial pain accompanies c.40% of URTIs including COVID-19. Moreover, in rare cases (2.5%), patients may complain of isolated facial pain without an accompanying headache. This finding might prove instrumental in the development of future editions of the International Classification of Orofacial Pain [27].

Rhinosinusitis is associated with a higher incidence of headache during COVID-19 and influenza [5, 28]. This is why APVRS has several features that made it especially interesting as a comparator in this study. On the one hand, it is a disease with prominent sinonasal inflammation. On the other hand, it is a sequel to viral infection with little systemic inflammatory response [19]. In other words, headache in APVRS could be promoted to a larger extent by rhinosinusitis than by systemic inflammatory factors. These mechanisms seem to result in a change in headache phenotype, as more often it is neither migraine nor TTH-like. Future studies on URTI-headache should take into account that both systemic (viral) and sinonasal factors contribute to this symptom and determine its final phenotype. As a footnote, it should be mentioned that non-nasal CAS observed in this study

were limited to lacrimation and conjunctival injection. Both these symptoms are highly prevalent in rhinitis, but are also reported by patients with different primary headache disorders [29].

This study is limited by several factors. Firstly, sampling was limited to patients actively seeking medical help. As a result, people who decided to treat their symptoms at home or via another healthcare provider (e.g. hospital A&E) were not included in the study. Some studies have shown that only 5–22% of people with RTI symptoms seek medical consultation, with high variability between countries and studies [30]. Secondly, the diagnostic process did not try to diagnose the particular viruses causing 'common cold'. The most important limitation associated with this might be the result of misdiagnosing other disorders with URTI symptoms (e.g. allergic rhinitis) as 'common cold'. In order to limit this possibility, strict exclusion criteria were applied, especially with regard to recurrent or chronic URT conditions. Moreover, a follow-up assessment helped to reduce the risk of this type of bias. It should also be noted that this study did not collect information about medications used by participants. Consequently, symptomatic URTI treatment that preceded their consultation or medications used for chronic disorders might have influenced the results. And finally, this study did not analyse the seroconversion status of participants. Therefore, data on immunisation is only valid in respect of registered COVID-19 cases or vaccinations. Thus patients who achieved immunity via other measures (e.g. unreported or subclinical disease), or patients immune to other virus variants, may have limited the strength of the observed associations.

In conclusion, not only headache, but also facial pain, seem to be prevalent during URTIs, and to be associated with general and sinonasal immune response rather than virus type. However, headache phenotype to some extent depends on causative microorganisms. This may not mean that viruses have a unique pain pattern, as this study suggests a change in headache phenotype in people who have been previously immunised against COVID-19. In other words, the symptomatology may evolve over time.

Clinical implications/future directions

Our observations may be relevant to ongoing scientific efforts to establish diagnostic criteria for acute headache attributable to COVID-19. Classification committees should consider the pros and cons involved in isolating different entities according to microorganisms because this may lead to a multiplication of classification entities — each for a different virus, but with similar symptoms.

In addition, this research indicates that prior immunisation against COVID-19, and possibly other URTIs also, may protect against migraine-like infection-related headache, although this is an observation requiring further scientific confirmation.

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RESEARCH PAPER

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Elevated tissue factor pathway inhibitor is associated with intracerebral haemorrhage of unknown cause in young adults

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ABSTRACT

Clinical rationale for study. We have reported that intracerebral haemorrhage (ICH) of unknown cause at a young age is associated with lower prothrombin and factor VII and higher antithrombin activity, along with the formation of looser fibrin networks displaying enhanced lysability. Patients with mild-to-moderate bleeding of unknown cause have elevated levels of free plasma tissue factor pathway inhibitor alpha (fTFPIα), inhibiting the tissue factor–factor VII complex and prothrombinase.

Aim of study. We hypothesised that patients with an intracerebral haemorrhage (ICH) of unknown cause may also exhibit higher fTFPIα.

Material and methods. We studied 44 adults aged ≤ 50 years following ICH of unknown cause at least three months after the incident, and 47 controls matched for age, sex, BMI, and hypertension. We assessed fTFPIα levels along with plasma fibrin clot permeability, turbidity and fibrinolytic capacity, thrombin generation, coagulation factors, antithrombin, and fibrinolysis proteins.

Results. Patients following ICH had 10.8% higher median fTFPIα levels than controls (8.3 [7.6–9.5] vs. 7.4 [6.9–8.5] ng/mL; p = 0.006). fTFPIα was higher in males than in females both in the ICH group (p = 0.0004) and in controls (p = 0.007), and correlated with age (r = 0.38; p = 0.01), fibrinogen (r = –0.39, p = 0.009), PAI–1 antigen (r = –0.32, p = 0.035), and clot maximum absorbance (r = –0.30, p = 0.049), but not with other laboratory variables. Nine patients had fTFPIα levels lower the upper limit of the reference range (i.e. 11.5 ng/mL) and they had a longer lag phase of the turbidity curve (p = 0.023) and clot absorbance (p = 0.042). In univariate analysis, a 1 ng/mL increase in fTFPIα was associated with a 61% greater chance of having an ICH (OR 1.61, 95% CI 1.19–2.18) even after adjusting for potential confounders.

Conclusions. Patients with ICH of unknown cause under the age of 50 are characterised by elevated fTFPIα associated with changes in fibrin clot formation and faster PAI–1–dependent lysis.

Clinical implications. Our study might suggest a novel potential mechanism underlying ICH.

Keywords: intracerebral haemorrhage, tissue factor pathway inhibitor, fibrin clot, blood coagulation

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Introduction

Intracerebral haemorrhage (ICH) occurs in c.5/100,000 individuals, is associated with substantial mortality [1], and carries an up to 15% risk of recurrence [2]. Apart from patients in whom the cause of bleeding is identified, up to 40% of patients classify as those with ICH of unknown cause [2, 3]. We have recently demonstrated that young adults with ICH of unknown cause are characterised by prohaemorrhagic fibrin clot phenotype, along with lower factor (F) II, lower FVII, and

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higher antithrombin (AT) activity [4]. Little is known about the role of natural anticoagulants in the pathogenesis of ICH, despite the fact that elevated levels of several natural anticoagulants, such as activated protein C, thrombomodulin or tissue factor pathway inhibitor (TFPI), have been demonstrated in haemorrhages of unknown cause [5].

Tissue factor pathway inhibitor (TFPI), a serine protease inhibitor occurring in two isoforms, TFPIα and TFPIβ, and synthesised mainly by endothelial cells, inhibits tissue factor (TF)–FVIIa complexes, whereas TFPIα additionally blocks the early forms of prothrombinase (complex of FXa and FVa) [5–8]. Up to 80% of the TFPIα isoform is bound to the endothelium and the remaining 20% circulates in the plasma, of which two thirds is associated with lipoproteins (mainly low–density lipoprotein [LDL]) and C–terminally degraded [6]. The remaining 20% that circulates in the plasma occurs in either free form i.e. full–length (10%, the active form) or carboxy–terminal truncated form (10%) [9].

It has been demonstrated that free TFPIα (fTFPIα) is increased in plasma obtained from patients with mild-to-moderate bleeding disorders such as epistaxis, easy bruising or menorrhagia, in particular in those with bleeding disorders of unknown cause and with platelet function disorders [10]. Interestingly, fTFPIα levels in such patients have been positively correlated with the lag time of the thrombin generation curve [10]. Lower levels of fTFPIα have been (albeit inconsistently) reported to increase the risk of thrombosis [11, 12]. In the context of intracerebral haemorrhage, total TFPI levels have been reported as unaffected in adults in the acute phase of a subarachnoid haemorrhage [13] and in acute ICH in children with haemophilia compared to control subjects [14].

Clinical rationale for study

To the best of our knowledge, elevated fTFPIα in ICH of unknown cause has not been previously investigated. We hypothesised that, as in bleeding of unknown cause in other locations, patients following ICH of unknown cause have elevated levels of this inhibitor. Therefore the aim of this study was to assess plasma fTFPIα levels and its associations with coagulation factors, fibrin clot properties and lysis in patients with ICH of unknown cause below the age of 50.

Material and methods

Patients

We recruited 44 consecutive patients who had suffered ICH of unknown cause at least three months prior to referral to the Centre for Coagulation Disorders, Krakow, Poland between 2013 and 2019. This patient group, and a control group matched for age, sex, body mass index (BMI), and hypertension, have been described in detail previously [4]. Briefly, the inclusion criteria were age 18–50 years and a diagnosis of ICH of unknown cause based on clinical symptoms, computed tomography scan, and according to the SMASH–U classification [15]. The key exclusion criteria were: known malignancy, kidney disease (acute up to stage G 3b and chronic up to stage G5), advanced liver injury (classes B and C on the Child–Pugh Score scale), diagnosed coagulation factor deficiencies, von Willebrand disease, thrombocytopenia (< 100,000/μl), brain aneurysm, arteriovenous malformation, and trauma. The patients did not show any clinical signs or symptoms of infection or deep venous thrombosis.

We collected data on demographics, comorbidities, current smoking, alcohol use and medications. The severity of neurological deficit was measured on admission using the National Institutes of Health Stroke Scale, and stroke outcome was assessed at discharge using the modified Rankin Scale. Definitions of all the comorbidities were as defined previously [16]. All participants gave their written informed consent, and the study was approved by the local Ethics Committee.

Laboratory investigations

Fasting blood samples were obtained from an antecubital vein, between the hours of 8am and 10am. Routine laboratory investigations included blood cell counts, glucose, creatinine, C–reactive protein, D–dimer, international normalised ratio, and activated partial thromboplastin time. Additionally, fibrinogen (von Clauss assay), FII, FV, FVII, FVIII, FIX, FX and FXI, AT activity, plasminogen activator inhibitor–1 antigen (PAI–1; ELISA, Hyphen, Neuville–sur–Oise, France) and prothrombin fragments 1 + 2 (F 1.2; ELISA, Siemens, Marburg, Germany) were assayed as previously described [4]. fTFPIα was determined with a commercially available ELISA kit (Diagnostica Stago, Asnieres, France). In our lab, the reference values for healthy individuals are 4.0–11.5 ng/mL.

Analysis of plasma fibrin clot variables was carried out as previously described [3]. Briefly, fibrin clot permeability (Ks) was measured using a hydrostatic pressure-driven system based on the volume of a percolating buffer using the formula: $Ks = Q \times L \times \eta/t \times A \times \Delta p$, where Q is the flow rate in time, L is the length of a fibrin gel, η is the viscosity of liquid (in poise), t is the percolating time, A is the cross–sectional area (in cm^2), and Δp is the differential pressure (in $dyne/cm^2$).

To measure fibrin clot turbidity, polymerisation was initiated by mixing plasma citrated samples 2:1 with a Tris buffer containing 0.6 U/mL human thrombin (Sigma–Aldrich, St. Louis, MO, USA) and 50 mmol/L calcium chloride. Using a Perkin–Elmer Lambda 4B spectrophotometer (Molecular Devices, San Jose, CA, USA), absorbance was read at 405 nm, and the lag phase of the turbidity curve, as well as the maximum absorbance at the plateau phase (ΔAbs), were recorded. The lag phase denotes the time required for initial protofibril formation, whereas ΔAbs indicates the number of protofibrils per fibre.

Fibrinolysis capacity was assessed in three assays. In the first, the turbidity method was used to determine clot lysis time (CLT), defined as the time from the midpoint of

the clear–to–maximum–turbid transition, representing clot formation, to the midpoint of the maximum–turbid–to–clear transition representing clot lysis. In this assay, the citrated plasma was mixed with calcium chloride (final concentration 15 mmol/L), recombinant human tissue factor (final concentration 0.6 pmol/L; Innovin, Siemens, Marburg, Germany), phospholipid vesicles (final concentration 12 µmol/L), and recombinant tissue–type plasminogen activator (rtPA, final concentration 60 ng/mL; Boehringer Ingelheim, Ingelheim, Germany). The second marker of fibrinolysis was the time required for a 50% decrease in clot turbidity ($t_{50\%}$). Here, 100 µL of citrated plasma was diluted with 100 µL of a Tris buffer containing 20 mM calcium chloride, 1 U/mL human thrombin (Sigma–Aldrich), and 14 µM rtPA (Boehringer Ingelheim). In the third assay, the lysis rate of the fibrin clots formed as described above and perfused with buffer containing a relatively high final concentration of rtPA *i.e.* 0.2 µmol/l (Boehringer Ingelheim) was determined by measuring the D–dimer concentrations (Abcam, Waltham, MA, US) every 15 min. in the effluent. The maximum rate of D–dimer increase ($D–D_{rate}$) and maximum D–dimer concentrations ($D–D_{max}$) were recorded.

Statistical analysis

Data was expressed as mean (standard deviation, SD) or median (interquartile range, IQR), according to its distribution assessed by the Shapiro–Wilk test. Differences in variables between the ICH group and controls were analysed using a Student t–test, U–Mann Whitney test, Chi^2 test or Fisher's exact test, as appropriate. Correlations were assessed using Pearson's correlation or Spearman's rank correlation coefficient, separately for ICH group and controls. Univariate and multivariate logistic regression were performed to assess the association between fTFPIα levels and the occurrence of ICH. In the multivariate regression, the model was adjusted for age, sex, hypertension, and platelet count. Two–sided p values of < 0.05 were considered statistically significant. Analysis was performed using the STATISTICA 12.0 software package (Stat Soft Inc., Tulsa, OK, USA, 2011).

Results

The ICH group comprised 44 patients with a median age of 41 (IQR 27–47) years, of whom 20 (45.5%) were female. As many as 23 (52.3%) were obese, 16 (36.4%) had hypertension, and 14 (31.8%) were current smokers. They did not differ from the controls (n = 47) in terms of demographics, comorbidities or medications, as shown previously [4]. Baseline patient characteristics are set out in Table 1.

Patients following ICH of unknown cause had 10.8% higher median fTFPIα levels than controls [8.3 (7.6–9.5) vs. 7.4 (6.9–8.5) ng/mL; p = 0.006; Fig. 1]. fTFPIα correlated with age both in the ICH group (r = 0.38; p = 0.01) and controls (r = 0.31, p = 0.03) and was higher in males than in females both in the ICH group (10.0 ± 2.5 vs. 7.8 ± 0.7 ng/mL; p = 0.0004) and in the controls (8.1 ± 1.4 vs. 7.1 ± 1.1 ng/mL; p = 0.007). However, fTFPIα was not related to any comorbidities, medications or routine laboratory investigations, including inflammatory markers or D–Dimer. In the ICH subjects, fTFPIα levels negatively correlated with fibrinogen, PAI–1 antigen and ΔAbs (Fig. 2 A, B, and C, respectively), but not K_s, CLT, $t_{50\%}$, $D–D_{rate}$ or $D–D_{max}$, coagulation factors or antithrombin. However, ΔAbs positively correlated with fibrinogen ($r = 0.68$, $p < 0.0001$), and inversely correlated with K_s ($r = –0.57$, $p = 0.0001$), while correlation with $t_{50\%}$ was of borderline significance ($r = 0.30$, $p = 0.05$). PAI–1 antigen demonstrated correlations with CLT ($r = 0.54$, $p = 0.0001$) and $t_{50\%}$ ($r = 0.48$, $p = 0.0009$). In the control group, fTFPIα was not associated with any variable apart from age.

In the ICH group, fTFPIα level >11.5 ng/mL was found in nine patients (20.5%). These individuals were all males, older and with lower platelet counts than the remaining ICH subjects (Tab. 1). Interestingly, they were also characterised by a longer lag phase of the turbidity curve and lower ΔAbs (Tab. 2). Analysis of the ICH subjects with fTFPIα in the top quartile (> 9.4 ng/mL, 11 patients) versus the remainder showed similar results. In the control group, none of the subjects had a fTFPIα level above the upper limit of the reference range (> 11.5 ng/mL).

In univariate analysis, a 1 ng/mL increase in fTFPIα was associated with a 61% greater chance of ICH (OR 1.61, 95% CI 1.19–2.18). After adjusting for potential confounders, this association remained significant, with area under the curve (AUC) for the full model (age, sex, hypertension, platelet count, fTFPIα) of 0.74, 95% CI 0.64–0.84, p = 0.021.

Discussion

To the best of our knowledge, the present study is the first to show that adult patients with a history of ICH of unknown cause under 50 years of age demonstrate elevated levels of fTFPIα, the main physiological regulator of the initiation of blood coagulation. Increasing concentrations of fTFPIα were associated with impaired fibrin clot formation, decreased clot density, and impaired inhibition of fibrinolysis. Our findings suggest a previously unreported mechanism that may contribute to the occurrence of ICH in young adults. Given recent advances in targeting TFPI with monoclonal antibodies [17], our findings might have therapeutic implications if validated in future studies and could help reduce the risk of ICH recurrence.

In the present study, the detected levels of fTFPIα were generally concordant with the literature, with higher levels of fTFPIα in males and older subjects [10. 18]. We did not observe the positive correlations with BMI that have been reported both in patients with mild bleeding and in controls [10]. In the studied ICH group, the levels of fTFPIα were mildly

Table 1. Demographic, clinical and basic laboratory variables in ICH group with respect to fTFPIα upper limit of reference range (left side of table) and comparison of these variables between ICH group and controls (right side of table)

Variable	fTFPIα > 11.5 ng/mL (n = 9)	fTFPIα ≤ 11.5 ng/mL (n = 35)	P–value	ICH group (n = 44)	Controls (n = 47)	P-value
Age (years)	44.8 (2.5)	37.8 (7.4)	0.008	41.0 (27.0–47.0)	40.0 (32.0–44.0)	0.46
Female sex, n [%]	0 (0)	20 (57.1)	0.007	20 (45.5)	22 (46.8)	0.90
BMI, kg/m^2	25.4 (3.4)	25.5 (4.1)	0.99	25.5 (3.9)	25.7 (4.3)	0.81
Medical history						
Hypertension, n [%]	2 (22.2)	14 (40.0)	0.55	16 (36.4)	21 (44.7)	0.42
Diabetes mellitus, n [%]	2 (22.2)	4 (11.4)	0.77	6 (13.6)	4 (8.5)	0.43
Coronary artery disease, n [%]	1 (11.1)	2 (5.7)	0.87	3 (6.8)	1 (2.1)	0.28
Previous myocardial infarction, n [%]	1 (11.1)	1 (2.9)	0.87	2 (4.5)	0 (0)	0.14
Current smoking, n [%]	3 (33.3)	11 (31.4)	0.77	14 (31.8)	14 (29.8)	0.83
Medications						
ACEI, n [%]	3 (33.3)	9 (25.7)	0.97	12 (27.3)	18 (38.3)	0.26
β–blockers, n [%]	2 (22.2)	7 (20.0)	0.75	9 (20.5)	9 (19.1)	0.88
Calcium channel blocker, n [%]	1 (11.1)	4 (11.4)	0.57	5 (11.4)	7 (14.9)	0.62
Diuretics, n [%]	1 (11.1)	5 (14.3)	0.77	6 (13.6)	13 (27.7)	0.10
Statins, n [%]	3 (33.3)	5 (14.3)	0.40	8 (18.2)	11 (23.4)	0.54
Laboratory investigations						
Haemoglobin, g/dL	13.6 (0.9)	13.8 (1.0)	0.73	13.7 (1.0)	13.9 (1.3)	0.43
White blood cells, 10^9/L	6.7 (6.1–7.1)	6.8 (5.7–8.0)	0.80	7.1 (6.4–8.1)	6.2 (5.5–7.5)	0.007
Platelets, 10^9/L	181.0 (156.0–205.0)	232.0 (189.0–289.0)	0.016	214.5 (179.5–257.5)	248.0 (211.0–298.0)	0.02
APTT, s	32.1 (30.8–33.1)	30.7 (29.2–33.0)	0.68	31.3 (29.3–33.0)	29.7 (27.2–32.3)	0.14
ALT, U/L	18.0 (14.0–29.0)	22.0 (17.0–30.0)	0.38	22.0 (17.0–29.5)	25.0 (19.0–30.0)	0.39
Creatinine, μM	87.6 (68.5–98.0)	73.0 (65.3–81.4)	0.36	74.1 (65.4–88.9)	73.0 (67.0–81.0)	0.73
C–reactive protein, mg/L	2.4 (2.1–4.4)	2.4 (1.6–3.4)	0.48	2.4 (1.8–3.8)	1.9 (1.2–3.4)	0.15
LDL cholesterol, mM	2.6 (2.5–3.1)	3.2 (2.5–3.9)	0.25	3.1 (2.5–3.5)	3.0 (2.4–3.5)	0.35
Coagulation variables						
Fibrinogen, g/L	2.4 (2.2–2.8)	2.7 (2.5–3.3)	0.06	2.7 (2.4–3.1)	3.0 (2.3–3.5)	0.46
D–Dimer, ng/mL	346.1 (110.0)	333.8 (116.6)	0.77	333.0 (218.0–422.5)	293.0 (218.0–398.0)	0.22
F1.2, nmol/L	121.0 (119.0–125.0)	128.0 (110.0–149.0)	0.78	124.0 (113.0–148.5)	119.0 (108.0–152.0)	0.61
Factor II, [%]	99.6 (6.3)	97.2 (10.4)	0.50	98.9 (90.2–104.2)	108.0 (98.0–120.0)	0.0001
Factor V, [%]	99.4 (10.8)	98.8 (9.0)	0.89	99.9 (95.2–104.1)	100.0 (93.0–114.0)	0.06
Factor VII, [%]	90.9 (89.4–107.1)	93.2 (87.9–103.1)	0.59	92.6 (88.2–104.6)	103.0 (95.0–114.0)	0.0003
Factor VIII, [%]	121.2 (91.6–126.9)	106.8 (86.5–126.3)	0.62	108.8 (87.6–126.6)	116.0 (102.0–134.0)	0.066
Factor IX, [%]	99.2 (12.6)	97.1 (11.8)	0.65	97.5 (11.8)	102.2 (11.8)	0.06
Factor X, [%]	100.6 (87.9–110.1)	99.4 (84.2–109.0)	0.73	99.5 (85.4–109.6)	101.0 (95.0–109.0)	0.14
Antithrombin, [%]	101.3 (16.1)	107.3 (11.9)	0.21	106.1 (12.9)	97.0 (10.9)	0.0004
fTFPIα, ng/mL	13.0 (11.9–13.3)	8.0 (7.5–8.6)	< 0.001	8.3 (7.6–9.5)	7.4 (6.9–8.5)	0.006

Data shown as median (IQR), mean (SD) or number (percentage). BMI — body mass index; ACEI — angiotensin–converting enzyme inhibitors; APTT — activated partial thromboplastin time; ALT — alanine aminotransferase; LDL — low–density lipoprotein; F1.2 — plasma prothrombin fragments 1.2

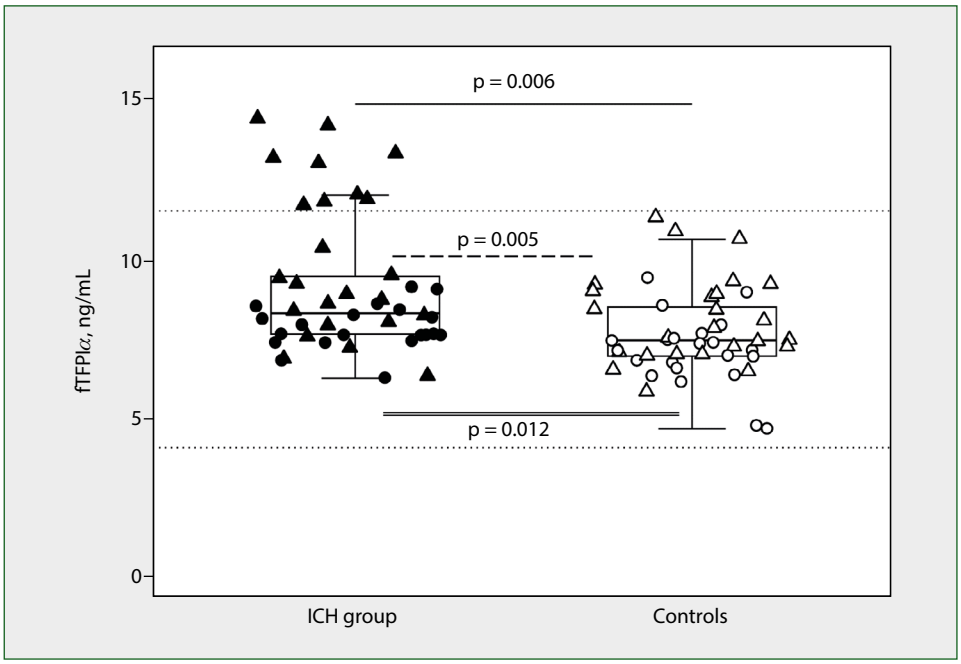

Figure 1. fTFPIα levels in ICH group (closed circles) compared to controls (open circles). Males are represented with triangles, females with circles. Boxes show IQR, whiskers +1.5 IQR and –1.5 IQR. Dotted lines represent reference range of fTFPIα in our laboratory. Solid line indicates difference between ICH group vs. controls; dashed line indicates difference between males with ICH vs. male controls; and double line indicates difference between females with ICH vs. female controls

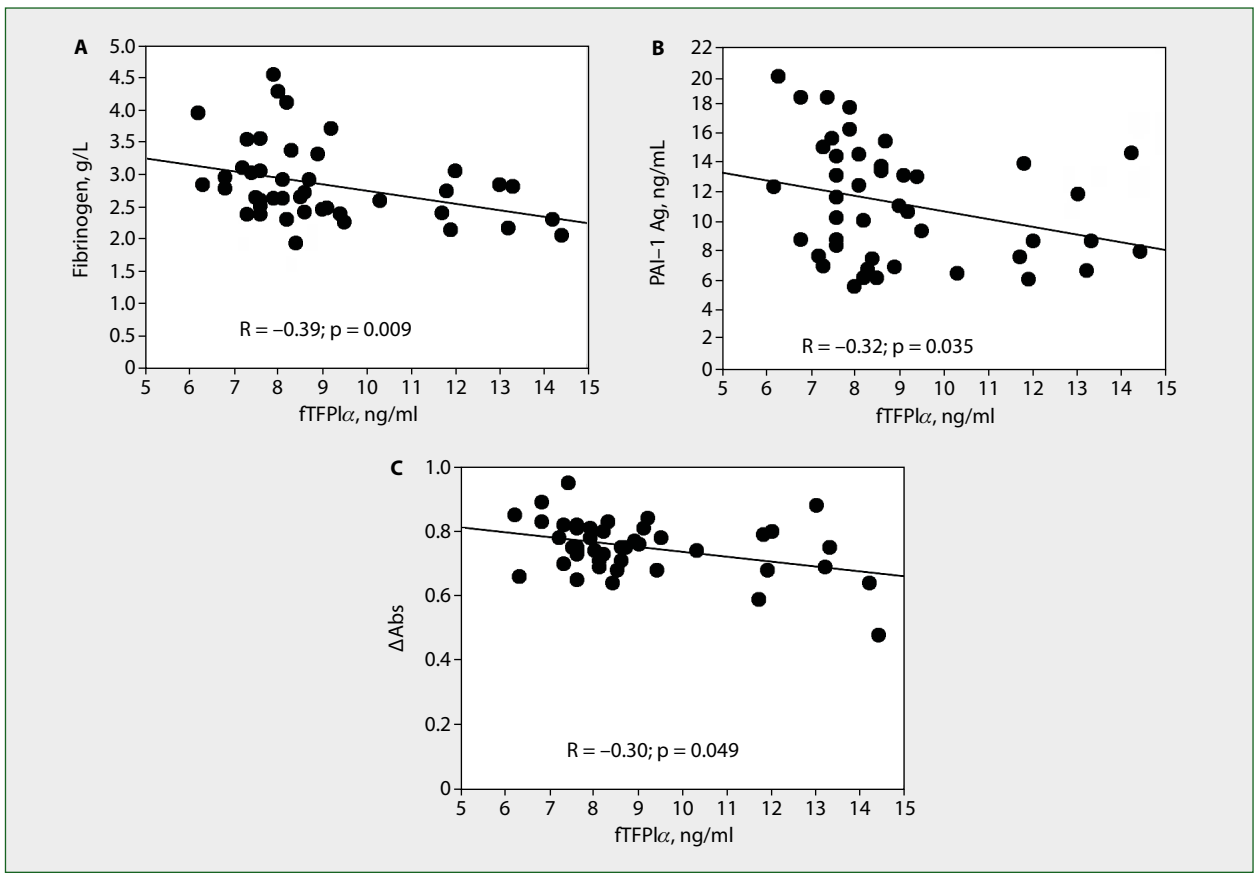

Figure 2. Linear correlations of fTFPIα with fibrinogen (A), PAI–1 (B), and ΔAbs (C) in ICH group. Correlation coefficients calculated using Spearman's rank correlation

Table 2. Fibrin clot and lysis variables in ICH group depending on fTFPIα below versus above upper limit of reference range

Variable	fTFPIα > 11.5 ng/mL (n = 9)	fTFPIα ≤ 11.5 ng/mL (n = 35)	P-value
K_s, 10^{-9} cm^2	9.5 (9.0–10.1)	9.0 (8.2–9.6)	0.16
Lag phase, s	49.1 (5.0)	44.9 (4.8)	0.023
ΔAbs	0.70 (0.12)	0.76 (0.07)	0.042
CLT, min	61.0 (56.0–75.0)	57.0 (57.0–82.0)	0.37
PAI–1:Ag., ng/mL	8.8 (7.7–12.0)	7.8 (7.8–14.7)	0.19
$t_{1/2}$, min	8.0 (1.1)	7.9 (0.9)	0.89
D–D_{rate}, mg/L/min	0.082 (0.007)	0.079 (0.006)	0.28
D–D_{max}, mg/L	3.5 (3.4–3.7)	3.4 (3.4–3.9)	0.31

Data shown as mean (SD) or median (IQR). K_s — indicates permeability coefficient; ΔAbs — maximum absorbance of fibrin gel at 405 nm determined by using turbidimetry; CLT — clot lysis time; $t_{1/2}$ — lysis time; D-D_{rate} — maximum rate of D-Dimer release in lysis assay; D-D_{max} — maximum D–dimer levels in lysis assay

elevated, which was similar to the results in patients with mild and moderate bleeding disorders [10]. Since it has been shown that males experience ICH more frequently and at a younger age than women [21], we speculate that elevated fTFPIα in male ICH survivors at least in part explains this observation.

Other potential factors that affect haemorrhage occurrence deserve comment. The prevalence of hypertension in the current sample was similar to other ICH cohorts [2]. Of note, in our patients it was mild and not considered to be a cause of the index event. More importantly, it was not associated with fTFPIα concentration. The rate of smokers and diabetics did not differ from other studies [22, 23]. LDL cholesterol levels and statin use among the current ICH group did not differ from the controls and was not associated with fTFPIα, and therefore it is unlikely to have influenced the results. Another potential contributor to ICH occurrence is thrombocytopenia, which has been also observed in patients with COVID–19 [24, 25]. The current ICH group had lower platelet count than controls (albeit within the normal range). However, after adjusing for platelet count, higher fTFPIα concentrations were still associated with a greater chance of ICH.

We have shown that fTFPIα levels negatively correlate with fibrinogen, which has not been described previously. Fibrinogen is the key determinant of fibrin clot structure and function [26, 27]. In our study, lower fibrinogen levels were in line with lower fibrin clot maximum absorbance in turbidimetry, which reflects the decreased density of the fibrin clot [28]. Interestingly, lower clot density was associated with higher fTFPIα, increased clot porosity and a tendency to clot lysis. ICH subjects with fTFPIα levels above the upper limit of the reference range also exhibited prolonged lag time of the turbidity curve. In patients with mild and moderate bleeding disorders, fTFPIα correlated positively with thrombin generation parameters: prolonged lag time and increased time to peak [10]. In the present study, we did not measure thrombin generation [4].

An important finding is the decreasing concentration of PAI–1 antigen with elevated levels of fTFPIα. PAI–1 is of key importance in regulating fibrinolysis by binding active tPA molecules, forming an inactive complex and preventing plasminogen activation. Its deficiency can cause hyperfibrinolytic bleeding [29]. Although in our subjects PAI–1 concentration was within reference limits, it could still contribute to bleeding [30]. PAI–1 also has an impact on the results of fibrinolysis assays [31]. In the present study, it strongly correlated with CLT and $t_{50\%}$, meaning that it might be another factor associated with fTFPIα that potentiates the lysis of the fibrin clot.

Our study has several limitations. Firstly, the number of participants was restricted, although the number of patients in the ICH group was similar to the subgroups with ICH of undetermined aetiology in young adults in other studies [2 ,22, 32]. Secondly, the results do not necessarily demonstrate a cause and effect relationship, and are not generalisable to the most severe ICH patients. The impact of clinical factors such as resistant hypertension [33] and alcohol abuse [34] cannot be excluded. We did not examine coagulation parameters in the acute period of ICH, although it has been shown that fTFPIα is unchanged in the acute phase of ICH [13, 14]. The fTFPIα assay is currently for research use only; perhaps further steps should be made towards its approval in clinical practice. The coagulation parameters were evaluated a few months after the index ICH; future studies could investigate fTFPIα levels as a prognostic factor for ICH.

To conclude, young adults who suffer from ICH demonstrate higher levels of a natural anticoagulant, fTFPIα, which is associated with prolonged fibrin clot formation, decreased clot density, and impaired inhibition of fibrinolysis.

Clinical implications/future directions

Our findings contribute to the understanding of the pathophysiology of ICH of unknown cause, and may form the foundations for future large-cohort studies of patients with ICH with long term follow–up.

Article information

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VIEWPOINT

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Challenges of equitable access to device-aided therapies for advanced Parkinson's Disease in Poland — expert consensus and treatment recommendations

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ABSTRACT

Introduction. In Poland, not all forms of device-aided therapies for advanced Parkinson's Disease (APD) are currently available.

Material and methods. We aimed to produce a consensus recommendation from Polish movement disorders experts after discussing gaps in the APD care pathway in Poland.

Results. Rescue therapy with apomorphine (APO) PEN injection and levodopa–entacapone–carbidopa intestinal gel infusion are not included in Poland's Specialist Therapeutic Programme, and are thus not reimbursed. For APO infusion, only the medication is reimbursed but not the device.

Conclusions. Consensus expert opinion is that APD patients in Poland would benefit from additional reimbursement access to these treatment options to improve APD patient care.

Keywords: advanced Parkinson's Disease, clinical practice, device-aided therapy

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Introduction

In the absence of a disease-modifying or curative therapy for Parkinson's Disease (PD), management of this progressive neurodegenerative condition currently relies on effective symptomatic treatments to control motor and non-motor symptoms, to ensure patients have the best possible quality of life, and to minimise the burden on caregivers. Thanks to research and development efforts over the past 25 years, we now have a range of effective oral, non-oral and surgical therapeutic options to offer to patients and meet the differing needs of individual patients as their disease progresses.

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While early stage PD can generally be managed effectively for several years with dopaminergic drugs, as the disease progresses to the advanced stage (APD), emerging motor and non-motor complications, the tapering off of therapeutic effect, and other treatment-related challenges such as gastrointestinal absorption issues, require a change of therapeutic strategy [1, 2].

At this point, methods of non-oral continuous drug delivery (CDD) that aim to provide continuous dopaminergic stimulation are used for sustained clinical efficacy, improvements in ON times without troublesome dyskinesias, and a reduction in OFF periods [3].

Given the wide range of device-aided advanced therapies (DAT) that are now available, the use of expert opinion-based clinically-driven personalised therapies in PD is an important concept that needs to be implemented, as the 'one size fits all' approach is not considered appropriate for the modern management of advanced PD [4].

Choosing the right DAT for each individual is, therefore, crucial to treatment success. Clear patient profiles of the individual characteristics that might best be addressed with a particular therapy are important to aid informed discussion with patients and carers and make the most appropriate treatment selection. A pragmatic and evidence-based clinical pathway, recently published as stepped care for PD, includes firstly confirmation of a diagnosis of APD, a process that can be aided by various screening tools [5], and secondly a decision as to which is the best DAT option based on the clinical profile supported by appropriate biomarkers where required (e.g. wearable sensors), patient choice, side effects profile, and age, as well as the stage of PD, the motor and non-motor burden, and patient lifestyle [6]. The patient's own viewpoint is critical in making any therapeutic choice and their preference for, or hesitancy about, particular DATs need to be considered and discussed [7].

To assist clinicians in correctly diagnosing APD, several validated screening tools are available for use in clinical practice [8]. Commonly used tools are the 5-2-1 criteria (≥ 5 doses of oral levodopa per day and/or ≥ 2 hours of OFF time per day and/or ≥ 1 hour of troublesome dyskinesia) which is based a consensus statement of European PD experts along with several non-motor symptoms such as non-motor fluctuations and sleep dysfunction as well as functional consequences affecting quality of life [9]. The MANAGE-PD paradigm has been developed based on these criteria, and is an online tool which can help determine whether current treatment needs further optimisation or if a device-aided option should be considered [10]. A recent comparison of the application of the 5-2-1 criteria and MANAGE-PD in clinical practice found that while both are valuable tools in the clinic, MANAGE-PD has a better screening potential for determining suitability for DAT than do the relatively simplistic 5-2-1 criteria [11]. The Dutch DAT Screening tool (D-DATS) has also been developed recently, and seems promising in promoting timely referral and appropriate treatment with DAT in APD [12].

When it comes to treatment selection, a range of DATs with proven efficacy and tolerability are now available in many countries for APD patients [13]. Since levodopa is the recognised 'gold standard' PD therapy, there has been particular focus on strategies to improve its delivery to overcome the limitations of oral and transdermal administration [14, 15].

While recent and ongoing developments in therapies for APD are to be welcomed, regulatory approval and marketing authorisation of treatments does not always equate to access or reimbursement at a national level in many countries, despite the availability of positive pivotal licencing studies-based data. In Poland, for instance, the prevalence of PD has significantly increased in recent decades, which aligns with global trends suggesting the disease burden has more than doubled over that time, possibly due to the increasing elderly population [16]. Despite this rise in PD cases, more costly and effective APD treatments are not routinely available to all and must be approved for national reimbursement in accordance with each country's specialist therapeutic programme. In addition, while particular medications themselves may be reimbursed, the newer delivery devices with inherent mechanical advantages may not. Classic examples of this are the non-availability of different formulations of apomorphine infusion, where one delivery system may be more bespoke to a patient's needs than another, or the availability of different types of intrajejunal levodopa infusion, where smaller, lighter and relatively silent devices may be preferred by patients [17].

Having taken account of all these challenges to providing effective treatment for patients, a group of key movement disorders experts from Poland, along with other European PD experts, convened to discuss the gaps in the current care pathway for APD in Poland and make recommendations as to how to improve this situation.

This article summarises that expert group's discussions and recommendations, which are intended to aid clinicians and their patients in making appropriate treatment choices from the existing pool of therapies as well as from the newer options discussed in this paper.

Material and methods

Polish movement disorders specialists and external stakeholders (the authors of this article) participated in an expert advisory meeting in June 2024 based on their extensive experience in clinical management of APD at tertiary centres within Poland or other European countries, and also their involvement in clinical research into both established DATs and those currently in development.

This article presents a narrative review of their discussions of the current, global APD treatment landscape, and their identification of gaps in the Polish market in terms of treatment options. It includes recommendations based on their expert opinion for an optimal APD management pathway in Poland.

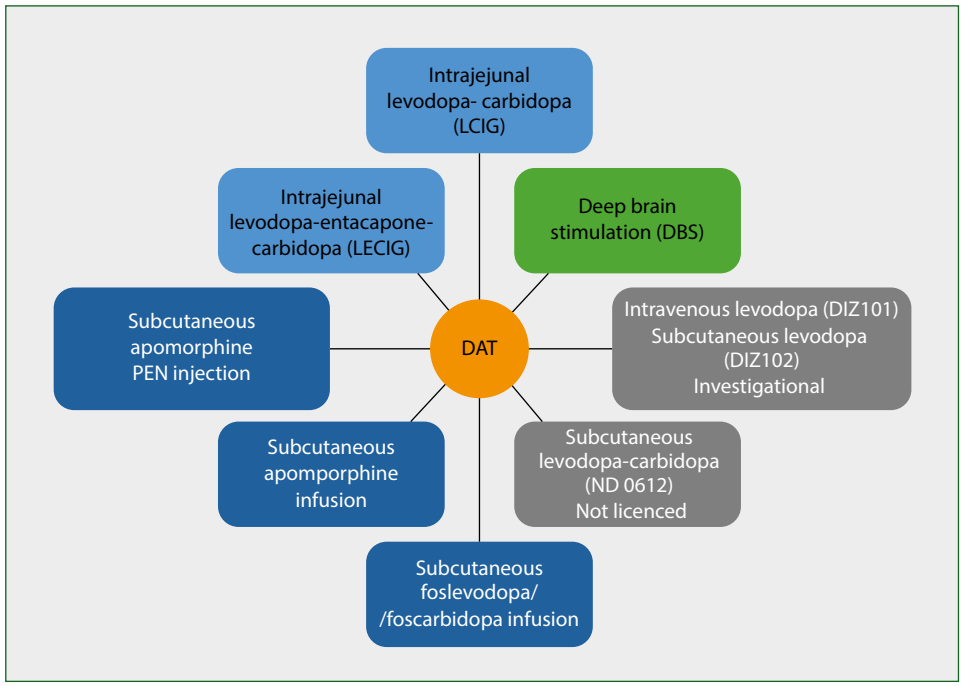

Figure 1. Approved device-aided therapy (DAT) options for advanced PD (dark blue: administered subcutaneously; light blue: administered by intrajejunal infusion; green: DBS, requires stereotactic brain surgery) along with some therapies not yet approved or under investigation (grey). DBS — deep brain stimulation; LECIG — levodopa-entacapone-carbidopa intestinal gel; LCIG — levodopa-carbidopa intestinal gel. *Not licenced indicates not licenced for commercial or clinical use*

Results

Global APD treatment landscape

Approved DAT options for the management of APD along with some therapies that are not yet approved or are under investigation are set out in Figure 1. For the early stages of APD, several minimally invasive non-oral 'on-demand' therapies are available that can provide rapid relief of troublesome motor OFF episodes as they occur, such as subcutaneous apomorphine (APO) injection, sublingual APO, or inhaled levodopa [18]. However, these therapies are administered intermittently and when APD becomes established and their daily use becomes too frequent, one of the more invasive continuous therapies may need to be considered to provide more effective control of PD symptoms. Where available, suitable patients can be considered for deep brain stimulation (DBS) or one of the infusion therapies, delivered either subcutaneously (APO infusion [19, 20] or the recently approved foslevodopa/foscarbidopa [13]) or via intestinal infusion (levodopa–carbidopa intestinal gel, LCIG) [21] or levodopa–entacapone–carbidopa intestinal gel (LECIG) infusion [17, 22]. However, it is important to take into account patient preferences when selecting therapy. A study evaluating the most common reason patients declined DBS and LCIG found that they were concerned about surgery, while the most common reason APO infusion was declined was the requirement for regular self-injection. DBS seemed to be preferred by younger patients with less severe disease, while APO infusion was generally preferred by older patients with a longer disease duration [7].

Further levodopa-based continuous therapies are in development, but have not yet received regulatory authority approval. These include transdermal levodopa pump patch, subcutaneous levodopa–carbidopa infusion (ND0612) delivered via a dual syringe and needle system, and concentrated acidic solutions of levodopa administered intravenously (DIZ101) or subcutaneously (DIZ102) [13, 23]. Continuous formulations of other non-levodopa therapies are also under investigation, including subcutaneous ropinirole and rotigotine, transdermal APO pump patch, and rotigotine implant. In addition, in selected cases, incisionless but lesioning techniques, e.g. transcranial magnetic resonance imaging (MRI)-guided focused ultrasound therapy (MRgfUS) or gamma knife therapies for unilateral thalamotomy or pallidotomy, can be used. One MRgFUS system has been approved in Europe (CE marked for essential tremor, PD tremor, and neuropathic pain) since 2012 [24] and since 2016 in the USA for the management of essential tremor [25]. Its use in parkinsonian tremor is based on a small study of only 20 patients on active treatment and seven on sham treatment [26], and currently the European Association of Neurology (EAN) does not recommend this for the management of PD tremor. There is also concern about its long-term safety [27]. If proven effective and safe in robust clinical trials, these will expand the range of options available to APD patients.

Current gaps in Polish APD therapy market

In Poland, DATs for APD treatment, which are more costly than oral or transdermal medications, are reimbursed in accordance with the Ministry of Health's Specialist Therapeutic Programme (STP). General neurologists will usually refer patients to specialist centres to determine and confirm a diagnosis of APD and, if the centres agree with the decision, an application is filed for consideration at the monthly meeting of the STP Committee to request advanced treatment which is assessed according to the 5-2-1 motor criteria along with recommended non-motor symptoms criteria and functional deficits which may affect quality of life [9].

Several therapeutic options in Poland are already available including DBS, intrajejunal LCIG infusion, and subcutaneous APO infusion. Normally, patients under the age of 70 are eligible for DBS if there is insufficient response to conventional pharmacological therapies and the emergence of clinically relevant motor fluctuations and dyskinesias along with a lack of significant cognitive impairment (excluding mild cognitive impairment), moderate-to-severe depression, significant white matter hyperintensities, or other vascular changes on brain MRI scan. Of relevance is the fact that the Polish criteria for suitability for DBS treatment mostly adopted the criteria established by a French group, as included in the recent EAN guidelines [28]. Severe dysarthria and severe gait disorder are additional exclusion criteria. Therefore, many patients who do not fulfil these criteria could potentially benefit from the available infusion-based advanced therapies, and the additional new product developments discussed in this paper.

As such, if patients are older than 70 and not eligible for DBS, then subcutaneous apomorphine infusion is considered the least invasive of all advanced therapies at this stage and can be used [19]. However, caution and vigilance about dopamine agonist-related side effects, such as impulse control disorder, somnolence and psychosis, still apply. Intrajejunal levodopa infusion was the predominant form of infusion therapy for advanced PD until the advent of subcutaneous foslevodopa/foscarbidopa, and is used globally with well-established long-term clinical efficacy [29, 30]. Foslevodopa/foscarbidopa is currently the only subcutaneous levodopa preparation available commercially and has recently become available in Poland. It is effective when used over a 24-hour period, which differentiates it from subcutaneous APO infusion which is usually administered over 16 hours in Poland. Selecting who is suitable for which therapeutic option is, therefore, a complex challenge, and a pragmatic flowchart is provided in this paper (Fig. 2) where we also consider the place of LECIG infusion as well as subcutaneous APO injection for rescue therapy.

However, if a request for advanced treatment is approved, according to the Ministry of Health's policy only the medication is reimbursed. As a result, patients wishing to start infusion therapy, such as LCIG infusion, may be offered older, larger pump systems, such as the Smith Medical CADD Legacy 1400 pump used for LCIG infusion, which may deter particularly younger and more active patients from commencing what might be for them an effective treatment option. Such rejections can be related to the weight of the pump, problems with body image, as well as general societal inconvenience.

Rescue therapy from predictable OFF periods remains a mainstay of management of fluctuating PD, especially in younger patients. In the case of on-demand (or 'rescue') treatments, there is currently a notable gap in the APD treatment pathway in Poland, with the only reimbursed options being soluble sustained-release levodopa tablets. Subcutaneous APO PEN injection is licenced in Poland but currently not reimbursed. It is envisaged that its wider use in early-stage APD might delay the transition of patients to more costly DAT treatments, and also reduce waiting lists for treatment in addition to improving self-confidence and quality of life of patients. APO is the only dopamine agonist with equivalent efficacy to levodopa and has a proven history of safety and tolerability in clinical use for more than 30 years. The PEN injection formulation has been shown in a range of clinical trials, and from extensive experience in clinical practice, to provide rapid and reliable resolution of motor OFF periods, returning patients to the ON state usually within 10–12 minutes which is not achievable by oral therapies or even sublingual apomorphine [31]. PEN formulation is also effective when there may be a 'no ON' state after oral levodopa use.

Unpredictable (and predictable) OFF periods for young PD patients remain among the greatest clinical challenges and have been rated as the most troublesome symptoms in a survey of advanced PD patients [32]. If reimbursed, an APO PEN injection would be a valuable addition to the range of options in APD treatment in Poland and fill gaps in the control of motor function alongside the patient's usual medication.

As of July 2024, Poland's STP for PD has been updated to include equal access to subcutaneous APO infusion, LCIG infusion and subcutaneous foslevodopa/foscarbidopa infusion. APO infusion has a well-established history of clinical use worldwide and its long-term efficacy and tolerability is supported by randomised controlled clinical trial (RCT) evidence and long-term open label study data [20, 31]. The European Academy of Neurology/Movement Disorder Society guidelines on the treatment of PD with invasive therapies recommend APO infusion for people with APD in whom fluctuations are not satisfactorily controlled with medication [28]. The UK's National Institute for Health and Care Excellence (NICE) guidelines suggest it should be started before patients are considered for foslevodopa/foscarbidopa and prior to invasive DATs such as DBS or LCIG, while an APO PEN injection can be used even earlier for managing troublesome predictable OFF periods [33].

Non-motor issues can drive management of advanced therapies and also device-aided therapies. The evidence is available from the EuroInf 2 study data and has been discussed by Leta et al. [6]. In addition to motor efficacy in PD, beneficial effects of APO infusion on PD non-motor symptoms (NMS) have been widely reported. EuroInf 2 was a prospective,

multicentre, international, observational study that compared clinical outcomes with APO infusion, LCIG infusion and DBS in clinical practice [34]. All three therapies provided good control of motor symptoms and improved quality of life but had different NMS effect profiles. APO infusion was found to provide particular improvement in Non-Motor Symptom Scale (NMSS) domains of mood/cognition, perceptual problems/hallucinations, attention/memory, and miscellaneous. It has also been known for some time that nocturnal use of continuous APO infusion has beneficial effects on sleep disorders in PD and can provide reduction of nocturnal awakenings, nocturnal OFF periods, pain, dystonia and nocturia [35]. More recently, the APOMORPHEE study was the first RCT to assess the safety, tolerability and efficacy of a night-time only APO infusion regimen, demonstrating fewer sleep disturbances in APD patients with moderate-to-severe insomnia [36]. Sleep issues are a common occurrence in PD, and this accumulating evidence suggests that APO infusion may be an effective option to help resolve them. However, despite the proven efficacy of APO infusion on motor PD symptoms and the reported benefits on common NMS such as sleep disorders, the newer pump systems are not reimbursed in Poland, thereby limiting patient choice and potentially dissuading patients from choosing this treatment option.

Another new development for APO infusion is the APO-go® POD system (Britannia Pharmaceuticals Ltd., Reading, UK) which extends the benefits of the currently pre-filled syringe. This has been designed to support patient autonomy as there is no liquid transfer required and set-up time is reduced. It would therefore represent a valuable addition to the Polish STP.

LECIG infusion is currently not included in Poland's STP for PD. LECIG is a combination of levodopa, carbidopa and entacapone in a single intestinal gel formulation, and requires the same surgical procedure as LCIG infusion [37]. Due to the presence of entacapone in the formulation, equivalent levodopa exposure can be achieved with a reduction in total daily levodopa dose ofc.35% [22, 38], and the treatment regimen can be somewhat simplified without the need for oral entacapone. The safety profile of LECIG is in line with data from published clinical studies of standard LCIG and oral entacapone [22]. However, a large, international observational study, ELEGANCE (NCT05043103), is now underway that aims to gather outcomes data for LECIG in clinical practice and this will add to the evidence base. LECIG is delivered using the Crono® LECIG pump which is smaller and lighter that the LCIG pump and has received favourable reports from patients [17].

In view of the growing evidence of the benefits of LECIG in the countries where it has been launched from both a clinical and practical perspective, our opinion is that LECIG should be added to the STP in Poland. If these suggested additions to the STP are implemented, we recommend that the treatment pathway for APD should be followed, as shown in the algorithm in Figure 2.

One of the key factors for successful implementation of device-aided infusion therapies, such as APO and LECIG, in other European countries has been the comprehensive education of PD Nurse Specialists (PDNS) about the products and their use, which allows them to feel empowered and confident when managing these treatment options. Currently, Poland has no official specialised training for PDNS, so this is a key strategic issue that needs to be addressed in relation to all DATs used for APD to maximise the success of each treatment.

Discussion

Effective control of PD motor and non-motor PD symptoms and the best possible quality of life should be paramount in the management of PD, particularly in APD.

Considering the evidence from published clinical trials for the efficacy of DATs such as subcutaneous APO PEN injection, subcutaneous APO infusion, and more recently LECIG infusion, our collective expert opinion is that APD patients in Poland would greatly benefit from reimbursement access to these proven treatment options, including the newer, smaller lightweight pump systems that are generally preferred by patients, and which may be important in encouraging treatment adherence.

In relation to APO infusion, the newer POD system would promote greater ease of use in fluctuating PD where APO offers the least invasive option, along with newly available foslevodopa/foscarbidopa therapy. In the rescue medication setting, time to ON after a subcutaneous APO injection is superior to oral therapies, and therefore of substantial potential benefit to patients who are active and working. LECIG also appears to be beneficial in APD in several regards. From a practical standpoint, the smaller pump is of great advantage and preferred by patients as reported in the original Swedish study undertaken by Öthman et al. [17]. Peripheral neuropathy has been described with intrajejunal levodopa infusion therapies and has been linked to malabsorption as well as possible hyperhomocysteinaemia [39,40]. While axonal neuropathy has been observed, there are also reports of concomitant co-pathologies as well as occasional cases of demyelinating polyneuropathy, although real-life data from a one-year follow up study of LECIG in PD showed no evidence of polyneuropathy thus far [41, 42]. The risk of polyneuropathy may in fact be lower with the use of LECIG due to the presence of the catechol-O-methyltransferase (COMT) inhibitor entacapone in the formulation.

There are theoretical advantages of combining a COMT inhibitor such as entacapone with levodopa, as it reduces levels of the metabolites 3-O-methyldopa (3-OMD) and homocysteine and therefore hyperhomocysteine-related rates of polyneuropathy may be lower. 3-OMD competes with levodopa at the blood brain barrier and so a reduction of the 3-OMD level is an additional advantage.

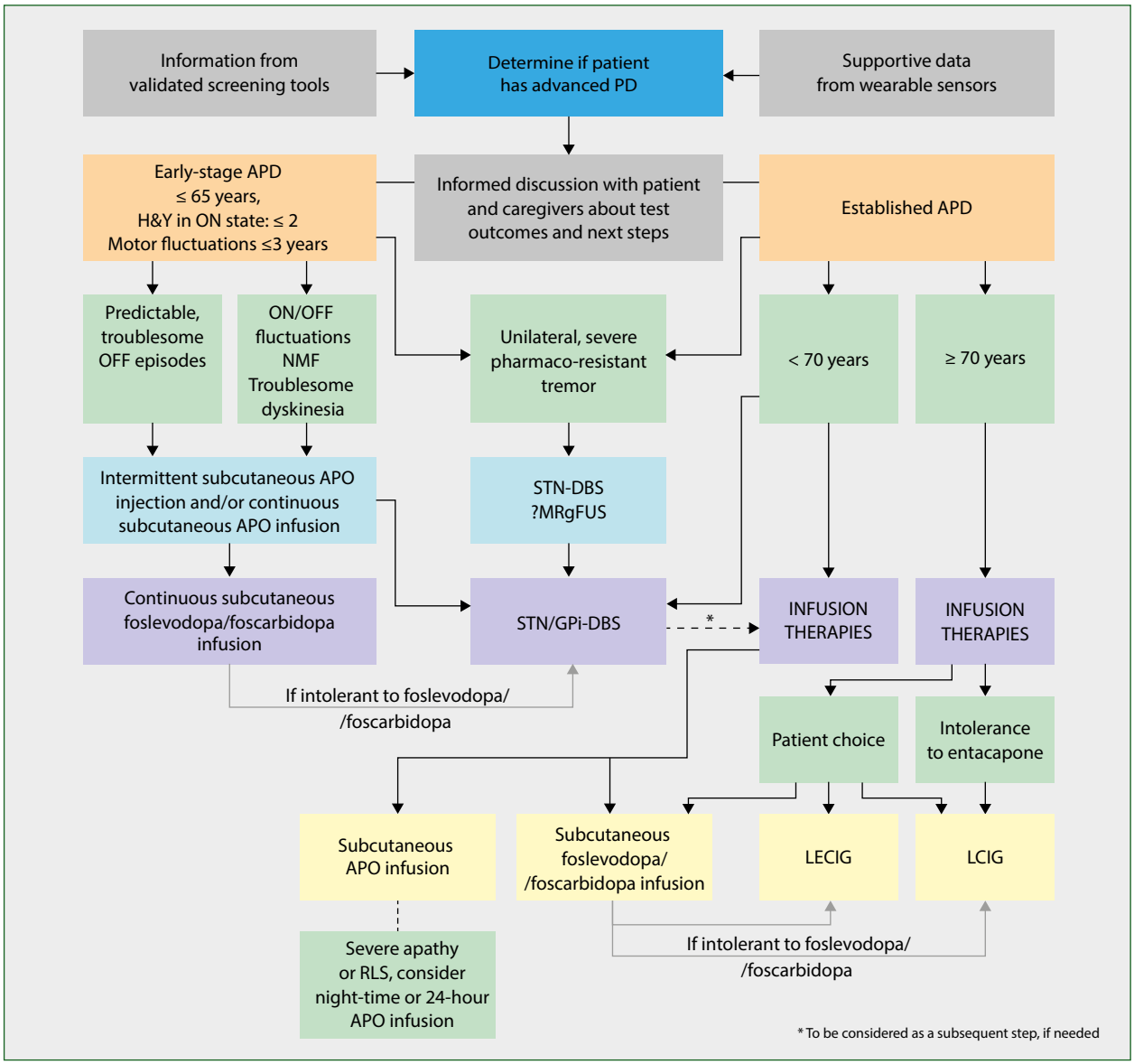

Figure 2. Suggested algorithm for clinical use of available device-aided therapies in Poland for advanced PD. Modified from Poplawska-Domaszewicz et al. [13]. APD — advanced PD; APO — apomorphine; DBS — deep brain stimulation; GPi — globus pallidus internus; H&Y — Hoehn & Yahr; NMF — non-motor fluctuations; MRgFUS — MRI-guided focused ultrasound; PD — Parkinson's Disease; PKG — Parkinson's KinetiGraph; RLS — restless legs syndrome; STN — subthalamic nucleus; LECIG — levodopa-entacapone-carbidopa intestinal gel; LCIG — levodopa-carbidopa intestinal gel; indicates possible consideration of technique if locally available

We acknowledge the inherent limitations in the development of these recommendations, as they are based on opinions and insights from a limited number of experts. However, the majority of participants have direct experience of the management of APD at a high level within Poland and have a detailed knowledge of its associated challenges. We are also aware that the experience at these specific centres may not necessarily be generalisable to all centres in the country, but it does raise important issues for further discussion in order to improve overall APD patient outcomes.

Conclusions

In the Polish clinical landscape of DATs for the management of APD, it is apparent that there are currently specific and important gaps in the availability of some effective therapeutic options. These include the use and availability of the most up-to-date versions of APO formulations i.e. an APO PEN injection that can be used for rescue therapy or an APO infusion using a modern POD system.

In addition, there is currently no availability of LECIG infusion, the levodopa–entacapone–carbidopa combination that can be administered with a substantially smaller pump than the currently available LCIG formulation. LECIG also provides pharmacological benefits in that a lower levodopa dose can be administered, reducing the accumulation of potentially harmful metabolites. The availability of these formulations in the therapeutic arena in Poland will improve patient care and enhance patient choice and quality of life in APD.

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JS has undertaken lectures and/or participated in Advisory Boards organised by AbbVie, Ever Pharma, Stada and Polpharma.

MR-B has received honoraria for lectures and participation in Advisory Boards organised by AbbVie, Stada and Vipharm.

SB has undertaken lectures and/or participated in Advisory Boards for: AbbVie, Ever Pharma, Stada, Polpharma and Orion Pharma.

DK has received honoraria for lectures and participated in Advisory Boards organised by AbbVie, Ever Pharma, Teva, GE HealthCare and Adamed.

AB has received honoraria for lectures and consultation fees from Merz, GE, Abbvie, Sandoz, Krka and Vipharm.

KRC is Editor in chief of JPM (Movement Disorders section), Nature Parkinson's Journal (Founder Editor). He has participated in recent Advisory Boards organised by AbbVie, UCB, GKC, Bial, Cynapsus, Lobsor, Stada, Zambon, Profile Pharma, Synovion, Roche, Therevance, Scion, Britannia Pharmaceuticals Ltd., Acadia, and 4D Pharma; Advisory Board over two years ago: Medtronic; he has received honoraria for recent lectures from AbbVie, Britannia Pharmaceuticals Ltd., UCB, Zambon, Novartis, Boehringer Ingelheim, Bial, Kyowa Kirin, SK Pharma, Scion, GKC, MDS, and EAN; recent grant (Investigator Initiated): Bial; grants (Investigator Initiated) over two years ago: Britannia Pharmaceuticals Ltd., AbbVie, UCB, and GKC; recent academic grants: EU Horizon 2020, Parkinson's UK, NIHR, Parkinson's Foundation, and the Wellcome Trust; academic grants over two years ago: Kirby Laing Foundation, MRC, and MDS (MDS NMS Project); royalties or licences (ongoing): Oxford (book), Cambridge publishers (book), MAPI institute (KPPS, PDSS 2); payment for expert testimony: GMC, NICE, and NIHR.

JSł is a Co-Editor in Chief of the Polish Journal of Neurology and Neurosurgery and has undertaken lectures and participated in Advisory Boards organised by AbbVie, Ever Pharma, Novartis, Roche, Woerwag Pharma, Stada, Exeltis, AskBio, Biogen and Polpharma.

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PRODUODOPA®
240 mg/ml+12 mg/ml roztwór do infuzji
foslewodopa/foskarbidopa

PRODUODOPA® znaczy WIĘCEJ

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Produodopa® to **pierwszy i jedyny podskórny, 24-godzinny wlew** umożliwiający utrzymanie stałego i stabilnego stężenia lewodopy we krwi.[1,2]

WIĘKSZA KONTROLA*

objawów ruchowych w sposób ciągły: rano, w dzień i w nocy†‡ bez konieczności przeprowadzenia inwazyjnego zabiegu.[1,3]

WIĘKSZA INDYWIDUALIZACJA*

zastosowanie Produodopy®, umożliwia podanie **do 6000 mg foslewodopy**, co odpowiada około **4260 mg lewodopy** na dobę. Podawana przez jedno miejsce infuzji i kaniulę, która może pozostać na miejscu do 3 dni. Może być stosowana w monoterapii.^[1]

* Większy komfort i większa kontrola odnosi się do czasu „włączenia" u pacjentów przyjmujących produkt leczniczy Produodopa® w porównaniu do doustnej lewodopy/karbidopy o natychmiastowym uwalnianiu. W 12. tygodniu obserwacji, u pacjentów przyjmujących produkt leczniczy Produodopa® zaobserwowano znaczną poprawę w kontroli objawów motorycznych w porównaniu z doustną lewodopą/karbidopą o natychmiastowym uwalnianiu, w tym czas „włączenia", bez uciążliwych dyskinez i czas „wyłączenia".[3]

† Pacjenci dokonywali wpisów w dzienniczku choroby Parkinsona tuż po przebudzeniu i co 30 minut w czasie aktywności.[3]

‡ Produodopa® jest lekiem zawierającym foslewodopę - prolek lewodopy, podawanym podskórnie w postaci 24-godzinnego wlewu.[1]

§ Zmiana miejsca infuzji i użycie nowego zestawu infuzyjnego musi nastąpić przynajmniej co 3 dni. Produodopa® umożliwia dawkowanie z 3 programowalnymi prędkościami przepływu (podstawową, wysoką i niską) oraz możliwością podawania dawki dodatkowej i dawki nasycającej. Szybkość infuzji można regulować stopniowo, w odstępach tak małych jak 0,01 ml/godzinę (równoważnik ~1,7 mg lewodopy/godzinę). Większa indywidualizacja odnosi się do pośredniego porównania z Duodopą®, która umożliwia podanie maksymalnie 4000 mg lewodopy dojelitowo (PEG-J), stopniowe dostosowywanie dawki podtrzymującej jest możliwe co 2 mg/godzinę (0,1 ml/godzinę), a dawka podtrzymująca ma stałą szybkość przepływu.[4]

^ Można przyjmować samodzielnie lub, jeśli to konieczne, z innymi jednocześnie stosowanymi produktami leczniczymi stosowanymi w leczeniu choroby Parkinsona.[1]

1. ChPL Produodopa® 11.2023
2. Rosebraugh M. et al; Journal of Parkinson's Disease 11 (2021) 1695–1702 DOI 10.3233/JPD-212813
3. Soileau M. et al; Lancet Neurol 2022; 21: 1099–109
4. ChPL Duodopa® 10.2023

PL-PRODD-240017

Produodopa®, 240 mg/ml + 12 mg/ml, roztwór do infuzji – skrócona informacja o leku

NAZWA PRODUKTU LECZNICZEGO: Produodopa®, 240 mg/ml + 12 mg/ml, roztwór do infuzji (foslewodopa + foskarbidoba) **SKŁAD JAKOŚCIOWY I ILOŚCIOWY:** 1 ml zawiera 240 mg foslewodopy i 12 mg foskarbidopy. 10 ml zawiera 2400 mg foslewodopy i 120 mg foskarbidopy. Foslewodopa i foskarbidopa są prolekami równoważnymi około 170 mg lewodopy i 9 mg karbidopy na 1 ml. *Substancja pomocnicza o znanym działaniu* Produodopa zawiera około 1,84 mmol (42,4 mg) sodu na ml. Pełny wykaz substancji pomocniczych, patrz Charakterystyka Produktu Leczniczego – ChPL. **POSTAĆ FARMACEUTYCZNA:** Roztwór do infuzji (infuzja). Produkt leczniczy Produodopa jest przezroczystym do lekko opalizującego roztworem w szklanej fiolce. Roztwór nie powinien zawierać cząstek stałych. Produkt leczniczy Produodopa może być bezbarwny, żółty lub brązowy i może mieć fioletowy lub czerwony odcień. Różnice w zabarwieniu są spodziewane i nie mają wpływu na jakość produktu. Roztwór może przybrać ciemniejsze zabarwienie po przekłuciu korka fiolki lub gdy jest w strzykawce. pH wynosi około 7,4. Osmolalność wynosi około 2200 do 2500 mOsmol/kg, ale może wynosić do 2700 mOsmol/kg. **WSKAZANIA DO STOSOWANIA:** Leczenie zaawansowanej choroby Parkinsona odpowiadającej na lewodopę u pacjentów, u których występują ciężkie fluktuacje ruchowe oraz hiperkinezy i (lub) dyskinezy, w przypadku gdy dostępne połączenia leków stosowanych w chorobie Parkinsona nie przynoszą zadowalających wyników. **DAWKOWANIE I SPOSÓB PODAWANIA:** Dawkowanie Produkt leczniczy Produodopa jest podawany w postaci ciągłego wlewu podskórnego, przez 24 godziny na dobę. Zalecana początkowa szybkość infuzji produktu leczniczego Produodopa jest określana poprzez przeliczenie dobowej dawki przyjmowanej lewodopy na dawkę równoważną lewodopy (ang. *levodopa equivalents*, LE), a następnie zwiększenie jej w celu uwzględnienia 24godzinnego podawania produktu (patrz Rozpoczęcie leczenia). Dawkę można dostosować w celu uzyskania odpowiedzi klinicznej, która maksymalizuje okres dobrej sprawności ruchowej (faza „włączenia" – ON) oraz minimalizuje liczbę i czas trwania epizodów „wyłączenia" – OFF oraz epizodów ON z uciążliwymi dyskinezami. Maksymalna zalecana dawka dobowa foslewodopy wynosi 6000 mg (lub 25 ml produktu leczniczego Produodopa na dobę, co odpowiada około 4260 mg lewodopy na dobę). Produodopa zastępuje leki zawierające lewodopę i inhibitory katecholoOmetylotransferazy (ang. *catechol-O-methyl transferase*, COMT). W razie potrzeby można stosować jednocześnie inne klasy produktów leczniczych stosowanych w leczeniu choroby Parkinsona. Rozpoczęcie leczenia Pacjenci zakwalifikowani do leczenia produktem leczniczym Produodopa powinni być w stanie zrozumieć działanie systemu podawania i stosować go samodzielnie lub z pomocą opiekuna. Pacjenci powinni zostać przeszkoleni w zakresie prawidłowego stosowania produktu leczniczego Produodopa i systemu podawania (patrz Sposób podawania) przed rozpoczęciem leczenia produktem leczniczym Produodopa oraz, w razie potrzeby, w późniejszym okresie. Rozpoczęcie leczenia produktem leczniczym Produodopa wymaga wykonania trzech czynności. Krok 1: Obliczenie dawki LE na podstawie leków zawierających lewodopę stosowanych w okresie aktywności pacjenta. Krok 2: Określenie godzinowej szybkości infuzji produktu leczniczego Produodopa. Krok 3: Określenie objętości dawki nasycającej. Krok 1: Obliczenie dawki LE na podstawie leków zawierających lewodopę stosowanych w okresie aktywności pacjenta. Ilość lewodopy ze wszystkich postaci zawierających lewodopę stosowanych w okresie aktywności pacjenta w ciągu dnia (zwykle 16 godzin/dobę) należy przeliczyć na LE, stosując odpowiedni mnożnik dawki z Tabeli 1, a następnie zsumować. W tych obliczeniach należy uwzględnić tylko lewodopę i inhibitory COMT. W obliczeniach nie należy uwzględniać lewodopy podawanej w ramach terapii ratunkowej ani żadnych innych leków lub terapii przeciwparkinsonowskich, w tym leków przyjmowanych poza okresem aktywności (np. w nocy). Jeśli w ciągu 24 godzin przyjmowane są jakiekolwiek inhibitory COMT, niezależnie od dawki inhibitora COMT, do sumy LE należy zastosować współczynnik korygujący, jak przedstawiono w Tabeli 1.

Tabela 1. Obliczanie dawek równoważnych lewodopy (LE)

Postać lewodopy	Mnożnik dawki
Produkty o natychmiastowym uwalnianiu, w tym zawiesina dojelitowa	1
Produkty o stopniowym uwalnianiu, o kontrolowanym uwalnianiu lub o przedłużonym uwalnianiu[a]	0,75
Jeśli stosowany jest jakikolwiek inhibitor COMT, należy pomnożyć sumę obliczonych dawek LE z powyższego punktu przez 1,33[a]	

[a] Lewodopa zawarta w produktach złożonych LD/CD/inhibitor COMT jest zaliczana do lewodopy o natychmiastowym uwalnianiu i należy ją dodać do dawki LE ze wszystkich innych źródeł lewodopy przed pomnożeniem sumy przez współczynnik korygujący dla inhibitorów COMT (tzn. nie należy stosować współczynnika korygującego COMT do pojedynczej dawki LE).
CD = karbidopa; LD = lewodopa; COMT = katecholoOmetylotransferaza; LE = dawka równoważna lewodopy.

Krok 2: Określenie godzinowej szybkości infuzji produktu leczniczego Produodopa. Sugerowaną początkową szybkość infuzji produktu leczniczego Produodopa na podstawie dawki LE obliczonej w kroku 1 przedstawiono w Tabeli 2. Godzinowa szybkość infuzji produktu leczniczego Produodopa w Tabeli 2 jest oparta na dawce LE przyjmowanej przez pacjenta podczas typowego 16godzinnego okresu aktywności (LE_{16}). Jeśli w kroku 1 dawka LE była określona na podstawie okresu aktywności dłuższym lub krótszym niż 16 godzin, dawka LE powinna zostać dostosowana do okresu 16godzinnego. Aby dostosować dawkę do okresu 16godzinnego, należy dawkę LE obliczoną w kroku 1 podzielić przez liczbę godzin, w których pacjent zazwyczaj nie śpi, a następnie pomnożyć przez 16. Następnie należy odnieść się do Tabeli 2, w której podano sugerowane początkowe szybkości infuzji produktu leczniczego Produodopa. Można również obliczyć początkową godzinową szybkość infuzji zgodnie ze wzorem podanym w Tabeli 2, gdzie X to liczba godzin czuwania pacjenta na dobę. Godzinowa szybkość infuzji określona w tym kroku powinna zostać wprowadzona jako podstawowa szybkość infuzji podczas programowania pompy (szczegółowe informacje znajdują się w instrukcji obsługi pompy).

Tabela 2. Sugerowana początkowa godzinowa szybkość infuzji produktu leczniczego Produodopa

LE_{16} (dawki LE wszystkich doustnych leków zawierających LD, przyjmowanych w ciągu 16godzinnego okresu aktywności (mg))	**Sugerowana początkowa godzinowa szybkość infuzji produktu leczniczego Produodopa (ml/godz)[a] podawanego w ciągu 24 godzin**
< 400	0,15
400–499	0,15–0,17
500–599	0,17–0,20
600–699	0,20–0,24
700–799	0,24–0,27
800–899	0,27–0,30
900–999	0,30–0,34
1000–1099	0,34–0,37
1100–1199	0,37–0,40
1200–1299	0,40–0,44
1300–1399	0,44–0,47
1400–1499	0,47–0,51
1500–1599	0,51–0,54
1600–1699	0,54–0,57
1700–1799	0,57–0,61
1800–1899	0,61–0,64
1900–1999	0,64–0,68
2000–2099	0,68–0,71
2100–2199	0,71–0,74
2200–2299	0,74–0,78
2300–2399	0,78–0,81
2400–2499	0,81–0,84
2500–2599	0,84–0,88
2600–2699	0,88–0,91
2700–2799	0,91–0,94
2800–2899	0,94–0,98
2900–2999	0,98–1,01
3000–3099	1,01–1,04
> 3100	1,04

[a] Godzinową szybkość infuzji można obliczyć według następującego wzoru, gdzie X oznacza liczbę godzin aktywności pacjenta użytą do określenia dawki LE (np. X = 16 w powyższej tabeli).
Godzinowa szybkość infuzji (ml/godz) = [(LE · 0,92 · 1,41)/240]/X
Założenia wykorzystane do wygenerowania „Sugerowanej początkowej godzinowej szybkości infuzji produktu leczniczego Produodopa":

- Całkowita dobowa dawka LE w ciągu 16 godzin jest zwiększona o 50%, aby uwzględnić dawkowanie 24godzinne
- Foslewodopa do podania podskórnego jest o 8% bardziej biodostępna niż lewodopa podawana dojelitowo
- Stosunek masy cząsteczkowej foslewodopy i lewodopy wynosi 1,41:1
- Jeden mililitr produktu leczniczego Produodopa zawiera 240 mg foslewodopy i 12 mg foskarbidopy
- Większość pacjentów z chorobą Parkinsona jest leczona doustnymi lekami przeciwparkinsonowskimi w okresie aktywności (okres leczenia zazwyczaj 16 godzin/dobę); po obliczeniu ilości foslewodopy potrzebnej w ciągu 16godzinnego okresu, wynik dzieli się przez 240 mg, aby określić liczbę mililitrów potrzebnych w ciągu 16godzinnego okresu, a następnie dzieli przez 16 godzin w celu ustalenia godzinowej szybkości infuzji

LE = dawka równoważna lewodopy; LD = lewodopa.

Krok 3: Określenie objętości dawki nasycającej. Dawkę nasycającą można podać bezpośrednio przed rozpoczęciem godzinowej infuzji w celu szybkiego osiągnięcia kontroli objawów w przypadku rozpoczynania leczenia produktem leczniczym Produodopa w stanie OFF (lub jeśli pompa była wyłączona przez ponad 3 godziny). Dawki nasycające można podawać za pomocą pompy lub doustnych tabletek karbidopy i lewodopy o natychmiastowym uwalnianiu. W Tabeli 3 podano zalecaną objętość dawki nasycającej (ml) produktu leczniczego Produodopa, którą należy zaprogramować w pompie (szczegółowe informacje znajdują się w instrukcji obsługi pompy) oraz odpowiadającą jej ilość lewodopy o natychmiastowym uwalnianiu (mg), niezależnie od tego, czy podawany jest jednocześnie obwodowy inhibitor dekarboksylazy DOPA (np. karbidopa, benserazyd).

Tabela 3. Określenie objętości produktu leczniczego Produodopa zalecanej do podania dawki nasycającej

Zalecana objętość dawki nasycającej (ml), którą należy zaprogramować w pompie	**Przybliżona odpowiadająca ilość lewodopy (mg)**
0,6	100
0,9–1,2	150–200
1,5–1,8	250–300
2,0	350
0,1 ml produktu leczniczego Produodopa zawiera 24 mg foslewodopy (co odpowiada około 17 mg lewodopy). Pompa może podawać dawkę nasycającą w zakresie od 0,1 ml do maksymalnie 3,0 ml, w odstępach co 0,1 ml.	

Optymalizacja i konserwacja Personel medyczny może dostosować początkową godzinową szybkość infuzji w celu uzyskania optymalnej odpowiedzi klinicznej u danego pacjenta. Godzinowa szybkość infuzji powinna być stosowana w sposób ciągły w czasie 24godzinnej infuzji. W razie potrzeby personel medyczny może zaprogramować i umożliwić 2 różne szybkości godzinowej infuzji (niska/wysoka). Wszystkie szybkości infuzji mogą być dostosowywane w odstępach co 0,01 ml/godzinę (co odpowiada około 1,7 mg lewodopy/godzinę) i nie powinny przekraczać 1,04 ml/godzinę (lub około 4260 mg lewodopy na dobę [6000 mg foslewodopy na dobę]). W pompie zastosowano funkcję bezpiecznego dostępu do konfiguracji dawki, aby uniemożliwić pacjentom wprowadzanie zmian w zaprogramowanych wartościach przepływu lub w funkcji dawki dodatkowej. Produkt leczniczy Produodopa może być przyjmowany samodzielnie lub, w razie konieczności, jednocześnie z innymi produktami leczniczymi stosowanymi w chorobie Parkinsona, w zależności od oceny lekarza. Podczas infuzji produktu leczniczego Produodopa można rozważyć zmniejszenie dawki innych jednocześnie stosowanych leków stosowanych w chorobie Parkinsona, a następnie dostosowanie dawki produktu leczniczego Produodopa. Nie badano jednoczesnego stosowania produktu leczniczego Produodopa z innymi lekami zawierającymi lewodopę lub z produktami leczniczymi, które w istotny sposób regulują synaptyczne stężenie dopaminy (takie jak inhibitory COMT). Inna prędkość przepływu Pompa umożliwia również zaprogramowanie dwóch innych szybkości infuzji dla pacjenta (niska/wysoka). Inne szybkości infuzji muszą być włączone i wstępnie zaprogramowane przez personel medyczny i mogą być wybierane przez pacjentów w celu uwzględnienia zmian w zapotrzebowaniu funkcjonalnym, np. obniżenia dawki w nocy lub zwiększenia dawki w przypadku długotrwałej intensywnej aktywności (szczegółowe informacje znajdują się w instrukcji obsługi pompy). Dawki dodatkowe Jeśli lekarz wyrazi na to zgodę, pacjent może samodzielnie podać sobie dodatkową dawkę w celu opanowania ostrych objawów OFF występujących podczas ciągłej infuzji. Objętość dawki dodatkowej można wybrać spośród 5 opcji (patrz Tabela 4). Funkcja dawki dodatkowej jest ograniczona do maksymalnie 1 dawki dodatkowej na godzinę. Jeśli pacjent zużyje 5 lub więcej dodatkowych dawek w ciągu 24godzinnego/dobowego okresu leczenia, należy rozważyć zmianę podstawowej szybkości infuzji. Możliwość włączenia tej funkcji, jak również minimalny czas wymagany między dawkami dodatkowymi, jest określana przez lekarza i nie może być modyfikowana przez pacjenta (szczegółowe informacje na temat programowania funkcji dodatkowej dawki znajdują się w instrukcji obsługi pompy).

Tabela 4. Opcja dawki dodatkowej produktu leczniczego Produodopa

Objętość produktu leczniczego Produodopa (ml)	Dawka równoważna lewodopy (mg)
0,10	17
0,15	25,5
0,20	34
0,25	42,5
0,30	51

Sposób podawania Produkt leczniczy Produodopa jest podawany podskórnie, najlepiej w brzuch, omijając obszar o promieniu 5 cm od pępka. Podczas przygotowywania i podawania tego produktu należy stosować technikę aseptyczną. Zestaw infuzyjny (kaniula) może pozostać na miejscu nawet przez 3 dni, jeśli lek jest podawany w sposób ciągły. Należy zmieniać miejsce infuzji i używać nowego zestawu infuzyjnego przynajmniej co 3 dni. Zaleca się, aby nowe miejsca infuzji były oddalone o co najmniej 2,5 cm od miejsc używanych w ciągu ostatnich 12 dni. Produktu leczniczego Produodopa nie należy podawać w miejsca, które są tkliwe, zasinione, zaczerwienione lub twarde w dotyku. Do podawania produktu leczniczego Produodopa należy stosować wyłącznie pompę Vyafuser (szczegółowe informacje znajdują się w instrukcji obsługi pompy) z użyciem sterylnych, jednorazowych elementów infuzyjnych (strzykawka, zestaw infuzyjny i adapter fiolki) zakwalifikowanych do użytku. Pacjenci powinni zostać przeszkoleni w zakresie prawidłowego stosowania produktu leczniczego Produodopa oraz systemu podawania (pompa, fiolka z roztworem, adapter fiolki, strzykawka, zestaw infuzyjny, akcesoria do przenoszenia, akumulator i ładowarka) przed rozpoczęciem leczenia produktem leczniczym Produodopa oraz, w razie potrzeby, po jego zakończeniu. W badaniu krzyżowym farmakokinetyki podawanie produktu leczniczego Produodopa w ramię i udo powodowało prawie taką samą ekspozycję na lek jak w przypadku brzucha (patrz ChPL). Nie oceniano długoterminowego bezpieczeństwa i skuteczności podawania leku w ramię i udo. Lek należy przechowywać i używać w sposób opisany w punkcie 6.4, Specjalne środki ostrożności podczas przechowywania. Fiolki z lekiem są przeznaczone wyłącznie do jednorazowego użytku. Po przeniesieniu zawartości fiolki do strzykawki, zawartość strzykawki należy podać w ciągu 24 godzin. Zużyte fiolki i strzykawki z lekiem należy usuwać zgodnie z lokalnymi przepisami. Strzykawki należy wyrzucić, nawet jeśli pozostały w nich resztki produktu, zgodnie z zaleceniami personelu medycznego (patrz ChPL). Przerwanie leczenia Zasadniczo należy unikać nagłego przerwania stosowania produktu leczniczego Produodopa lub szybkiego zmniejszania jego dawki, bez zastosowania alternatywnego leczenia dopaminergicznego (patrz ChPL). Podawanie produktu leczniczego Produodopa można przerwać bez podejmowania dalszych działań na krótki okres, np. gdy pacjent bierze prysznic. W przypadku przerw dłuższych niż jedna godzina należy użyć nowego zestawu infuzyjnego (zgłębnika i kaniuli) i zmienić miejsce infuzji. Jeśli infuzja została przerwana na dłużej niż 3 godziny, pacjent może również samodzielnie podać sobie dawkę nasycającą, jeśli zezwoli na to lekarz, w celu szybkiego przywrócenia kontroli objawów. Jeśli leczenie produktem leczniczym Produodopa zostanie przerwane na dłuższy czas (> 24 godzin) lub zostanie trwale przerwane, lekarz powinien określić odpowiednie alternatywne leczenie dopaminergiczne (np. doustna lewodopa/karbidopa). Leczenie produktem leczniczym Produodopa może być wznowione w dowolnym czasie, zgodnie z instrukcjami dotyczącymi rozpoczęcia leczenia tym produktem (patrz ChPL). Szczególne populacje Farmakokinetyka produktu leczniczego Produodopa nie była oceniana w żadnej szczególnej populacji. Produkt leczniczy Produodopa jest przeznaczony do stosowania u pacjentów z chorobą Parkinsona, którzy przyjmują już stałą dawkę lewodopy doustnie. Różnice w ekspozycji nie są uważane za kliniczne istotne, ponieważ dawka produktu leczniczego Produodopa jest optymalizowana po rozpoczęciu leczenia. W związku z tym nie oczekuje się, że efekty zmiennych towarzyszących będą miały wpływ na skuteczność kliniczną lub bezpieczeństwo. Więcej informacji na temat farmakokinetyki lewodopy i karbidopy w szczególnych populacjach, patrz ChPL. **PRZECIWWSKAZANIA:** Produkt leczniczy Produodopa jest przeciwwskazany u pacjentów z: nadwrażliwością na substancje czynne lub na którąkolwiek substancję pomocniczą wymienioną w punkcie 6.1; jaskrą z wąskim kątem przesączania; ciężką niewydolnością serca; ostrą fazą udaru; ciężkimi zaburzeniami rytmu serca; przeciwwskazane jest stosowanie z produktem leczniczym Produodopa nieselektywnych inhibitorów MAO i selektywnych inhibitorów MAO typu A. Należy przerwać podawanie tych inhibitorów co najmniej na 2 tygodnie przed rozpoczęciem leczenia produktem leczniczym Produodopa. Produkt leczniczy Produodopa można podawać równocześnie z zalecaną przez wytwórcę dawką inhibitora MAO o wybiórczym działaniu na MAO typu B (np. selegiliny chlorowodorek) (patrz ChPL); chorobami, w których podawanie leków adrenomimetycznych jest przeciwwskazane, np. guz chromochłonny, nadczynność tarczycy oraz zespół Cushinga. Lewodopa może aktywować czerniaka złośliwego i dlatego nie należy stosować produktu leczniczego Produodopa u pacjentów z podejrzanymi, nierozpoznanymi zmianami skórnymi lub z czerniakiem w wywiadzie. **SPECJALNE OSTRZEŻENIA I ŚRODKI OSTROŻNOŚCI DOTYCZĄCE STOSOWANIA:** Kilka poniższych ostrzeżeń i środków ostrożności dotyczy wszystkich produktów zawierających lewodopę, a zatem dotyczy również produktu leczniczego Produodopa. Produkt leczniczy Produodopa nie jest zalecany w leczeniu polekowych reakcji pozapiramidowych. Należy zachować ostrożność, podając produkt leczniczy Produodopa pacjentom z ciężką chorobą sercowonaczyniową lub płuc, astmą oskrzelową, chorobą nerek, wątroby lub endokrynną, lub z chorobą wrzodową albo drgawkami w wywiadzie. U pacjentów z zawałem mięśnia sercowego w wywiadzie, u których utrzymują się zaburzenia rytmu serca, pochodzące z węzła przedsionkowokomorowego lub komorowe, podczas początkowego dostosowania dawki należy szczególnie dokładnie monitorować czynność serca. Wszystkich pacjentów leczonych produktem leczniczym Produodopa należy dokładnie monitorować pod kątem rozwoju zaburzeń psychicznych, depresji z tendencjami samobójczymi i innych poważnych zaburzeń psychicznych. Należy zachować ostrożność podczas leczenia pacjentów z psychozami występującymi w przeszłości lub obecnie. Większa częstość omamów może wystąpić u pacjentów leczonych agonistami dopaminy i (lub) innymi lekami dopaminergicznymi zawierającymi lewodopę w tym produkt leczniczy Produodopa. W takich przypadkach zaleca się przeanalizowanie stosowanego leczenia. Należy zachować ostrożność przy równoczesnym podawaniu leków przeciwpsychotycznych o właściwościach blokowania receptorów dopaminowych, szczególnie antagonistów receptora D2, a pacjenci powinni być dokładnie obserwowani pod kątem utraty skuteczności działania przeciwparkinsonowskiego lub nasilenia objawów parkinsonizmu (patrz ChPL). Pacjentów z przewlekłą jaskrą z szerokim kątem przesączania można leczyć produktem leczniczym Produodopa z zachowaniem ostrożności, pod warunkiem, że ciśnienie wewnątrzgałkowe jest dobrze kontrolowane, a pacjent jest dokładnie monitorowany w kierunku zmian ciśnienia wewnątrzgałkowego. Produkt leczniczy Produodopa może wywoływać niedociśnienie ortostatyczne. Dlatego należy zachować ostrożność, jeśli produkt leczniczy Produodopa jest podawany pacjentom przyjmującym inne produkty lecznicze mogące powodować niedociśnienie ortostatyczne (patrz ChPL). U pacjentów z chorobą Parkinsona stosowanie lewodopy wiązano z sennością i epizodami nagłego zasypiania. Dlatego należy zachować ostrożność podczas prowadzenia pojazdów lub obsługiwania maszyn (patrz ChPL). Po nagłym odstawieniu leków przeciwparkinsonowskich obserwowano objawy przypominające złośliwy zespół neuroleptyczny (ang. *Neuroleptic Malignant Syndrome*, NMS), w tym sztywność mięśni, podwyższoną temperaturę ciała oraz zmiany stanu psychicznego (np. pobudzenie, splątanie, śpiączka), a także zwiększoną aktywność fosfokinazy kreatynowej w surowicy. U pacjentów z chorobą Parkinsona rzadko obserwowano rabdomiolizę, wtórną do złośliwego zespołu neuroleptycznego, lub ciężkich dyskinez. Dlatego po nagłym zmniejszeniu dawki lub przerwaniu podawania lewodopy z karbidopą należy dokładnie obserwować pacjentów, a szczególnie pacjentów przyjmujących leki przeciwpsychotyczne. Nie zgłaszano występowania NMS ani rabdomiolizy w związku z podawaniem produktu leczniczego Produodopa. Należy regularnie monitorować pacjentów pod kątem rozwoju zaburzeń kontroli impulsów. Należy poinformować pacjentów i ich opiekunów, że u osób leczonych agonistami dopaminy i (lub) innymi produktami dopaminergicznymi zawierającymi lewodopę, w tym produktem leczniczym Produodopa, mogą wystąpić behawioralne objawy zaburzeń kontroli impulsów, a w tym: uzależnienie od hazardu, zwiększone libido i hiperseksualność, kompulsywne wydawanie pieniędzy lub kupowanie oraz kompulsywne lub napadowe objadanie się. W takich przypadkach zaleca się przeanalizowanie stosowanego leczenia. Badania epidemiologiczne wykazały, że u pacjentów z chorobą Parkinsona, w porównaniu do populacji ogólnej, występuje zwiększone ryzyko rozwoju czerniaka. Nie wyjaśniono, czy zaobserwowane zwiększone ryzyko było spowodowane chorobą Parkinsona czy innymi czynnikami, takimi jak leki stosowane w chorobie Parkinsona. Dlatego podczas stosowania produktu leczniczego Produodopa, w każdym ze wskazań, zaleca się pacjentom i personelowi medycznemu regularną kontrolę w celu wykluczenia czerniaka. Najbardziej właściwe jest prowadzenie przez specjalistów (np. dermatologów) okresowych badań skóry. Zespół dysregulacji dopaminowej (ang. *Dopamine Dysregulation Syndrome*, DDS) jest uzależnieniem prowadzącym do nadmiernego stosowania produktu, obserwowanym u niektórych pacjentów leczonych karbidopą z lewodopą. Przed rozpoczęciem leczenia należy ostrzec pacjenta i jego opiekunów o możliwym ryzyku DDS. W celu uniknięcia dyskinez wywołanych przez lewodopę może być konieczne zmniejszenie dawki produktu leczniczego Produodopa. Podczas długookresowej terapii produktem leczniczym Produodopa zaleca się okresową kontrolę czynności wątroby, układu krwiotwórczego, układu sercowonaczyniowego oraz nerek. Produkt leczniczy Produodopa zawiera hydrazynę, produkt rozpadu foskarbidopy, która może być genotoksyczna i potencjalnie kancerogenna. Mediana dawki dobowej produktu leczniczego Produodopa wynosi około 2541 mg/dobę foslewodopy i 127 mg/dobę foskarbidopy. Maksymalna zalecana dawka dobowa wynosi 6000 mg foslewodopy i 300 mg foskarbidopy. Obejmuje to hydrazynę przy medianie ekspozycji do 0,2 mg/dobę i maksymalnej dawce 0,5 mg/dobę. Znaczenie kliniczne takiej ekspozycji na hydrazynę nie jest znane. Obniżona zdolność do obsługiwania systemu podawania leku może prowadzić do powikłań. W przypadku takich pacjentów, choremu powinien pomagać opiekun (np. pielęgniarka lub bliski krewny). Nagłe lub stopniowe nasilenie bradykinezji może wskazywać na niedrożność urządzenia i wymaga sprawdzenia w celu ustalenia przyczyny. U pacjentów leczonych produktami zawierającym lewodopę z karbidopą notowano polineuropatię. Przed rozpoczęciem leczenia należy określić, czy u pacjenta w przeszłości występowały objawy polineuropatii oraz znane czynniki ryzyka, a następnie regularnie obserwować. U pacjentów otrzymujących produkt leczniczy Produodopa zgłaszano zdarzenia w miejscu infuzji (patrz ChPL). W celu zmniejszenia ryzyka zaleca się przestrzeganie zasad aseptyki podczas stosowania tego leku oraz częste zmienianie miejsca infuzji. W badaniach klinicznych u niewielu pacjentów, u których wystąpiły reakcje w miejscu infuzji, wystąpiły również zakażenia w miejscu infuzji. Dlatego zaleca się uważne monitorowanie ciężkich reakcji w miejscu infuzji i zakażeń w miejscu infuzji. Produodopa zawiera sód Produkt leczniczy Produodopa zawiera 42,4 mg (około 1,84 mmol) sodu na ml, co odpowiada 2,1% zalecanej przez WHO maksymalnej dobowej dawki sodu. Maksymalna dawka dobowa tego leku zawiera 54% zalecanej przez WHO maksymalnej dobowej dawki sodu. Produodopa zawiera dużą ilość sodu. Należy to wziąć pod uwagę zwłaszcza u pacjentów stosujących dietę o niskiej zawartości soli. **WPŁYW NA PŁODNOŚĆ, CIĄŻĘ I LAKTACJĘ:** Ciąża Brak danych dotyczących stosowania produktu leczniczego Produodopa u kobiet w ciąży. **Badania lewodopy z karbidopą na zwierzętach wykazały szkodliwy wpływ na reprodukcję** (patrz ChPL). Produkt leczniczy Produodopa nie jest zalecany do stosowania w okresie ciąży oraz u kobiet w wieku rozrodczym nie stosujących skutecznej metody antykoncepcji, chyba że korzyści dla matki przeważają nad możliwym ryzykiem dla płodu. Karmienie piersią Lewodopa, a być może także metabolity lewodopy przenikają do mleka ludzkiego. Istnieją dowody, że w czasie leczenia lewodopą laktacja ulega hamowaniu. Nie wiadomo, czy karbidopa lub jej metabolity przenikają do mleka ludzkiego. Badania na zwierzętach wykazały przenikanie karbidopy do mleka. Brak wystarczających danych dotyczących działania produktu leczniczy Produodopa lub jego metabolitów u noworodków i niemowląt. Podczas leczenia produktem leczniczym Produodopa należy przerwać karmienie piersią. Płodność W badaniach wpływu na reprodukcję nie wykazano oddziaływania na płodność szczurów otrzymujących lewodopę/karbidopę. **WPŁYW NA ZDOLNOŚĆ PROWADZENIA POJAZDÓW I OBSŁUGIWANIA MASZYN:** Produkt leczniczy Produodopa może wywierać znaczny wpływ na zdolność prowadzenia pojazdów i obsługiwania maszyn. Lewodopa i karbidopa mogą powodować zawroty głowy i niedociśnienie ortostatyczne. Dlatego należy zachować ostrożność podczas prowadzenia pojazdów oraz obsługiwania maszyn. Pacjentów leczonych produktem leczniczym Produodopa, u których występuje senność i (lub) epizody nagłego zasypiania, należy poinformować o konieczności unikania prowadzenia pojazdów lub wykonywania czynności, podczas których osłabienie czujności mogłoby stanowić zagrożenie dla nich samych lub dla innych osób, z ryzykiem ciężkich obrażeń lub śmierci (np. podczas obsługiwania maszyn), dopóki takie nawracające epizody i senność nie ustąpią (patrz ChPL). **DZIAŁANIA NIEPOŻĄDANE:** Podsumowanie profilu bezpieczeństwa Najczęstszymi działaniami niepożądanymi (≥ 10%) zgłaszanymi we wszystkich badaniach fazy III przez pacjentów przyjmujących produkt leczniczy Produodopa były zdarzenia w miejscu infuzji (rumień w miejscu infuzji, zapalenie tkanki łącznej w miejscu infuzji, guzek w miejscu infuzji, ból w miejscu infuzji, obrzęk w miejscu infuzji, reakcja w miejscu infuzji i zakażenie w miejscu infuzji), omamy, upadek i niepokój. Tabelaryczne zestawienie działań niepożądanych Działania niepożądane zgłaszane we wszystkich badaniach fazy III u pacjentów narażonych na produkt leczniczy Produodopa (379 pacjentów z całkowitą ekspozycją wynoszącą 414,3 pacjentolat, 230 pacjentów z całkowitą ekspozycją wynoszącą ≥ 6 miesięcy, 204 pacjentów z całkowitą ekspozycją wynoszącą ≥ 12 miesięcy) lub dane z badań produktu Duodopa żel dojelitowy w oparciu o częstość występowania w trakcie leczenia, niezależnie od przypisanej przyczynowości, przedstawiono w Tabeli 5 zgodnie z klasyfikacją układów i narządów MedDRA. Częstość występowania jest oparta na następującej konwencji: bardzo często (≥ 1/10), często (≥ 1/100 do < 1/10), niezbyt często (≥ 1/1 000 do < 1/100), rzadko (≥ 1/10 000 do < 1/1 000) lub bardzo rzadko (< 1/10 000).

Tabela 5. Tabelaryczne zestawienie działań niepożądanych

Klasyfikacja układów i narządów	Częstość występowania	Działania niepożądane
Zakażenia i zarażenia pasożytnicze	Bardzo często	Zapalenie tkanki łącznej w miejscu infuzji Zakażenie w miejscu infuzji Zakażenie układu moczowego[b]
	Często[a]	Ropień w miejscu infuzji
Zaburzenia krwi i układu chłonnego	Często	Niedokrwistość[b]
	Niezbyt często	Leukopenia[b] Trombocytopenia[b]
Zaburzenia układu immunologicznego	Nieznana	Reakcja anafilaktyczna[b,e]
Zaburzenia metabolizmu i odżywiania	Często	Zmniejszenie apetytu

Zaburzenia psychiczne	Bardzo często	Niepokój Depresja Omamy[c]
	Często	Nietypowe sny[b] Pobudzenie[b] Stan splątania Złudzenia Zaburzenie kontroli impulsów Bezsenność Paranoja Zaburzenie psychotyczne Napady snu[b] Zaburzenie snu[b] Myśli samobójcze
	Niezbyt często	Samobójstwo dokonane[b] Otępienie[b] Dezorientacja[b] Zespół dysregulacji dopaminowej Nastrój euforyczny[b] Strach[b] Zwiększone libido[b] Koszmary senne[b] Próba samobójcza[b]
	Rzadko	Nietypowe myśli[b]
Zaburzenia układu nerwowego	Często	Zaburzenia funkcji poznawczych Zawroty głowy Ortostatyczne zawroty głowy Dyskinezy Dystonia Bóle głowy Hipestezja Zjawisko ONOFF Parestezje Polineuropatia[d] Senność Omdlenia Drżenie[b]
	Niezbyt często	Ataksja[b] Drgawki[b] Zaburzenia chodu[b]
Zaburzenia oka	Niezbyt często	Jaskra z zamkniętym kątem przesączania[b] Kurcz powiek[b] Podwójne widzenie[b] Niedokrwienna neuropatia nerwu wzrokowego[b] Niewyraźne widzenie[b]
Zaburzenia serca	Często	Nieregularna częstość pracy serca[b]
	Niezbyt często	Kołatanie serca
Zaburzenia naczyniowe	Często	Nadciśnienie tętnicze Niedociśnienie tętnicze Niedociśnienie ortostatyczne
	Niezbyt często	Zapalenie żył[b]
Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia	Często	Duszność Ból jamy ustnej i gardła[b]
	Niezbyt często	Dysfonia[b]
	Rzadko	Nieprawidłowy oddech[b]
Zaburzenia żołądka i jelit	Często	Rozdęcie brzucha[b] Bóle brzucha Zaparcia Biegunka Suchość w jamie ustnej Zaburzenie smaku[b] Niestrawność[b] Utrudnione połykanie[b] Wzdęcie z oddawaniem gazów[b] Nudności Wymioty
	Niezbyt często	Nadmierne wydzielanie śliny[b]
	Rzadko	Bruksizm[b] Przebarwienie śliny[b] Ból języka[b] Czkawka[b]
Zaburzenia skóry i tkanki podskórnej	Często	Kontaktowe zapalenie skóry[b] Nadmierna potliwość[b] Świąd Wysypka
	Niezbyt często	Łysienie[b] Rumień[b] Pokrzywka[b]
	Rzadko	Przebarwienie potu[b] Czerniak złośliwy[b]
Zaburzenia mięśniowoszkieletowe i tkanki łącznej	Często	Skurcze mięśni Ból szyi[b]
Zaburzenia nerek i dróg moczowych	Często	Nietrzymanie moczu Zatrzymanie moczu
	Niezbyt często	Niewłaściwe zabarwienie moczu[b]
	Rzadko	Priapizm[b]

Zaburzenia ogólne i stany w miejscu podania	Bardzo często	Rumień w miejscu infuzji Reakcja w miejscu infuzji Guzek w miejscu infuzji Obrzęk w miejscu infuzji Ból w miejscu infuzji
	Często[a]	Astenia Uczucie zmęczenia Zasinienie w miejscu infuzji Złuszczenie w miejscu infuzji Wynaczynienie w miejscu infuzji Krwiak w miejscu infuzji Krwotok w miejscu infuzji Stwardnienie w miejscu infuzji Stan zapalny w miejscu infuzji Podrażnienie w miejscu infuzji Naciek w miejscu infuzji Grudka w miejscu infuzji Świąd w miejscu infuzji Wysypka w miejscu infuzji Opuchlizna w miejscu infuzji Złe samopoczucie Obrzęk obwodowy Ból[b]
	Niezbyt często	Bóle w klatce piersiowej[b]
Badania diagnostyczne	Często	Zwiększenie stężenia aminokwasów (zwiększenie stężenia kwasu metylomalonowego)[b] Zwiększenie stężenia homocysteiny we krwi[b] Obniżona zawartość witaminy B_6 Niedobór witaminy B_{12}[b] Zmniejszenie masy ciała Zwiększenie masy ciała[b]
Urazy, zatrucia i powikłania po zabiegach	Bardzo często	Upadki

[a] Wspólne działania niepożądane odnoszące się do zdarzeń w miejscu infuzji włączono, jeśli częstość występowania ≥ 2%.
[b] Te działania niepożądane stwierdzono w przypadku produktu leczniczego Duodopa żel dojelitowy jako działania niepożądane związane ze stosowaniem leku. Jednakże działania te nie były uznawane za działania niepożądane produktu leczniczego Produodopa.
[c] Omamy obejmują omamy, omamy wzrokowe, omamy słuchowe, omamy węchowe, omamy dotykowe i omamy mieszane.
[d] Polineuropatia obejmuje neuropatię obwodową, polineuropatię, osłabienie czucia wibracji, obwodową neuropatię czuciową, zaburzenia czucia i utratę czucia.
[e] Na podstawie danych po wprowadzeniu produktu do obrotu

Opis wybranych działań niepożądanych Zdarzenia *w miejscu infuzji* W badaniach fazy III najczęstszymi zdarzeniami niepożądanymi związanymi z produktem leczniczym Produodopa były reakcje w miejscu infuzji 77,6% (N=294) i zakażenia w miejscu infuzji 41,4% (N=157). W badaniach klinicznych obserwowano zdarzenia w miejscu infuzji, w tym reakcje w miejscu infuzji i zakażenia, często występujące w przypadku infuzji podskórnej produktu leczniczego Produodopa. Większość zdarzeń w miejscu infuzji nie była ciężka, miała łagodne lub umiarkowane nasilenie i ustępowała samoistnie lub po zastosowaniu leczenia, takiego jak antybiotyki i (lub) nacięcie i drenaż. U trzech uczestników z zakażeniami w miejscu infuzji wystąpiło powikłanie w postaci posocznicy, które skutkowało hospitalizacją. Należy monitorować wszelkie zmiany na skórze w miejscu infuzji, które mogą wskazywać na potencjalne zakażenie, takie jak zaczerwienienie połączone z ciepłem, obrzęk, ból i odbarwienie po uciśnięciu. Podczas stosowania tego leku należy przestrzegać zasad aseptyki i rozważyć częstszą niż co 3 dni zmianę miejsca infuzji, używając nowego zestawu do infuzji, jeśli pojawią się takie zmiany na skórze. Zaleca się, aby nowe miejsca infuzji były oddalone o co najmniej 2,5 cm od miejsc używanych w ciągu ostatnich 12 dni. *Badania laboratoryjne:* Zgłaszano następujące nieprawidłowości w badaniach laboratoryjnych podczas leczenia lewodopą z karbidopą, które należy brać pod uwagę podczas leczenia pacjentów produktem leczniczym Produodopa: podwyższone stężenie azotu mocznikowego we krwi, zwiększona aktywność fosfatazy alkalicznej, zwiększenie aktywności AspAT, AlAT, LDH, zwiększone stężenie bilirubiny, glukozy we krwi, kreatyniny, kwasu moczowego, dodatni odczyn Coombsa oraz zmniejszenie stężenia hemoglobiny i wartości hematokrytu. Notowano obecność leukocytów, bakterii oraz krwi w moczu. Lewodopa z karbidopą, a zatem również produkt leczniczy Produodopa, mogą powodować fałszywie dodatni wynik, gdy stosowany jest test paskowy do wykrywania ciał ketonowych w moczu; reakcja ta nie ulega zmianie pod wpływem gotowania próbki moczu. Zastosowanie testu na obecność glukozy w moczu z oksydazą glukozową może dać fałszywie ujemne wyniki. Zgłaszanie podejrzewanych działań niepożądanych Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem Departamentu Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych, Al. Jerozolimskie 181C, PL-02 222 Warszawa, tel.: + 48 22 49 21 301, faks: + 48 22 49 21 309, Strona internetowa: https://smz.ezdrowie.gov.pl Działania niepożądane można zgłaszać również podmiotowi odpowiedzialnemu. **WYKAZ SUBSTANCJI POMOCNICZYCH:** Sodu wodorotlenek 10N (do ustalenia pH), Kwas solny stężony (do ustalenia pH), Woda do wstrzykiwań **RODZAJ I ZAWARTOŚĆ OPAKOWANIA:** Całkowita ilość 10 ml w fiolce z bezbarwnego, przezroczystego szkła typu I, zamykanej szarym korkiem z gumy bromobutylowej, aluminiowym wieczkiem i turkusowym plastikowym kapslem typu *flip-off*. Opakowanie zewnętrzne (tekturowe pudełko) zawiera 7 fiolek. Sterylne, jednorazowe elementy do infuzji (strzykawka, zestaw infuzyjny i adapter fiolki), które zostały zakwalifikowane do użytku, są dostarczane oddzielnie. Pompa Vyafuser jest dostarczana oddzielnie. **PODMIOT ODPOWIEDZIALNY POSIADAJĄCY POZWOLENIE NA DOPUSZCZENIE DO OBROTU:** AbbVie Sp. z o.o., ul. Postępu 21B, 02-676 Warszawa **NUMER POZWOLENIA NA DOPUSZCZENIE DO OBROTU:** 27625, wydane przez Prezesa URPL,WMiPB. Lek wydawany z przepisu lekarza – Rp. Niniejsza informacja została zaktualizowana dnia 25 czerwca 2024 r. na podstawie Charakterystyki Produktu Leczniczego z 11/2023, z którą należy się zapoznać przed zastosowaniem leku. Pełny tekst Charakterystyki Produktu Leczniczego jest dostępny na stronie internetowej Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych http://urpl.gov.pl Dodatkowe informacje dostępne są w AbbVie Sp. z o.o., ul. Postępu 21B, 02-676 Warszawa, tel.: +48 22 372 78 00, fax: +48 22 372 78 01, www.abbvie.pl. Produkt refundowany w programie lekowym numer B.90. Cena (urzędowa) detaliczna: brak, maksymalna kwota dopłaty ponoszona przez pacjenta: 0 PLN.

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Uveitis in multiple sclerosis patients: a case series

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To the Editors

We have read with interest the paper by Wawrzyniak et al. [1], wherein the authors investigate the coexistence of multiple sclerosis (MS) and other autoimmune disorders. Although they found in their cohort common comorbidities such as thyroid autoimmunity, rheumatological disorders and inflammatory bowel disease, they did not report uveitis.

We would like to share a series of patients with uveitis who subsequently developed MS. We strongly believe that uveitis, while it is typically regarded as a sign of a different autoimmune disorder such as, e.g., sarcoidosis, Crohn's disease, systemic lupus erythematosus or ankylosing spondylitis, may be yet another initial manifestation of MS alongside other atypical syndromes [2].

In patients without a clear cause of uveitis who subsequently develop MS, it is unclear whether uveitis should be treated as MS prodrome or MS manifestation, or as the independent rheumatological sign of a concurrent autoimmune disease. On the other hand, central nervous system demyelination may be a complication of tumour necrosis factor-alpha (TNF-alpha) inhibitors used in patients with uveitis.

Undoubtedly, uveitis is an interdisciplinary disorder that often requires cooperation between neurologists, ophthalmologists and rheumatologists.

Uveitis is an inflammation of the uvea – the vascular layer of the eye which comprises the iris, ciliary body and choroid. The inflammatory process can also involve other structures, such as the retina, sclera, cornea, vitreous humour and, importantly in the context of MS, optic nerve. Uveitis, based on the primary location of the inflammatory activity, can be categorised as: anterior uveitis (with the iris and ciliary body being affected), intermediate uveitis (predominantly affecting the vitreous humour), posterior uveitis (affecting the retina and/or choroid) or panuveitis that refers to anterior, intermediate and posterior uveitis combined. Uveitis can be further divided into unilateral or bilateral and acute (less than three months), chronic (longer than three months) or recurrent (when a flare up occurs after a previous episode has fully resolved). Uveitis aetiology can be infectious, noninfectious (e.g. due to sarcoidosis, Behçet's disease, Vogt-Koyanagi-Harada disease or juvenile idiopathic arthritis-associated uveitis) or masquerade (neoplastic, non-neoplastic) [3–4, also see The Standardisation of Uveitis Nomenclature (SUN) Working Group].

Although optic neuritis is the most common ophthalmic manifestation of MS, uveitis can present similarly and occurs in c. 1–3% of MS patients (in whom the risk is 10 times higher than in the general population). Intermediate uveitis accounts for 10–20% of uveitis cases overall, but 61–80% of MS-associated uveitis, making it the most frequent uveitis type in MS [5].

We present three cases of patients with uveitis who eventually developed MS fulfilling the 2017 revised McDonald criteria (Tab. 1, Fig. 1).

The first patient (female) developed chronic intermediate uveitis in the right eye at the age 21. After eight years she developed left-sided hemiparesis and was diagnosed with relapsing-remitting MS (RRMS). Magnetic resonance imaging (MRI) detected demyelinating lesions periventricularly, in the pons and cerebellum.

The second patient (male) developed recurrent intermediate bilateral uveitis at the age of 20. Aged 33 he presented with Lhermitte's sign and dysesthesias in his lower limbs up to the thoracic sensory level corresponding to spinal cord lesions on MRI. At that time he was diagnosed with RRMS. However, his first clinical episode of MS was preceded by the incidental finding of multiple T2-hyperintense lesions supratentorially and in the cerebellum after two years of treatment with TNF-alpha inhibitor (adalimumab). At that point adalimumab was

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Table 1. Clinical profiles of uveitis patients subsequently diagnosed with MS.

Case number	Age (now)	Sex	Eye	Uveitis location	Uveitis course	Year of first uveitis diagnosis	Year of MS diagnosis	TNF-alpha inhibitor therapy	OB restricted to CSF
1	30	F	OD	Intermediate	Chronic	2015	2023	No	Present
2	37	M	OU	Intermediate	Recurrent	2007	2020	Yes (2015–2020)	Present
3	41	F	OU	Intermediate	Acute	2009	2012	No	Present

CSF – cerebrospinal fluid; F – female; M – male; MS – multiple sclerosis; OB – oligoclonal bands; OD – right eye; OU – both eyes; TNF – tumour necrosis factor

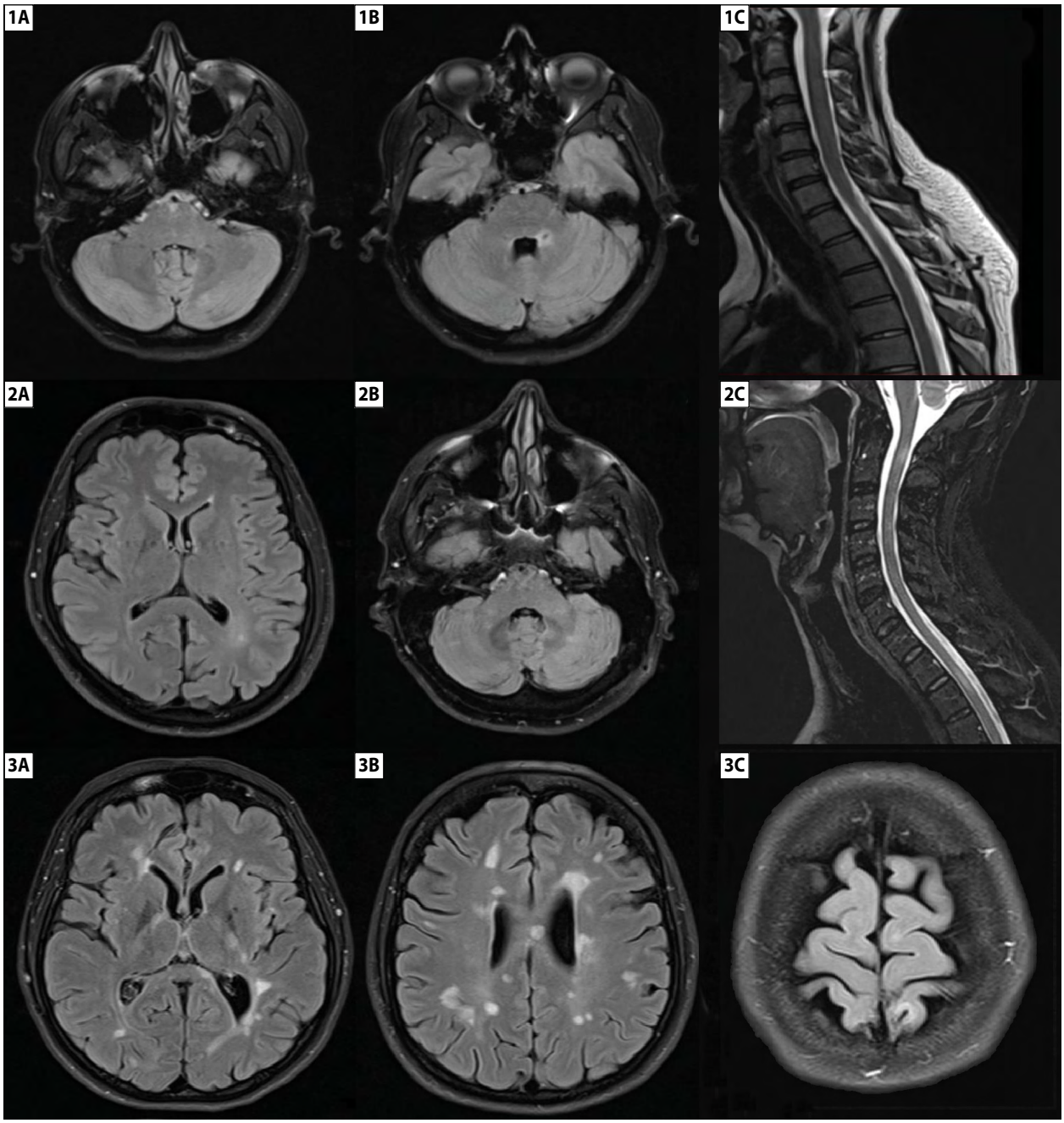

Figure 1. Case 1 (1A–1C): FLAIR-T2 hyperintense demyelinating lesions periventricularly in pons and cerebellum (1A–1B); no lesions in cervical and thoracic spinal cord (1C). Case 2 (2A–2C): multiple FLAIR-T2 hyperintense lesions supratentorially in cerebellum and cervical spinal cord (T2). Case 3 (3A–3C): multiple FLAIR-T2 hyperintense lesions periventricularly (3A–3B) and juxtacortically (3C)

stopped. It remains unclear whether demyelination is a side effect of TNF-alpha inhibitors or if it induces MS [6]. Abraham et al. [4] recommended that all patients with intermediate uveitis should have a brain MRI before the introduction of TNF-alpha inhibitors.

The third patient (female) developed acute intermediate bilateral uveitis aged 26 and three years later was diagnosed with RRMS when she presented with paraparesis, dysarthria and central facial palsy. MRI detected demyelinating lesions periventricularly, subcortically, in right optic radiation, on the line between right internal capsule and thalamus and in the pons.

To date uveitis has not been considered an MS relapse. Therefore, disease modifying therapy for MS does not target uveitis *per se* and the patient may require additional localised or generalised treatment for a severe uveitis course (with TNF-alpha inhibitors being contraindicated in MS).

More studies are needed to understand the immunological basis of MS-associated uveitis and these might aid in establishing novel therapeutic approaches in such cases.

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Good results of neurorehabilitation of ischaemic stroke — locked-in syndrome in a pregnant woman with delivery of healthy child

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To the Editors

The mortality rate in locked-in syndrome (LIS) is significant. Patients usually die after a few days, and up to 87% of deaths occur within the first four months. If patients survive the first year, 86% of them will still be alive four years later. LIS patients have low quality of life scores, mainly due to motor dysfunction [1].

A 21-year-old woman in the 8th week of pregnancy was admitted to the Accident & Emergency Department (A&E) of her local District Hospital (DH) due to headache accompanied by dizziness, vertigo, balance disorders, and numbness of the upper and lower limbs that had been increasing gradually for c.16 hours. Speech disorders and limb ataxia were observed, and verbal contact with the patient had become difficult. Before the incident, the patient had been healthy, without addictions, and was not taking any medications. CT scan and CT angiogram of the head showed a stroke in the left cerebellar hemisphere (Fig. 1A, B) and a thrombus in the basilar artery (Fig. 1C).

Initially admitted to the Department of Neurology of the DH, due to increasing disturbances of consciousness and breathing, the woman was transferred to the Intensive Care Unit (ICU) of the University Medical Centre (Uniwersyteckie Centrum Kliniczne, UCK) in Katowice, Poland c.12 hours after arriving at A&E.

In the ICU, the patient was unconscious, with respiratory and circulatory failure. A divergent position of the right eyeball, vertical nystagmus, flexion reaction to pain in the right limbs, extension in the left limbs, and bilateral Babinski sign were observed (NIHSS = 33 points, mRS = 5 points, GCS score = 6 points). Due to the exceeded time window (i.e. more than 24 hours) and the presence of an ischaemic area visible in CT and CT angiography, the patient was not qualified for either thrombolysis or thrombectomy according to the guidelines of the Polish Neurological Society [2]. In the ICU, low molecular weight heparin (LMWH) 5,000 U.I./day and ASA 150 mg/day were administered. After 20 days, these doses were reduced to LMWH 2,500 U.I./day and ASA 75 mg/day. The patient

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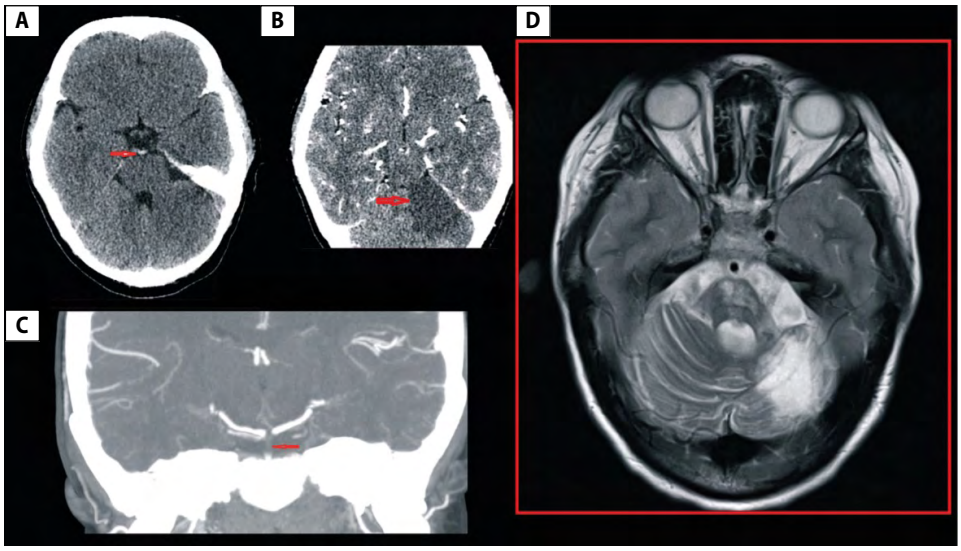

Figure 1. Neuroimaging examinations performed at Accident & Emergency Department of a district local hospital, and an ambulatory follow up two years after the onset of symptoms. **A.** Head Computed Tomography (CT) scan: hyperdensity of the basilar artery and an early signs of the left cerebellar hemisphere ischemic stroke; **B.** Head Angio-CT scan: irreversible left cerebellar hemisphere damage – ischemic stroke; **C.** Head Angio-CT scan: 9 mm in long axis thrombus in the basilar artery. Posterior cerebral arteries were supplied by posterior communicating arteries; **D.** Brain MRI (2 years after the stroke): malacic lesions in the upper part of the left cerebellar hemisphere, in middle cerebellar peduncle, in the central part of the pons and partially in the medulla *(courtesy of Helimed-Diagnostic imaging)*

Table 1. Specific laboratory test results

Test		Result	Unit	Reference range
Activity of S-protein		66	%	64–126
Activity of C-protein		> 149.9	%	70–140
Homocysteine		5.36	µmol/L	4.44–13.56
Activity of factor VIII		212.1	%	70–150
Activity of factor IX		130.3	%	70–120
Anti-cardiolipin antibodies	IgG	< 2	RU/mL	< 20
	IgM	6.32	RU/mL	< 20
Beta-2 glycoprotein		Negative		
Lupus anticoagulant		Negative		
Factor V Leiden		No mutation		
Mutation of prothrombin (20210 G-A)		No mutation		
Tests for HIV, VDRL and Lyme disease		Negative		
ANA, ANCA, dsDNA antibodies		Negative		

was mechanically ventilated (percutaneous tracheostomy was performed). Catecholamines and anti-oedematous treatment were used.

Seeking the cause of the stroke, vascular malformations were excluded via CT angiography. Transthoracic echocardiography was normal. Similarly, ultrasonographic examinations of the vessels of the lower limbs and abdominal cavity did not reveal any pathology, including thrombosis. In the diagnostic considerations, various causes of congenital and acquired thrombophilia were considered, including autoimmune diseases, and inflammatory factors. The activity of C-protein and factors VIII and IX were increased, possibly due to pregnancy. Several laboratory tests were performed, as set out in Table 1.

On the 56th day of her stay in hospital, the patient was transferred to the Neurological Rehabilitation Department (NRD). She was circulatory and respiratory-efficient, and showed symptoms of locked-in syndrome. She was conscious, non-verbal contact in the form of eyelid movements was possible, but with abolished eye movements, and features of

bulbar syndrome with paralysis of nerves IX, X, XII and V, VII on both sides and quadriplegia except for movement in the left foot. Paroxysmal crying and laughter were observed. The patient was fed through a gastric tube, and later a percutaneous endoscopic gastrostomy (PEG) was performed. In the NRD, doses of LMWH and ASA were continued until 32 weeks of pregnancy. Later, the dose of LMWH was doubled and ASA was discontinued. During hospitalisation, the patient was consulted many times by obstetricians and foetal vital signs were monitored.

In NRD, an extensive rehabilitation programme was introduced based on therapy according to the Bobath and PNF methods, starting with bedside rehabilitation. Breathing exercises, positioning, orofacial exercises, passive motor exercises, and classical massage were used. Thereafter, active exercises, motor coordination exercises, and general rehabilitation exercises were introduced. From a lying position, through gradual verticalisation, the patient was led to walking using a walker, initially with the assistance of a physiotherapist.

Speech therapy with PNF elements, some sensory integration, the Masako maneuver and Shaker exercises were introduced. After 94 days of hospitalisation, the tracheostomy tube was removed. The mobility of the limbs, swallowing and logical thinking improved. Semi-liquid oral nutrition was introduced, and then the physiological way of eating was gradually returned. After 111 days, the PEG was removed.

On the day of discharge from the NRD (after a 142-day stay in the NRD), the woman was conscious, being orally fed, in logical verbal contact, but emotionally unstable. Neurological examination revealed slight weakening of the muscle strength of the left limbs (grade 4 of the MRC scale) and cerebellar symptoms of ataxia, dysdiadochokinesia and disturbances of dynamic balance. The patient had gained the ability to feed herself and to move independently with the aid of a walker (NIHSS = 3 points, mRS = 1 point).

A caesarean section was performed in the 38th week of pregnancy. The newborn was in a good condition. The puerperium was uncomplicated.

15 months after the stroke, the presence of a patent foramen ovale (PFO) was diagnosed and a Septal Occluder was implanted (RoPE score = 9 points). The RoPE scale is used in patients who have had a cryptogenic stroke and who have been diagnosed with PFO. A result of 9 points (max = 10) confirms the need for an occluder (which was also performed on the patient after delivery). Head MRI revealed malacic lesions in the left cerebellar hemisphere, affecting also the left middle peduncle, in the central part of the pons and the medulla oblongata (Fig. 1D). Outpatient tests for thrombophilia were repeated and were negative.

At the time of writing, the patient is moving independently, without assistance. The latest neurological examination has shown minor deficits i.e. mild ataxia in the left upper limb, and tandem gait slightly disturbed (NIHSS = 1 point, mRS = 1 point). The woman has got married, and is taking care of her two children on a daily basis.

If an acute stroke is diagnosed in a pregnant woman, reperfusion treatment should be seriously considered. However, each such case should be treated individually, considering the risk of intrauterine bleeding [2, 3].

The presented case of a severe ischaemic stroke in a young pregnant woman with PFO in whom neither thrombolysis nor thrombectomy could be performed, shows that the neuroplasticity of a young person's brain and many months of arduous, comprehensive rehabilitation can give unexpectedly good results [4, 5]. Our presented case suggests that pregnancy may promote repair mechanisms after stroke.

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Anti-DPPX encephalitis mimicking Creutzfeldt-Jakob Disease: first case report in Poland

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To the Editors

Anti-DPPX (dipeptidyl-peptidase-like protein-6) encephalitis, discovered in 2013, is a rare autoimmune disorder affecting the central nervous system (CNS), characterised by a range of neurological and gastrointestinal symptoms. The disease is caused by antibodies targeting DPPX, a regulatory subunit of Kv4.2 potassium channels, which are crucial for controlling neuronal excitability. DPPX is expressed in various brain regions, including the hippocampus and cerebellum, as well as in the myenteric plexus of the gastrointestinal system. The widespread distribution of the receptors explains the multifocal disease manifestations. The disruption of these potassium channels by anti-DPPX antibodies leads to a cascade of symptoms, which are both neurological and gastrointestinal in nature [1, 2].

Early signs of anti-DPPX encephalitis often include unexplained weight loss and gastrointestinal disturbances, particularly severe diarrhoea. These symptoms are typically followed by a range of neurological issues, including cognitive dysfunction, agitation, hallucinations, and exaggerated startle responses. In addition to these neuropsychiatric symptoms, patients may experience motor disturbances such as resting tremors, rigidity, myoclonus, and even seizures. Sleep disorders such as REM sleep behaviour disorder, are also common. Most patients are middle-aged, with a median age at onset of c.52 years, and men appear to be more frequently affected than women. Diagnosis is confirmed by identifying anti-DPPX autoantibodies in the patient's blood or CSF [1, 2].

The disease typically progresses subacutely over several months, which can make an early diagnosis challenging. Anti-DPPX encephalitis has often been misdiagnosed as other conditions, such as Creutzfeldt-Jakob Disease (CJD), due to overlapping symptoms such as cognitive decline and myoclonus. However, unlike CJD, anti-DPPX encephalitis is a treatable condition, especially when identified early. Immunotherapy, including corticosteroids, intravenous immunoglobulin, plasmapheresis, azathioprine, rituximab, cyclophosphamide, and mycophenolic acid has shown promise in managing the disease and improving outcomes for patients. Anti-DPPX encephalitis may be associated with malignancy in up to 10% of cases, most commonly B-cell lymphoma, although cases related to small cell lung cancer, breast cancer, and hepatocellular carcinoma have also been described [1–6].

A 54-year-old Caucasian woman without a history of chronic diseases was admitted to hospital for evaluation of rapidly progressive cognitive deficit. 18 months before admission, she experienced persistent diarrhoea lasting for about two months, loss of appetite, and a weight loss of c.10 kg. The patient was diagnosed with erosive gastritis and *helicobacter pylori* infection, and her symptoms subsided after treatment.

After a few months, the patient became apathetic, had memory problems, and her mood slightly deteriorated. She consulted a psychiatrist, who diagnosed her with depression and started treatment, which was ineffective. She was hospitalised twice in the psychiatric ward, without improvement. At that time, she exhibited slowed speech and disorientation — she wandered around the department and required constant

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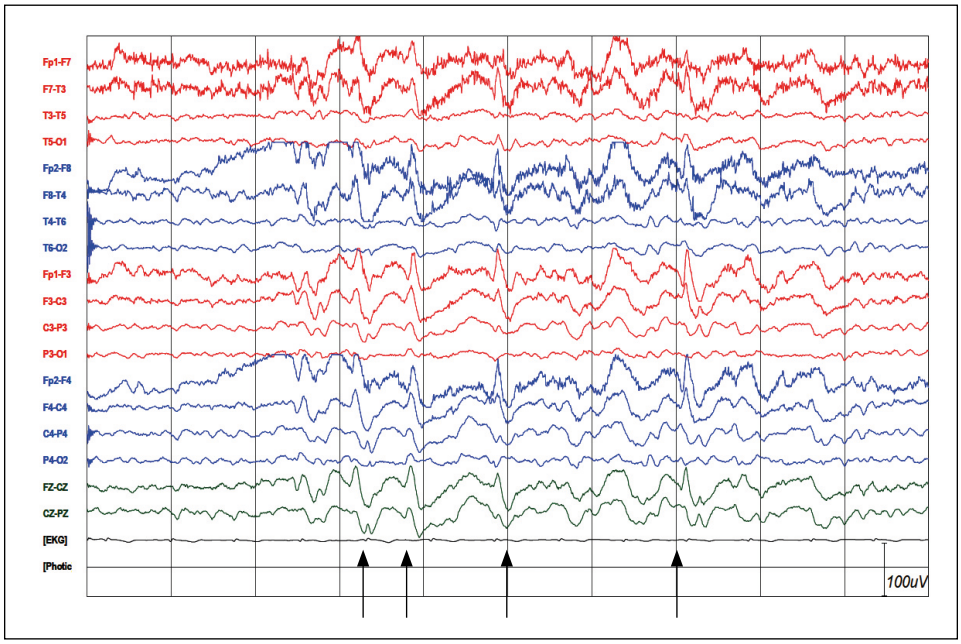

Figure 1. Wake electroencephalography: triphasic sharp wave complexes (arrows) and background slowing in theta-delta range

supervision by staff, with a progressive decline in cognitive function being observed. Balance issues and eating disorders also appeared: the patient refused meals but consumed a lot of sweets, which she had previously disliked, and smoked heavily. Over the following months, the patient was hospitalised several times in the psychiatric, internal medicine, and neurology departments. Brain MRI showed non-specific demyelinating changes, and a cerebrospinal fluid examination returned normal results. A salivary gland tumour was diagnosed, with a biopsy result suggesting cancer, requiring further evaluation after the tumour's removal. No surgery was performed due to the patient's condition.

Neurological examination upon admission to our department: conscious; non-verbal; does not follow commands; reacts with fear during examination; significantly increased rigidity of all four limbs and trunk; pupils round, equal, and symmetrically reactive to light; bedridden; and cachectic.

During this stay, EEG and brain MRI were performed. In the EEG, periodic discharges of triphasic sharp wave complexes and background slowing were recorded (Fig. 1). Brain MRI, performed twice, revealed non-specific, small vascular lesions, progressive subcortical brain atrophy, and a tumour of the right salivary gland (Figs. 2, 3). In two cerebrospinal fluid tests, normal general parameters were obtained: clear, WBC count 3 (normal range 0–5), RBC count 0, protein 13.6 mg/dL (normal range 20–40), glucose 3.42 mmol/L (normal range 2.20–4.16). Immunophenotyping showed no sign of a proliferative process. The presence of oligoclonal bands was detected. Due to the EEG findings, cerebrospinal fluid was tested for Creutzfeldt-Jakob Disease: the RT-QuIC test was negative, and no presence of the 14-3-3 protein was detected in cerebrospinal fluid using the Western blot method. However, anti-DPPX antibodies were detected using the indirect immunofluorescence method at a titre of 1:32 and were tested only in CSF.

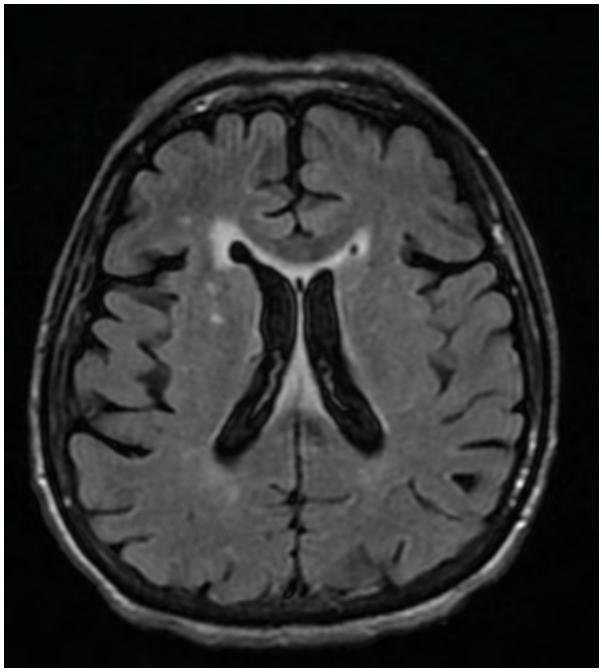

Figure 2. Brain MRI. T2 FLAIR. Cortical and subcortical atrophy. Leukoaraiosis

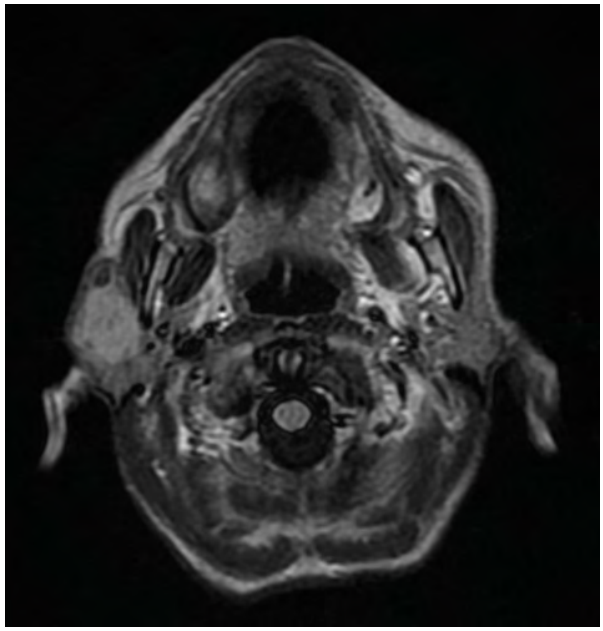

Figure 3. Brain MRI. Tumour of right salivary gland

Chest and abdominal CT scan showed enlarged axillary lymph nodes with strong enhancement after intravenous contrast administration. A biopsy was postponed due to the patient's neurological condition.

Due to elevated cancer markers, the patient was gynaecologically and oncologically consulted. No malignancy was found, except for the salivary gland tumour. The salivary gland tumour was removed, and histopathological examination revealed acinic cell carcinoma.

Based on the clinical presentation and additional test results, autoimmune encephalitis with anti-DPPX antibodies was diagnosed. Intravenous treatment with methylprednisolone (1 g/day for five days) and immunoglobulins (18 g/day for five days) was administered, but no neurological improvement was achieved. Subsequently, treatment with rituximab (five doses of 375mg/m^2 for seven days) was initiated. Over the following days, the patient's neurological condition showed a slight improvement — she began to utter single words, follow simple commands, and eat some parts of the meals she was offered.

Anti-DPPX encephalitis typically presents with a subacute to chronic onset of encephalopathy, along with hyperkinetic movement disorders and myelopathy, often preceded by prodromal diarrhoea. Less common manifestations include neurological conditions such as opsoclonus-myoclonus syndrome, progressive encephalomyelitis with rigidity and myoclonus, and stiff-person syndrome. Diagnostic tests tend to produce nonspecific and variable results. Brain MRI might show increased signal on T2/fluid-attenuated inversion recovery sequences in temporal lobes. CSF examination may reveal increased protein, mild pleocytosis and positive 14-3-3 protein. EEG is abnormal in the majority of patients, showing e.g.. slow background, triphasic periodic complexes, and epileptiform discharges. Autoimmune encephalitis (AE) can manifest primarily as significant cognitive impairment, even in the absence of clear inflammatory changes on MRI or in cerebrospinal fluid. Cognitive decline may also be observed in encephalitis other than anti-DPPX-related cases, including anti-NMDAR ab-mediated AE, anti-leucine-rich glioma-inactivated-1 (LGI-1) contactin-associated protein-like 2 (CASPR-2) ab-mediated AE, and anti-γ-aminobutyric acid type-B (GABA B) ab-mediated AE [6, 7].

Our case report contains some limitations including the lack of certain clinical and laboratory data such as: medications used for the treatment of depression, the number of oligoclonal bands in the CSF, the method of RT-QuIC detection, and a whole body PET-CT scan (not performed).

In summary, anti-DPPX encephalitis is a rare but increasingly recognised autoimmune condition characterised by a combination of gastrointestinal symptoms, weight loss, and progressive neurological deficits. When evaluating acute/subacute neuropsychiatric symptoms, it is crucial to take into account both prion and immune-mediated disorders in the differential diagnosis, bearing in mind that EEG and 14-3-3 protein levels in CSF are not definitive in distinguishing between these conditions.

To diagnose autoimmune encephalitis and determine the correct treatment, identifying specific antineuronal antibodies in serum or CSF can be highly informative.

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Paraneoplastic cerebellar degeneration — raising awareness for early diagnosis

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Keywords: paraneoplastic cerebellar degeneration, anti-Yo antibodies, ovarian cancer

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To the Editors

Paraneoplastic neurological syndromes are caused by hormones and cytokines synthesised by tumours, and occur in 1–3% of all cancer patients. They can have impacts on both the central and peripheral nervous systems [1].

We present a case report of a 68-year-old postmenopausal woman who was admitted to our hospital's Accident & Emergency with a 7-day history of unsteadiness of gait, ataxia and speech disorder. Similar, transient symptoms were observed in 2022 when the patient was discharged from hospital with a TIA diagnosis.

In neurological examination, lower limbs ataxia, slurred speech, and bilateral positive Babinski sign were observed. Brain CT and MRI scan were normal. Basic laboratory tests revealed slightly elevated TSH levels. Tumour biomarkers were negative in serum. A general cerebrospinal fluid (CSF) examination showed normal results. However, a paraneoplastic antibody screening detected anti-Yo antibodies in both CSF and blood serum.

To identify an underlying neoplasm, we conducted a whole-body CT scan and PET-CT scan (Fig. 1). The whole-body CT revealed a tumour in the right ovary. In the PET-CT, an increased metabolism of fludeoxyglucose (FDG) in the right ovary was observed and the patient was qualified to laparoscopy followed by laparotomy. A histopathological evaluation showed G3 adenocarcinoma of the right fallopian tube. IVIG treatment was implemented, with no improvement of neurological symptoms. Due to her poor neurological and general condition, chemotherapy was not implemented and palliative care was recommended. Six months later, she has stable neurological symptoms with limbs ataxia and slurred speech.

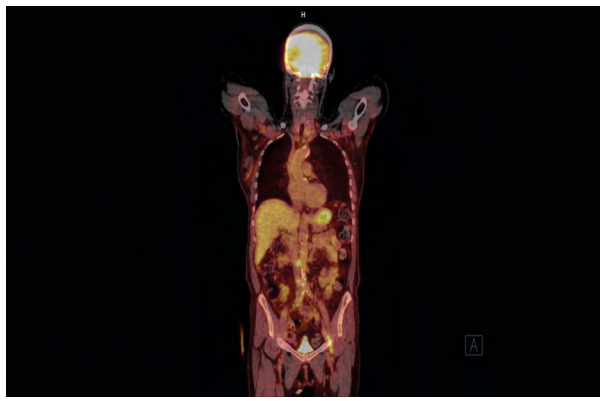

Figure 1. Whole-body PET-CT scan revealing increased metabolism of FDG in right ovarian tube

Paraneoplastic cerebellar degeneration (PCD) is a very rare condition occurring in less than 1% of cancer cases. It is usually associated with breast and gynaecological malignancies, but can also occur in small-cell carcinoma and Hodgkin's lymphoma. The neurological symptoms include subacute cerebellar ataxia, dysarthria, kinetic tremor, diplopia and/or

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Table 1. Antibodies associated with PCD

Antibody (alternative name)	Frequency of cancer [%]	Usual tumours
Yo (PCA-1)	> 90	Ovarian cancer, breast cancer
Anti CRMP5(CV2)	> 80	SCLC, thymoma
Anti-mGLuR1	30	Mostly haematological
Anti Ri (ANNA2)	> 70	Breast > lung (SCLC and NSCLC)
PCA-2	80	SCLC, NCLC, breast cancer
P/Q VGCC	50 (LEMS, nearly 90 for rapidly progressive cerebellar syndrome)	SCLC
SOX1	> 90	SCLC
Tr (DNER)	90	Hodgkin's lymphoma

ANNA — antineuronal nuclear antibody; CRMP5 — collapsin-responsive mediator protein 5; DNER — delta/notch-like epidermal growth factor-related receptor; LEMS — Lambert-Eaton myasthenic syndrome; mGluR1 — metabotropic glutamate receptor; NSCLC — non-small cell lung cancer; PCA — Purkinje cell antibody; P/Q VGCC — P/Q type voltage-gated calcium channel; SCLC — small cell lung cancer

oscillopsia. Specific antibodies are reported in both serum and CSF (Tab. 1).

The Anti-Yo antineuronal antibody against Purkinje cells is the most commonly detected antibody in connection with PCD [2, 3]. They affect the vermis and midline cerebellum. Anti-Hu, anti-Tr, anti-Ri and anti-mGluR1 have also been identified in PCD patients [2]. The antibodies could be specific for different kind of tumours. Therefore, it helps in directing cancer diagnosis, even several months to years before local mass effect [4, 5].

Outcomes of PCD are typically poor, and treatment is limited, including tumour resection, chemotherapy, and immunosuppressive treatment [5]. Early treatment initiation provides better prognosis.

PCD poses a significant challenge both in diagnosis and treatment. Due to its unspecific nature, it is under-recognised. Moreover, because of its rarity, no randomised controlled trials have been conducted to establish the optimal treatment approach.

This letter highlights the critical need to address the under-recognition of PCD by neurologists and oncologists. An early diagnosis significantly improves patient outcomes and reduces the risk of severe, irreversible complications. By incorporating targeted PCD-associated antibody screening into routine workups, we can ensure timely diagnosis and improve patient outcomes.

Article information

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