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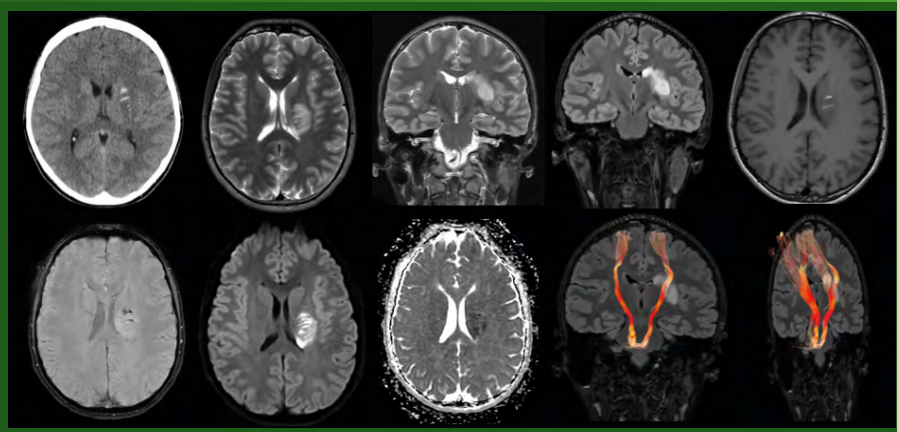

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Herpes zoster prevention in multiple sclerosis and neuromyelitis optica spectrum disorders

Consensus of Section of Multiple Sclerosis and Neuroimmunology of Polish Neurological Society, Polish Society of Family Medicine and Polish Society of Vaccinology on supplementary data to recommendations of expert group of Polish Society of Vaccinology, Polish Society of Family Medicine, Polish Dermatological Society, Polish Association for the Study of Pain, and Polish Neurological Society and ECTRIMS/EAN of 2023

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ABSTRACT

A working group convened by the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society, the Polish Society of Family Medicine, and the Polish Society of Vaccinology has developed a consensus on supplementary data to the recommendations of the expert group of the Polish Society of Vaccinology, the Polish Society of Family Medicine, the Polish Dermatological Society, the Polish Association for the Study of Pain, and the Polish Neurological Society, and ECTRIMS/EAN of 2023 with regard to the currently available in Poland recombinant herpes zoster vaccine (RZV).

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It is intended for the prevention of herpes zoster and postherpetic neuralgia in individuals aged > 50 and individuals aged ≥ 18 who belong to herpes zoster risk groups. In Poland it is available with 50% reimbursement exclusively for patients aged 65 and older who have an increased risk of developing herpes zoster.

This statement is based on the literature available as of 12 July 2024. The guidance will be updated as new data emerges. All data regarding the above-mentioned vaccine comes from clinical trials which have been reviewed, published and approved by the regulatory authorities and an increasing number of recommendations that might have an impact on real world data.

Keywords: herpes zoster, multiple sclerosis, neuromyelitis optica spectrum disorders, risk of herpes zoster, indications for vaccination

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Herpes zoster prevention

Herpes zoster is an infectious viral disease that represents symptomatic reactivation of a latent varicella-zoster virus (VZV) infection. For herpes zoster to develop, the patient has to have a history of primary VZV infection, usually in the form of varicella, less frequently in the form of an oligosymptomatic or intrauterine infection, and occasionally after varicella vaccination with a live product containing an attenuated Oka VZV strain. Varicella vaccination has not been shown to increase the risk of herpes zoster on the population level [1, 2]. Usually, herpes zoster presents as vesicles on an erythematous base, preceded by pain in a single dermatome. Severe complications can develop in the course of the disease, with postherpetic neuralgia being the most clinically significant one. This occurs in up to 30% of patients, leads to a considerable decrease in the quality of life, and causes chronic suffering. Its treatment is long-term, often ineffective and constitutes a significant challenge for the healthcare system.

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) are autoimmune disorders managed with disease-modifying therapies (DMTs). According to the ongoing drug programme reimbursed by the Polish National Health Fund (NFZ) 'Treatment of patients with MS' (B.29), patients found eligible for treatment with sphingosine-1-phosphate (S1P) receptor modulators or cladribine tablets have to be tested for the presence of anti-VZV antibodies.

If a high titre of IgG antibodies and no IgM antibodies are found, VZV vaccination is not necessary, although the patient can still be vaccinated against herpes zoster. If there is no history to confirm varicella and the patient has no IgG antibodies against VZV, it is recommended to fully vaccinate them, i.e. administer two doses of a varicella vaccine at least six weeks apart.

Currently, there are two vaccine products against varicella available in Poland: Varilrix® and Varivax®. It should be remembered that the varicella vaccine contains live attenuated viruses and is completely different to the herpes zoster vaccine, which is a recombinant vaccine (Shingrix®). A history of varicella is an indication for herpes zoster vaccination, and varicella vaccination does not rule out the possibility of being given a herpes zoster vaccine.

When discussing the risk of developing herpes zoster, one should remember that a considerable number of DMTs used to treat MS and NMOSD have immunosuppressive effects.

According to the recommendations on herpes zoster vaccination published in 2023, which were developed by experts representing several Polish scientific societies including the Polish Neurological Society, the risk factors for herpes zoster are the following:

1) age > 50 years,
2) congenital or acquired immunodeficiency, including iatrogenic immunosuppression, human acquired immunodeficiency virus (HIV) infection, neoplastic disease (leukaemia, lymphoma, multiple myeloma), solid organ transplantation or haematopoietic stem-cell transplantation (HSCT),
3) chronic heart disease,
4) chronic liver disease,
5) chronic lung disease,
6) chronic kidney disease,
7) autoimmune diseases,
8) diabetes,
9) depression [2].

Although MS is typically diagnosed in people aged between 20 and 40, it is a chronic disorder that patients usually live with for many years. Data provided by the Polish National Health Fund (NFZ, Narodowy Fundusz Zdrowia) shows that patients aged 56 to 65 were the largest age cohort of MS patients receiving healthcare services in 2019 [2]. Moreover, as MS or NMOSD patients age, and thus the duration of their treatment (including immunosuppressive treatment) increases, they often develop other chronic disorders such as depression, which can result from, among other factors, the effects of some DMTs.

Consequently, MS and NMOSD patients are in a group of patients at a particularly high risk of herpes zoster. According to the summary of product characteristics of the approved herpes zoster vaccine (recombinant protein vaccine) [4] and the published recommendations, due to the epidemiology of herpes zoster and the occurrence of its complications,

the vaccination is recommended to all people aged > 50 and younger adults (≥ 18) with risk factors for herpes zoster [2, 5].

ECTRIMS/EAN recommendations on administration of recombinant herpes zoster vaccine

According to the ECTRIMS/EAN recommendations published in 2023, herpes zoster vaccine is recommended for MS patients aged > 18 if they have a history of varicella or were vaccinated against varicella and in whom treatment with drugs increasing the risk of herpes zoster, e.g. cladribine tablets, alemtuzumab, S1P receptor modulators, natalizumab, or anti-CD20 monoclonal antibodies, is being planned. Varicella vaccination should be considered in other cases [6]. Moreover, herpes zoster vaccination is recommended in older MS patients, who according to the recommendations should also receive a pneumococcal vaccine and flu vaccine every year [6]. Polish recommendations for this population take into consideration RSV vaccine (for those over 60) and diphtheria tetanus pertussis vaccine (once every 10 years) [5]. Vaccinations against hepatitis B and COVID should also be recommended for this group of patients [6]. Herpes zoster vaccination should optimally be done at least two weeks before the start of immunosuppressive treatment, or as early as possible if the treatment has already started. Ideally, it should be during the period when the likelihood of achieving an immune response is the highest.

Herpes zoster vaccine

The recombinant herpes zoster vaccine (RZV) available in Poland (Shingrix®) was approved in the European Union in 2018; it has been available in Poland since the spring of 2023. Due to the epidemiology of herpes zoster and the occurrence of its complications, the vaccine is intended for the prevention of herpes zoster and postherpetic neuralgia in individuals aged > 50 and individuals aged ≥ 18 who belong to herpes zoster risk groups. The full vaccination schedule consists of two doses of the vaccine given 2–6 months apart. In special cases, the interval between doses may be shortened to one month. The need for booster doses has not been determined [4], but based on the duration of follow-up and previous experience with the use of the vaccine [7], the administration of two doses results in effective immunisation lasting c.10 years. New information on the durability of vaccination efficacy is expected to be obtained over time as the vaccine remains on the market. No data on the need for booster doses is currently available. Observational studies that are ongoing are assessing the efficacy of the vaccine beyond 10 years after completion of the full vaccination schedule. The need for booster doses requires confirmation in further studies.

The vaccine product for herpes zoster prevention that is approved in Poland may be given to people previously vaccinated with a live attenuated varicella vaccine. It is not, however, indicated for use in the prevention of varicella as a primary VZV infection. The RZV vaccine is only intended for prevention, and should not be used to treat clinically confirmed disease [4]. Due to the risk of recurrent herpes zoster, the vaccination is also recommended in patients who previously had herpes zoster, but not until acute herpes zoster symptoms have resolved.

Efficacy

The recombinant vaccine has a very high efficacy. It has been shown to reduce the risk of developing herpes zoster by > 90% over an average follow-up of 3.1 years in people aged ≥ 50 and to reduce the risk of postherpetic neuralgia by 91.2% over an average follow-up of 3.1 years in people aged ≥ 50 and by 88.8% over 4 years in people aged ≥ 70. The safety and efficacy of the vaccine have also been demonstrated in groups at high risk of herpes zoster i.e. autologous HSCT recipients, patients with haematological or solid neoplasms, patients with HIV infection, and individuals after kidney transplantation [7].

Safety

The most common (> 1/10) side effects of the RZV vaccine include injection site reactions such as pain, redness, and swelling, also fatigue, chills, fever and headache, gastrointestinal symptoms including nausea, vomiting, diarrhoea and/or abdominal pain.

Common (≥ 1/100 to < 1/10) adverse effects are pruritus at the injection site and malaise. Severe side effects occur in a small percentage of patients, and overall the frequency of some side effects is higher in younger age groups, for example:

- pain at the injection site, fatigue, muscle pain, headache, chills and fever are more frequent in people aged 18–49 compared to people aged 50 and older,
- muscle pain, fatigue, headache, chills, fever and gastrointestinal symptoms are more frequent in people aged 50–69 compared to people aged 70 and older.

The analysis of data from a passive reporting system for suspected adverse events following immunisation (VAERS, the Vaccine Adverse Event Reporting System) from the first eight months of the use of Shingrix®, after the distribution of c.3.2 million doses, showed that the safety profile of the vaccine was similar to that seen in premarketing clinical studies. Reports of serious adverse events following the administration of the vaccine have been published, including several cases of herpes zoster both in immunocompetent individuals and in patients with immunodeficiency. However, once the reported cases had been analysed, it was determined that the relationship was only temporal, and the cases were not confirmed as having been caused by the administration of the vaccine [8].

Reimbursement in Poland

According to the Polish national recommendations on vaccinations [5] and a position paper of several Polish Medical Associations [2] on herpes zoster vaccination, the administration of recombinant herpes zoster vaccine (RZV) should be also considered in all individuals over > 50 and in individuals aged ≥ 18 who undergo immunosuppressive treatment. Moreover, the vaccine should be considered in all patients with chronic conditions which increase the risk of herpes zoster. These are:

- inherited or acquired immunosuppression, including: iatrogenic immunosuppression, HIV, cancer, haematological malignancies, haematopoietic cell transplant, solid organ transplant,
- chronic pulmonary conditions (i.e. asthma, COPD),
- chronic cardiological conditions (i.e. heart failure),
- chronic kidney disease,
- chronic liver disease,
- autoimmune diseases,
- diabetes,
- depression.

The announcement by the Polish Minister of Health on 11 December 2023 concerning the list of reimbursed medicines and foodstuffs intended for particular nutritional uses and medical devices [9] as of 1 January 2024, included the herpes zoster and postherpetic neuralgia vaccine to be available in Poland, with 50% reimbursement for patients aged 65 and older who have an increased risk of developing herpes zoster [10]. This 50% reimbursement for Shingrix® is accessible for individuals aged 65 and older from the following risk groups:

- chronic heart disease,
- chronic lung disease,
- diabetes,
- chronic renal failure,
- congenital or acquired immunodeficiency,
- generalised neoplastic disease,
- HIV infection,
- Hodgkin's lymphoma,
- iatrogenic immunosuppression,
- leukaemia,
- multiple myeloma,
- following solid organ transplantation,
- rheumatoid arthritis,
- psoriasis,
- psoriatic arthritis,
- inflammatory bowel disease,
- ankylosing spondylitis,
- multiple sclerosis,
- systemic lupus erythematosus.

50% reimbursement of the vaccine's cost means that the price of the product available in Poland for patients is c.400 PLN per dose (c.800 PLN for a full vaccination schedule; data as of 4 March 2024). It is worth noting that reimbursement before the start of treatment is available to patients with multiple sclerosis, but only those aged 65 and older. Taking into consideration the risk factor that is iatrogenic immunosuppression, the reimbursement may apply to MS and NMOSD patients (aged at least 65) during immunosuppressive treatment.

Conclusions

A. Herpes zoster develops in people who have previously had varicella. Varicella vaccination does not protect against herpes zoster and its complications, including postherpetic neuralgia.
B. Vaccination against herpes zoster should be considered in every newly diagnosed MS/NMOSD patient before the initiation of DMTs, especially ones with immunosuppressive effects, regardless of previous infection caused by the varicella zoster virus (VZV) or previous immunisation against the varicella zoster virus.
C. Herpes zoster vaccination in this group should optimally be done at least two weeks before the start of immunosuppressive treatment, or at the earliest possible date if the treatment has already been started (ideally, it should be during the period when the likelihood of achieving an immune response is the highest).
D. Use of the RZV vaccine while taking DMTs is possible and safe (the product available in Poland is not a live vaccine), but it is difficult to fully predict its efficacy based on the available data.
E. The reimbursement of the RZV vaccine is limited to the risk groups. It is important to note that these are not the same as the risk groups listed in the SPC and in the previously published recommendations provided by scientific societies, including the Polish Neurological Society. Reimbursement is also needed in adult patient groups with MS and NMOSD who are at risk of herpes zoster, including all adults found eligible for the use of medicines that significantly increase the risk of developing herpes zoster, such as cladribine, alemtuzumab, S1P receptor modulators, natalizumab, and anti-CD20 monoclonal antibodies, regardless of their age.

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Update on diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD) — recommendations of Section of Multiple Sclerosis and Neuroimmunology of Polish Neurological Society

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ABSTRACT

Introduction. An expert panel of the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society has developed principles for the management of neuromyelitis optica spectrum disorders (NMOSD). These principles are based on expert opinion and data from the literature published up to May 2023. Recommendations were developed based on the results of the most recent clinical trials, guidelines of foreign and international scientific societies, and the authors' clinical experience.

Clinical implications. The principles for diagnosing NMOSD are discussed, with particular emphasis on serological and neuroimaging diagnosis. Recommendations for the treatment of relapses and chronic immunosuppressive treatment, including the most recent methods of immunotherapy, are also presented. Additionally, the principles of monitoring treatment efficacy and safety are included. Therapy regimens are completed with recommendations for symptomatic treatment. The paper also includes an algorithm for vaccination in patients with NMOSD. Therapeutic management in pregnant women with NMOSD is discussed.

Keywords: recommendations, diagnosis and treatment, neuromyelitis optica spectrum disorders, NMOSD

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Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are rare autoimmune conditions of the central nervous system (CNS) characterised by inflammatory demyelination, axonal loss and astrocytopathy that lead to the occurrence of pathological lesions within the optic nerves, brain and spinal cord. This condition was first described in the late 19th century.

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However, the relationship between neuromyelitis optica (NMO) and multiple sclerosis (MS) was debated for many decades [1–8]. Researchers and clinicians long considered NMO to be a subvariant of MS. It was not until the discovery of anti-aquaporin-4 antibody (AQP4-IgG) specific to this nosological entity that this syndrome was considered a separate disease. Serum AQP4-IgG is recognised as a diagnostic biomarker and is found in most patients (≥ 80%) with the NMO phenotype [9].

The diagnostic criteria for NMOSD were devised in 2015 (Tab. 1) [10]. Despite the defined diagnostic criteria, early and adequate diagnosis of NMOSD remains challenging in clinical practice. Particular diagnostic problems are related to seronegative cases that require detailed differential diagnosis, which is also sometimes difficult due to the lack of diagnostic biomarkers to differentiate heterogeneous conditions with the same NMOSD phenotype. Serum antibodies against myelin oligodendrocyte glycoprotein (MOG-Ab) are found in some NMOSD patients seronegative for AQP4-IgG [9–19]. Notwithstanding this, anti-MOG antibodies may be associated with a clinical presentation different from that typical of NMOSD.

The development of diagnostic and therapeutic principles is an urgent necessity, as new molecules with the potential to alter the prognosis of NMOSD have emerged in recent years [20–27].

To date, expert recommendations have been developed on a national (e.g. in Germany, USA, and Canada) and international scale (e.g. in Central and South America) [8, 28–35]. Our recommendations summarise the experience of the team specialising in MS and NMOSD and working within the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society.

Diagnosis of NMOSD

NMOSD should be suspected in patients who have experienced clinical involvement of at least one of the following structures: optic nerve, spinal cord, area postrema, brainstem, or diencephalon [9]:

1) diagnosis is based on fulfilling the diagnostic criteria proposed by the international panel of experts chaired by Wingerchuk in 2015 (Tab. 1) [10];
2) management varies according to the serostatus of AQP4-IgG. In the population of patients with negative or unknown AQP4-IgG serostatus, both clinical and radiological criteria must be fulfilled (via a typical image of the spinal cord and/or brain on magnetic resonance imaging, MRI) [8, 28, 31–34];
3) differential diagnosis should primarily exclude MS and diseases with a similar clinical picture (Tab. 2–3) [8, 11, 16–18, 30, 32, 36–38];
4) patients with suspected NMOSD should be diagnosed in a centre with experience in diagnosing and treating demyelinating inflammatory diseases of the central nervous system.

Serological diagnosis of NMOSD

Serum AQP4-IgG titres should be determined in patients with symptoms suggestive of NMOSD. Negative results may be related to the NMOSD phenotype with a different pathomechanism (other unidentified antibodies) or to the low sensitivity of the diagnostic methods. Cell-based assays (CBAs) are the recommended diagnostic methods. Enzyme-linked immunosorbent assays (ELISA) are less sensitive — a positive ELISA result does not need to be confirmed, while a negative ELISA result should be confirmed by CBAs [40–44].

Serological testing should be performed in patients before steroid treatment and plasma exchange. However, this should not delay treatment. Note that false negative results can occur. The samples should be secured for testing before treatment. In the case of negative serological test results for AQP4-IgG in a patient with typical NMOSD symptoms, the test should be repeated 3–6 months after the first determination.

Serum AQP4-IgG testing should be performed in the case of symptoms suggestive of NMOSD, such as optic neuritis, myelitis, or area postrema syndrome, in patients diagnosed with a systemic disease (e.g. systemic lupus erythematosus, Sjögren's syndrome) [8, 36–41].

A comprehensive differential diagnosis should be performed in patients with symptomatology typical of NMOSD with imaging findings (MRI) suggestive of MS (Tables 2 and 3). Serum MOG-Ab titres should be determined using CBAs in patients with symptomatology suggestive of NMOSD in whom anti-AQP4 antibodies are not detected using CBAs.

MOG antibody-associated disease (MOGAD) is diagnosed based on the criteria developed by Jarius et al. [21]. New diagnostic criteria have recently been proposed [22]. The diagnosis of MOGAD should be considered in patients with symptomatology similar to that of the NMO spectrum (optic neuritis, myelitis, brainstem encephalitis, or encephalitis) in whom AQP4-IgG is not detected (Fig. 1) [18, 21].

Neuroimaging diagnosis of NMOSD

In NMOSD, MRI should be performed according to a standard and reproducible protocol applied in the diagnostic process and follow-up of the disease course and activity. Neuroimaging studies should be performed in reference centres, using at least 1.5 T MRI according to the protocol for MS patients with extended imaging. The 2015 diagnostic criteria are still valid (Tab. 1) [8, 10, 45]. A brain MRI should

Table 1. NMOSD diagnostic criteria for adult patients (from Wingerchuk et al. 2015 [10]; with the authors' permission)

Diagnostic criteria for NMOSD with AQP4-IgG
1. At least one core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses
Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status
1. At least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
a. At least one core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
b. Dissemination in space (two or more different core clinical characteristics)
c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method
3. Exclusion of alternative diagnoses
Core clinical characteristics
1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions
Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status
1. Acute optic neuritis: requires brain MRI showing
a. normal findings or only nonspecific white matter lesions, OR
b. optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over > 1/2 optic nerve length or involving optic chiasm
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥ 3 contiguous segments (LETM) OR ≥ 3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions

AQP4 — aquaporin-4; IgG — immunoglobulin G; AQP4-IgG — anti-aquaporin-4 antibody; LETM — longitudinally extensive transverse myelitis lesions; NMOSD — neuromyelitis optica spectrum disorders

Table 2. Comparison between AQP4-IgG-positive NMOSD, MOGAD and MS (modified from Jarius et al., 2023; Carnero Contentti et al., 2023; Kim et al., 2017 [8, 23, 38])

	NMOSD	MOGAD	MS
Prevalence/mln	12	20	1,342
Incidence/mln	2	3.4	68
Age at onset	Mostly adults, mean age at onset – 40	Often children, young adults	Adults, mean age at onset — 30
Sex (F:M)	9:1	1:1	3:1
Other antibodies or autoimmune disorders	30–50%	Not so often, anti-NMDAR encephalitis	Not so often
Optic neuritis	Bilateral or unilateral severely impaired visual acuity at onset posterior part, longitudinally extensive lesions, often optic chiasm involvement	Bilateral or unilateral severely impaired visual acuity at onset anterior part, longitudinally extensive lesions, often oedema of optic disc	Typically unilateral mild to moderately impaired visual acuity at onset, short optic nerve lesions
Myelitis	Severe deficit 85% LETM (cervical and thoracic spinal cord); involvement of central part	Severe deficit at onset usually LETM (cervical and thoracic spinal cord), conus; 40% STM; grey matter involvement forming an H-sign	Mild or moderate deficit at onset usually STM, typically affects periphery of spinal cord along dorsal or lateral columns
Area postrema	20%	Rare	Never
Recovery after a relapse	Risk for poor recovery	Usually good recovery	Usually good recovery
Course	Relapsing	Monophasic or relapsing	Relapsing, secondary progressive, or primary progressive
Oligoclonal bands	10–20%	10–20%	> 90%

LETM — longitudinally extensive transverse myelitis; STM — short transverse myelitis; NMOSD — neuromyelitis optica spectrum disorders; MOGAD — MOG antibody-associated disease; MS — multiple sclerosis; NMDAR — anti-N-methyl-D-aspartate receptor

Table 3. Diseases mimicking NMOSD (based on [8, 38])

Diagnosis	Symptoms suggestive of diagnosis	Diagnostic examinations
Autoimmune inflammatory		
Acute disseminated encephalomyelitis (ADEM)	**Clinical:** • fever, meningeal syndrome, convulsions, alteration in consciousness • age < 18 years • history of infection preceding disease **Radiological:** • simultaneous enhancement of many lesions on MRI after contrast administration • lesions within basal ganglia	No specific differential tests • note abnormalities on MRI (see opposite column) • follow-up of clinical and radiological evolution over time
Systemic lupus erythematosus (SLE)	**Clinical:** • nephropathy • arthritis • facial erythema • haematological disorders (anaemia)	• serum antinuclear antibodies (ANA) • serum anti-ds-DNA-antibodies
Sjögren's syndrome	**Clinical:** • keratoconjunctivitis sicca and xerostomia, especially in presence of another autoimmune connective tissue disease (mostly rheumatoid arthritis) • polyneuropathy or myopathy	Anti-Ro (SS-A) and/or anti-La (SS-B)
Behçet's disease	**Clinical:** • oral and genital ulcers • uveitis **Radiological:** • lesions within basal ganglia	
Neurosarcoidosis	**Clinical:** • uveitis • optic and facial nerve involvement • polyneuropathy or multiple mononeuropathy **Radiological:** • focal changes in lungs (X-ray, CT) • meningeal enhancement on MRI after contrast administration • simultaneous enhancement of many lesions on MRI after contrast administration	Chest X-ray or CT • assessment of serum angiotensin-converting enzyme (ACE) and cerebrospinal fluid (CSF) • gallium scintigraphy of whole body • FDG-PET • ENG • biopsy
Autoimmune GFAP astrocytopathy	Fever, myelitis, meningitis, encephalitis, involuntary movements, psychosis, seizures, sphincter disorders, hyponatremia	• GFAP-IgG in CSF • in CSF, pleocytosis and elevated protein concentration • on MRI, linear radial perivascular enhancement after contrast administration; periventricular • paraneoplastic syndrome (ovarian tumour — teratoma) in 20–25%
Neoplasms		
Meningeal carcinomatosis	symptoms of meningeal irritation, headache, nausea, vomiting, impaired consciousness, behavioural changes, balance disorders, speech disorders, radicular pain	• linear meningeal enhancement on MRI • immunophenotyping of cerebrospinal fluid cells
Lymphomas	headache, impaired consciousness, behavioural changes, focal symptoms	• significant radiological variability (MRI) • immunophenotyping of cerebrospinal fluid cells
Paraneoplastic		
Encephalitis associated with collapsin response mediator protein 5 (CRMP5)	psychotic disorders, polyneuropathy, dysautonomia	• anti-CRMP5 antibodies (anti-CV2 antibodies) • small cell lung cancer
Metabolic		
Vitamin B12 deficiency	**Clinical:** • concomitant polyneuropathy • gastrointestinal symptoms • megaloblastic anaemia **Radiological:** • in cases of myelopathy, typical thoracic spinal cord involvement (posterior funiculi) with hyperintense lesions on T2 and FLAIR sequences, often with atrophy on MRI	• determination of serum B12 vitamin • in borderline levels of serum B12 concentrations, levels of methylmalonic acid (MMA) and homocysteine should be determined • intrinsic factor antibodies • Schilling test

→

Table 3 cont. Diseases mimicking NMOSD (based on [8, 38])

Diagnosis	Symptoms suggestive of diagnosis	Diagnostic examinations
Genetic		
Adrenomyeloneuropathy	**Clinical:** • concomitant polyneuropathy **Radiological:** • symmetrical periventricular lesions	• VLCFA assessment • genetic testing • ENG
Hereditary spastic paraplegia	Progressive spastic paraparesis of lower limbs, sphincter disorders	• genetic testing • brain and spinal cord MRI
Hereditary Leber optic neuropathy	Slow, painless loss of vision, Possibility of abnormal colour discrimination and impaired pupillary response to light	• genetic testing

ADEM — acute disseminated encephalomyelitis; MRI — magnetic resonance imaging; CT — computed tomography; ANA — antinuclear antibodies; SLE — systemic lupus erythematosus; anti-ds-DNA-antibodies — anti-(double stranded)-DNA antibodies; GFAP-IgG — glial fibrillary acidic protein immunoglobulin G; CRMP5 — collapsin response mediator protein 5; FDG-PET — fluorodeoxyglucose-positron emission tomography; MMA — methylmalonic acid; VLCFA — very long chain fatty acids; ENG — electroneurography

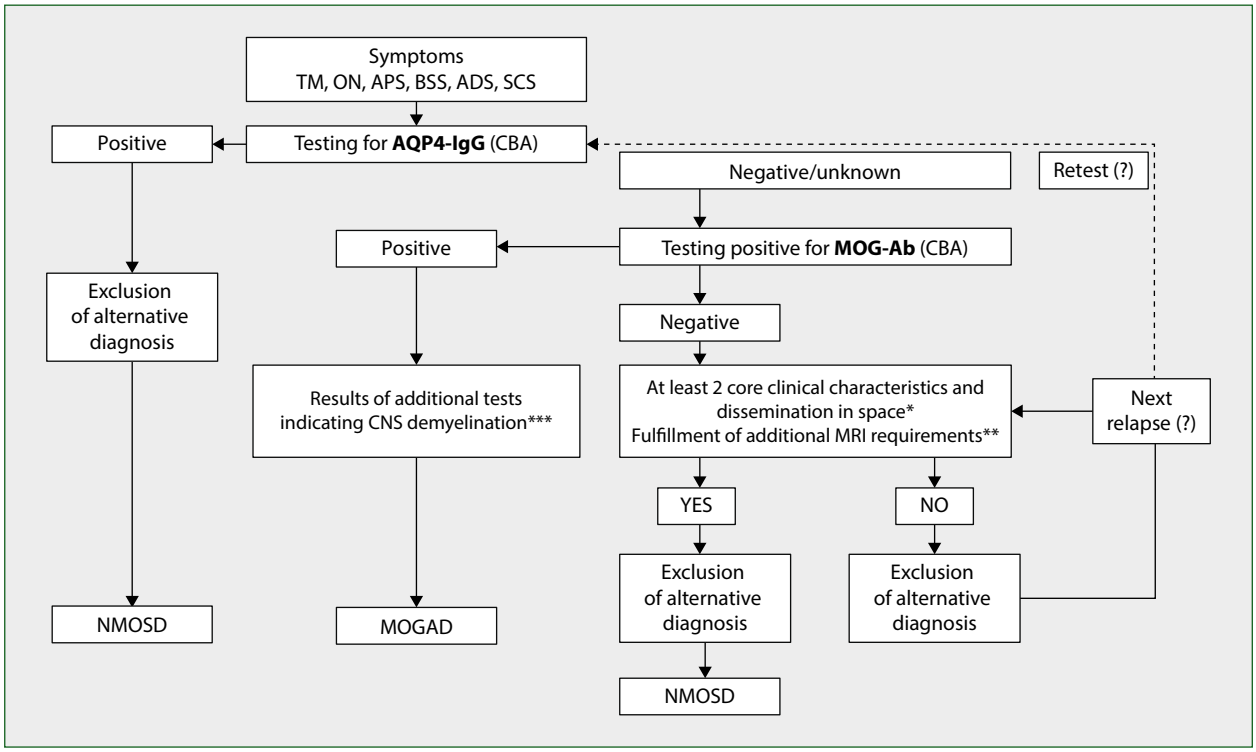

Figure 1. Diagnostic algorithm for neuromyelitis optica spectrum diseases (NMOSD). ON — optic neuritis; TM — transverse myelitis; LETM — longitudinally extensive transverse myelitis; APS — area postrema syndrome; BSS — brainstem syndrome; ADS — acute diencephalic syndrome; SCS — symptomatic cerebral syndrome; AQP4-IgG — anti-aquaporin-4 antibody; MOG-Ab — antibodies against myelin oligodendrocyte glycoprotein; MOGAD — MOG antibody associated disease; *at least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of following requirements: ON, TM with LETM or APS; dissemination in space (two or more different core clinical characteristics); **according to Table 1; ***MRI or electrophysiological test results (VEP in patients with isolated ON)

be performed before and after contrast administration to differentiate between NMOSD and MS. Although most lesions are not typical of MS, some 10-20% of patients fulfill the radiological Barkhof criteria.

An MRI scan of the spinal cord should be performed in patients with suspected NMOSD before and after contrast administration. This should include at least two segments of the spinal cord (i.e. cervical and thoracic). In the acute phase of the disease, the presence of longitudinally extensive transverse myelitis (LETM) typical of NMOSD is often reported. LETM includes lesions extending the length of three or more vertebral segments. In short-segment myelitis (STM), defined as spinal cord lesions extending fewer than three vertebral segments and a normal brain MRI or MRI not meeting the MS criteria, AQP4-IgG should be tested and a follow-up spinal MRI should be considered [23, 46–50].

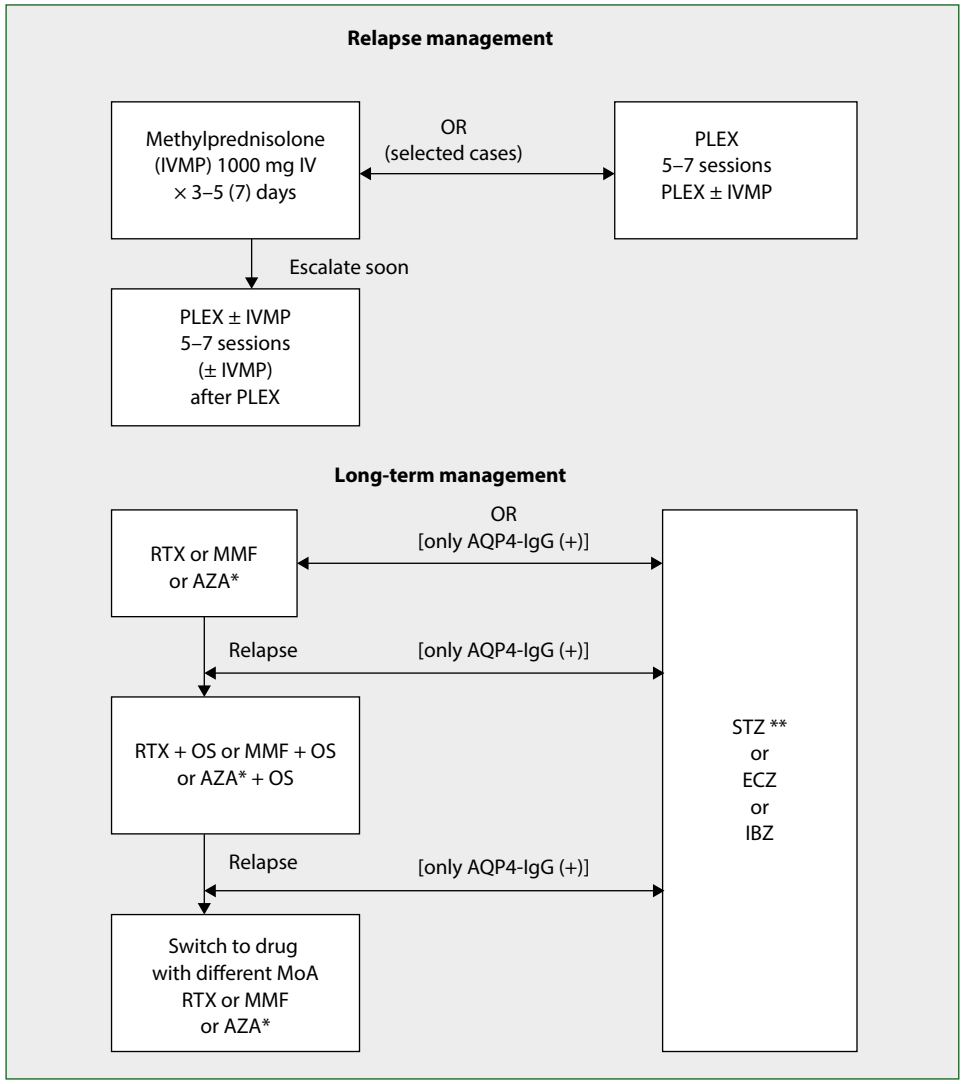

Figure 2. Recommended treatment algorithm for acute and long-term management for patients with NMOSD. IV — intravenous; PLEX — plasma exchange; IVIG — intravenous immunoglobulins; AZA — azathioprine; OS — oral steroids; AQP4-IgG — anti-aquaporin-4 antibody; STZ — satralizumab; ECZ — eculizumab; IBZ — inebilizumab; MoA — mechanism of action; *recommended if rituximab (RTX) or/and mycophenolate mofetil (MMF) is unavailable; **available in Poland in drug programme reimbursed by National Health Fund (NFZ, *Narodowy Fundusz Zdrowia*) since 2022

In patients with optic neuritis and suspected NMOSD, orbital MRI, including T1-weighted sequences before and after contrast administration, should be taken into consideration. MRI shows extensive (more than half of the nerve) unilateral or bilateral optic nerve involvement and/or involvement of the optic chiasm typical of NMOSD [47–49].

Treatment of NMOSD

Recommendations for relapse management

The mainstay of treatment of NMOSD relapses includes methylprednisolone intravenous — *i.v.* (1 g/d for 3–5 days, in some cases up to seven days) and/or plasma exchange (PLEX) (Fig. 2) [31, 32]. Oral steroid therapy should be continued with gradual dose tapering, depending on the severity of the relapse. Severe relapses should be treated with PLEX as the first-line treatment. Plasmapheresis is also used in patients who did not previously respond to methylprednisolone *i.v.* [33, 51–54]. An algorithm for treatment with PLEX is given in Table 6. In addition, administration of polyvalent immunoglobulins *i.v.* should be considered (Fig. 2) [33, 34, 55].

Recommendations for chronic immunosuppressive treatment

Please note that the following recommendations do not apply to MOGAD.

Table 4. Recommended immunosuppressive therapy in long-term management for seronegative and seropositive patients with neuromyelitis optica spectrum disorders (NMOSD) (modified from [29, 33, 57–60])

Medication and dosage	Mechanism of action	Most common and important side effects	Recommendations and comments
Oral steroids (OS) ***Methylprednisolone/prednisone*** • **Relapse managemen** • **Methylprednisolone** *i.v.* 1,000 mg/d; 3–5 (max 7) days with oral tapering • **Bridging therapy** (start of therapy with AZA/MMF/RTX) **Prednisone** or equivalent (OS) 1mg/kg once daily for 3–6 mo. + AZA/MMF or 1–2 mo. + RTX; then slow tapering over 3–6 mo. • **Add-on therapy** (in case of suboptimal response to AZA/MMF) **Prednisone** or equivalent (OS) 5–10 mg once daily	Binding to intracellular receptors → modulation of gene transcription; anti-inflammatory and immunosuppressive	Infections, weight gain, oedema, hyperglycaemia, hypertension, gastric irritation, insomnia, psychosis, rash, avascular necrosis of hip, cushingoid appearance	Could be used during pregnancy
Azathioprine (AZA) Target dose: 2.5–3 g/kg/daily in divided doses; *p.o.* • **Inpatient**: start 25mg daily and then increase by 25 mg daily • **Outpatient**: start 25 mg daily and then increase by 50 mg weekly	Inhibits purine synthesis resulting in inhibition of DNA, RNA and protein synthesis; T- and B--lymphocyte apoptosis	Infections, diarrhoea, vomiting, elevated LEs, rash, hypersensitivity, increased risk of malignancy depending on therapy duration (lymphoma, skin cancers and other cancers), bone marrow suppression	AZA is recommended if MMF or RTX is unavailable AZA should be combined with OS until its full effect (at least 6 months) lymphopenia (< 500–1,000/µL) or an elevated MCV (at least 5 points from baseline) is a useful marker of adequate dose TPMT activity and metabolites could help to monitor use of AZA AZA could be used during pregnancy
Mycofenolate mofetil (MMF) Target dose: 750–1,500 mg twice daily (median dose: 1,000 mg, twice a day), *p.o.* • start at 500 mg twice a day for 1–2 weeks and then increase to 1,000 mg twice a day	Prodrug of mycophenolic acid, an inhibitor of inosine-5′ — monophosphate dehydrogenase → interference with proliferation of T- and B- lymphocytes	Leukopenia, diarrhoea, vomiting, sepsis, increased risk of malignancy (lymphoma, skin cancers and other cancers), teratogenicity, reports on development of progressive multifocal leukoencephalopathy (PML) (not in NMOSD)	MMF should be combined with OS until its full effect (at least 4–6 months) lymphocyte count should decrease to 1,000–1,500/µL, following a plasma trough level of 1–2 µg/mL is a useful marker of adequate dose
Rituximab (RTX) Drug given *i.v.* following premedication: clemastine *i.v.* + paracetamol (acetaminophen) *i.v.* + + methylprednisolone *i.v.* • **Induction therapy:** — 1 g with retreatment at 2 weeks — 100 mg with retreatment at 2 weeks — 375 mg/m^2 *i.v.* once weekly for 4 weeks — 100 mg *i.v.* once weekly for 3 weeks • **Maintenance therapy with fixed time intervals:** — 1 g *i.v.* every 6 mo. — 375mg/m^2 *i.v.* every 6 mo. • **Maintenance therapy based on lymphocyte CD19(+) or CD27(+) count:** 1 g *i.v.* or 100 mg *i.v.* or 375 mg/m^2 *i.v.* when — CD19(+) count: > 0.01% × 10^9/L or > 0.1% of total lymphocytes; > 0.5% PBMC or — CD27(+) count: > 0.05% PBMC in first 2 years and then > 0.1% PBMC	Chimeric monoclonal antibody against human CD20	Minor infections (urinary and respiratory tract), non-serious infusion-related reactions, HBV and TBC reactivations	RTX + OS until its full effect (at least 1–2 mo.) Monitoring B cells [CD19(+)/CD20(+)/CD27(+)] could be useful to plan retreatment RTX could be used during pregnancy or overlapping syndrome (NMOSD and MS) In severe hypogammaglobulinaemia (< 150 µg/dL) and/or frequent or severe infections with IgG levels between 150 and 300 µg/dL supplementation of IVIg 400 mg/kg every 4 weeks targeting a serum level > 800–1,000 µg/dL is recommended

i.v. — intravenous; mo — month/s; AZA — azathioprine; MMF — mycophenolate mofetil; RTX — rituximab; PBMC — peripheral blood mononuclear cells; MCV — mean corpuscular volume; TPMT — thiopurine methyltransferase; MS — multiple sclerosis; IgG — immunoglobulin G; IVIg — intravenous immunoglobulins; DNA — deoxyribonucleic acid; RNA — ribonucleic acid; LEs — liver enzymes (aspartate aminotransferase and alanine aminotransferase); HIV — human immunodeficiency virus; HBV — hepatitis B virus; VZV — varicella zoster; TBC — tuberculosis; ECG — electrocardiogram; HAHA — Human Anti-human Antibody

Table 5. Recommended registered therapy in long-term management for seropositive patients with neuromyelitis optica spectrum disorders [NMOSD AQP4-IgG (+)] (modified from [8, 26–29])

Medication and dosage	Mechanism of action	Most common and important side effects	Recommendations and comments
Eculizumab (ECZ) **Intravenous *(i.v.)*** 900 mg weekly during the first 4 doses starting on day 1, followed by 1,200 mg every 2 weeks starting at week 4th	Humanised monoclonal antibody, which inhibits complement protein C5 → inhibition of terminal complement cascade	Minor infections (respiratory tract, nasopharyngitis and urinary), non-serious infusion-related reactions, increased risk of meningococcal and encapsulated bacterial infections	Efficacy and safety obtained in PREVENT Trial (randomised, placebo-controlled time-to-event trial in AQP4-IgG-positive NMOSD patients); All NMOSD patients must receive meningococcal vaccination 14 days prior to first dose of ECZ
Satralizumab (STZ)* **Subcutaneous (SC)** 120 mg at weeks 0, 2 and 4 and then every 4 weeks	Humanised anti-interleukin 6 receptor (IL-6R) monoclonal antibody type IgG2	Minor infections Non-serious infusion-related reactions	Data from pooled analysis from two phase III, randomised, double-blind, placebo-controlled studies in + and – AQP4-IgG NMOSD patients; Sakura-Sky was an add-on therapy study (STZ with AZA, MMF or OS); Sakura-Start was a monotherapy study
Inebilizumab (IBZ) **Intravenous *(i.v.)*** 300 mg in 2 doses on days 1 and 15 and then 3,000 mg every 6 mo.	Humanised monoclonal antibody against CD19	Minor infections (urinary and respiratory tract), non-serious infusion-related reactions, arthralgia	Efficacy and safety obtained in N-MOmentum study (double blind, randomised placebo-controlled phase II/III trial in (+) and (–) AQP4-IgG NMOSD patients)
Tocilizumab (TCZ) **Intravenous (IV)** 8 mg/kg every 4 weeks	Humanised monoclonal antibody against interleukin-6 receptor (IL-6R)	Anaemia, non-serious infusion-related reactions, infections (TBC, opportunistic), Elevated LEs, hypertension	Efficacy and safety obtained in TANGO (randomised, open-label, parallel-group study comparing TCZ vs AZA in (+) and (–)AQP4-IgG NMOSD patients) TCZ could be considered in pregnant women with severe NMOSD

*Available in Poland in drug programme reimbursed by National Health Fund (NFZ, *Narodowy Fundusz Zdrowia*) since 2022; SC — subcutaneous; AZA — azathioprine; MMF — mycophenolate mofetil; OS — oral steroids; ECZ — eculizumab; *i.v.* — intravenous; AQP4-IgG — anti-aquaporin-4 antibody; LEs — liver enzymes (aspartate aminotransferase and alanine aminotransferase); TBC — tuberculosis; IL-6R — interleukin-6 receptor

Table 6. Principles of PLEX procedure at Department of Neurology, Medical University of Warsaw

- 5–7 PLEX sessions every other day (it is possible to perform first two sessions day by day)
- during each PLEX session, c.110% of plasma volume should be exchanged (equivalent of 50–55 mL plasma/kg)
- 3.5% solution of human albumin as replacement fluid is recommended. It is also possible to use frozen plasma
- continuous vital signs monitoring, including blood pressure and ECG during PLEX session
- laboratory tests: complete blood count, albumin level, electrolytes determined before and c.4 hours (or next day depending on session schedule) after each PLEX session
- if a coagulation profile is checked, a decreased level of fibrinogen or extended APTT with no clinical signs of haemorrhagic diathesis are not contraindications to PLEX session
- following last PLEX session, removal of central vein catheter and sending it for bacteriological testing is recommended

Once NMOSD is diagnosed, chronic treatment should be started as early as possible to reduce the risk of relapse because in NMOSD each relapse is associated with a high risk of irreversible neurological deficits [31, 32]. The recommended types of immunotherapy in NMOSD (Tab. 4–5) [24, 29, 36, 56–60] are as follows:

I. Drugs used in seropositive and seronegative NMOSD:
— non-selective immunosuppressants, such as:
  - azathioprine (AZA);
  - mycophenolate mofetil (MMF);
  - long-term oral corticosteroids or combination therapy (immunosuppressants + corticosteroids);
— monoclonal antibody: *i.v.* cycles of rituximab (RTX) also in combination therapy [29–33, 58].

II. Drugs used in seropositive NMOSD in which the following antibodies show high efficacy (they can be used as the first-line treatment):
— eculizumab (ECZ) *i.v.* as monotherapy;
— inebilizumab (IBZ) *i.v.* as monotherapy;
— satralizumab (STZ) *s.c.* as monotherapy or combination therapy with other immunosuppressive drugs (e.g. corticosteroids, AZA, or MMF) [27–34].

Monitoring treatment of NMOSD

In chronically treated patients, the effectiveness of therapy should be monitored by clinical evaluation (assessment

Table 7. Pharmacological options for symptomatic therapy in NMOSD (modified from [30, 61])

Symptomatic therapy	Indications	Common daily dosage	Side effects
Anticonvulsants			
Gabapentin	Neuropathic pain	300–3,600 mg	Dizziness, drowsiness, fatigue, falls
Pregabalin	Tonic spasms	50–300 mg	Dizziness, drowsiness, fatigue, falls
Carbamazepine	Neuropathic pain	100–1,200 mg	Dizziness, drowsiness, nausea, vomiting, ataxia, hyponatremia, agranulocytosis, skin rash
Oxcarbazepine	Tonic spasms	150–1,200 mg	
Levetiracetam	Neuropathic pain	250–1,000 mg	Irritability, agitation, drowsiness
	Tonic spasms		
	Neuropathic pain		
	Tonic spasms		
	Neuropathic pain		
Muscle relaxants			
Oral baclofen	Spasticity	50–80 mg	Sedation, dizziness, drowsiness, nausea, vomiting, urinary retention
Tizanidine	Tonic spasms	2–36 mg	Sedation, dizziness, drowsiness, nausea, liver injury
Botulinum toxin injections	Spasticity,	50–300 units	Focal weakness, dysphagia, dry mouth, urinary retention (depending on site of injection)
	Tonic spasms		
	Focal spasticity or dystonia		
	Overactive bladder		
	Tonic spasms		
	Neuropathic pain		
Antidepressants			Nausea, somnolence, hypertension, liver injury, serotonin syndrome
Duloxetine	Neuropathic pain	30–120 mg	
Venlafaxine	Depression and anxiety	37.5–225 mg	Nausea, somnolence, hypertension, liver injury, serotonin syndrome
Amitriptyline	Neuropathic pain	12.5–150 mg	Sedation, dry mouth, constipation
	Depression and anxiety		
	Neuropathic pain		
	Depression and anxiety		
Medications for bladder dysfunction	Overactive bladder	5–30 mg	Dry mouth, constipation, urinary retention, cognitive decline
Oxybutynin		7.5–15 mg	
Darifenacin		5–10 mg	
Solifenacin			
Mirabegron	Overactive bladder	25–50 mg	Hypertension, constipation, urinary retention

of relapse rates, progression of disability) and periodic MRI of the brain and/or spinal cord with the frequency depending on clinical condition [31–33].

Symptomatic treatment

Immune-modulating therapies for relapse prevention of NMOSD have evolved rapidly over the past few years. However, a significant unmet need is the determination of best practice related to chronic symptomatic management [30, 61]. Chronic symptoms have a profound effect on a patient's quality of life. Pharmacological options for symptomatic therapy in NMOSD are set out in Table 7.

Specific situations of patients with NMOSD

Disease activity in NMOSD can be increased in the postpartum period, but, unlike in MS, also appears to be increased during pregnancy. Furthermore, obstetric complications, including miscarriage and preeclampsia, may also commonly occur in patients with NMOSD. Therefore, stabilisation of the disease before conception is recommended [61, 62]. Several case series have reported an elevated relapse risk during pregnancy compared to the prepartum period, which can result in an accumulation of disability [63, 64]. Moreover, pregnancy-related hyperemesis gravidarum, severe nausea, or vomiting may be confused with area postrema syndrome (NMOSD-associated

Table 8. Therapies for patients with NMOSD and pregnancy[a, b] (modified from [62])

Therapy	Length of washout period per label	Length of washout period per pharmacokinetic/ /pharmacodynamic placental transfer and potential risksc	Characteristics
Azathioprine (aza)	No recommendations	Continuation during pregnancy could be considered	Reassuring safety data across case series for various indications
Mycophenolate Mofetil (mmf)	6 Weeks	6 Weeks	Embryotoxicity, pregnancy loss
Rituximab (rtx) Anti-cd20 (igg1)	6 Months (fda) 12 Months (ema)	2 Months; could be continued if Maternal benefits outweigh potential foetal risks	Intermediate half-life but prolonged biological activity after administration; reassuring emerging safety data with pregnancy exposures; consider Checking newborn b cells and lymphocytes
Satralizumab (stz) Anti-il6r (igg2)	No recommendations	2 Months	In monkeys treated during pregnancy, no adverse effects on maternal animals or foetal development, however, some neonatal immune concerns
Inebilizumab (ibz) Anti-cd19 (igg1)	6 Months (fda) 12 Months (ema)	2 Months; could be continued if maternal benefits outweigh potential foetal risks	Intermediate half-life but prolonged biological activity after administration; consider checking newborn b cells and lymphocytes
Eculizumab (ecz) Igg2/4 kappa anti-c5 antibody	No recommendations	2 Months; could continue if Maternal benefits Outweigh potential foetal risks	Reassuring safety data for infants of women with paroxysmal nocturnal haemoglobinuria treated during pregnancy
Tocilizumab (tcz) Anti-il6r (igg1)	No recommendations	3 Months	Abortifacient and embryotoxic, possible delayed delivery in monkeys treated during pregnancy; In humans, possible increased risk of miscarriage, preterm birth, and lower birth weight in women with rheumatoid arthritis but potentially confounded by methotrexate comedication

IgG — immunoglobulin G; a — treatments reviewed in Wallach et al. [70]; b — pregnancy data reviewed in Mao-Draayer et al. [71]; c — washout refers to period during which drug has to be stopped before conception attempts can begin

symptoms of intractable nausea, vomiting, or hiccups) [61]. If new neurological symptoms arise and doubt exists about their nature, an MRI without gadolinium should be obtained [65]. During pregnancy, short courses of glucocorticoids are generally considered safe. Methylprednisolone, prednisone, and prednisolone are preferred in pregnancy, as they do not enter the foetal circulation. In contrast, c.80% of a maternal dose of dexamethasone can cross the placenta into the foetal circulation unmetabolised [56, 66]. Either PLEX or intravenous immunoglobulins (IVIg) can be used in NMOSD for steroid-resistant relapses. IVIg (0.4 g/kg/d) is preferred in pregnancy because of lower risks of circulatory instability (such as maternal hypotension, which potentially can result in decreased placental perfusion and foetal oxygenation) [67, 68]. Therefore, when PLEX is chosen, maintaining an adequate maternal intravascular volume by saline infusions during the procedure is essential. In the second or third trimester, the patient should lay on her left side to avoid compression of the inferior vena cava by the gravid uterus [67, 68]. Recommendations for immunosuppressive therapies in relation to pregnancy are set out in Table 8 [70, 71].

In NMOSD, infection, vaccination and therapies interact with each other, and these interactions need to be managed to minimise the risk of infection and maximise the benefits of vaccination. Vaccinations that reduce the risk of infection have been shown to stabilise the course of the disease. Some therapies alter the course, increase the risk of specific infections, and affect the efficacy of vaccinations. The effects of vaccination depend on various factors, including the vaccination type (live attenuated or inactivated) or the patient's vaccination history (primary vaccination, revaccination, or booster vaccination). The effects of these factors can also be influenced by a variety of patient-specific characteristics, including age, sex, comorbidities, immune status, or co-medication and drug interactions (Tab. 9) [72–76].

Table 9. Suggested intervals between immunotherapies and vaccinations (modified from [72–76])

Main mechanism of action	Drug	Interval from vaccine to treatment (weeks)		Live vaccine during therapy permitted	Interval from treatment to live vaccine
		Inactivated vaccine	Live vaccine		
Direct depletion or cytolysis	Rituximab (RTX)	> 4	> 4	No	12 months + normal B cell count
	Inebilizumab (IBZ)	> 4	> 4	No	After B cell repletion
Impairment of cell proliferation	Azathioprine (AZA)	2–4	4	No	> 3 months
	Mycophenolate mofetil (MFM)	2–4	> 4–6	No	> 2 months
Pleiotropic effects	Tocilizumab (TCZ)	4[a]	4	No	Not studied
	Satralizumab (STZ)	2–4	4	No	Not studied
	Eculizumab (ECZ)	2–4	4	Not advised	Not studied
	Glucocorticosteroids[b]	0	0	Yes	None
	Glucocorticosteroids[b] for > 2 weeks	2–4	4	No	> 2 months
	IVIg	2–4	2–4	Yes	> 3 months (diminished response to measles vaccine up to one year)
	PLEX	2–4	2–4	Not advised	None

Information based on prescribing information and [1–4]. IVIg — intravenous immunoglobulin; [a] — where possible, shorter intervals can lead to reduced immune response. If shorter intervals are unavoidable, testing for antibody responses to vaccination and/or additional vaccination might be necessary; [b] — equivalent to < 20 mg prednisolone daily

Conclusions

The diagnosis and treatment of NMOSD continue to be challenges that require specific clinical experience. The diagnosis should be made according to the 2015 criteria. Immune therapy of NMOSD is undergoing dynamic changes related to the registration of new generation drugs, i.e. monoclonal antibodies with different mechanisms of action and high efficacy in inhibiting disease progression, mainly in patients with anti-AQP4 antibodies [24–27, 30–33].

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GUIDELINES

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Recommendations of Multiple Sclerosis and Neuroimmunology Section of Polish Neurological Society and Immuno-oncology Section of Polish Society of Oncology on oncological risk in patients with multiple sclerosis undergoing immunomodulatory therapy

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ABSTRACT

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS) that is usually diagnosed between the ages of 20 and 40. Changes in the immune system also observed in cancer may suggest a higher prevalence of cancer in the MS patient population. In recent years, many highly effective immunosuppressive drugs have been introduced into disease-modifying therapy (DMT) which may be associated with a higher risk of cancer development in patients with MS. This paper presents current data on the oncological risk of individual drugs. In addition, it provides recommendations on the management for qualifying for DMT and monitoring the safety of the therapy from anoncological perspective.

Keywords: multiple sclerosis, oncological risk, cancer, immunomodulatory therapy

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Introduction

Multiple sclerosis (MS) is a relatively common inflammatory and neurodegenerative disease of the central nervous system (CNS) that is usually diagnosed between the ages of 20 and 40. Women are affected 2–3 times more often than men [1, 2]. It involves engagement of the immune system, acute inflammatory injury of axons and glia, post-inflammatory gliosis, and neurodegeneration [1]. Relapsing-remitting MS (RRMS) is the most common type of MS, accounting for c.85–90% of cases at onset and affecting especially young people. Its course is characterised by fully or partly reversible episodes (known as relapses) of neurological disability and the differential involvement of motor, sensory, visual, and autonomic systems [3]. The era of disease-modifying therapies (DMTs) began in the 1990s. In the 21st century, many new drugs have been introduced that have improved treatment, not only in terms of effectiveness but also safety. Because most DMTs are immunosuppressive, they may be associated with a higher risk of cancer.

Risk of developing cancer in general population

In Poland, the number of cancer cases has more than doubled in the last two decades. According to the National Cancer Registry, over 146,000 new cancer cases and 99,900 cancer-related deaths were reported in 2020. Malignant neoplasms are the second most common cause of death, and account for over 20% of all deaths [4].

The risk of developing cancer depends on age and sex. In 2020, the number of new cases in young people (i.e. those aged 20–44) in Poland amounted to over 7,000 cases annually in women and over 3,500 in men. In turn, in middle-aged individuals (45–64 years) and people aged 65 and over, the numbers were as follows: over 25,000 cases in women and 21,000 in men, and 40,000 in women and 45,000 in men, respectively [4].

The most prevalent malignancy in women is breast cancer (23.8%), with an increasing incidence, followed by lung cancer (9.9%) and colorectal cancer (8.5%). Endometrial cancer (7.1%) and ovarian cancer (4.1%) are slightly less common. In 2020, the highest mortality was related to lung cancer and breast cancer. In turn, the most prevalent carcinoma in men is prostate cancer (19.6%); followed by lung cancer (15.9%) and colorectal cancer (11.2%). Bladder cancer (6.6%) is less common. The highest mortality is associated with lung cancer [4].

The prevalence of cancer depends on the age structure of the population. In young women (aged 20–44), breast cancer is most prevalent (29% of cases and 29% of deaths due to all cancers), followed by cervical cancer (5% and 9%, respectively), ovarian cancer (5% and 8%, respectively) and colorectal cancer (3% and 9%, respectively). In middle-aged women (aged 45–64), breast cancer is also the most frequently diagnosed carcinoma (31% of cases, 18% of deaths due to all cancers) followed by lung cancer (9% and 20%, respectively), colorectal cancer (8% and 9%, respectively), ovarian cancer (5% and 8% respectively) and endometrial cancer (9% and 3%, respectively) [4]. In young men (aged 20–44), testicular cancer is the most common (26% of cases, 7% of deaths due to all cancers), followed by colorectal cancer (7% and 10%, respectively) and melanoma (7% and 5%, respectively) [4]. In middle-aged men (aged 45–64), the most common cancers are lung cancer (17% of cases, 29% of deaths due to all cancers), prostate cancer (16% and 4%, respectively), and colorectal cancer (13% and 11%, respectively). Bladder cancer (5% and 4%, respectively) and gastric carcinoma (4% and 6%, respectively) are less prevalent [4].

Cancer risk in patients with multiple sclerosis

Early analyses showed a higher risk of cancer among patients with MS, especially brain and urinary tract cancers [5–7]. Recent studies have not confirmed these figures [6, 8, 9], which is in line with a meta-analysis from 2020 that did

not show a higher prevalence of cancer in the population of patients with MS compared to the general population [10].

However, there are still reports suggesting differences in the prevalence of some cancers in patients with MS compared to the general population [7, 11, 12]. Analysis of a Norwegian database (n = 6,949) confirmed a higher cancer incidence in endocrine glands, brain, meninges and respiratory organs [12]. Breast, cervical and gastrointestinal cancers were found to be more common in the MS patient population, especially in women, compared to the control group, which was also demonstrated in a meta-analysis in 2015 [7, 12]. Analysis of a Danish database of MS patients (n = 11,817) showed an increased risk of melanoma [13]. There are reports of a higher incidence of bladder cancer than in the general population, which could be influenced by recurrent urinary tract infections associated with urinary incontinence [7, 14].

The stage of the disease and the phenotype of MS (i.e. clinically isolated syndrome [CIS], relapsing-remitting MS [RRMS], secondary progressive MS [SPMS] or primary progressive MS [PPMS]) do not correlate with a higher risk of cancer development [9]. Many reports have attempted to determine in more detail the risk factors for cancer in the population of patients with MS. However, no clear conclusions can be drawn from them [12, 15, 16]. It is known that age is an important risk factor for the development of cancer. In the population of patients with MS, the risk of carcinoma increases with age. It is higher in individuals over 60 and in patients whose disease occurs later and lasts longer [12, 16].

DMT and cancer risk

Drugs that are effective in inhibiting clinical and radiological activity and disease progression have been registered in the DMT of MS. However, the long-term impact of most of them, especially in terms of adverse effects, is as yet insufficiently understood. Mechanisms of action, including the impact on the immune system, vary between drugs. By inhibiting the immune system, the immunosuppressive effect can cause significant lymphopenia and increase the risk of cancer development, the frequency of infections, or the development of opportunistic infections [17, 18].

Comparing data on the prevalence of cancer in the period before the use of DMT and after its introduction, no clear conclusions can be drawn [12, 13]. To date, data on the safety of DMT does not allow for estimation of the risk, because patients over 55 and those who have had MS for more than 10 years have rarely been enrolled in clinical trials. It has been found that DMT switching could carry a risk of cancer. Patients with a single switch of DMT carry double the risk of developing cancer, and for patients who change therapy two or more times this risk is more than trebled. It has not been demonstrated that the therapy model (i.e. escalation vs. induction) has an impact on the risk of cancer development [16].

Statements of risk of cancer during DMT treatment, and recommendations on the management for DMT and monitoring the safety of the therapy from an oncological perspective, are set out in Table 1.

Beta interferons (IFN-β)

In vitro studies have not found the mutagenic effects of these substances, and no potential carcinogenic effects have been demonstrated. Carcinogenicity studies of IFN-β in animals have not been conducted (Suppl. Tab. 1) [19–22]. No cases of cancer have been reported in clinical registration trials of anyinterferon beta products [23–26].

To date, data on the safety assessment of IFN-β has not shown an increased risk of cancer associated with the use of drugs from this group. Analysis of data from 12 clinical trials on IFN-β 1a s.c. (subcutaneous route) and clinical practice (n = 3,746) did not show a higher incidence of cancer in the group of patients treated with IFN-β compared to the group treated with a placebo [27]. A lack of increased risk of IFN-β 1a i.m. (intramuscular injection) was confirmed in analysis of a very large group of patients from an American population (n = 402,250) [28]. Similarly, in a French study that evaluated patients from 12 MS centres (n = 9,269) treated with IFN-β 1a s.c., IFN-β 1a i.m. and IFN-β 1b, no higher incidence of cancer was noted [29]. No increased cancer risk was demonstrated in a 12-year follow-up of patients treated with IFN-β registered in the British Columbia MS Database (n = 5,146). In this group, a trend toward an increased risk of breast cancer was observed, but with no statistical significance [30].

Glatiramer acetate (GA)

In vitro data has not found genotoxicity or carcinogenicity. No animal studies have been performed (Suppl. Tab. 2) [31]. No cases of cancer have been reported in clinical trials [32].

Most real-world evidence (RWE) studies donot show an increased risk of cancer in patients treated with GA. Based on the data from the British Columbia MS Database, only 2.3% of patients treated with GA were reported to have had cancer. The French study found no association between cancer risk and GA [29, 30]. In a study of patients from an Israeli population, a higher incidence of breast cancer in women was found, depending on the duration of GA therapy. However, the data was not statistically significant [33]. Isolated cases of cutaneous lymphoma and melanoma have been reported in patients exposed to GA [34].

Dimethyl fumarate (DMF)

In vitro genotoxicity studies have not demonstrated the mutagenic effects of DMF. In preclinical studies, mice were found to have an increased prevalence of kidney cancer and

Table 1. Statements and recommendations for DMTs

DMT	Statement	Recommendation
Beta interferons	No increased risk of cancer associated with beta interferon therapy was found	**Recommendation 1** There are no special recommendations related to IFN-β regarding cancer prevention
Glatiramer acetate	There was no evidence of an increased risk of cancer associated with glatiramer acetate therapy	**Recommendation 2** There are no special recommendations for cancer prevention associated with glatiramer acetate therapy
Dimethyl fumarate	No increased risk of cancer associated with dimethyl fumarate therapy has been demonstrated yet. However, this needs to be confirmed in long-term observations	**Recommendation 3** There are no specific recommendations for cancer prevention associated with dimethyl fumarate therapy
Teriflunomide	No increased risk of cancer associated with teriflunomide therapy has been demonstrated yet. However, this needs to be confirmed in long-term observations	**Recommendation 4** There are no special recommendations for cancer prevention associated with teriflunomide therapy

Sphingosine 1-phosphate (S1P) receptor modulators

Recommendation 5

- Patient education in terms of skin observation and self-examination
- Patients are advised to perform regular self-assessment of body, taking into account changes occurring within existing pigmented nevi and appearance of new lesions on skin, especially in areas not associated with exposure to ultraviolet radiation
- Patients are advised to follow rules of safe exposure to sun and to use skin protection against ultraviolet radiation, both natural and artificial (indoor tanning)
- Periodic physical examination and history taking, including a comprehensive skin examination, should be performed
- Periodic dermatology consultation with skin assessment prior to initiation of treatment and during treatment is recommended in accordance with the current SmPC of a given drug (recommended primarily before therapy with fingolimod or siponimod, and to be considered before treatment with ozanimod or ponesimod)
- Phototherapy with UV-B radiation or photochemotherapy with psoralens (PUVA) is contraindicated during treatment
- Use of fingolimod, ozanimod and siponimod is contraindicated in patients with active malignancy. It is recommended to discontinue therapy if active malignancy is diagnosed. (Recommendation 5a, 5c and 5d)
- Use of ponesimod is contraindicated in patients with active malignancy. (Recommendation 5b)
- Caution should be exercised when ponesimod or siponimod is administered concomitantly with anti-cancer drugs, immunomodulatory or immunosuppressive agents due to risk of additive immune effects during such therapy and weeks after its completion (Recommendation 5b, 5d)
- Fingolimod and ozanimod should not be administered concomitantly with anti-cancer drugs, immunomodulatory, or immunosuppressive agents due to risk of additive effects on immune system (Recommendation 5a, 5c)
- It is recommended to perform screening tests for cervical cancer (including a cervical smear every three years in women aged 25–59, or every 1–2 years in women at increased risk, depending on the previous result) and vaccination against human papillomavirus (HPV) in accordance with current standards of care (Recommendation 5a)

DMT	Statement		Recommendation
Fingolimod	An increased risk of cancer associated with fingolimod therapy, especially skin cancers, has been demonstrated		**Recommendation 5a**
Ponesimod	No increased risk of cancer associated with ponesimod has been demonstrated yet. However, long-term observations are warranted In turn, an increased risk of skin malignancies has been found in combination with another S1P receptormodulator (SmPC)		**Recommendation 5b**
Ozanimod	No increased risk of cancer associated with ozanimod has been demonstrated yet. However, further long-term follow-up is necessary An increased risk of skin malignancies has been found in combination with another S1P receptor modulator (SmPC)		**Recommendation 5c**
Siponimod	An increased risk of cancer, especially skin cancers, associated with siponimod has been demonstrated		**Recommendation 5d**
Natalizumab	No increased risk of cancer associated with natalizumab has been demonstrated yet. However, further long-term observations are warranted	Patient education in terms of skin observation and self-examination Patients are advised to regularly self-assess body, taking into account changes within existing pigmented nevi and appearance of new lesions on skin, especially in areas not associated with exposure to ultraviolet radiation Patients are advised to follow rules of safe exposure to sun and to use skin protection against ultraviolet radiation, both natural and artificial (indoor tanning) Periodic physical examination and history taking, including a comprehensive skin examination, should be performed Use of natalizumab is contraindicated in patients with active malignancy, except for basal cell carcinoma (SmPC). Basal cell carcinoma should be removed	**Recommendation 6**

Table 1. cont. Statements and recommendations for DMTs

Ocrelizumab	A higher incidence of cancer, especially breast cancer, was observed in registration trials of ocrelizumab compared to controls RWE observations have not confirmed this yet. Further long-term observations are warranted	Female patients should undergo standard breast cancer screening in accordance with current guidelines: • breast ultrasound every 2 years in women aged 20–30 • ultrasound once a year in women after age 30 • mammography once every 2 years in women over 45 Patients with known risk factors for malignancy and patients who are actively monitored for risk of cancer recurrence should be individually assessed for benefit-risk ratio Use of ocrelizumab in patients with active malignancy is contraindicated	**Recommendation 7**
Ofatumumab	No increased risk of cancer associated with ofatumumab therapy has been demonstrated yet. However, further long-term observations are warranted	Patients with known risk factors for malignancy and patients who are actively monitored for risk of cancer recurrence should be individually assessed for benefit-risk ratio Use of ofatumumab is contraindicated in patients with active malignancy	**Recommendation 8**
Alemtuzumab	No increased risk of cancer associated with alemtuzumab has been demonstrated yet. However, autoimmune thyroid disease alone may be a risk factor for thyroid cancer Further long-term observations are warranted	In cases of autoimmune thyroid disease, patient should be monitored for thyroid cancer also after completion of therapy Caution should be exercised in patients with pre-existing and/or active malignancy	**Recommendation 9**
Cladribine	A higher incidence of cancer was observed in registration studies of cladribine tablets compared to controls However, this has not been confirmed in RWE observations yet. Further long-term observations are warranted	Patients treated with cladribine should be advised to follow Standard Cancer Screening Guidelines (SmPC) Cladribine therapy is contraindicated in cases of active malignancy Individual benefit-risk assessment should be performed in patients with pre-existing malignancies prior to treatment initiation	**Recommendation 10**

Recommendations for eligibility for DMT:

When qualifying a patient with MS for DMT, it is necessary to:

1. Perform an oncological medical interview to check for active and past cancer disease and collect a family history of cancer
2. Inform patient that risk of developing cancer increases with age and thatuse of immunosuppressive therapies may be an additional risk factor for cancer formation
3. Tests should be performed to rule out active malignancy according to standard screening guidelines, depending on risk factors, age and planned DMT
4. Recommend modification of risk factors for the development of cancer (ban on smoking and alcohol abuse, maintenance of normal body weight: BMI < 25)
5. Educate patients in terms of observation and self-examination of skin and breasts
6. Inform patient about need to protect skin from sun exposure using UV filters

Recommendations for monitoring DMT:

When monitoring DMT, recommendations are:

1. Tests for cancer detection:
   a) Performing tests for detection of skin cancers:
      • Educating patients in field of skin observation and self-examination
      • Patients are recommended to regularly self-assessbody, taking into account lesions occurring within existing pigmented nevi and appearance of new lesions on skin, especially in locations not associated with exposure to ultraviolet radiation
      • Patients should be advised to follow rules of safe sun exposure and use skin protection products against ultraviolet radiation – natural and artificial (indoor tanning)
      • Periodic physical examination and history taking, including a comprehensive examination of skin (basal cell carcinoma, melanoma) should be performed. In cases of a suspicious skin lesion, immediate dermatology consultation should be sought
   b) Conducting tests for detection of breast cancer:
      • Educating patients in terms of breast observation and self-examination
      • Regular breast self-examination
      • Breast imaging studies in accordance with current recommendations for general population
   c) Performing tests for detection of cervical cancer in accordance with current recommendations for general population
2. When switching to DMT, an analysis of potential benefit-risk of cancer development should be carried out, considering patient's age, number of previous DMTs, and duration of immunosuppressive treatment

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Table 1. cont. Statements and recommendations for DMTs

Preventive cancer screening – current screening programmes	
Breast Cancer Prevention Programme	In women > 45, mammography once every 2 years
Cervical Cancer Prevention Programme	In women aged 25–64, cytology once every 3 years
	Once a year in women with risk factors (HIV infection, intake of immunosuppressive drugs, and HPV infection of a high-risk type)
Colorectal Cancer Screening Programme	Colonoscopy:
	— In people aged 50–65
	— In people aged 40–49 if a first-degree relative has been diagnosed with colorectal cancer
	— In people aged 25–49with a family history of colorectal cancer unrelated to polyposis
Pilot programme for early detection of lung cancer	Chest computed tomography in former and active smokers > 55

Risk factors for development of cancer disease in a patient treated with DMT: checklist

No.	Risk factors
1.	Patient age > 50
2.	A history of cancer
3.	Oncological history: confirmed oncogenic germline mutations in patient or a family history of cancer in first-degree relative confirmed by genetic consultation
4.	Duration of DMT therapy > 10 years
5.	DMT switching at least twice
6.	Prior immunosuppressive DMT
7.	Current therapy with a drug with a confirmed increased risk of cancer (fingolimod, siponimod, ocrelizumab, cladribine)
8.	Current immunosuppressive therapy (ponesimod, ozanimod, ofatumumab, alemtuzumab)

forestomach cancer. Two times higher exposure than the recommended human dose resulted in a higher incidence of renal cancer and testicular Leydig cell adenoma in rats (Suppl. Tab. 1) [35].

In the DEFINE and CONFIRM registration studies, the prevalence of cancer in patients treated with DMF was not higher than in the placebo group (Suppl. Tab. 2) [36, 37]. In long-term follow-up of patients from the ENDORSE registration trial (median follow-up 8.76 years), a similar number of cancers was recorded in the group treated with DMF from the beginning and the group initially on a placebo (16 cases; 3% vs. 8 cases; 3%). The incidence of cancer in patients treated with DMF was 459 per 100,000 persons per year. This did not differ significantly from the incidence rate in the general population (442 per 100,000 persons per year) [38]. Despite lymphopenia in patients, no higher incidence of cancer was noted in RWE observations. In a Spanish study, the incidence of cancer in patients treated with DMF (n = 886) was low and amounted to 0.9% (n = 8) at a mean follow-up of 39.5 months, with as many as 62% of patients developing cancer (n = 5) over the age of 50 [39].

Teriflunomide (TER)

Thisdrug was not mutagenic *in vitro* or clastogenic *in vivo*. Its metabolite caused mutagenicity and a clastogenic effect *in vitro,*but not *in vivo*. In preclinical studies in rats and mice, no evidence of carcinogenicity of the drug was observed (Suppl. Tab. 1) [40].

The TEMSO and TOWER registration trials did not show an increased risk of cancer in patients treated with TER compared to a placebo group (Suppl. Tab. 2) [41]. In long-term follow-ups (median 13 years) of patients (n = 1,978) from phase II and III clinical trials (i.e. TEMSO, TOWER, TOPIC, TENERE, TERI-PRO, and TAURUS MS I), a total of 19 (0.9%) cases of cancer were reported [42]. In patients on 14 mg TER, no increased risk of cancer was confirmed [43].

Sphingosine 1-phosphate (S1P) receptor modulators: fingolimod, ponesimod, ozanimod, siponimod

Fingolimod (FTY)

In preclinical studies in rats, no evidence of carcinogenicity of FTY was reported. In mice, an increased incidence of lymphomas was demonstrated at the drug dose equivalent of six times the human dose (Suppl. Tab. 1) [44].

According to the Summary of Product Characteristics (SmPC), FTY may induce lymphopenia. It has an immunosuppressive potential, and may therefore increase the risk of cancer, especially skin cancer and lymphomas. In clinical trials and observations after the drug's introduction to the market,

cases of various types of lymphomas were found, and their incidence in clinical trials was higher than would be expected in the general population [45].

The first reports of increased cancer risk came from the FREEDOMS and TRANSFORMS registration trials (Suppl. Tab. 2) [45, 46]. In a long-term (up to 4.5 years) follow-up of patients from the TRANSFORMS trial, an increased risk of non-melanocytic skin cancer was confirmed. No higher risk of melanoma was found [47]. In the INFORMS trial, 25 cases of malignancies (7.4%) were reported in patients with PPMS (n = 336), including particularly skin cancers such as basal cell carcinoma (n = 14), squamous cell carcinoma (n = 6), and melanoma (n = 1), and also breast cancer (n = 1), lymphoma (n = 1), lung cancer (n = 1), ovarian cancer (n = 1) and prostate cancer (n = 1). No correlation was found between the degree of lymphopenia and skin cancer [48]. Cases of basal cell carcinoma (n = 36) were reported in the LONGTERMS trial, which was a long-term (14 years) follow-up of patients treated with FTY (n = 3,480). It was the most common serious adverse event, while eight cases of breast cancer were also reported [49].

There have also been reports of cancer in RWE observations of patients treated with FTY. Cases of melanoma (n = 5) were reported in patients with short-term (12–32 months) therapy with FTY[50]. Additionally, cases of Kaposi's sarcoma were described [45]. In a German study evaluating the efficacy and safety of FTY treatment after five years (n = 4,068), the following cancers were described: basal cell carcinoma (n = 21), melanoma (n = 6) and other skin cancers (n = 4) [51]. In an analysis of a Swedish database of patients with MS, patients treated with FTY (n = 1,620) presented with a 1.5--fold increased risk of malignancy compared to the general population, especially for basal cell carcinoma (n = 15) and cervical intraepithelial neoplasia grade 3 (CIN3) (n = 17). In addition, breast cancer (n = 4), prostate cancer (n = 3), melanoma (n = 4), skin cancers other than melanoma (n = 3), and lymphoma (n = 2) were reported [52].

In 2020, a meta-analysis of 34 studies (n = 64,135) estimated the incidence of cancer in the population of patients treated with FTY at 2% (n = 2,561). A higher incidence of cancer was observed in patients on a higher dose (1.25 mg) (3.0%) compared to 0.5 mg (2.0%) [53]. In connection with reports of an increased incidence of cancer, especially skin cancer, in patients treated with FTY, the European Medicines Agency (EMA) recommended monitoring the patient's skin, which was included in the SmPC in 2015 [44]. Cases of human papillomavirus (HPV) infections, including highly oncogenic variants, were reported in women treated with FTY, which may increase the risk of secondary cervical cancers [54, 55]. In the longitudinal open-label LONGTERMS trial, cases of cervical precancerous stages (n = 7) were found in women on FTY [49].

Ponesimod

In preclinical studies, ponesimod did not show a genotoxic potential *in vitro* or*in vivo*. In the carcinogenicity studies in rats, no cancerous lesions were observed. In mice, however, an association was found with sarcoma and haemangioma at high drug doses (Suppl. Tab. 1) [56].

In the OPTIMUM registration trial, six cases of cancer (1.0%) were reported in the group on ponesimod (n = 567), including five skin cancers, comprising basal cell carcinoma (n = 4) and melanoma (n = 1) (Suppl. Tab. 2) [57].

In a long-term (median 7.9 years) follow-up of patients from the phase II study and extension phases who continued ponesimod therapy (n = 214), eight (1.8%) cases of non-skin cancers were reported: invasive ductal breast cancer (n = 3), breast cancer (n = 2), B-cell lymphoma (n = 1), cervical adenocarcinoma (n = 1) and oesophageal adenocarcinoma (n = 1). Six (1.4%) cases of skin cancer were observed, i.e. basal cell carcinoma (n = 5), squamous cell carcinoma (n = 1) plus anunspecified skin cancer (n = 1) [58]. To estimate the risk of cancer formation in patients treated with ponesimod, long-term observations of large cohorts are warranted.

Ozanimod

In preclinical studies, ozanimod and its major active metabolites were not genotoxic *in vitro* or*in vivo*. No tumours were found in studies evaluating carcinogenicity in animals (Suppl. Tab. 1) [59].

In the SUNBEAM and RADIANCE clinical trials, half of the cancer cases involved malignant skin cancers other than melanoma, the most common being basal cell carcinoma (Suppl. Tab. 2) [60, 61].

An analysis of patient data from phase I, II, and III clinical trials and open-label studies involving 2,787 patients on ozanimod for an average of 32 months showed a total of 25 (1.1%) cases of cancer, including skin cancers (n = 12): basal cell carcinoma (n = 9), squamous cell carcinoma (n = 1), non-melanoma skin cancer (n = 1), and melanoma (n = 1); and 13 cases of other cancers such as ductal breast cancer (n = 1), breast cancer (n = 5), cervical cancer (n = 1), testicular cancer (n = 1), kidney cancer (n = 1), glioma (n = 1), pancreatic cancer (n = 1), thyroid cancer (n = 1) and an unspecified malignant neoplasm (n = 1) [62]. These analyses did not show a higher cancer incidence than in the registration trials. Long-term observations are required.

Siponimod (SIP)

Siponimod is not genotoxic *in vitro* or *in vivo*. In animal studies, it has caused lymphomas, haemangiomas and haemangiosarcomas in mice, and follicular adenomas and thyroid carcinomas in male rats. The occurrence of these tumours was considered species-specific, and the relevance of these studies to humans is unclear (Suppl. Tab. 1) [63]. Basal cell carcinoma and other skin cancers, including squamous cell carcinoma, have been reported in patients on siponimod.

In the EXPAND registration trial in patients with SPMS, cases of skin cancer were observed (Suppl. Tab. 2) [64]. Analysis of patients in the EXPAND trial after five years of

follow-up (n = 1,651) showed an increased risk of skin cancer (n = 78; 5.1%), with an incidence rate of 1.6 per 100 patient-years, mostly basal cell carcinoma, compared to the registration study (n = 21, 1.9%), where the incidence rate was 1.2 per 100 patient-years [65]. These observations are consistent with the data on fingolimod.

Natalizumab (NAT)

Preclinical studies in mice showed no carcinogenic, clastogenic, or mutagenic effects (Suppl. Tab. 1) [66]. The AFFIRM clinical trial did not show a higher incidence of cancer in patients treated with NAT than in a placebo group (Suppl. Tab. 2) [67].

RWE observations indicated cancer cases. In a study of a Swedish population treated with NAT (n = 1,670), 17 (1.01%) cancer cases were described, including basal cell carcinoma (n = 8), breast cancer (n = 2), melanoma (n = 2) and precancerous conditions of the cervix (CIN3) (n = 15). No increased cancer risk was found compared to the general population [52]. In 2017, the World Health Organisation issued a warning regarding NAT therapy, as 16 cases of primary central nervous system lymphoma (PCNSL) had been reported in the VigiBase® database by May 2015, the analysis of which showed that NAT could affect more rapid progression of B-cell lymphoma of the CNS [68]. Case reports of PCNSL in patients treated with NAT are emerging. Acorrelation between PCNSL and NAT is still under discussion [69, 70]. The first suggestions from the analysis of clinical trial data and reported cases after the introduction of the drug to the market highlighted acoincidence between melanoma and NAT therapy. The incidence of melanoma in NAT patients was estimated at 5/100,000 patient-years, which was half that in the general population (10/100,000 patient-years) [71]. Case reports of melanoma still appear in patients on NAT. Additionally, cases of melanoma are reported in adverse event registries [72–74].

Ocrelizumab (OCR)

No preclinical studies of the carcinogenic or mutagenic effects of OCR have been conducted (Suppl. Tab. 1) [75]. In clinical trials, patients with RRMS (OPERA I, OPERA II) showed a higher incidence of cancer, especially breast cancer, in the OCR group (Suppl. Tab. 2) [76]. During the extension phase of the trial (five years in total), further cases of cancer (n = 5) were reported, of which two were associated with breast cancer. An increase in the incidence of breast cancer was observed in the 3rd and 4th years of therapy [77]. The ORATORIO study (PPMS) showed a higher incidence of cancer in the OCR group compared to a placebo group (Suppl. Tab. 2) [78]. During the extension phase of the study, two more cases of skin cancer were reported: basal cell carcinoma (n = 1) and squamous cell carcinoma (n = 1). In a 6.5-year follow-up of patients in the ORATORIO trial, 14 cases of cancer were reported in the group of patients treated with OCR: basal cell carcinoma (n = 4), histiocytoma (n = 1), pancreatic cancer (n = 1), lymphoma (n = 1), endometrial cancer (n = 1), breast cancer (n = 3) and squamous cell carcinoma (n = 2). In the group of patients initially treated with a placebo and then switched to OCR, 10 cases of cancer were reported: bladder cancer (n = 2), lung cancer (n = 1) and basal cell carcinoma (n = 7) [79]. Until January 2020, cancers had been reported with a higher incidence than in the control group in all clinical trials of OCR (11 studies) and their extended phases (n = 5,680) in a 7-year follow-up (0.46/100 patient-years vs. 0.21/100 patient-years in the control group) [80]. Similarly, in a 10-year follow-up (n = 6,155), the incidence of cancer was confirmed (0.49/100 patient-years) [81], although no higher incidence of cancer was found compared to the MS population and the general population [80, 81]. The incidence of breast cancer in women treated with OCR was not higher than in the MS population, but breast cancer was slightly more prevalent compared to the general population, findings which require further follow-up [80]. A higher incidence of cancer was observed in the group of patients with PPMS, which may be associated with the higher age of patients in this study group.

Proper risk assessment will be possible in the long-term follow-up after publishing the results of the VERISMO trial assessing cancer risk in patients treated with OCR in daily clinical practice.

Ofatumumab (OFT)

No *in vitro* or *in vivo* studies have been performed to assess the carcinogenicity and mutagenicity of OFT (Suppl. Tab. 1) [82].

In the ASCLEPIOS I and ASCLEPIOS II registration clinical trials, no higher cancer incidence was shown in the group on OFT compared to the control group treated with teriflunomide (Suppl. Tab. 2) [83]. There have beenno long-term observations to assess the safety of this therapy.

Alemtuzumab (ALZ)

No *in vitro* or *in vivo* studies have been performed to assess the carcinogenic and mutagenic potential of ALZ (Suppl. Tab. 1) [84].

The CARE-MS I and CARE-MS II clinical trials found no higher cancer risk in patients treated with ALZ compared to the control group (Suppl. Tab. 2) [85, 86]. No increased incidence of cancer was observed in the long-term follow-up of patients from the registration studies. Six cases of cancer were reported in a 5-year follow-up of patients with CARE-MS I (n = 376) (0.3/100 patient-years) [87]. After 3–5 years of follow-up of

patients from the CARE-MS II trial (n = 412), two more cases of cancer were found. In total, four cases of cancer were found in the 5-year follow-up (n = 435), which included thyroid cancer (n = 2), melanoma (n = 1) and basal cell carcinoma (n = 1) [88].

In a study evaluating the long-term (8-year follow-up) safety of ALZ, 17 (0.8%) cases of cancer were reported in the ALZ group (n = 811), seven of which occurred in people aged 45 and over. The incidence of cancer increased with age. Cancer was found in 0.9–2.2% of people in younger groups, while malignancies were present in as many as 8.1% of patients aged 45+ [89].

Cancer cases were also described in RWE observations. In a Finnish study, four cases of cancer (3.0%) were reported in a 2-year follow-up (n = 121). They included breast cancer (n = 2), cervical cancer (n = 1) and cervical cancer in situ (n = 1) [90]. Up to 35% of patients treated with ALZ developed secondary autoimmune thyroid diseases, such as Graves-Basedow disease (65%), followed by hypothyroidism (20%) and subacute thyroiditis (12%). They were most often observed in the 3rd and 4th years after the completion of therapy [91]. It is believed that autoimmune thyroid diseases may be a factor increasing the risk of thyroid cancer. Therefore, it is necessary to monitor patients, even after treatment completion [92].

Cladribine

In preclinical studies, no carcinogenicity was found in mice or monkeys (Suppl. Tab. 1) [93]. The carcinogenic potential of cladribine has been demonstrated in indications other than MS. An increased risk of secondary cancers (hairy cell leukaemia) has been reported in patients on cladribine [94].

The CLARITY clinical trial in patients with RRMS showed an increased number of cancers in the group treated with cladribine tablets (0.29/100 patient-years), which resulted in refusal to approve the drug by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2011 (Suppl. Tab. 2) [95, 96]. A higher incidence of a specific cancer type was not demonstrated. However, patients who developed cancer were, on average, seven years older. In the CLARITY extension study, 11 (1.06%) cases of cancer were reported in the next two years of therapy: melanoma (n = 2), basal cell carcinoma (n = 1), breast cancer (n = 1), cervical cancer (n = 1), ovarian cancer (n = 1), kidney cancer (n = 1), colorectal cancer (n = 1), thyroid cancer (n = 1), squamous cell carcinoma (n = 1) and bile duct cancer (n = 1). These findings were not more common than those found in the general population [97]. It was demonstrated that the cancer risk did not increase with the duration of therapy. The above data allowed the drug to be registered.

Analysis of patients from CLARITY, CLARITY EXTENSION, ORACLE-MS and those continuing follow-up in the PREMIERE registry (n = 923) confirmed that the incidence of cancers did not increase with the duration of therapy. From 1–4 years after the first dose, it was 0.29/100 patient-years, and after 5–8 years, it was 0.28/100 patient-years and was not higher compared to other DMTs [98]. A proper risk assessment will be possible in the long-term follow up after publishing the results of the ongoing CLARION trial.

Recommendations

1. Currently, there are no international recommendations regarding how to reduce the risk of cancer formation in patients with MS treated with DMT.
2. Age over 55 and age-related comorbidities, as well as qualitative changes in the immune system (immunosenescence), are risk factors for cancer development.
3. There is insufficient data on the risk of cancer formation from clinical trials in patients over 55 on DMT, which should be reported to patients in this population.
4. Data on the long-term safety of DMT must be collected because the two-year duration of clinical registration trials is insufficient to assess cancer risk.
5. The increasing age of the patient, the duration of therapy, and the number of previously used drugs, especially those with an immunosuppressive mechanism, may lead to an accumulation of the risk of cancer formation.
6. Considering the immunological mechanism of action of individual DMTs, special caution should be exercised in the cases of therapy with alemtuzumab, cladribine, S1P receptor modulators, and natalizumaband anti-CD20 antibodies.
7. If cancer occurs, most DMTs should be discontinued. In a patient with active malignancy, alemtuzumab, cladribine, S1P receptor modulators, natalizumab and anti-CD20 antibodies should not be used in the treatment of MS.

*Beta interferons, glatiramer acetate, dimethyl fumarate and teriflunomide are however not contraindicated.

8. The concomitant use of DMT with anti-cancer drugs has not been studied.
9. Possible DMT continuation/switching in a patient with MS and cancer should lead to consultation with an oncologist to choose the optimal therapy considering the existing cancer disease and the risk of possible rebound effects in the course of MS.
10. The effect of anti-cancer treatment on MS has not been studied.

**Preparations of alemtuzumab, cladribine, ofatumumab and ocrelizumab are used to treat cancers of the bone marrow and the lymphatic system.

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Validation analysis of Polish version of Neuropathic Pain Questionnaire — Short Form (NPQ-SF-PL) and assessment of quality of life in patients with chronic neuropathic pain

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ABSTRACT

Aim of the study. The aims of this study were to translate and culturally adapt the Polish version (PL) of the Neuropathic Pain Questionnaire-Short Form (NPQ-SF), as well as to compare this questionnaire to other diagnostic tools in terms of reliability and psychometric validity.

Clinical rationale for the study. Neuropathic pain (NP) affects up to 10% of the general population. Despite a large number of studies, almost 50% of patients have a poor therapeutic outcome. Diagnostic tools are intended to distinguish between NP and non-NP (NoP) and to guide the examiner to perform further diagnostics in accordance with the guidelines.

Material and methods. A total of 140 patients with chronic pain (ChP), 90 with NP and 50 with NoP, were enrolled into this study. NPQ-SF-PL has been developed following the guidelines for translation and cultural adaptation. Reliability of the translated version was examined using internal consistency, predictive validity, and intraclass correlation coefficient (ICC).

Results. In the study, women predominated over men, and the average age was 53.22. Cronbach's α value for the entire scale was 0.76 and ICC for test-retest reliability was 0.631. Receiver-operating characteristic curve analysis gave a sensitivity of 90.0% and a specificity of 88.0%. Area under the curve was 0.94. NPQ-SF-PL was moderately associated with self-completed Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) and weakly associated with the Numerical Rating Scale (NRS). The NP group obtained statistically significantly lower scores than the NoP group in all domains of the 36-Item Short Form Health Survey (SF-36), thus indicating worse health status. Patients aged over 41 years presented a worse quality of life compared to younger ones. Also, more than half of the patients with NP of both genders experienced symptoms of mild or more severe depression.

Conclusions. NPQ-SF-PL is a valid screening tool for assessing NP in Polish chronic pain patients. The obtained results showed very good psychometric properties and adequate internal consistency. The repeatability of the questionnaire indicated moderate reliability.

Clinical implications/future directions. We believe this study will provide physicians with a new instrument for the evaluation of NP for clinical and research purposes.

Keywords: aging, cross-cultural adaptation, depression, diagnostic tool, neuropathic pain, Neuropathic Pain Questionnaire, non-neuropathic pain, Quality of Life

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Introduction

Neuropathic pain (NP) is a condition that affects 7–10% of the general population. In patients with diabetes, this can be as much as 20–30%. The latest cross-sectional cohort UK Biobank data indicates a NP prevalence of 9.2%, accounting for 18.1% of people with chronic pain (ChP). Despite a large number of studies and analysis, almost 50% of patients have a poor therapeutic outcome i.e. they either do not respond to the proposed treatment or the response is only moderate at best. Therefore, NP should be considered as a major unmet clinical need [1, 2]. Increased sensitivity to pain, or spontaneous pain in paradoxical combination with reduced or loss of function, may be a consequence of damage to the somatosensory nervous system. This happens in the case of NP, which often later becomes chronic, i.e. lasting ≥ 3 months, and manifests in recurrent pain episodes or persistent pain [3, 4].

According to the International Association for the Study of Pain (IASP) classification, chronic NP consists of peripheral and central pain. The first type combines units such as postherpetic or trigeminal neuralgia, nerve lesions, painful neuropathy, and radiculopathy. The 'central pain' category includes sequelae of diseases such as multiple sclerosis, stroke, and brain or spinal cord injury [3]. The most characteristic features of NP, regardless of its aetiology, are ongoing pain, paroxysmal pain, and allodynia. These result from various pathophysiological mechanisms [5].

To guide clinical decisions, a three-level grading system for certainty of NP has been designed: possible, probable, and definite. The 'possible' level of certainty contains the use of screening tools because a combination of several different descriptions has high distinctive value and may be indicative of NP. It is indispensable that the patients' history indicates neurological disease or lesions with an anatomically related pain distribution [6]. Diagnostic tools are also intended to distinguish between NP and non-NP; nevertheless, they should not be used in patients with widespread pain [7]. Also, their use alone does not enable the identification of a patient with NP, but is intended to direct the examiner to carry out further diagnostics, in accordance with the guidelines [6]. The subsequent full examination for NP can be time-consuming but is extremely important for initiating appropriate treatment. Therefore, a practical, quick and easy screening assessment is very helpful [8, 9].

At the same time, pain has a complex impact on the patient's life, and can lead to physical, mental and even spiritual suffering. Fighting pain should always be a priority, but even so coping strategies can also help to manage and reduce the consequences of pain [10]. Biological and genetic factors appear to underlie the co-occurrence of NP and mental illness. On the other hand, some behavioural and social factors can be modified by patients themselves and seem to be important in the prevention of NP [11].

Having considered the above, physicians should actively recognise and treat pain and its complications, as well as encouraging and supporting the patient in finding appropriate coping strategies.

Clinical rationale for the study

To the best of our knowledge, the Neuropathic Pain Questionnaire-Short Form (NPQ-SF) has never been translated into or validated for the Polish language. The aims of this study were to translate and culturally adapt the Polish version of the NPQ-SF, as well as to compare this questionnaire to other diagnostic tools in terms of reliability and psychometric validity.

Material and methods

This single-centre prospective observational study began in January 2021 and was conducted over 24 months in the University Clinical Hospital No. 4 in Lublin, affiliated to the Medical University of Lublin, Poland. A total of 140 ChP patients who met the eligibility criteria were included in the study. All patients had previously been assessed for pain type (i.e. NP, non-neuropathic pain, or other) according to the IASP guidelines. The following inclusion criteria were adopted: (1) age 18 years or over; (2) men or women with ChP for ≥ 3 months; (3) patients able to speak and read Polish; and (4) patients expressing written consent to participate in the study. In order to obtain sociodemographic data and medical history, an interview was conducted with each patient. In cases of cognitive or communication impairments that prevented the completion of the questionnaire, as well as a previous history of severe psychiatric diseases, patients were excluded from the research. Additional exclusion criteria were an unidentifiable nerve injury and pain syndromes associated with diffused pain. Study participants obtained all relevant information about this research and provided written informed consent before undergoing screening. If patients had any doubts about completing the survey, the physician explained the content of the survey and/or clarified the type of pain. Ethical approval to conduct this study was obtained from the Institutional Ethics Committee of the Medical University of Lublin, Poland (KE-0254/147/2020).

Instruments

The NPQ-SF [12] is a self-report assessment consisting of three items; tingling pain, numbness, and increased pain due to touch. These three have been selected from the original Neuropathic Pain Questionnaire (NPQ) [13]. These three items are significant predictors able to distinguish NP from non-NP (NoP) and are consistent with clinical symptoms and signs (positive and negative phenomena) occurring in NP [14].

For each item, participants numerically rate their usual pain on a scale of 0 (i.e. none) to 100 (the worst pain imaginable). To obtain a total discriminant function score, the results for each item are multiplied by the coefficient of the discriminant function and the structure coefficients, and then summed up using a given constant value. Thus, a result ≥ 0 predicts NP, while scores below 0 denote NoP. NPQ-SF is characterised by sensitivity of 64.5% and specificity of 78.6%, and total predictive accuracy of 73.0%. The NPQ-SF has been translated into and validated for the Turkish [8] and Arabic [15] languages.

In order to make comparisons between NPQ-SF and some commonly used scales, the Polish version of the NPQ-SF (the NPQ-SF-PL) was administered to patients, together with the self-completed Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) [16, 17], the Numerical Rating Scale (NRS) [18], the Hamilton Rating Scale for Depression (HRSD) [19], and the 36-Item Short Form Health Survey (SF-36) [20]. For the purpose of test-retest reliability evaluation, 50 of the patients filled out the NPQ-SF-PL for a second time after 14–21 days.

Translation and cross-cultural adaptation

Translation and cross-cultural adaptation followed the guidelines proposed by Beaton et al. [21]. The NPQ-SF-PL was first developed by forward translation of the original version of the questionnaire by two independent bilingual translators with different profiles whose native language is the target language (i.e. in this case Polish). The second step was to create one common translation from these two translations. Blind back-translation was then performed by two professional translators, and the resulting versions were evaluated and compared to the original version of the tool. The unified, pre-final version of the tool was tested by patients in order to look for a missing element or unclear sentence. The final version, re-evaluated based on the reports obtained, was approved and accepted by the participating scientists and validated in clinical settings. Permission to translate the NPQ-SF into Polish was granted by Dr Miroslav Bačkonja, who created the original version of this tool.

Statistical analysis

Statistical analysis was performed with Statistica software (version 13.3, StatSoft, Lublin, Poland). Data expressed on a qualitative scale was presented as number or mean, standard deviation (SD) and interquartile ranges (IQRs). For statistical significance, a value of $p < 0.05$ was assumed. Regardless of missing data, patients were included in the analysis if the entire NPQ-SF was completed. Incomplete or unclear data from other questionnaires used was omitted from statistical analysis. Frequencies and descriptive statistics were examined for each variable. Statistical comparisons were made between the NP and NoP subgroups in terms of demographic characteristics and the results of individual questionnaires. A chi-squared test (χ^2) was used to compare the relationships between variables expressed on a qualitative scale. A non-parametric Mann-Whitney U test was used to compare the means of two independent samples and Dunn's multiple comparison tests to evaluate differences among the groups. Also, to measure reproducibility and consistency of results, test-retest reliability was performed with the intraclass correlation coefficient (ICC) with corresponding 95% confidence intervals (CI) between first and second total scores [22]. The Cronbach's alpha (α) coefficient was calculated to analyse the internal consistency of this 3-item questionnaire. Internal consistency indicates the degree of correlation between the items and is the measure of scale homogeneity. Alpha is assumed to be from 0 to 1, but given a negative correlation between elements, the reliability result may be below 0. Some authors recommend a maximum value of 0.90 to avoid redundancy among the items. A Cronbach's alpha of > 0.80 indicates good internal consistency [23, 24]. To assess the relationship between variables and to calculate the correlation between different scales, we used Spearman's correlation coefficient (R). The relations were interpreted as strong (0.7–0.9), moderate (0.4–0.6), or weak (0.1–0.3) [25]. The predictive validity was estimated using receiver operator characteristic (ROC) curves. The area under the curve (AUC), and its 95% CI for the ROC curve, were calculated. Also, to maximise the sum of sensitivity and specificity for all the possible values of the cut-off point, the Youden index was calculated [26].

Results

The final version of the NPQ-SF-PL is attached as Supplementary material.

General information

The study group consisted of 140 patients with ChP of differing origins. Patients with NP accounted for 64.29% and patients with NoP for 35.71%. The mean age (SD) of patients was 53.22 (15.81). There was no significant difference between the gender distribution of the two groups ($p > 0.05$). A significant relationship was found between the place of residence distribution ($p < 0.05$), with the NP group predominantly living in towns/cities and the NoP group in the countryside. Detailed data on the clinical and demographic characteristics of the NP and NoP groups is set out in Table 1, and can be found in our previous article concerning validation of the Polish version of the NPQ [27]. According to Yates's chi-squared test, a statistically significant difference in the occurrence of NP by using NPQ-SF-PL was obtained between the study group and the control group ($p < 0.05$). The average NPQ-SF-PL score (SD) for the total group was –0.09 (0.97). The NPQ-SF-PL was compared to different questionnaires. There was no statistically significant difference between the assessment of the NP group in NPQ-SF-PL compared either to the S-LANSS questionnaire or to the NRS.

Table 1. Brief clinical and demographic characteristics of whole group

	NP n = 90	NoP n = 50	Female n = 85	Male n = 55
Mean age (SD)	55.82 (15.26)	48.54 (15.87)	52.42 (16.44)	54.45 (14.85)
Gender F/M	53/37	32/18		
Diagnosis	– central pain (n = 15) – CIDP (n = 9) – metabolic neuropathy (n = 17) – malignant neuropathy (n = 9) – trigeminal neuralgia (n = 4) – postherpetic neuralgia (n = 3) – painful polyneuropathy (n = 8) – painful radiculopathy (n = 25)	– primary or secondary musculoskeletal pain (n = 25) – primary or secondary headache or orofacial pain (n = 7) – primary or secondary visceral pain (n = 6) – cancer-related pain (n = 3) – postsurgical or post-traumatic pain (n = 9)		
NPQ-SF-PL score (SD)	0.41 (0.81)	–0.99 (0.38)	–0.002 (1.04)	–0.23 (0.82)
HDRS score (SD)	10.37 (8.04)	6.92 (7.15)	9.28 (7.74)	8.90 (8.17)

CIDP — chronic inflammatory demyelinating polyneuropathy; F — female; HDRS — Hamilton Depression Rating Scale; M — male; NoP — non-NP; NP — neuropathic pain; NPQ-SF — Neuropathic Pain Questionnaire short form; SD — standard deviation

Table 2. Mean scores obtained by using Hamilton Depression Rating Scale (HDRS) divided into tested (NP) and control (NoP) groups

HDRS scores (meaning)	NoP group	NP group					
	Total (%)	Total (%)	Females (%)	Males (%)	21–40 years (%)	41–60 years (%)	61+ years (%)
0–6 (no depression)	31 (62.00)	42 (46.67)	25 (47.17)	17 (45.94)	9 (50.00)	15 (46.88)	17 (42.50)
7–12 (mild depression)	8 (16.00)	11 (12.22)	5 (9.43)	6 (16.22)	2 (11.11)	4 (12.50)	6 (15.00)
13–17 (moderate depression)	7 (14.00)	20 (22.22)	13 (24.53)	7 (18.92)	4 (22.22)	8 (25.00)	8 (20.00)
18–29 (severe depression)	3 (6.00)	14 (15.56)	9 (16.98)	5 (13.51)	2 (11.11)	3 (9.37)	9 (22.50)
30–52 (very severe depression)	1 (2.00)	3 (3.33)	1 (1.89)	2 (5.41)	1 (5.56)	2 (6.25)	0 (0.00)
Total	50 (100.00)	90 (100.00)	53 (100.00)	37 (100.00)	18 (100.00)	32 (100.00)	40 (100.00)

Hamilton Depression Rating Scale (HDRS)

At enrollment in this study, patients were evaluated using the HDRS. The average HDRS score (SD) was 9.14 (7.89). Dividing into NP and NoP groups and into genders gave higher HDRS results for the NP group and for women [27]. There was no significant difference in the level of depression between the NP and NoP groups ($p > 0.05$). Taking into account only the NP group, there was no statistically significant difference in the level of depression between women and men ($p > 0.05$) or between respondents depending on age ($p > 0.05$) (Tab. 2). Nevertheless, according to the results, most NP patients of both genders experienced symptoms of mild or more severe depression, which is noteworthy. For the group of women this figure was 52.83%, and for men 54.06%. We also noted an increase in the incidence of depression with the increasing age of respondents, with the highest percentage of moderate, severe and very severe depression in the oldest group (61+ years), amounting to 42.50%.

Short Form Health Survey (SF-36)

Due to missing items, the SF-36 questionnaire was analysed for a group of 124 patients, 83 with NP and 41 with NoP. The NP group obtained statistically significant ($p < 0.05$) lower scores than the NoP group in all domains of the SF-36, thus indicating the poorest health status and significant impairment of quality of life. The results are shown in Figure 1A. The NP group was also analysed in all subscales by gender, place of residence, and age. There were no statistically significant differences ($p < 0.05$) between genders or between places of residence. However, statistically significantly better quality of life in terms of physical function was demonstrated in the group of respondents aged 21–40 compared to the groups aged 41–60 and 61+ (Fig. 1B).

Cronbach's alpha (α) coefficient and ROC

To analyse the internal consistency of the scale, Cronbach's α was calculated. The Cronbach's α value for the entire scale was 0.76, and ranged from 0.52 to 0.87 when the value of one of three subscales was suppressed.

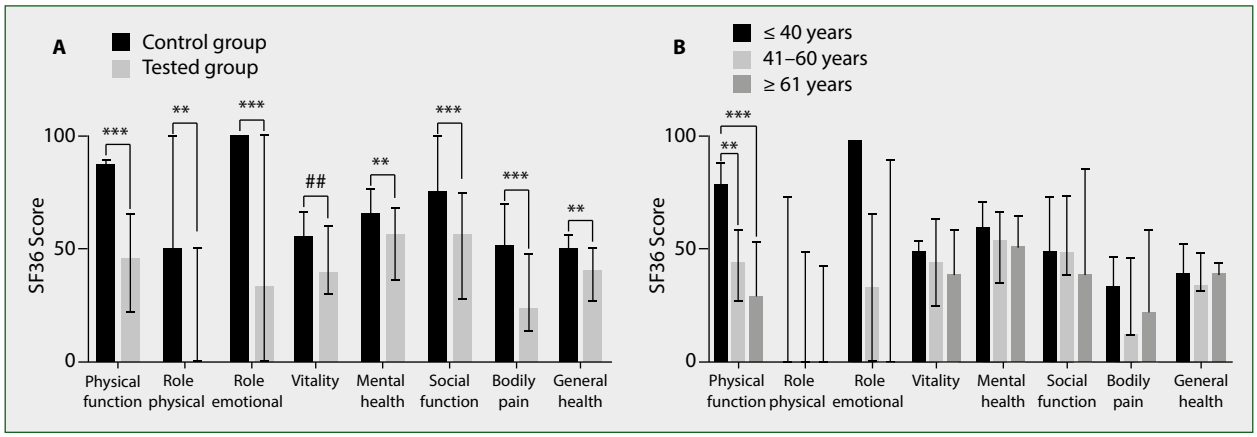

Figure 1. Short Form Health Survey (SF-36) score, median with interquartile range (IQR). **A.** Results for whole group divided into studied group — NP group (83 subjects) and control group — NoP group (41 subjects). Mann-Whitney U test; ** $p < 0.01$; *** $p < 0.001$ and student's t-test for independent samples; ## $p < 0.01$; **B.** Studied group (NP group) divided into groups according to age, post hoc Dunn's multiple comparisons test; ** $p < 0.01$; *** $p < 0.001$

When the repeatability of the questionnaire was assessed using the ICC, reliability was 0.631 (with 95% CI) which indicated moderate reliability [28]. Predictive validity was assessed based on ROC curves for which the area under the curve (AUC) was calculated. The AUC was 0.94, which means very good diagnostic power of the test. The cut-off diagnostic value was determined based on sensitivity, specificity, and Youden's index, corresponding to different total scores. The ROC curve analysis, as the best cut-off value distinguishing NP from NoP, showed a result of 0.481 (Fig. 2), which gives a sensitivity of 90.0% and a specificity of 88.0%.

Correlations between NPQ-SF-PL and various scales used in this study

The Spearman's rank correlation coefficient (R) was estimated separately for the NP and NoP groups ($p < 0.001$). For the NPQ-SF-PL NP group, a moderate correlation with the S-LANSS and a weak correlation with the NRS was found (R = 0.42 and R = 0.32, respectively). The NoP scores revealed a statistically significant moderate correlation with the S-LANSS (R = 0.50). The results are presented in Supplementary material Table 1.

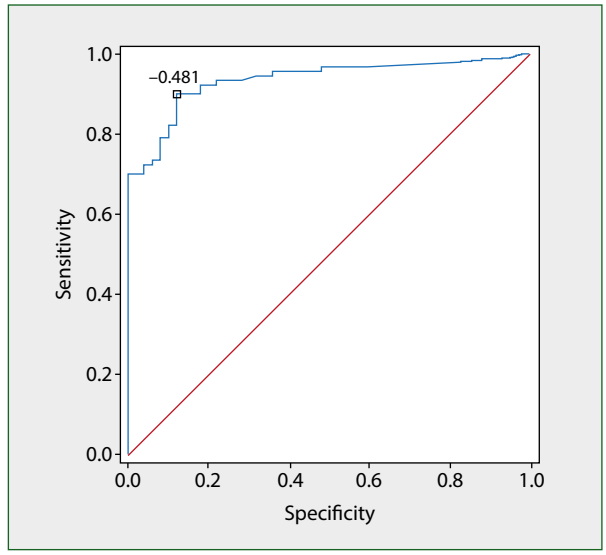

Figure 2. Receiver operating characteristic (ROC) curve for NPQ-SF-PL

Discussion

The present research paper reports on the validation and cross-cultural adaptation of the NPQ-SF to confirm that this tool is an acceptable and psychometrically satisfactory measure of data collection, especially as a screening tool, in Polish patients with chronic neuropathic conditions. The type of neuropathy was assessed by symptoms, clinical examination, and detection tools such as nerve conduction studies, imaging studies and laboratory investigations.

The reliability of the questionnaire was assessed using internal consistency, which assesses both the homogeneity of the test and the degree of correlation between the scale items [24]. The analysis showed appropriate Cronbach's α values for the entire questionnaire, even if individual items scored in the range of 0.52–0.87. The Cronbach's α value for this Polish version was higher than for other validation studies [8, 15, 29]. Other studies' low α values may be related to many reasons including a small number of items or a short test length, poorly related items, or items measuring heterogeneous constructs [29, 30].

The stability of the questionnaire over time was assessed using test-retest reliability. The reliability of the ICC was

moderate and lower than in other studies [8, 15], but these results are probably associated with the earlier re-testing time of the remaining questionnaires. Additionally, the original versions of the NPQ and NPQ-SF did not examine test-retest reliability [12, 13]. A good correlation as obtained between the NPQ-SF and S-LANSS was expected due to the existence of common verbal descriptions such as numbness, increased pain due to touch, and tingling pain. There have been few articles comparing questionnaires. Similar to our study, Spearman's rank correlation was used by Abolkhair et al. [29]. Their results indicated a moderate correlation between NPQ-SF and S-LANSS total scores, as well as a fair correlation between the NRS score and the NPQ-SF total score. Yurdakul et al. [8], using the Pearson's correlation test, provided a moderate correlation between the NPQ-SF and the NRS, as well as a high correlation between the NPQ-SF and LANSS total scores. Using the same Pearson's correlation test, Terkawi et al. [15] found that NPQ-SF items and total score were moderately-to-strongly associated with S-LANSS. Our study also included patients with mixed pain conditions, which could have influenced the results. These conditions are still poorly defined, and clinically manifest as a combination of various pain components which act simultaneously, concurrently and/or overlap to cause pain in the same area of the body [31]. The diagnosis of mixed pain is currently based on clinical assessment following a detailed history and physical examination, rather than a formal confirmation in the absence of diagnostic criteria or screening tests. Many studies have excluded patients with mixed pain conditions from analysis, and studies including these patients have not yielded consistent results regarding changes in specificity and/or sensitivity, limiting the generalisability of the results. However, it is acceptable to use validated screening tools to detect the presence of the NP component [32, 33].

With the exception of place of residence, the demographic data obtained is consistent with previously published results [11, 34–36]. This can be explained by the high references of our centre and the fact that patients from suburban areas are primarily referred to district hospitals. A higher neuropathic ChP prevalence was observed in women and in middle-aged patients, peaking at age 50–64. Additional non-genetic components contributing to this ailment include physical work and social deprivation [11, 37]. In the assessment of pain management, an increasingly important role is attributed to quality of life, everyday functioning and pain-related psychological factors, rather than just to the intensity of pain itself, and therefore these factors are increasingly being taken into account [38]. Nevertheless, patients with NP report higher pain intensity compared to patients with different types of pain, and exacerbations occur without obvious precipitatory factors [34, 39, 40]. A study conducted in patients with peripheral neuropathic (PNP) conditions as the primary diagnosis has shown that SF-36 is a sensitive indicator of ChP. Compared to the general population, patients with PNP had statistically significant lower results. Lower scores on physical function and bodily pain were also found in the non-working PNP group, so these may refer to work ability [41]. Also, reduced scores in all SF-36 domains were observed in patients with chronic NP identified by the S-LANSS questionnaire compared to the chronic non-NP group and the group without ChP. This indicates severely impaired functioning in patients with NP on every measured dimension of overall health, even when compared to patients with other types of ChP. Domains such as physical function, role physical (i.e. role limitations due to physical health problems), bodily pain, and role emotional (i.e. role limitations due to personal or emotional problems), were the most strongly associated with chronic NP [42]. This decline in the scores is consistent with our data, and indicates a reduced quality of life in patients with chronic NP. Another study [43] suggests that as many as 85% of patients with ChP may suffer from depression, and that these patients have a worse prognosis compared to patients diagnosed with ChP only. Moreover, these two diseases are closely related and are able to mutually promote their own progression in severity. Hypothetically, the common pathogenetic factor between ChP and depression may be chronic, subclinical inflammation of the nervous system [44]. According to reports, the coexistence of depression occurs in up to 60% of NP patients; this co-occurrence worsens prognosis and intensifies the severity of pain [45]. Due to the common neuro-mechanism between NP and depression, it appears that the latter may increase the risk of pain or escalate pain sensation, leading to a reduction in quality of life [46], whereas it is ChP that may lead to depression (chronic pain-induced depression) [43]. Some studies also highlight the close relationship between NP, quality of life and depression, especially in long-duration and more severe pain conditions [47]. In the elderly, persistent and untreated pain can lead to social isolation, functional deterioration, poor sleep, and an increased risk of falls. Moreover, the impact of NP on quality of life may be as great as the impact of some other chronic diseases [42, 48]. Epidemiological studies have shown that the prevalence of ChP and depression is higher in women than in men. These differences may be related not only to cultural and social factors, but also to biological factors resulting from gender differences [45, 49].

The results obtained should be interpreted with some caution due to the limitations of our study. The inclusion of patients with mixed pain syndromes in our study may have an impact on the psychometric properties and our conclusions. The usefulness of the questionnaire may also be limited by the fact that the study was conducted only on patients with ChP. It is also undeniable that screening questionnaires are not considered to be a gold diagnostic standard, but rather a guide for further diagnostics. However, their ease of use and availability should encourage doctors of various specialities to use them in practice and, if indicated, to further refer the patient for detailed examinations.

Clinical implications/future directions

To the best of our knowledge, this is the first cross-cultural adaptation of NPQ-SF in a Polish-speaking population. We have demonstrated that the NPQ-SF-PL questionnaire is a valid tool for assessing neuropathic pain in Polish chronic pain patients. The obtained results showed very good psychometric properties and adequate internal consistency. The repeatability of the questionnaire indicated moderate reliability. Also, the correlation with other questionnaires used in the study was moderate or weak. We believe this study will provide physicians with a new tool to evaluate neuropathic pain for clinical and research purposes.

The next step would be to compare the use of the questionnaire in patients with acute NP or to use the self-completion format in epidemiological studies. Growing evidence points to a role of neuroinflammation in the development of both ChP and depression, but robust, large-scale data on this topic is still lacking.

Another interesting issue requiring further research is the use of non-pharmacological therapies to counteract depression, pain and a decline in the quality of life.

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Supplementary material: *The final version of NPQ-SF-PL; Suppl. Table 1. Correlations between NPQ-SF-PL, S-LANSS, NRS and HDRS.*

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Measuring multifidus muscles atrophy after midline lumbar fusion with cortical bone trajectory screws due to spinal instability and spondylolisthesis: a retrospective case series

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ABSTRACT

Introduction. This study aimed to assess the impact of midline lumbar fusion with cortical bone trajectory screws (MIDLF/CBT) on the multifidus muscles, focusing on the evaluation of their postoperative atrophy.

Clinical rationale for the study. MIDLF/CBT is a relatively new technique increasingly used to treat spinal instability. Despite its reduced invasiveness compared to traditional posterior lumbar interbody fusion with traditional pedicle screws (PLIF/TP), concerns remain about potential damage to the multifidus muscles that are crucial for spinal stability. Understanding the extent of muscular atrophy post-MIDLF/CBT is vital for improving surgical outcomes, and potentially patient rehabilitation strategies.

Material and methods. This study retrospectively analysed preoperative and postoperative MRI scans of patients who underwent MIDLF/CBT for degenerative segmental spondylolisthesis. The bilateral width of the multifidus muscles at the operated segment and adjacent segments was measured using axial T2-weighted MRI scans. Statistical comparisons were made using a paired *t* test, with significance set at $p < 0.05$.

Results. The study included 16 patients with an average age of 57 ± 10 years, 10 of whom (62.5%) were women, and featured a mean follow-up period of 37 ± 25 months. Postoperative measurements showed a significant reduction in the width of the multifidus muscles at the operated segment (mean difference −3.3 mm, $p = 0.02$) and the inferior adjacent segment (−7.4 mm, $p < 0.01$). A decrease in muscle width at the superior adjacent segment was also observed, although this was not statistically significant.

Conclusions and clinical implications. Our study concluded that MIDLF/CBT results in significant multifidus muscle atrophy at and below the operated segment, potentially impacting postoperative rehabilitation and recovery. These findings highlight the need for further research comparing MIDLF/CBT to other spinal stabilisation techniques. Additionally, incorporating functional electromyographic assessments of paraspinal muscles could provide deeper insights into the long-term consequences of spinal surgeries and helpdevelop new approaches and strategies to mitigate paravertebral muscles atrophy, thus enhancing patient outcomes.

Keywords: cortical bone trajectory, midline lumbar fusion, multifidus muscles, spinal fusion, spinal instability, spinal stabilisation

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Introduction

Midline lumbar fusion with cortical bone trajectory screws (MIDLF/CBT) is a less invasive technique used to treat numerous spinal conditions such as spinal instability and spondylolisthesis [1]. In recent years, this procedure has grown in popularity among spinal surgeons [2], setting itself apart from other techniques, notably posterior lumbar interbody fusion with so-called traditional pedicle screws (PLIF/TP), in a multitude of ways, with particular emphasis on its screw placement methodology. Unlike PLIF, where the TP screws are inserted lateromedially, MIDLF employs CBT to position screws in a mediolateral and caudocranial direction. This insertion trajectory enhances surgical precision and lowers the risk of nerve injury and soft tissue dissection [1, 3].

Nonetheless, lumbar fusion surgeries, in general, are commonly associated with intraoperative paravertebral muscle injury, potentially leading to muscular atrophy, reduced mobility, and persistent postoperative back discomfort [4]. Additionally, the multifidus muscle appears to be especially prone to damage since it is solely innervated by the medial branch of the dorsal ramus and lacks intersegmental nerve supply [4, 5].

Other studies have utilised computer tomography (CT) and magnetic resonance imaging (MRI) to evaluate muscle atrophy by using measures such as relative cross-sectional area (CSA) and muscle density of the multifidus and other paravertebral muscles [6–10]. However, because of the screw's midline position, the presence of artefacts rendered these methods unsuitable for our investigation. Therefore, we opted for MRI and focused on measuring the width of the multifidus muscles at the operated segment level, as well as the superior and inferior adjacent segments, both before and after surgery.

Our previous work confirmed good clinical long-term outcomes in patients after MIDLF/CBT [11]. For this present study, we aimed to radiographically assess the impact of this supposedly less invasive technique on the vitality of the multifidus muscles and explore potential signs of their postoperative atrophy. Furthermore, our article presents a new, easy-to-use method of indirectly evaluating the paravertebral muscle mass. This comprehensive analysis addresses a gap in previous research.

Clinical rationale for the study

The MIDLF/CBT technique is gaining popularity due to its less invasive nature, which theoretically reduces tissue damage and promotes quicker recovery compared to traditional methods such as PLIF/TP. However, despite its advantages, there is a concern regarding its impact on the multifidus muscles, which are crucial for maintaining spinal stability and posture. The multifidus muscle is particularly susceptible to atrophy due to its medial anatomical position and innervation. By evaluating the extent of multifidus muscle atrophy postoperatively, this study sought to fill a gap in existing research and provide a more comprehensive understanding of the long-term effects of MIDLF/CBT on spinal health. Such knowledge is essential for further refining surgical techniques, improving postoperative care protocols, and ultimately enhancing patient outcomes in those suffering from spinal instability and spondylolisthesis.

Material and methods

Our study included all patients who underwent spinal stabilisation surgery using the MIDLF/CBT technique due to degenerative segmental spondylolisthesis and who had both preoperative and postoperative control MRI scans performed. Following our previous study evaluating the clinical effects of the MIDLF/CBT approach, we retrospectively analysed the radiographic pictures of the paravertebral muscles at, below, and above the operated spinal segment.

On the axial T2-weighted MRI scans, we measured the width of the multifidus muscles as the maximal distance between its two most lateral borders. Overall, the width of the muscle mass was assessed at five different levels: the operated segment, the middle of the upper and lower adjacent vertebra, and the upper and lower adjacent intervertebral disc (Figs. 1–6).

As described in our previous study, the MIDLF CD Horizon® Solera™ (Medtronic plc, Minneapolis, MN, USA) or mPACT (medialised posterior approach cortical trajectory; DePuy Synthes, Raynham, MA, USA) screws and rods were applied [11]. The procedure was started with a midline skin incision and continued with paravertebral muscle dissection and retraction towards the medial joint facets of the operated segment. Then we inserted translucent carbon retractors and decompressed the dural sac with the outgoing neural roots if appropriate. When indicated, we proceeded with bilateral discectomy, intervertebral space preparation, and intervertebral fusion using a polyetheretherketone or titanium prosthesis with bioactive properties and filled with osteogenic material. Following that, we identified the entry points for the screws in the pars interarticularis of the vertebrae. Next, we prepared canals for the screws and inserted them in the mediolateral and caudocranial direction through the pedicles. In the final step, we put in the longitudinal rods, repositioned the operated segment if needed, and tightened the screws. The surgical wound was sutured layer by layer.

All analyses were performed in R 4.4.11 and RStudio 2024.04.2 [12, 13]. Continuous parameters were expressed as means and standard deviations, categorical variables as counts and percentages. Post-operation and pre-operation multifidus muscle diameters were compared using a paired *t* test and expressed as mean difference (i.e. post-operation minus pre-operation) with a 95% confidence interval (CI). A p value < 0.05 was considered statistically significant.

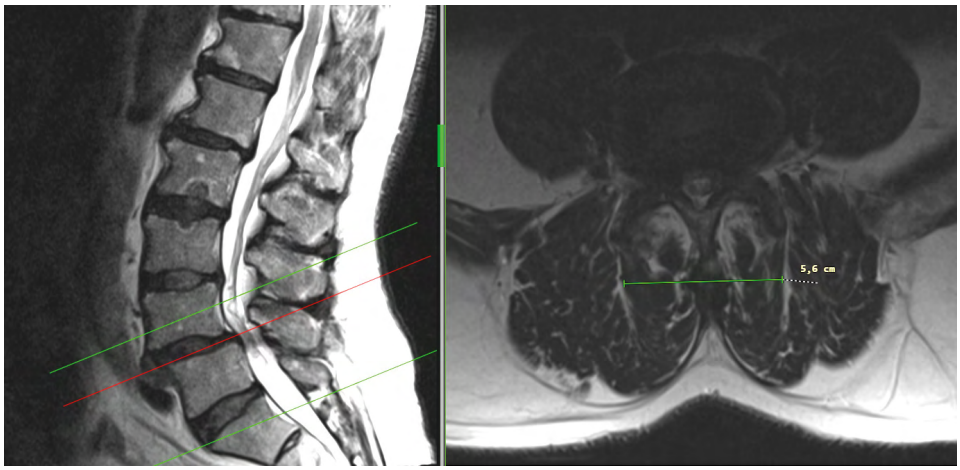

Figure 1. Preoperative T2-weighted MRI scan of a patient with L4/5 spondylolisthesis — measuring bilateral width of multifidus muscles in the operated segment

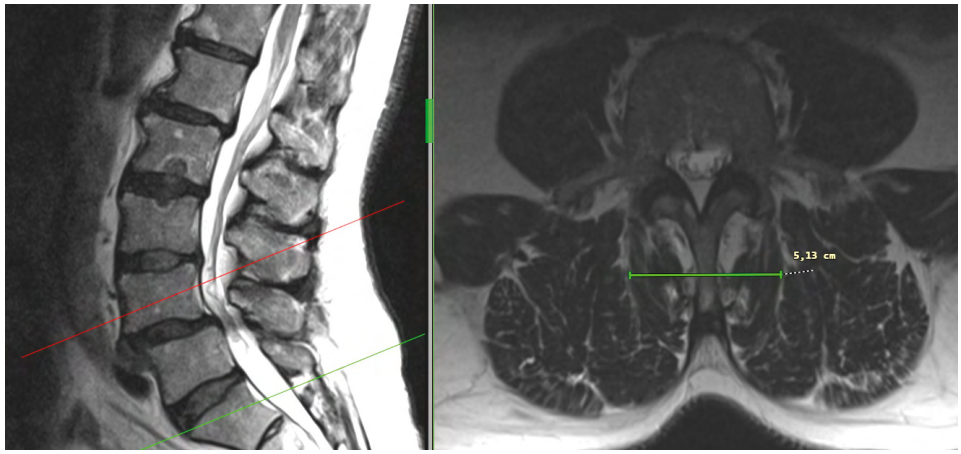

Figure 2. Preoperative T2-weighted MRI scan of a patient with L4/5 spondylolisthesis — measuring bilateral width of multifidus muscles in the middle of the upper vertebra (L4)

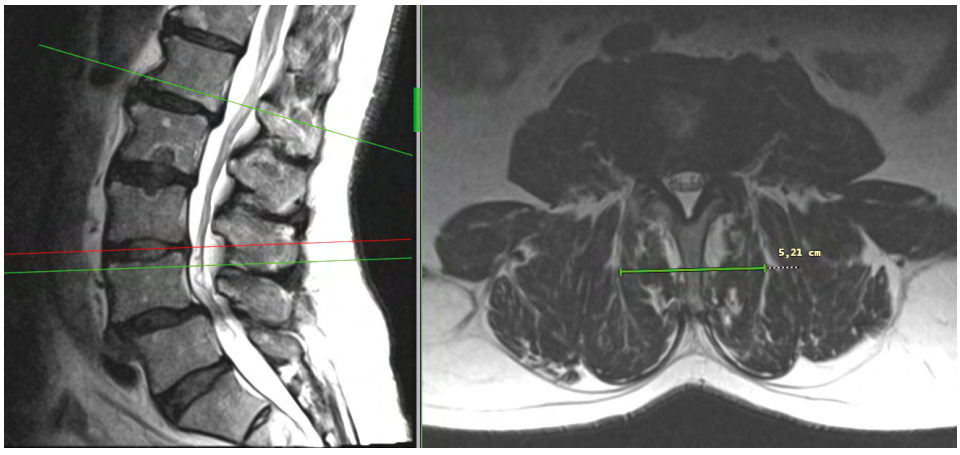

Figure 3. Preoperative T2-weighted MRI scan of a patient with L4/5 spondylolisthesis — measuring bilateral width of multifidus muscles in the upper adjacent segment (L3/4)

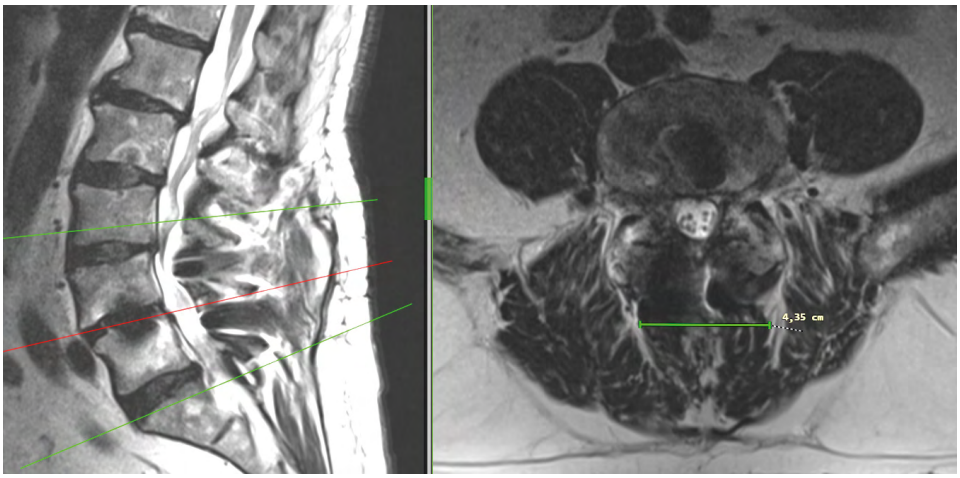

Figure 4. Postoperative T2-weighted MRI scan of a patient after MIDLF/CBT in L4/5 due to spondylolisthesis — measuring bilateral width of multifidus muscles in the operated segment

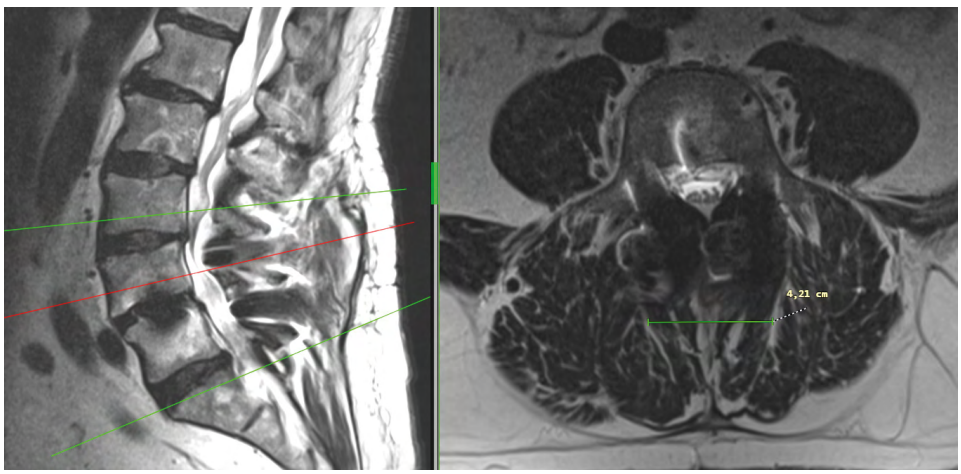

Figure 5. Postoperative T2-weighted MRI scan of a patient after MIDLF/CBT in L4/5 due to spondylolisthesis — measuring bilateral width of multifidus muscles in the middle of upper vertebra (L4)

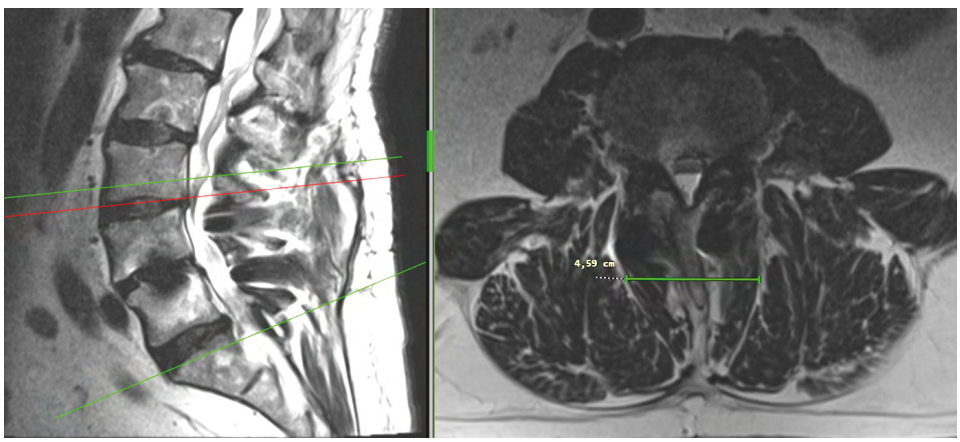

Figure 6. Postoperative T2-weighted MRI scan of a patient after MIDLF/CBT in L4/5 due to spondylolisthesis — measuring bilateral width of multifidus muscles in the upper adjacent segment (L3/4)

We ensured that our study conformed to the guidelines issued in the 1964 Declaration of Helsinki and was approved by the respective institutional Ethics Committees.

Results

We identified 16 patients with an average age of 57 ± 10 years, of whom 10 were women (62.5%), who were operated for spinal instability with the use of the MIDLF/CBT technique between 2014 and 2017. The mean time of the control MRI scan post-operation was 37 ± 25 months.

The diameter (width) of the multifidus muscles was significantly smaller in and below the operated segment. It was also decreased cranially to the stabilised intervertebral space, albeit not significantly (Tab. 1, Fig. 7).

Discussion

Drawing on recent advances in the MIDLF/CBT approach and our own extensive and successful clinical experience with it [11], the present article aimed to evaluate the significance of postoperative muscle atrophy and its variation across different spinal segments. MRI scans of 16 patients before and after the operation were analysed, during which the width of the multifidus muscles was measured at the level of the operated segment, along with the superior and inferior adjacent segments. Ultimately, findings of significant muscle reduction were obtained, suggesting probable muscle atrophy secondary to intraoperative injury. Additionally, the method we applied appears to be sufficiently reliable for indirectly assessing the volume of the multifidi, as well as other spinal muscles.

Santoni et al. introduced the CBT screw insertion approach in 2009 [3], and in 2014 Mizuno et al. first described MIDLF/CBT as a less invasive option for lumbar spine fusion [1]. This approach contains several advantages over previous techniques, especially a lower risk of nerve injury due to the mediolateral and caudocranial screw trajectory, as well as less tissue and muscle damage thanks to its medial starting point. Multiple studies have additionally pointed out that MIDLF/CBT is associated with shorter hospital stays, reduced operating time, and less blood loss, ultimately rendering patients a superior quality of life [14–18].

The multifidus muscle is one of the three most surgically significant paraspinal muscles, along with the longissimus and iliocostalis. It contributes considerably to the dynamic stability of the lumbar spine rather than its motion, which is particularly important during lumbar flexion [19]. It also has a higher CSA, rendering it an even greater force production. This suggests that if damaged, other spinal muscles are compensate for the deficit [20, 21]. We chose to analyse the multifidus width because of its unique features, as stated above, and due to the better visualisation provided by the evident fibrous cleavage between the multifidus and the longissimus sections of the sacrospinalis muscle group [21].

There are two plausible explanations for the postoperative muscular atrophy. The first is related to the use of retractors; this instrument has been reported to cause intraoperative muscle damage, both directly through surface contact pressure and indirectly by increasing intramuscular pressure, which subsequently lowers blood perfusion through the muscles. Gejo et al. noted that the retracting time correlates to muscle injury, suggesting a shorter retraction exposure is beneficial for its prevention [22].

Secondly, postoperative muscle atrophy is also linked to iatrogenic muscle denervation. The multifidus muscle is at a particularly increased risk due to its exclusive innervation by the medial branch of the dorsal ramus [4, 20, 23, 24]. In MIDLF on the other hand, a less extensive retraction and skeletisation of the paravertebral muscles is sufficient due to the mediolateral and caudocranial trajectory of the CBT screws compared to the TP ones.

Hyun et al. compared the paramedian interfascial approach (PIA) to the traditional midline approach (MA) by measuring the CSA, thickness, and width of the multifidus muscles on CT scans. In contrast with the PIA, patients undergoing the MA presented with lower multifidus CSA and muscle thickness, indicating a higher degree of muscle atrophy. Nevertheless, the authors found that the difference in width between the MA and PIA was statistically insignificant [6].

Hung et al. measured postoperative (6 months) MRI scans of a group of patients undergoing minimally invasive posterior interbody fusion with CBT screws to those of another group undergoing conventional PLIF/TP. Patients after CBT screws

Table 1. Summary of measured parameters

Variable	Pre-operation		Post-operation		Mean difference (95% CI)	P-value
	n	mean (SD)	n	mean (SD)		
Operated segment	16	57.7 (5.8)	16	54.4 (8.4)	−3.3 (−6.0, −0.6)	0.02
Middle of upper vertebra	16	52.7 (7.2)	16	51.4 (6.7)	−1.2 (−3.4, 0.9)	0.24
Middle of lower vertebra	16	64.9 (6.8)	16	59.2 (10.3)	−5.6 (−9.4, −1.9)	< 0.01
Upper adjacent segment	16	51.7 (7.1)	10	48.8 (6.0)	−1.5 (−3.5, 0.5)	0.12
Lower adjacent segment	12	69.2 (6.8)	12	61.5 (9.0)	−7.4 (−11.2, −3.5)	< 0.01

CI — confidence interval; SD — standard deviation

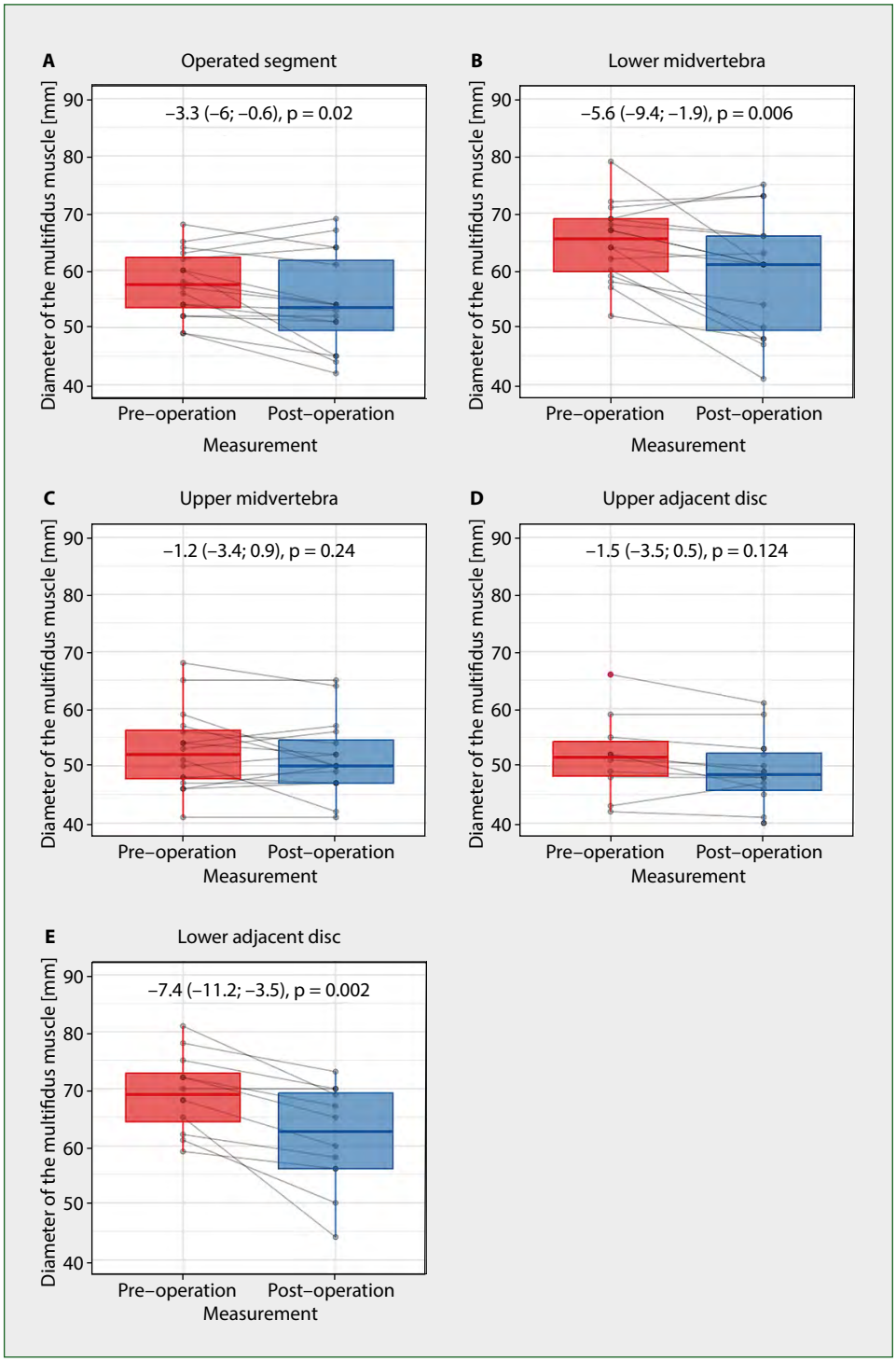

Figure 7. Summary of measured parameters

placement presented with a reduced fat infiltration ratio ($p < 0.05$), suggesting less intraoperative multifidus damage [8]. Similarly, Li et al. noted that the minimally invasive posterior lumbar interbody fusion with CBT screws has no significant impact on paravertebral muscles after evaluating the erector spinal muscle volume and fat infiltration of the operated and adjacent segments [25].

To determine postoperative muscle changes, Kameyama et al. evaluated and compared CT images of patients before and after PLIF/TP, and of those undergoing a minimally invasive lateral lumbar interbody fusion with percutaneous pedicle screws (LLIF/PPS). The results showed a marked decrease in multifidus muscle density only in the PLIF/TP group; no change in CSA of the paraspinal muscles was observed in

either group [7]. Fan et al. utilised pre- and postoperative MRI scans and correlated the CSA values and the extent of fatty infiltration of the multifidi between a minimally invasive and conventional open PLIF/TP; markedly less muscle atrophy in the minimally invasive approach was reported [10]. Moreover, Cho et al. investigated MRI and CT scans one year after patients underwent PLIF/TP at L4/5 and measured the volume of paraspinal muscles using a particular formula; the multifidus muscle volume was significantly decreased both on CT and MRI. On the other hand, the erector spinae and psoas major muscles were preserved mostly intact. Interestingly, younger patients experienced greater muscular damage [26].

Unlike evaluating postoperative muscular atrophy in open vs percutaneous minimally invasive approaches for spinal stabilisation, as was done in many of the abovementioned studies [e.g. 7, 8, 10], the comparison between MIDLF/CBT and PLIF/TP techniques bears a much closer resemblance as far as paraspinal muscles and their perioperative retraction and hypoperfusion are concerned. Given that reliable volumetric measurement of the multifidi post-MIDLF/CBT is problematic due to severe artefacts associated with the medial position of the screw heads, we had to choose a different approach to assess the muscles, which we described in our methodology.

Our results suggest the multifidus muscles of the upper adjacent segment are relatively spared in contrast to those of the operated and lower adjacent segments. This finding most probably correlates with the caudocranially oriented position of the retractor, copying the caudocranial insertion trajectory of the CBT screws, in which its pressure exerted upon the muscles (and thus their propensity for potential ischaemia) is presumably much lower in the upper parts of the incision.

Nevertheless, regardless of the postoperative changes to the multifidus muscles visible on the MRI scans, nearly 90% of patients have reported favourable outcomes for pain relief two years after surgery, and their functioning in day-to-day activities has significantly improved, as we described in our previous study on MIDLF/CBT [11]. 86.9% reported fair, good, or excellent outcomes in terms of pain relief based on MacNab score 2 years after surgery. Patients' level of function in activities of daily living improved significantly based on Oswestry Disability Index score: from 66.8 ± 9.8 before surgery to 33.9 ± 16.5 2 years after surgery ($p < 0.001$).

The strengths of our present study lie in the novelty and simplicity of the applied measuring method. Furthermore, we have achieved extensive average and median follow-up times which, in our opinion, demonstrate the long-term effect of the MIDLF/CBT technique on the multifidus muscle mass that we assessed both in and around the operated segment. This provides important additional information due to the potential risk of adjacent segment disease developing after the surgery [27].

Our study has several limitations. Firstly, its sample size is relatively small. Given the difference in the width of the multifidus muscles before and after the operation, however, our results were statistically significant. Secondly, the postoperative follow-up period was of various lengths, i.e. patients experienced different times for recovery when evaluated on the control MRI scan. And thirdly, the artefacts originating from the heads of the CBT screws did not allow for an elaborate CSA or volumetric assessment of the multifidus muscles, leading us to decide upon a novel approach to measure their maximum bilateral diameter.

Clinical implications and future directions

The width of the multifidus muscle mass as a marker of its atrophy is significantly reduced after spinal stabilisation with the MIDLF/CBT technique years after the operation. The biggest changes were observed in and immediately below the operated segment; milder atrophy also occurred in the superior adjacent segment.

These results indicate that the MIDLF/CBT approach, despite its anticipated lesser invasiveness, still noticeably impacts the vitality of the multifidus muscles, and thus potentially hampers postoperative rehabilitation and recovery. Measuring the width of the multifidus muscles appears to be a reliable method for their pre- and postoperative assessment. Further investigation and comparison to other spinal stabilisation techniques is warranted. Also, a functional electromyographic examination of the paravertebral muscles before and after surgery would be of benefit.

Article information

Authors' contributions: *AS, AV collected and analysed data, co-wrote manuscript; FS revised manuscript with significant amendments; MF operated on patients and collected data; PH revised manuscript; PL operated on patients, collected data, and revised manuscript; PW statistically analysed data on patients.*
Ethical approval: *The present study conforms to the guidelines issued in the 1964 Declaration of Helsinki. This study was approved by the jnstitutional Ethics Committees (Ethics Committees of University Hospital Kralovske Vinohrady and Tomas Bata Regional Hospital Zlin).*
Consent to participate: *Informed consent was obtained from all individual participants included in the study.*
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Conflicts of interest: *None.*

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RESEARCH PAPER

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Safety and efficacy of short percutaneous fixation in AO3 and AO4 lumbar fractures: a single-centre experience of 35 cases

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ABSTRACT

Introduction. Spinal fractures with subsequent bone fragment dislocation are among the injuries most feared by patients and physicians. The surgical strategy is tailored to the individual patient's characteristics and often consists of pedicle instrumentation with rod-screw systems. Short instrumentation has been associated with worse spinal correction and increased complications. However, recent studies have suggested similar results in terms of kyphosis correction and the maintenance of sagittal alignment compared to longer instrumentation.

Material and methods. This single-center retrospective study was conducted between January 2018 and April 2021. We included 35 single lumbar burst fractures AO Spine grade A3 or A4 with evidence of intra-canal fragments. Patients underwent minimally invasive percutaneous posterior lumbar instrumentation with pedicle screws. Patients received short segmental fixation involving only one level above and below the fractured vertebra.

Results. An immediate postoperative computed tomography (CT) scan demonstrated a significant reduction in vertebral kyphotic deformation (11.7° ± 1.6 vs 16.7° ± 5, p<0.001) and sagittal Cobb angle (9.8° ± 1.3 vs 11.7° ± 1.5, p < 0.001). The correction was slightly reduced but remained significant at 12 months for both kyphotic (12.3° ± 1.4, p = 0.03) and sagittal Cobb (10.3° ± ± 0.9, p = 0.04). Upper lumbar vertebrae showed even larger correction indices compared to lower lumbar segments. No implant failure or screws pullout was seen at the last follow-up.

Conclusions. Short spinal fixation is a safe and effective treatment of complete and incomplete burst fractures with posterior bone fragment dislocation. All included patients fared well and achieved good kyphotic correction with no perioperative or long-term complications.

Keywords: spine, trauma, short fixation, posterior fixation

(*Neurol Neurochir Pol 2025; 59 (1): 49–55*)

Introduction

spinal fractures with subsequent bone fragment dislocation are among the injuries most feared by patients and physicians. Their consequences can be devastating, ranging from mild pain and discomfort to paralysis and death [1–3]. Incomplete and complete burst fractures affect millions of patients every year, accounting for c.10–20% of all spine fractures, with c.25% occurring at the lumbar level [1, 4].

Lumbar burst fractures result in spinal instability and possible nerve damage; they often require surgery to achieve sufficient decompression, vertebral height restoration, and

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stability while at the same time correcting and avoiding kyphosis and the onset of neurological deficits. Traditionally, posterior fixation with rod-screw systems has been widely used for the treatment of these fractures. More recently, the minimally invasive percutaneous pedicle screw placement technique has been advocated because it involves smaller incisions, less bleeding, less dissection of paraspinal muscle tissue, less pain, and rapid postoperative recovery [5, 6].

The length of spinal fixation is still a matter of debate, with some studies demonstrating a more favorable course with longer instrumentations [7–10], while recent studies have reported similar results in terms of kyphotic correction and long-term complications, but with the additional advantage of reduced operating time as well as a lower risk of screw malposition and related neurological complications observed with shorter constructs. Short-segment stabilization has also shown faster pain relief, less tissue destruction than long-segment, and good biomechanical stability [11–19].

This retrospective study analyzed the clinical and neuroradiological outcomes of patients undergoing a minimally invasive percutaneous short posterior vertebral fixation, with additional laminectomy in selected cases.

Material and methods

Ethical considerations

Ethical approval was not required for this study. All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants.

Design of study

This was a single-center retrospective study conducted between January 2018 and April 2021 in patients treated for traumatic lumbar fractures with significant intracanal fragments at the Neurosurgery Unit, Vito Fazzi Hospital, Lecce, Italy. Of the 142 patients treated for spinal fractures during the period in question, 35 fulfilled our enrollment criteria and were included in the final analysis.

We included single lumbar burst fractures classified according to the AO Spine classification system [20] as grade A3 or A4. Neurological status was assessed using the American Spinal Injury Association International Standards for Neurological Classification of Spinal Cord Injury (AIS) [21]. Included patients shared normal or only slightly impaired neurological function (AIS grades D or E) and underwent short posterior instrumentation with percutaneous polyaxial pedicle screws insertion after exclusion of the need for anterior approaches assessed by means of the Load Sharing Score (LSS) [22].

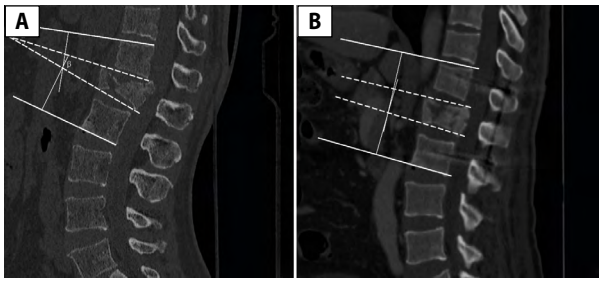

Figure 1. Example of sagittal measurement of kyphotic deformation following burst fracture. L1 AO A4 fracture before (**A**) and after (**B**) vertebral instrumentation. Dotted lines define vertebral kyphotic deformation angle (alpha — α), whereas solid lines define sagittal Cobb angle (beta — β)

Patients were included if their LSS score was > 7. Posterior wall failure and an intracanal fragment causing a reduction of at least 15% of the vertebral canal diameter were two of the inclusion criteria. Pedicle screws were interconnected to posterior rods to exert a lordotic force to restore the vertebral height and correct the spinal kyphosis. No screws were placed in the affected vertebrae.

Patients were excluded if they presented with severe neurological deficits (AIS grades A, B, or C), multilevel vertebral fractures, osteoporotic or pathological fractures, or a previous history of lumbar spine instrumentation.

Clinical and radiological evaluation

Demographic data, as well as clinical details and the entity of neurological impairment, were carefully recorded after patient admission. Data relevant to the study was retrieved from medical records. Patients were clinically followed up at one, eight, and 12 months.

Upon hospital admission, patients received baseline computed tomography (CT) and magnetic resonance imaging (MRI). The key radiological features included in the final analysis were the vertebral height and deformity of the spine before and after surgery, as well as the long-term implant integration and integrity. Figures 1 and 2 depict the pre-operative diagnostic workout and the calculation of spinal canal compression and peri-operative angular radiological outcomes.

Spinal alignment was assessed using the regional kyphosis angle between the upper plate of the overlying vertebra and the lower plate of the vertebra underlying the fracture (here named the sagittal Cobb angle) and the kyphotic deformation of the fractured vertebra, measured as the angle between the upper plate and the lower plate of the injured vertebra (Fig. 1). The average mid-sagittal canal diameter for the two adjacent vertebrae, one above and one below the fractured vertebra, was considered to be the normal mid-sagittal diameter of the fractured vertebra. The percentage of spinal canal compromise at presentation was calculated using the method described by Hashimoto et al. [23] set out in Figure 2.

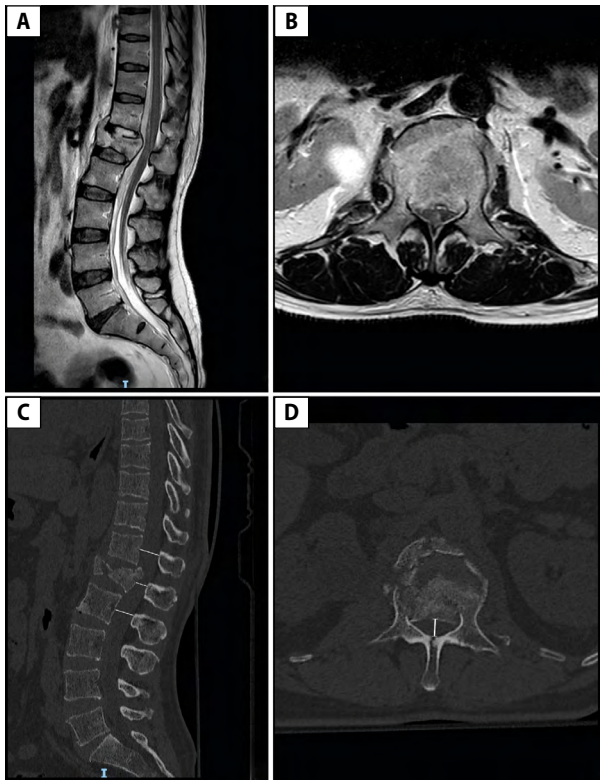

Figure 2. Pre-operative radiological evaluation. All included patients received pre-operative magnetic resonance (MRI, panels **A**, **B**) and computed tomography imaging (CT, panels **C** and **D**). Extent of maximal spinal canal compression has been systematically evaluated on CT images. Maximal reduction in canal diameter was defined as distance from posterior aspect of bone fragment and anterior wall of posterior arch on a midsagittal location, as shown in panel **D**. This measure was compared to mean canal diameter measured at upper and lower levels (as depicted in panel **C**). All measures were performed on axial CT slices. See text for further details

All patients received an additional CT scan within six days after surgery. Two independent neuroradiologists used sagittal, coronal, and axial slices with bone windows to detect screw positioning, angular changes, and early complications. Long-term follow-up was conducted using plain 2-projection X-rays at 8- and 12-month follow-ups to address late kyphotic correction angles and the occurrence of complications (Fig. 3).

Statistical analysis

Categorical variables are reported as absolute numbers and percentages, whereas continuous variables are reported as the median and interquartile range (IQR). The Kolmogorov-Smirnov and Skewness tests were used to assess the normality of the distribution of continuous variables. Between-group differences evaluation and unadjusted univariate analyses were performed using the t-test or Mann-Whitney U-test in accordance with normality and the Chi-square or Fisher's exact test, where appropriate. The results of all tests are presented as p-values and statistical significance was set as a probability value of 0.05 (95% confidence interval). Statistical analysis was performed using STATA Statistical Software 2015: Release 14 (StataCorp LLP, College Station, TX, USA).

Results

Overall characteristics

A total of 35 patients (23 males and 12 females) fulfilled the inclusion criteria for this study. The mean age at presentation was 51.4 years (range 12.8–80.8). Road accidents were the most common cause of lumbar trauma (n = 19, 54%), followed by falls (n = 16, 46%).

All enrolled patients suffered moderate to severe lumbar pain and tenderness to compression of spinous processes. In

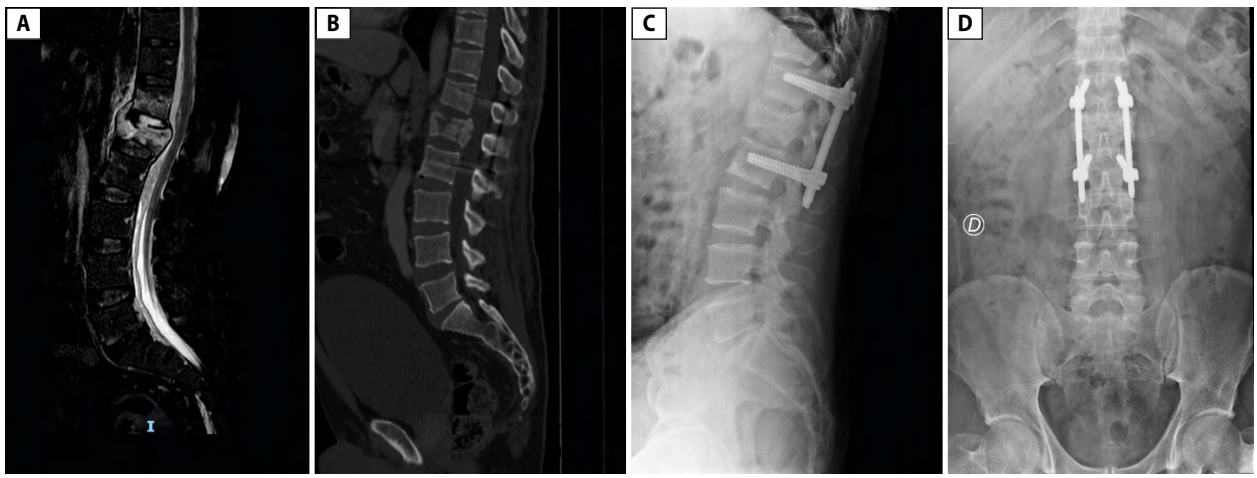

Figure 3. Follow-up of radiographical changes after short spinal instrumentation in a 56-year-old man with an AO A4 L1 fracture due to a road accident. **A**. Preoperative STIR MRI imaging; **B**. Immediate postoperative CT scan; **C**. 12 months later, lateral X-ray follow-up; **D**. 12-month anteroposterior X-ray follow-up

six cases, the pain was irradiated with a radicular pattern to the inferior limbs. Five patients showed mild sensory deficits with a radicular distribution. Only two patients showed initial neurological deficits (motor weakness and sphincteric dysfunction) and were classified as AIS grade D.

The most affected level was L1 (62.8%), followed by L2 (25.7%), L3 (5.7%), L4 and L5 (2.8% each). See Table 1 for a summary of demographic and lesion characteristics. We observed a mean post-traumatic vertebral kyphotic deformation of 16.7° ± 5 and a mean sagittal Cobb angle of 11.7° ± 1.5. This value was slightly inferior for L1–L2 lumbar vertebrae (10.3° ± 2.3). The vertebral canal impaction ranged from 15-73% with a mean of 36.5% ± 12.5%. Baseline MRI demonstrated initial radiological signs of damage to the conus medullaris in 11 cases (31%), corresponding to patients with L1 or L2 fractures with severe dislocation of posterior fragments (mean canal compression of 49% ± 15).

Radiographic outcomes

An immediate (obtained within six days) postoperative CT scan demonstrated a significant reduction in vertebral kyphotic deformation (11.7° ± 1.6 vs 16.7° ± 5, $p < 0.001$) and sagittal Cobb angle (9.8° ± 1.3 vs 11.7° ± 1.5, $p < 0.001$). The correction resulting from posterior instrumentation was sustained over time, although slightly decreased, and remained significant at the 12-month follow-up for both kyphotic deformation (12.3° ± 1.4, $p = 0.03$) and Cobb angle (10.3° ± 0.9, $p = 0.04$). The overall radiological outcomes are set out in Table 2. We performed a subgroup analysis including only L1–L2 fractures (n = 31, 88% of the entire series). In this subgroup, the extent of the correction was larger than that observed in the entire series (3.4° ± 1.9; $p < 0.001$ relative to the pre-operative values) and was well sustained at the final follow-up (4.5° ± 2; $p < 0.001$). Patients requiring laminectomy shared a mean 52% ± 10% reduction in vertebral canal diameter. After surgery, these patients gained significant dural sac decompression. At the final follow-up, we did not experience implant failure or screws pullout.

Table 1. Baseline characteristics of patients included in this study

Overall population		Patients (n = 35)
Demographics	Age	51.4 ± 19.7
	Age > 50	21 (60)
	Male	23 (65.1)
	Female	12 (34.2)
Fractures AO grade	AO A3	17 (48.5)
	AO A4	18 (51.3))
Aetiology	Road accident	19 (54)
	Fall	16 (46)
Location	L1	22 (62.8)
	L2	9 (25.7)
	L3	2 (5.7)
	L4	1 (2.8)
	L5	1 (2.8)
Intracanal fragment	Severe (> 25%)	17 (48)
	Moderate (< 25%)	18 (52)
	Mean canal compression	36% ± 17
	Mean compression in severe	52% ± 10
Damage	Conus medullaris	11 (31)
Symptoms	Lumbar pain	35 (100)
	Irradiated pain	6 (17.1)
	Sensory disturbances	5 (14.2)
	Motor weakness	2 (5.7)
	Sphincteric dysfunction	2 (5.7)
Clinical outcome at last follow up	Improved	32 (91.4)
	Stable	3 (8.5)
	Worse	0 (0)
Surgery	Short posterior fixation	35 (100)
	cement augmented	10 (28)
	+ laminectomy	17 (48.5)
	Mean hospital stay (d)	5 ± 2.5

Continuous variables are expressed as mean ± standard deviation or median [range], whereas dichotomic variables are expressed as frequency (%); d — days; AO — AO spine classification of thoracolumbar fractures

Table 2. Radiological changes after short lumbar posterior fixation

Timepoint	Vertebral kyphotic deformation (n = 35)	Sagittal Cobb angle (n = 35)	Sagittal Cobb angle — upper lumbar (L1–L2, n = 31)
Pre-operative	16.7° ± 5	11.7° ± 1.5	10.3° ± 2.3
Postoperative	11.7° ± 1.6	9.8° ± 1.3	3.4° ± 1.9
p-value	< 0.001	< 0.001	< 0.001
Pre-operative	16.7° ± 5	11.7° ± 1.5	10.3° ± 2.3
12-month follow up	12.3° ± 1.4	10.3° ± 0.9	4.5° ± 2
p-value	0.03	0.04	< 0.001

Continuous variables are expressed as mean ± standard deviation

Clinical outcomes

Twelve months after surgery, we recorded a 91.4% improvement in presenting symptoms (Tab. 1). Lumbar pain without leg irradiation was consistently the first symptom to recede following posterior instrumentation. Pain irradiating to the lower limbs and segmentary motor weakness started to improve later during the follow-up and had completely resolved at eight months. Sensory and sphincteric disturbances had a slower course. Sensory disturbances showed complete resolution only at the final follow-up in three cases while remaining stable in two patients. Similarly, patients presenting with sphincteric disturbances did not achieve any improvement at the final follow-up.

Discussion

Surgery is the mainstay of treatment for the correction of lumbar burst fractures with neurological deficits. Over recent decades, posterior decompression with pedicle screw fixation has played an increasing role, overcoming the limitations of laminar hooks and allowing for good rigid fixation [24]. The advantages of posterior instrumentation include immediate spinal canal decompression, intracanal fragments identification, and ligamentotaxis [25]. However, the differences between long and short posterior instrumentation are not obvious [26, 27].

Traditionally, pedicle screws were only inserted above and below the injured vertebral body. Although this surgical procedure is known to save the segmental motion of the vertebral body, poor surgical outcomes such as spinal non-union, implant failure, and increased kyphosis have been reported [28, 29]. Longer posterior instrumentation, on the contrary, is generally perceived as achieving a better distribution of biomechanical stress across the fused metamers and ensuing complications [27]. However, the notion of poorer surgical outcomes obtained with short instrumentation has been recently questioned [27], and recent works have reported similar results in terms of kyphosis correction, maintenance of sagittal alignment, and complications rate attained by both surgical strategies [11]. Moreover, we must remember that the biomechanical needs of a lumbar burst fracture are mainly relevant only in the first year after the traumatic event. Once spinal fixation has been achieved, long constructs exert a toll in terms of spinal stiffness and patient compliance [27].

This study presents our experience with short instrumentation of burst lumbar fractures using polyaxial screws. Some authors have advocated a slightly better outcome in patients implanted with monoaxial screws in terms of restoration of vertebral height [30]. However, the same study observed similar vertebral kyphotic angles (N.B. named Cobb angle in the original publication), admitting a prominent role played by the rods in achieving a good kyphosis correction.

In accordance with previous reports [11–19], we observed good immediate correction of the kyphosis resulting from vertebral fracture. Specifically, we recorded a satisfactory correction of kyphotic deformation at the level of the fractured vertebra and a reduction of the sagittal kyphotic Cobb angle. The reported immediate postoperative value of 9.8° ± 1.3 for sagittal Cobb angle refers to the whole series. Owing to the physiological lordosis of lower lumbar levels (L3–L5), burst fractures at these levels contributed to most of the overall kyphotic deformation.

We, therefore, performed a subgroup analysis including only L1–L2 fractures (88% of the entire series) and found an even larger correction index at this level. The extent of the correction is comparable to that shown in reports of posterior fixation with the inclusion of the fractured level [11] and fixation followed by anterolateral fusion (about 3° immediate post-op) [27]. It has been traditionally argued [8] that, despite immediate satisfactory results, in the long term, there could be loss of correction and fixation failure due to the four-pedicle screw fixation (being a double plane fixation) inducing simultaneous quadrilateral and suspension effects [16]. We did observe a slight decrease in the correction of both kyphotic angles; however, this correction was still significantly sustained at the 12-month follow-up and was attested at 4.5°. We note that Todeschi et al. reported an 8.5° sagittal Cobb angle at 24 months following short posterior fixation + anterolateral fusion [27].

In addition to this, we did not observe screws pullout or implant failure, although the relatively short follow-up might have been insufficient to detect late complications or further loss of correction. Importantly, no intraoperative complications, CSF leaks, screw malpositions, or implant pullouts were recorded at the final follow-up. Although patients with severe neurological deficits were excluded from this series, we observed a good rate of resolution of presenting symptoms, except for three cases with L1 burst and conus medullaris damage, whose symptoms remained stable at the final follow-up.

Limitations

The limitations of this study include its retrospective design, the lack of a control group, and the relatively short follow-up. Due to our strict inclusion and exclusion criteria, the number of cases meeting our requirements was relatively small. Further investigations are therefore necessary to evaluate longer follow-ups and determine the long-term efficacy of these interventions in treating lumbar burst fractures.

Conclusions

Given the aforementioned limitations, this experience with short instrumentation of complete and incomplete lumbar fractures suggests that limiting spinal instrumentation to one

level above and below is a safe and effective treatment. Patients experience an almost global resolution of symptoms, while no peri-operative complications, late implant failure, or screws pullouts were recorded. All our included patients fared well.

These results suggest that short instrumentation might not be inferior to longer lumbar spine fixation, although further, larger studies are needed to confirm this.

Article information

Data availability statement: *The authors confirm that the data supporting the findings of this study is available within the article, figures, and tables.*

Ethics statement: *All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.*

The ethical review process and approval by our ethics committee were not required for the present study because it is a retrospective study on patients that required a life-saving intervention. Furthermore, the research data analysis does not affect the participants and their medical care.

Authors' contributions: *Conceptualization: PDD, AM; Data collection: PDD, RP, DC, MR, AM; Statistical analysis: PDD; Manuscript drafting: PDD, RP; Revision and final approval: MR, AM.*

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Screening for *PRKN* and *PINK1* mutations in Ecuadorian patients with early-onset Parkinson's Disease

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ABSTRACT

Introduction. Early-onset Parkinson's Disease (EOPD) is a neurodegenerative disease with the clinical manifestation of movement symptoms before the age of 50. Patients with EOPD frequently have a positive family history of disease, with bi-allelic loss of function mutations in *PRKN* and *PINK1* as the most common genetic cause. To date, the majority of genetic studies have been conducted on patients with European ancestry, limiting the understanding of the genetic heterogeneity of EOPD across populations. The aim of this study was to screen the *PRKN* and *PINK1* genes in an Ecuadorian EOPD cohort, and improve the understanding of the genetic profile of patients in this population.

Material and methods. Seventy unrelated patients with EOPD and with an average age at onset of 42.6 ± 5.6 years were recruited at the Hospital Eugenio Espejo in Quito, Ecuador, and screened for the presence of *PRKN* and *PINK1* single nucleotide and copy number variations.

Results. Sanger sequencing identified six *PRKN* variants, and five resulted in nonsynonymous amino acid substitutions. Seven *PINK1* variants were identified: four nonsynonymous, and three common (MAF > 1%), among the EOPD cohort. Multiplex ligation-dependent probe amplification (MLPA) identified three carriers with *PRKN* copy number variants. Overall, across the series, two patients carried pathogenic homozygous deletions of exons 3 and 4.

Discussion. Gaining insights into the genetics of EOPD in Latin America is important. In this study, we have identified two carriers of pathogenic *PRKN* copy number variants in a relatively large group of Ecuadorian patients with EOPD. Additional, familial, early-onset and sporadic PD studies are warranted to further expand the knowledge base regarding Latin American populations.

Keywords: Parkinson's Disease, EOPD, genetics, risk factors

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Introduction

Parkinson's Disease (PD) is a common progressive neurodegenerative disorder, and its clinical manifestation is a combination of motor (bradykinesia, rigidity, tremor, postural instability) and non-motor (sleep disorders, smell disturbances, neuropsychiatric symptoms, dysautonomia, sensory abnormalities) features [1–4]. As the signs of preclinical PD are non-specific and often go unreported by patients, there is an urgent need to find biomarkers to identify individuals at risk. Therefore, studying the genetic architecture of PD may better our understanding of early pathophysiology and identify preclinical patients for therapeutic intervention trials [5].

The average age at onset of motor symptoms in PD is 60 years. However, up to 10% of patients develop their first clinical motor symptom before the age of 50 years (the definition of early-onset PD, EOPD) [6, 7]. Compared to patients with later onset PD (> 50 years), EOPD patients more frequently have a positive family history (7% vs 20%) and are diagnosed with monogenic forms of PD [6, 8]. Additionally, the genetic landscape differs, with recessive pathogenic variants in *PRKN* and *PINK1* being most common, as opposed to pathogenic heterozygous variants in *LRRK2* and *VPS35* which are more common in later onset PD patients [1, 9].

The majority of genetic studies on EOPD have focused on patients with European ancestry, and very few have investigated the genetics of EOPD in South America. In a study from 2010, Marder et al. demonstrated that *PRKN* variants were almost three times as frequent in Hispanic populations compared to white non-Hispanic populations with EOPD [10]. This was consistent with a previous Latin American study, which described a significant enrichment in copy number variants (CNV) in the known PD genes, specifically *PRKN* [11]. In a study including 12 Ecuadorian and 26 Colombian patients with EOPD, only one variant in *PRKN* was identified, and this was within the Colombian EOPD cohort [12].

Underrepresented populations should be studied, as there may be population-specific variations in gene variation. Investigation of Hispanic populations would lead to greater understanding of the pathophysiology of PD and contribute to an inclusive understanding of the disease's clinical heterogeneity. To address the paucity of information regarding PD genetics in Latin America, we aimed to characterise variations in the *PRKN* and *PINK1* genes in 70 unrelated patients with EOPD from Quito, Ecuador.

Material and methods

Whole blood was collected from 70 unrelated patients with EOPD (33 females, 37 males) from Hospital Eugenio Espejo in Quito, Ecuador. The patients were from central and northern Ecuador and self-reported as being either mestizo or of indigenous descent. The average age at diagnosis was 42.6 ± 5.6 years (24–49), and the average age at blood collection was 54.3 ± 10.1 years (31–79). All individuals provided written informed consent and were approved by the local Institutional Review Board (IRB) and Mayo Clinic IRB (1087–98). DNA was extracted using a QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany) following the standard protocol. Bidirectional Sanger sequencing was performed on all coding exons of *PRKN* and *PINK1* using custom primers designed using human genome build GRCh38/hg38. All PCR products were purified using Agencourt Ampure XP and CleanSeq purification systems performed on the Beckman Coulter Biomek Fxp automated workstation (Beckman Coulter Life Sciences, Indianapolis, IN, USA). Sequence chromatograms were visualised using Seqscape Software v3.0 (Thermo Fisher Scientific, Waltham, MA, USA). For CNV analysis, we used MLPA version P051 Parkinson mix 1 and performed the analyses using Coffalyser.Net™ (MCR Holland, Netherlands). Microsatellite haplotyping was performed using 10 microsatellite markers (D6S255, D6S437, D6S1581, D6S1579, D6S1550, D6S253, D6S305, D6S1599, D6S1277, D6S386) previously described by Pineda-Trujillo et al. [13]. PCR conditions followed the standard protocol, and allelic sizes were determined using a Thermo Fisher Scientific Applied Biosystems DNA analyser 3730xl and GeneMapper Software 6 (Thermo Fisher Scientific).

Results

Sanger sequencing for 70 patients identified six *PRKN* and seven *PINK1* variants (Tabs. 1 and 2). All *PRKN* variants identified were nonsynonymous, and two of them *i.e.* p.S167N and p.V380L (rs1801474 and rs1801582, respectively) were common (MAF > 1%) in the Ecuador EOPD cohort. Of the seven coding variants in *PINK1,* four were nonsynonymous, and three were common (MAF > 1%). The PINK1 p.Q115L (rs148871409) carrier also carried two other *PINK1* variants *i.e.* p.A340T (rs3738136) and p.N521T (rs1043424), both common.

MLPA analysis identified three patients with *PRKN* CNVs. Two patients, aged 24 and 33, had homozygous deletions of exons 3 and 4. One patient, aged 47, was observed with heterozygous duplication of exons 3 and 4. Sanger sequencing did not identify any variants within PRKN for these three patients with PRKN CNVs. Microsatellite haplotyping identified a shared haplotype between the two unrelated patients carrying homozygous deletion of exons 3 and 4.

Of the 70 EOPD patients screened, two were found to have monogenic PD explained by our study. Both of these patients carried homozygous deletions of PRKN exons 3 and 4, accounting for ~3% of the cohort.

Discussion

Seventy patients with EOPD of mestizo and indigenous descent, from Hospital Eugenio Espejo, Quito, Ecuador, were screened to identify variations present in *PRKN* and *PINK1*.

Table 1. *PRKN* single nucleotide polymorphisms identified within Ecuadorian EOPD cohort

Chr: position	SNP ID	Exon	Amino Acid	Geno-types	Major	Het	Minor	MAF (%)	GnomAD v4.1.0 MAF (%)			CADD--score	ClinVar
									Admixed American	African/ /AA	European (non--Finnish)		
Single nucleotide polymorphisms													
6:162201165	rs1801474	4	S167N	G > A	42	19	7	24.26	39.10	7.20	1.70	14.1	Benign
6:161785844	rs114696251	7	Y267H	T > C	69	1	0	0.71	0.02	0.23	0.0001	27.0	VUS
6:161785806	rs149433924	7	H279H	C > T	69	1	0	0.71	0.02	0.001	0.03	0.51	Likely benign
6:161548880	rs1460011098	9	E353K	G > A	69	1	0	0.71	0.002	0.000	0.002	20.7	VUS
6:161386823	rs1801582	10	V380L	G > C	63	6	1	5.71	13.11	17.43	16.58	0.69	Benign
6:161350195	rs949479970	12	M434I	G > T	69	1	0	0.71	0.00	0.003	0.00025	28.9	VUS
Copy number variants													
		3		Duplication		1		1.43					
		3		Deletion			2	2.86					
		4		Duplication		1		1.43					
		4		Deletion			2	2.86					

MAF — minor allele frequency; gnomAD — MAF obtained from version v4.1.0; AA — African American; VUS — variant of uncertain significance. CADD scores were obtained from version GRCh38-v1.7

Table 2. *PINK1* single nucleotide polymorphisms identified within Ecuadorian EOPD cohort

Chr: position	SNP ID	Exon	Amino Acid	Geno-types	Major	Het	Minor	MAF (%)	GnomAD v4.1.0 MAF (%)			CADD-score	ClinVar
									Admixed American	African/ /AA	European (non--Finnish)		
1:20633728	rs1557559211	1	G60G	G > A	69	1	0	0.71	0.002	0.00	0.00	14.45	N/R
1:20633737	rs45530340	1	L63L	C > T	51	18	1	14.29	14.93	6.56	19.84	11.92	Benign
1:20633892	rs148871409	1	Q115L	A > T	69	1	0	0.71	2.40	0.86	5.48	18.63	Benign
1:20645618	rs3738136	5	A340T	G > A	57	11	2	10.71	8.66	1.48	4.59	9.67	Benign
1:20648554	rs45499398	6	D391D	T > C	69	1	0	0.71	0.33	3.62	0.005	5.09	Benign
1:20649169	rs115477764	7	E476K	G > A	69	1	0	0.71	0.34	3.79	0.01	5.53	Benign
1:20650507	rs1043424	8	N521T	A > C	44	20	6	22.86	23.07	25.98	27.83	16.93	Benign

MAF — minor allele frequency; gnomAD — MAF obtained from version v4.1.0; AA — African American; N/R — not reported; VUS — variant of uncertain significance. CADD scores were obtained from version GRCh38-v1.7

Together, the encoded enzymes mediate a critical mitochondrial quality control (mitophagy) that is lost in disease [14]. PRKN p.Y267H (rs114696251) was identified in one patient with EOPD in a heterozygous state, and although this variant was formerly categorised as a variant of uncertain clinical significance (ClinVar, VCV000649511.5) [15], this substitution was observed in a Taiwanese patient with EOPD [16], and functionally it restructures the RING1 domain of the Parkin protein, leading to the loss of E2 coenzyme binding and inhibiting the translocation of Parkin to the mitochondria [17]. Two common *PRKN* variants, p.S167N and p.V380L (rs1801474 and rs1801582, respectively), have been reported to be benign in various populations. Within our EOPD cohort, rs1801474 and rs1801582 MAF were 24.64% and 7.64% respectively. Neither of these common *PRKN* variants were functionally impaired [18, 19].

PINK1 p.Q115L (rs148871409) had a Combined Annotation Dependent Depletion (CADD) score of 21.3 and was three times less frequent in the Ecuadorian patients compared to the gnomAD (Genome Aggregation Database) Admixed American population. The carrier bearing p.Q115L also carries two common (MAF > 1%) *PINK1* variants, (rs3738136; p.A340T) and (rs1043424; p.N521T), and has an age at onset of 31 years. Although predicted to be benign, p.Q115L reduces PINK1 kinase activity, while rs3738136 and rs1043424 showed only minor functional defects, if any [18, 20].

Two patients carried a homozygous deletion of *PRKN* exons 3 and 4, and one patient carried a heterozygous duplication of *PRKN* exons 3 and 4. *PRKN* exon 3 encodes the linker domain and exon 4 encodes the RING0/unique Parkin domain thought to mediate phospho-binding on damaged mitochondria [21]. A homozygous deletion of both exons leads to a loss of function for the PRKN protein, interfering with its structure and disrupting its ability to tag damaged mitochondria for degradation. The duplication encompassing exons 3 and 4 observed in one patient could be a heterozygous joint duplication on one allele, or one exon on each respective allele that would result in a compound heterozygous status. Additional screening of family members would inform as to the heterozygosity status of the two duplications, *i.e.* same allele or compound heterozygous.

The use of advanced single-strand or ultra-long-read sequencing technologies enables the detection of duplications by allowing long reads to span entire exons, capturing both the original and duplicated exon in a single read. Additionally, long-read sequencing supports allele phasing, which helps to determine whether the duplicated exons are on the same or different chromosomes, thereby clarifying whether the duplication is homozygous or heterozygous. In patient specimens, biochemical measurements of protein levels and enzymatic activity would provide definitive answers regarding PRKN expression and function [22].

Our presented study examined a relatively large cohort of patients with EOPD from Ecuador, a population into which there has been limited genetic research. The limitations of this study include the deep longitudinal clinical phenotype data, and large population-based genetic characterisation of patients and controls from Ecuador. A recent genome wide association study exploiting multi-ancestry sample series for association of common variants has highlighted the need for studies encompassing diverse populations [23]. Further studies, at both the familial and population levels, are warranted to expand our understanding of the genetic profile of EOPD in Latin American populations.

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Authors' contributions

TF performed genetic screening and composed/revised manuscript.

RP performed genetic screening and composed/revised manuscript.

AS-B performed genetic screening and assisted in manuscript composition.

AS obtained specimens, revised and approved final version of manuscript.

RW performed genetic screening and assisted in manuscript composition.

SK-H provided input as clinical geneticist, revised and approved final version of manuscript.

WS performed clinical examinations on patients, collected specimens, revised and approved final version of manuscript.

JD provided intellectual input, revised and approved final version ofmanuscript.

OR conceptualized this study, led genetic analysis and advised manuscript composition.

GJ-K collected and processed specimens in Ecuador, provided intellectual input, revised and approved final version of manuscript.

FA organised and coordinated study in Ecuador, obtained IRB approval, performed clinical examinations on patients, collected specimens, revised and approved final version of manuscript.

ZW conceptualised this study, obtained IRB approval, coordinated study logistics, obtained funding, and revised/edited manuscript.

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Conflicts of interest

TF: no disclosures.

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RESEARCH PAPER

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Levodopa and dopamine agonist phobia in Parkinson's Disease — does it really matter? A survey on treatment patterns in Polish tertiary centres

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ABSTRACT

Aim of study. To investigate the treatment strategies of Parkinson's Disease (PD) among movement disorder specialists in tertiary centres in Poland, and how literature warnings (levodopa and dopamine agonist phobia) have influenced their practice.

Material and methods. The survey was conducted between 30 November, 2020 and 18 October, 2021, in four Polish tertiary referral centres for PD (two in Gdansk, one in Sosnowiec, and one in Warsaw). Movement disorder specialists collected information on the treatment of 494 consecutive patients diagnosed with PD. The questionnaire included information on the age of the patient, the duration of PD, the Hoehn&Yahr (H&Y) stage, comorbidities, pharmacotherapy, and advanced PD therapies i.e. deep brain stimulation (DBS), levodopa/carbidopa intestinal gel (LCIG), and continuous subcutaneous apomorphine infusions (CSAI).

Results. Levodopa was the most prescribed medication (n = 465/494), followed by dopamine agonists (n = 292/494). The mean dose of levodopa was 810.58 ± 473.11 mg, and it did not exceed 2,000 mg/d in 98.5% of patients. The mean doses of dopamine agonists used were relatively low (ropinirole 8.64 ± 3.94 mg, pramipexole base 1.76 ± 0.65mg). Amantadine (n = 197/494) and MAO-B inhibitors (n = 202/494) were prescribed less frequently. Catechol-o-methyltransferase (COMT) inhibitors (n = 7/494) and anticholinergics (n = 4/494) were rarely used in the studied population. Complex polytherapy with three or more PD medications was the most often used treatment strategy (n = 223/494).

Conclusions and clinical implications. Levodopa remains the gold standard in PD treatment in tertiary movement disorder centres in Poland. Dopamine agonists formed the second most frequently prescribed group of medications; however, the observed low dosages of both levodopa and dopamine agonists may suggest a cautious approach by clinicians. Amantadine and MAO-B inhibitors (mainly rasagiline) constituted important elements of PD pharmacotherapy. The high prevalence of complex polytherapy underlines the complexity of PD management, the cautious use of single medication at high doses, and the need for personalised therapeutic strategies.

Keywords: Parkinson's Disease, levodopa phobia, dopamine agonist phobia, prescription patterns

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Introducion

Parkinson's Disease (PD) is a progressive neurodegenerative disease characterised by motor and non-motor symptoms [1]. Pharmacotherapy plays a critical role in managing PD, significantly enhancing both the quality and length of a patient's life [2]. Currently available treatments have only symptomatic effects, with most therapeutic strategies focusing on improving motor symptoms. Historical shifts in treatment approaches, driven by concerns over levodopa-related complications raised two decades ago (known as 'levodopa phobia') and the more recent 'dopamine agonist phobia', may influence current practice [3, 4]. Motor symptom management, such as bradykinesia, tremor, rigidity and gait impairment, is mostly based on dopaminergic medications, such as levodopa (LD) with a dopa decarboxylase inhibitor and non-ergot dopamine agonists (DA) such as ropinirole, pramipexole, piribedil, apomorphine, and rotigotine. Additionally, MAO-B inhibitors (rasagiline, selegiline), COMT inhibitors (entacapone being the only one available in Poland), amantadine and anticholinergics (biperiden, pridinol and trihexyphenidyl) contribute to the therapeutic landscape [5–11]. Advanced therapies, which are specialised treatment options for patients whose symptoms cannot be effectively managed with oral medications, include deep brain stimulation (DBS), levodopa/carbidopa intestinal gel (LCIG), continuous subcutaneous apomorphine (CSAI), and recently continuous subcutaneous levodopa-carbidopa infusions. These therapies are available and fully reimbursed in Poland, although the last-named one was introduced only after the completion of data collection for our study. The complexity of PD management is further compounded by the multitude of available therapeutic options, their adverse effects and interactions, along with inevitable progression of the disease. Furthermore, the availability and reimbursement of PD medications vary in Poland, with some medications being not licensed (e.g. opicapone, safinamide, trihexyphenidyl, istradefylline) or being licenced but not reimbursed (e.g. rasagiline, rotigotine, entacapone). This study aimed to investigate the treatment strategies of PD among movement disorder specialists in tertiary centres in Poland.

Material and methods

The survey was conducted between 30 November, 2020 and 18 October, 2021 in four Polish tertiary referral centres for PD (two in Gdansk, one in Sosnowiec, and one in Warsaw). Movement disorder specialists collected information on the treatment of 494 consecutive patients diagnosed with PD either according to UK Brain Bank Criteria [12] for patients diagnosed before 2015, or Movement Disorders Society criteria [13] for those diagnosed after 2015. The material was collected during the COVID-19 pandemic and the aim of our previous study was to assess the role of amantadine as a preventive SARS-CoV-2 medication [14]. The questionnaire included information on the age of the patient, the duration of PD, the Hoehn&Yahr (H-Y) stage, comorbidities, pharmacotherapy, and advanced PD therapies i.e. DBS, LCIG, and CSAI. Patients were divided into groups based on age (< 50, 50–59, 60–69, ≥ 70 years), H&Y stage (I–V), and disease duration (0–5, 6–10, > 10 years). The mean doses of the most often prescribed medications with standard deviation were calculated in groups depending on age, H&Y stage score, and disease duration. Rasagiline was excluded from these calculations due to its fixed dosing.

The collected data is part of routine history taking and did not include any additional interventions nor influence medical decisions, and therefore Bioethical Committee approval was not required.

Results

Basic demographic data

Movement disorder specialists collected data from 494 patients (301 males, 60.93%). The mean age of the patients was 64.75 years (SD ± 10.62, range: 27-89). The mean H&Y score was 2.45 (SD ± 0.68, range: 1–5), and the mean duration of PD was 9.54 years (SD ± 5.80, range 1–30). 270/494 (54.66%) patients had at least one comorbidity. Full data concerning comorbidities can be found in the Supplementary Material.

Mono and polytherapy

A total of 119 patients (24.09%) were on monotherapy only, with 104 on LD, 14 on DA (pramipexole n = 7, ropinirole n = 7), and one on rasagiline. A further 152 patients (30.77%) were treated with two medications, and 151 (30.57%) and 72 (14.57%) with three and four medications respectively. The distribution of pharmacotherapy in the study population is set out in Figure 1.

Age

The number of individuals with specific medications in groups related to patient age (< 50, 50–59, 60–69, ≥ 70 years) is set out in Figure 2A.

Hoehn&Yahr stage

The number of patients with specific medications at different stages of PD according to Hoehn&Yahr stage (I–IV) is set out in Figure 2B.

Duration of disease

The number of patients with specific medications in groups related to disease duration (0–5, 6–10 years, > 10 years) is set out in Figure 2C.

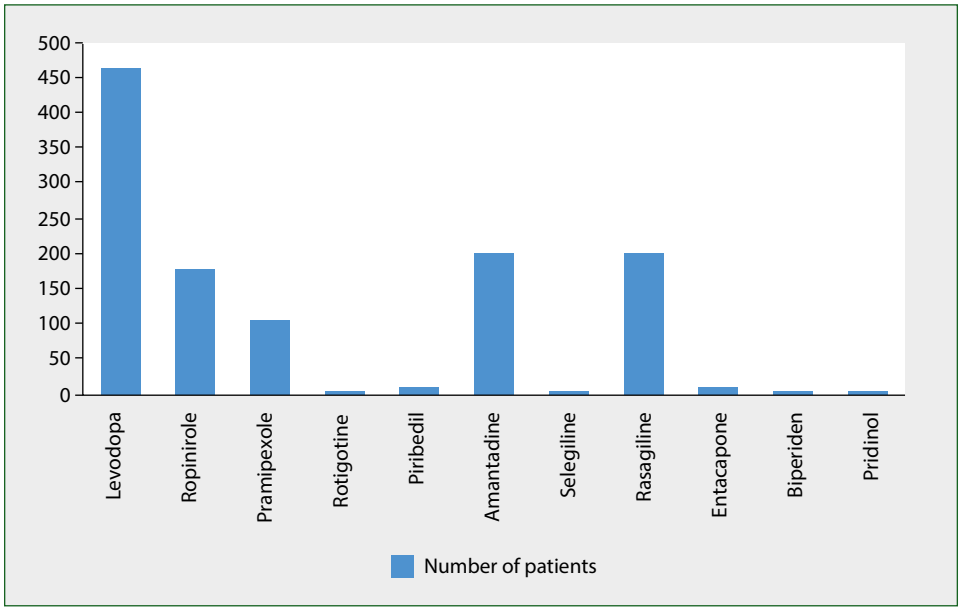

Figure 1. Number of patients treated with each medication

Mode of therapy

In the studied group, 394/494 patients (79.76%) received oral pharmacotherapy exclusively, whereas 84 (17%) were treated with DBS, 12 patients (2.43%) were on LCIG, and four patients (0.81%) were on CSAI. In the DBS group, 80 (95.25%) patients were on levodopa, 51 (60.71%) on DA (ropinirole 43, pramipexole seven, piribedil one), 41 (48.81%) on amantadine, 20 (23.81%) on MAO-B inhibitors (all on rasagiline), one (1.19%) on entacapone, and one (1.19%) on anticholinergics (i.e. biperiden).

Mean doses

The mean dose of each selected medication across the whole study population was as follows: LD 810.58 mg (SD ± 473.11), ropinirole 8.64 mg (SD ± 3.94), pramipexole (base) 1.76 mg (SD ± 0.65), and amantadine 254.57 mg (SD ± 78.11). Mean doses of patients treated with DBS were slightly different: levodopa 892.5 mg (SD ± 550.05), ropinirole 8.47 mg (SD ± 4.11), pramipexole (base) 1.65 mg (SD ± 0.82), and amantadine 285.36 mg (SD ± 85.33). The doses adjusted to age, H&Y, and disease duration are set out in Table 1. LD dose distribution is set out in Table 2. All ropinirole or pramipexole medications were prescribed in extended release preparations.

Discussion

'LD phobia', which emerged at the start of the 21st century, was driven by unproven hypotheses of LD toxicity and studies suggesting that DA might delay the onset of motor complications [3]. Consequently, clinical guidelines in the early 2000s recommended the use of DA as initial therapy. 'DA phobia' is a more recent phenomenon that has potentially led to reduced use of this group of medications by clinicians [4]. The concern primarily stems from warnings about side effects associated with DA treatment, including excessive daytime sleepiness, sleep attacks, postural hypotension with the associated risk of falls and injuries, peripheral oedema, and above all neuropsychiatric symptoms such as the increased risk of impulse control disorder [15, 16].

According to data collected by the Polish National Health Fund, there were 99,471 patients diagnosed with PD who were provided with health services in 2021 in Poland. A substantial amount (494) of patients took part in our study, which makes our cohort a representative sample of the population (0.50%).

Our results show that LD was the most frequently prescribed medication across all patient groups, regardless of age, H&Y scale score, disease duration, or type of therapy. Specifically, LD was used by 361 patients (96.27%) on polytherapy and 104 patients (87.40%) on monotherapy. The lowest but predominant use of LD was observed among patients under 50 and those who also had an H&Y scale score of 1 (Fig. 2). The overall prescription rate of LD in our cohort (94.12%) was higher than reported in studies from Japan in 2023 (85.4% [17] and 74% [18]), international cohorts in 2023 (79.5% [19]), India in 2017 (92.2% [20]), and the United States in 2016 (90% [21]).

As expected, there was a gradual increase in the mean LD dose with advancing age, higher H&Y scale score, and longer disease duration (Tab. 1). In most patients, the prescribed doses of LD were below 1,000 mg, with doses exceeding 2,000 mg in only seven (1.50%) cases (Tab. 2). The mean LD dose in our study (810.58 ± 473.11 mg) was higher than that reported in 2021 in a study from the United Kingdom

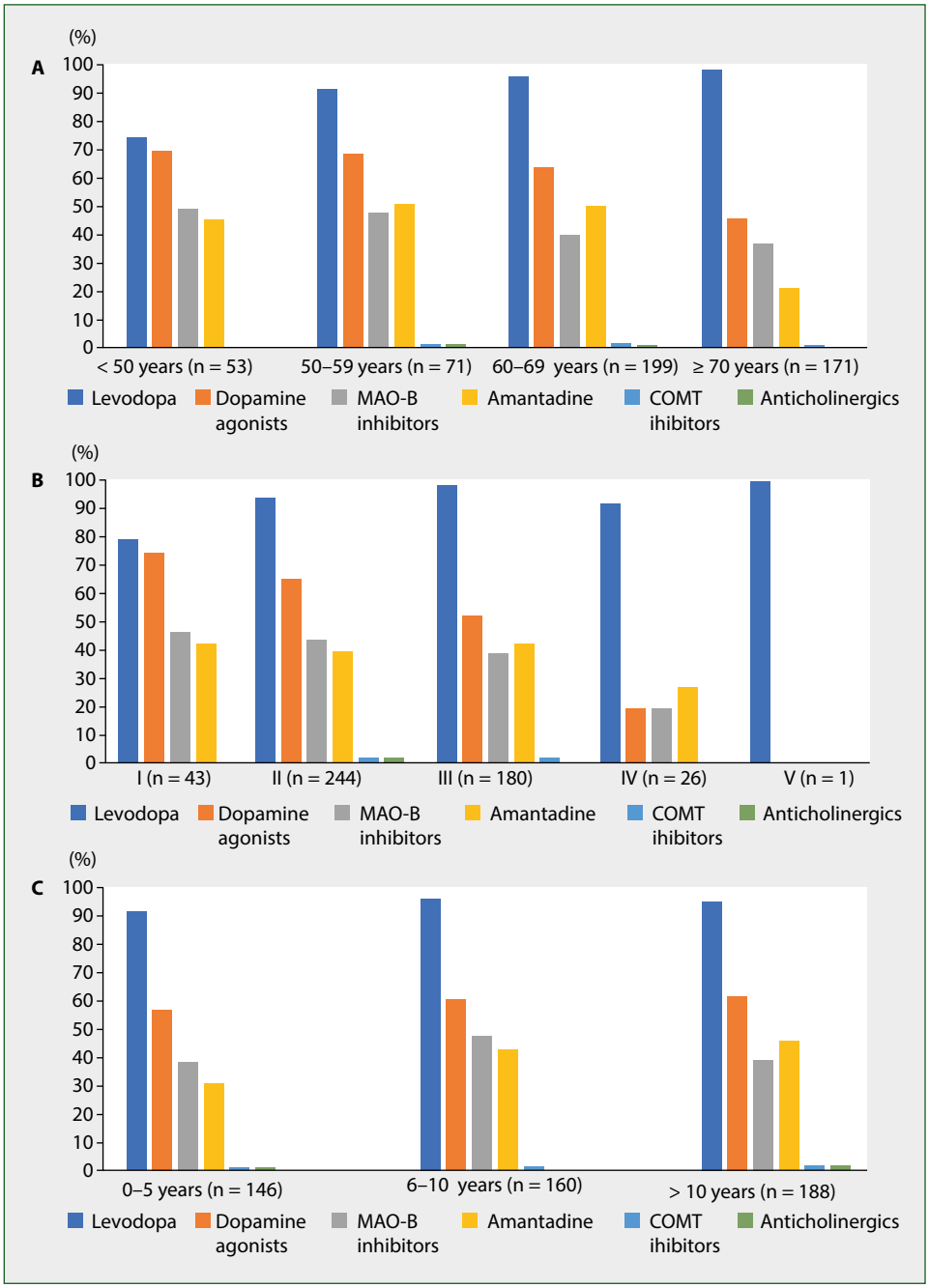

Figure 2. Medications used regarding age distribution (**A**), H&Y staging (**B**), and disease duration (**C**)

and the United States (658.57 ± 503.55 mg) [22], and in earlier studies from the United States in 2012 (two groups: 684.0 ± 412.8 and 559.7 ± 310.6 mg) [23], and Poland in 2011 (801.11 ± 430.58 mg) [24].

However, previous studies from the United Kingdom published in 2003 [25] and Poland in 2004 [26] documented comparatively higher mean doses of LD, of 955.8 ± 540.4 mg and 871 ± 446 mg, respectively. The compared studies examined slightly younger [25], similar [24], and older populations [22, 23, 26] in terms of mean age, whereas mean duration of disease was slightly shorter in two studies [22, 24], longer in two [25, 26], and no information was provided in one [23].

The high prescription rates suggest that there is no reluctance to use LD in tertiary centres in Poland. However, results reported in the abovementioned studies suggest that the paradigm of LD treatment might have changed over the past 20 years, as today's mean doses of LD might be lower than those of two decades ago.

DAs constituted the second most important component of the PD treatment strategy in the studied population. They

Table 1. Mean doses of selected medications regarding age, H&Y staging, and duration of disease

Drug	Age			
	< 50 years	50–59	60–69	≥ 70
Levodopa	723.44 mg (± 558.43)	714.23 mg (± 471.74)	781.17 mg (± 414.12)	902.23 mg (± 502.78)
Ropinirole	8.77 mg (± 3.95)	8.75 mg (± 3.76)	8.65 mg (± 4.19)	8.47 mg (± 3.70)
Pramipexole (base)	1.57 mg (± 0.70)	1.89 mg (± 0.79)	1.79 mg (± 0.61)	1.77 mg (± 0.59)
Amantadine	262.50 mg (± 96.96)	261.11 mg (± 54.91)	243.00 mg (± 79.46)	274.32 mg (± 77.84)
Drug	**H&Y stage**			
	I	II	III	IV
Levodopa	397.06 mg (± 263.98)	772.09 mg (± 458.42)	879.40 mg (± 424.64)	1,250 mg (± 669.52)
Ropinirole	6.29 mg (± 3.91)	8.41 mg (± 3.65)	9.57 mg (± 4 .20)	–
Pramipexole (base)	1.49 mg (± 0.58)	1.83 mg (± 0.65)	1.86 mg (± 0.64)	1.31 mg (± 0.53)
Amantadine	233.33 mg (± 76.70)	244.79 mg (± 79.30)	266.45 mg (± 74.56)	314.29 mg (± 69.01)
Drug	**Disease duration**			
	0–5 years	6–10 years	> 10 years	
Levodopa	598.50 mg (± 328.91)	778.22 mg (± 397.09)	997.05 mg (± 547.84)	
Ropinirole	7.42 mg (± 4.21)	9.00 mg (± 3.40)	9.09 mg (± 4.03)	
Pramipexole (base)	1.50 mg (± 0.50)	1.90 mg (± 0.61)	1.88 mg (± 0.75)	
Amantadine	221.59 mg (±5 7.46)	247.76 mg (± 78.54)	276.74 mg (± 80.69)	

Table 2. Distribution of levodopa doses

Levodopa dose (mg)	≤ 500	> 500 to 1,000	> 1,000 to 1,500	> 1,500 to 2,000	> 2,000
Number of patients	161 (34.62%)	189 (40.65%)	75 (16.13%)	33 (7.10%)	7 (1.50%)

were used by 278 patients (74.13%) on PD polytherapy and 14 patients (11.76%) on monotherapy, totalling 59.11% of the whole cohort. Their prescription rate was higher than those reported in recent studies from Japan (30.4% [17] and 52.8% [18]), the international cohort (57.4% [19]), India (22.9% [20]), and the United States (29–31% [21] and 24–27% [27] in 2021).

In our study, we observed a relatively higher use of DA among younger patients (< 50) and those in the early stages of the disease (Fig. 2). Their use declined with advancing age and disease progression (Fig. 2). Ropinirole was prescribed nearly twice as often as pramipexole (Fig. 1), despite reports of comparable efficacy and tolerability between the two [28]. This may be influenced by the prescriber's routine, as ropinirole was the first new generation (non-ergotamine) DA licenced and reimbursed in Poland, while pramipexole entered the market several years later. The mean doses of ropinirole in patients with an H&Y scale score of I and disease duration of less than 5 years were lower than the suggested clinically meaningful dose of 8 mg [29, 30]. We observed a gradual increase in ropinirole dosing with disease progression and higher H&Y scale scores. Mean doses of pramipexole exceeded reported minimal effective dose of 1.05 mg (1.50 mg of salt) [31, 32], although were relatively low compared to a maximum daily dose of 3.15 mg (4.50 mg of salt). Piribedil was used only by eight patients, most likely due to its burdensome dosing regimen, which requires intake several (3–5) times a day [33]. The prescription rate for rotigotine transdermal patch was very low, despite evidence of its effectiveness, tolerability, and ease of use [34], probably because it is not reimbursed in Poland.

Overall, the mean doses of DA in our cohort were relatively low compared to maximum range of ropinirole (24 mg/d) and pramipexole (3.15 mg/d of base). However, there is a scarcity of studies on DA dosing in real-world populations for direct comparison. The lower prescription rate of DAs compared to LD may reflect, to some extent, the influence of DA phobia. On the other hand, these medications were more frequently prescribed in Poland (in terms of the number of treated patients).

MAO-B inhibitors were frequently prescribed in our study population, regardless of age, H&Y stage, and disease duration. Specifically, 201 patients received MAO-B inhibitors as a part of polytherapy and one patient as monotherapy, totalling 40.69% of the studied cohort. This prescription rate was higher than those reported in previous studies from Japan (21.1% [17] and 12.3% [18]), international cohorts (37.9% [19]), India (3.3% [20]), and the United States (9–11% [21] and 28–30% [27]). Despite similar costs and evidence of the effectiveness of selegiline and rasagiline [7, 8], the use of the former was considerably lower (Fig. 1). This disparity may be attributable to the numerous side effects and drug interactions associated with selegiline treatment [35] and more recent and

extended clinical trials with rasagiline showing its safety and good profile for the treatment of tremor.

Amantadine was prescribed to 197 patients (39.88%), a usage higher than those reported in recent studies from Japan (10% [17] and 13.4% [18]), international cohorts (21% [19]), India (16.6% [20]), and the United States (7–8% [21]). In our study, we observed an increase in the prescription rate of amantadine with progression of disease and with age (in groups < 50, 50–59, and 60–69 years), followed by a decrease after the age of 70 (Fig. 2). This trend was probably due to its cardiovascular contraindications and potential side effects in older patients [8]. However, an increase of amantadine use with duration of the disease (Fig. 2), and of its mean doses with duration of the disease and H&Y scale score, was observed (Tab. 1), presumably due to the growing need for its anti-dyskinetic properties as the disease progresses [9, 36]. The minimal effective dose of amantadine in the treatment of PD has not been clearly defined [36], and to the best of our knowledge data concerning mean doses of amantadine in real-world populations for direct comparison is limited. Nevertheless, amantadine was used from early disease stages, and nowadays due to reports of its possibly preventive anti-dyskinetic effect, such treatment (i.e. polytherapy from the very beginning) seems to be the rational approach [37]. The amantadine extended release preparation is unavailable in Poland.

COMT inhibitors were rarely used in the studied population. Entacapone was only prescribed to seven patients (1.42%), despite its good safety profile and proven effectiveness in combination with LD [38, 39]. This prescription rate was much lower compared to reported usage of COMT inhibitors in studies from Japan (17.6% [17] and 20.9% [18]), international cohorts (49.7% [19]), India (3.3% [20]), and the United States (6–8% [21] and 7–18% [27]). The relatively high monthly therapy cost and lack of reimbursement for entacapone in Poland were presumably the reasons for its low usage. However, since our data collection period ended, the price of entacapone has fallen, which has increased its prescription rate.

We observed a very low use of anticholinergics in the studied population, as they were prescribed to only four patients (0.81%). This prescription rate was lower than in recent studies from Japan (12.7% [17] and 1% [18]), international cohorts (1.5% [19]), and the United States (5–6% [21] and 2% [27]). The difference was even more pronounced compared to a study based on data from India (38.6% [20]), in which the high prescription rate of anticholinergics presumably resulted from their affordability. Low usage of anticholinergics in our cohort probably stemmed from contraindications and possible side effects associated with treatment with this group of medications, in particular a deterioration of cognitive functions and higher risk of psychotic events, as well as the risk of constipation [40, 41].

Most patients (79.76%) in the studied group were treated only with oral pharmacotherapy. However, a relatively high number of patients (17%) were treated with DBS, underlining the importance of this method in tertiary centres in Poland. LCIG and CSAI therapies are reimbursed through a special medication programme in Poland, which requires one-day inpatient visits. As the predominant part of our data collection took place in outpatient settings, many of these patients did not participate in this study and are thus underrepresented. The assessment of therapy in patients treated with advanced methods requires further, extended research.

Our results show a significantly lower share of PD monotherapy than in studies from Japan [17, 18, 42], India [20], China [43], and the US [27] published between 2017 and 2023. A substantial group of patients in our study (45.14%) were treated with three or more medications (Fig. 2), in contrast to the 18% [42] reported in a recent Japanese study. Complex polytherapy with at least two drugs, and often three or more, constitutes a leading strategy in tertiary centres in Poland. This reflects a nuanced approach to PD treatment, allowing for personalised pharmacotherapy tailored to the specific needs of each patient, especially those experiencing motor fluctuations, dyskinesias, LD resistant tremor and the need to decrease the possible side effects when using more medications.

Clinical implications and future directions

LD remains the gold standard in PD treatment, with its widespread use dispelling concerns about LD phobia. However, the overall doses are lower than 20 or 30 years ago. While DAs constitute the second most frequently prescribed group of medications, their relatively low doses may suggest a cautious approach, possibly reflecting lingering 'DA phobia'. Other medications, particularly MAO-B inhibitors and amantadine, also play important roles in PD management and are more commonly used in Poland. The high prevalence of complex polytherapy, whereby nearly half of patients are treated with three or more medications, underlines the complexity of PD management and the need for personalised therapeutic strategies.

Future studies, particularly in non-tertiary care settings involving general neurologists, are essential to provide a more comprehensive understanding of PD treatment patterns in Poland. Conducting interviews with providers about their approach to pharmacotherapy could provide valuable additional insights. Continued monitoring of these trends will inform best practice and optimise patient outcomes.

The main limitation of this study is that the analysis of movement disorder specialists' practices may not fully represent the general pharmacotherapy landscape for PD in Poland. Tertiary care settings typically involve patients with more advanced stages of the disease, which could influence prescription patterns. Clinical practices at the time of publication may have changed since our data collection took place in 2020 and 2021. The influence of published data and congress

discussions on possible side effects of PD medications and real-world clinical practice is difficult to assess. Such assessment should take a long term perspective that takes into account local limitations e.g. availability, reimbursement.

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SHORT COMMUNICATION

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Whole exome sequencing-based testing of adult epilepsy in a Polish population

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ABSTRACT

Aim of the study. Genetic panel testing in paediatric and mixed adult and children populations has demonstrated clinical utility and provided a diagnostic yield of 18–40%. The data on adult epilepsies is limited. We aimed to investigate the diagnostic yield and analyse genetic diagnoses in whole exome sequenced adult patients with epilepsies in Poland.

Material and methods. We recruited 151 patients from 42 clinical centres across Poland. The patients had a diagnosis of epilepsy/seizures, were 18 or older at the time of the genetic testing, and did not have a genetic diagnosis. All patients were tested with whole exome sequencing after an initial testing with a panel of 47 epilepsy-related genes.

Results. We reached a diagnostic yield when considering pathogenic/probably pathogenic variants according to ClinVar of 8.6% (n = 13) and 17% (n = 26) when applying the American College of Medical Genetics (ACMG) criteria. Most patients had a pathogenic/probably pathogenic variant in epilepsy-related genes (54%), followed by potential epilepsy-related genes (19%), and neurodevelopment-associated epilepsy genes (15%).

Conclusions. Our study shows that whole exome sequencing-based testing reaches a slightly higher diagnostic yield that the traditional 300 gene panel. Genes related to childhood onset neurodevelopmental disorders and epilepsy should be considered as well.

Clinical implications/future directions. Patients may have had a diagnosis related to a childhood syndrome, but due to limited diagnostic possibilities, it was not possible to diagnose them in childhood. We would consider testing adult patients with epilepsy with whole exome or genome sequencing (or if not possible with a panel) in cases of a diagnosis of epilepsy with no hints suggesting secondary epilepsy, and especially with clinical features indicating a genetic epilepsy diagnosis, such as neurodevelopmental delay and early onset of seizures.

Keywords: epilepsy, genetics, whole exome sequencing, Polish population

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Introduction

In Poland, there are c.643,000 adults and children with epilepsy [1]. Although epilepsy can develop in people of any age, genetic epilepsy in children is more common than in adults, in which secondary causes such as structural and traumatic epilepsy play an important role. For this reason, children undergo genetic testing more often than adults.

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Currently, there are three main methods for the diagnosis of epilepsy available: next generation-based panel, whole exome sequencing (WES), and whole genome sequencing (WGS). Panel focuses on selected genes and therefore provides quicker and more cost-effective variant interpretation, and reduces the burden of secondary findings and the interpretation of variants of unknown significance. However, panel has also several limitations. Most importantly, it does not permit reanalysis of the gene (unless NGS-based) and the identification of the structural and copy number variants that can be provided with whole genome sequencing, and recently also with whole exome sequencing. The available studies for epilepsy in adults usually use a broad panel of 89–500 genes as a first testing strategy [2–4].

Genetic testing in pediatric populations has demonstrated clinical utility and provided a diagnostic yield of 18-40%, depending on the cohort tested [5–7]. However, the diagnostic yield and data on the potential classification of adult epilepsies are limited. In the largest adult epilepsy study so far, of over 2,000 individuals, as many as 10.9% obtained a genetic diagnosis with a panel testing [4]. Two small studies of adults with epilepsy, primarily those with intellectual disability (ID) or childhood-onset seizures, reported a diagnostic yield of 22-23% [2, 3]. In the Polish population, there has been no study on adults with epilepsy only. A recent paper including mostly children, but also adults, with epilepsy from Poland, reported a monogenic cause of epilepsy in over 20% of patients [8]. Therefore our aim was to investigate the diagnostic yield and analyse genetic diagnoses in adult patients with epilepsies in Poland in a large whole exome sequenced population across the country tested in a single reference genetic centre.

Material and methods

We performed a retrospective analysis. We included 150 patients from 42 clinical centres across Poland. The patients had been referred to the MEDGEN laboratory (Warsaw, Poland) by a treating physician or presented without referral. The patients had a diagnosis of epilepsy/seizures, were 18 or over at the time of the genetic testing, and did not have a genetic diagnosis. Although details regarding family history were not available in all cases, the cohort was enriched with patients with intellectual disability and early seizures onset, suggesting a genetic background of epilepsy. Patients with known epilepsy causes (e.g. stroke, traumatic brain injury, tumour) were excluded. Commercial panel testing of 47 genes followed by whole exome sequencing based on the current literature has been performed commercially since 2017. The list of genes included in the panel is available as Supplementary material. The patients were classified according to the indications for genetic testing according to the International League Against Epilepsy (ILAE) [9], and according to the manifestation of epilepsy in phenotypes into variants of epilepsy-related genes, potential epilepsy genes, neurodevelopment-associated epilepsy genes, and epilepsy genes [10].

This study was conducted in accordance with the Declaration of Helsinki and there were no significant risks to the participants. We ensured the privacy of the participants and their personal information was kept confidential and anonymised for the analysis. Consent for the genetic testing was provided by all patients or their caregivers.

The enriched DNA libraries were sequenced by the Illumina NovaSeq 6000 instrument, 2 x 100 bp. All procedures for exome sequencing were conducted by CeGaT (Tübingen, Germany). Raw sequencing reads were mapped to the human reference genome GRCh37 and GrCh38 assembly using BWA MEM (bwa-mem 2.avx2 mem 0.7.17-r1188) [11]. Duplicates were removed using biobambam2 version 2.0.183 [12]. Variants were identified using HaplotypeCaller (GATK v4.2.6.1) [13], FreeBayes v1.3.2, and named using Variant Effect Predictor (VEP109) [14]. The presence of the variant in control populations was checked in the 1,000 Genomes [15] and gnomAD (v.4) (Broad Institute) databases [16]. A filtering criterion of 1% frequency was applied. The in silico splicing analysis was performed using algorithms embedded in Alamut Visual Plus software (Sophia Genetics), i.e. SpliceSiteFinder-like, MaxEntScam, NNSPLICE, GeneSplicer and SpliceAI [17]. The presence of the detected pathogenic/probably pathogenic variants was confirmed by Sanger sequencing.

Results

The median age of the patients was 28 years (18–61). We reached a diagnostic yield when considering pathogenic/probably pathogenic variants according to ClinVar of 8.6% (n = 13) and 17% (n = 26) when applying the American College of Medical Genetics (ACMG) criteria. According to the indications for genetic testing according to the ILAE [9], most adult patients were tested for epilepsy + (n = 100, 66%), 21 patients were tested for drug-resistant epilepsy (14%), 17 for encephalopathy (5%), and six for familial epilepsy (4%). According to the classification of epilepsy in phenotypes [10], most patients had a pathogenic/probably pathogenic variant in epilepsy-related genes (54%), followed by potential epilepsy genes (19%), neurodevelopment-associated epilepsy genes (15%), and epilepsy genes (12%). ID/NDD was the most common comorbidity present in 49% of patients (n = 76). In a cohort with NDD/IDD, the diagnostic yield was 22% (n = 17 patients with a genetic diagnosis). Four patients were diagnosed with Rett syndrome and in the other 22 patients, pathogenic/probably pathogenic variants in 22 different genes were identified. A full list of variants and phenotypes is set out in Table 1.

Table 1. Phenotypic and genetic data of patients with a molecular diagnosis. Variants reported as pathogenic according to American College of Medical Genetics (ACMG) criteria

Patient number	Indications according to ILAE [9]	Additional features	Molecular results
1	epilepsy +	ID/NDD, no speech, obstructed breathing, generalised weakness	Rett syndrome
2	epilepsy +	cerebellar atrophy	Rett syndrome
3	familial epilepsy		Rett syndrome
4	familial epilepsy		Rett syndrome
5	epilepsy +	abnormal muscle tone disorders, dysmorphic features, autism, NDD	*AP4B1*, p.Leu142Arg/p.Arg102Ter
6	drug-resistant epilepsy	atypical autism, NDD	*CHD4*, c.439-2A > C
7	drug-resistant epilepsy	autism, NDD	*TSC2*, p.Val126Phe
8	epilepsy +	neuropathy, epilepsy, binocular cataract, spastic paraparesis	*KIF1A*, p.Ser274Leu
9	epilepsy +	psychogenic epilepsy, muscular hypotonia	*KMT2E*, p.Pro350Ser
10	epilepsy +	childhood autism, anxiety, auditory hypersensitivity	*BBS5*, c.817-1G >T; *BBS10*, p.Ala296Thr
11	drug-resistant epilepsy	cortical dysplasia	*CHRNA4*, p.Met314Thr
12	epilepsy +	cerebellar syndrome, myoclonus-dystonia	*KCNC1*, p.Arg320His
13	epilepsy +	NDD, high iron levels in blood, congenital cataract	*CYP27A1*, p.Arg127Trp/p.Arg127Trp
14	drug-resistant epilepsy	autism spectrum disorder, profound mental retardation, nystagmus, scoliosis, flat-valgus feet, joint laxity, neuropsychiatric disorders	*DYRK1A*, p.His545GlnfsTer18
15	epilepsy +	hereditary epilepsies, dystonia, NDD, hypoglycaemia	*MED12*, c.6268-2A>G
16	epilepsy +	epilepsy, dysmorphia (protruding ears, prominent lips), NDD	*CHD2*, p.Arg1074Trp
17	epilepsy +	atypical autism, NDD	*NBEA*, p.Gly719ValfsTer4
18	epilepsy +	severe mental retardation, dysmorphia, short stature, microcephaly	*KDM3B*, p.Asp377GlyfsTer102
19	epilepsy +	severe mental retardation, hypothyroidism, obesity, neuropsychiatric disorders	*TSC1*, p.Arg420GlyfsTer20
20	epilepsy +	increased muscular tone in all extremities, severe mental retardation, aphasia, agenesis of left kidney, microgyria	*SON*, p.Val629AlafsTer56
21	epilepsy +	NDD, microcephaly, obesity	*ANKRD11*, p.Arg1188Ter
22	epilepsy +	Cornelia de Lange syndrome, moderate mental retardation	*ARID1B*, p.Pro557AlafsTer10
23	epilepsy +	severe mental retardation, wheelchair bound	*NSD1*, p.Lys1938Arg
24	epilepsy +	mild NDD, cerebral palsy	*ATP1A3*, p.Pro775Leu
25	epilepsy +	cerebellar syndrome of unclear aetiology, tics, myotonias, flaccid paraparesis, cerebellar cortex atrophy	*POLG*, p.Trp748Ser/p.Ala143Val
26	drug-resistant epilepsy	cerebral palsy, speech and language disorders, significant ID, spastic quadriparesis, swallowing disorders – PEG-fed	*TCF4*, p.Ala323Val

Discussion

We present the first study in a Polish adult population investigating the genetic background of adult epilepsies only. We showed a diagnostic yield of 8.6% when applying ClinVar criteria, and of 17% when applying ACMG criteria. We also applied the ILAE classification criteria to an adult only population in Poland.

Polish patients tend to obtain access to genetic testing later than in the US and Western Europe, so it should be expected that the diagnostic rate will be higher. However, the diagnostic yield reported in our study is lower than in some studies where the diagnostic yield reached 22–23% [2, 3], while it was higher than in the biggest study on adults available so far [4].

It must be taken into consideration that the patients were tested with a panel of 47 genes only, followed by the WES, whereas many laboratories apply an epilepsy panel of around 300 genes. Currently, there is no consensus regarding how many genes should be included in a diagnostic panel. In other studies, panels have ranged from 89 to 580 genes [2–4]. The highest diagnostic yield has been reported for panels consisting of 100–299 genes, and the inclusion of additional genes did not increase the diagnostic yield.

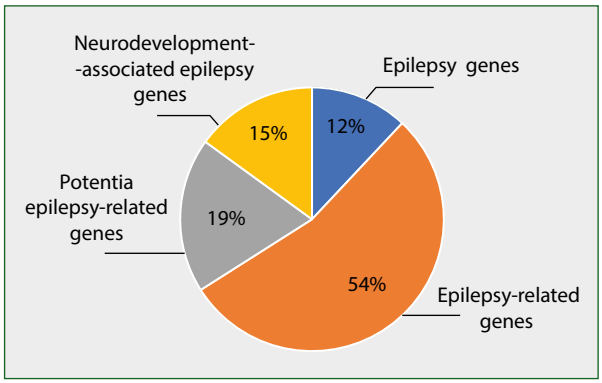

Figure 1. Categories according to manifestation of epilepsy in phenotypes, as in Wang et al. [10]

Our patients obtained diagnoses of differing origins. Only four patients were diagnosed with the same molecular diagnosis. This was of Rett syndrome, which is characterised by a high prevalence of epilepsy, of up to 67% [18], and may still pose a diagnostic challenge in some cases. Most importantly in some patients, a clinically actionable genetic finding was identified, such as pathogenic/probably pathogenic variants in *TSC1* and *TSC2*. For the diseases associated with these genes, there exists a recently approved therapy with mechanistic target of rapamycin complex 1 (mTORC1) [19].

Our study has some limitations. Firstly, it may be biased by the fact that we induced the commercial testing, so that patients with a suspected genetic diagnosis and comorbidities such as NDD/ID or a positive family history may have been mainly those who were tested. For the ID/IDD cohort, we also reached a diagnostic yield higher than in other cohorts i.e. 22% diagnostic yield vs 16% diagnostic yield as described in McKnight et al. [5]. Furthermore, the methodology did not permit the detection of CNVs and structural variants. Nevertheless, our study is a valuable contribution to the discussion on the testing of adult patients with epilepsy.

Ours is the first study on an adult Polish population applying whole exome sequencing. Taking into account that currently more than 900 genes are involved in epilepsy, broad testing with whole genome or exome sequencing is recommended as the first choice testing in ILAE guidelines [20]. Panels should be performed only in particular situations, e.g. if exome or genome sequencing are not available or not covered by the insurance [20]. In cases of epilepsy with neurodevelopmental delay, an indicative phenotype and no diagnosis after panel, structural variants should be considered. Also, in cases of a clear hereditary component in the pedigree without a genetic diagnosis after the panel, new genes and deep splicing variants should be sought. CNVs and structural variants as well as splicing variants may reliably be detected with WGS.

Conclusions

Our study shows that whole exome sequencing-based testing reaches a slightly higher diagnostic yield that the traditional 300 gene panel. Adults in Poland may be affected by childhood onset disease with epilepsy, so that genes related to childhood onset neurodevelopmental disorders and epilepsy should be considered as well.

Clinical implications/future directions

Patients may have had a diagnosis related to childhood syndrome, but due to limited diagnostic possibilities, it was not possible to diagnose them in childhood. We suggest testing adult patients with epilepsy with whole exome or genome sequencing (or if not possible with panel) in cases of a diagnosis of epilepsy, and especially in patients with clinical features indicative of a genetic epilepsy diagnosis, such as neurodevelopmental delay and early onset of seizures.

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Erdheim-Chester disease is often complicated by neurological disorders

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Keywords: Erdheim-Chester disease, histiocytosis, brain, neurological involvement

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To the Editors

We were interested to read the article by Kaleta et al. about a 39-year-old man with Erdheim-Chester disease (ECD) who was diagnosed on the basis of typical clinical findings, a tibial plateau fracture, infiltration of CD68-positive histiocytes, and the presence of the V600E variant in BRAQ1 [1]. Clinically, he showed weight loss, gait disturbance, dysarthria, divergent strabismus, left hemiataxia, upper limb hypotonia and lower limb spasticity, pleural fibrosis, thickening of the interlobar septum, fibrosis of the kidneys, and fibrosis of the aorta [1]. Cerebral MRI showed thickening of the dura mater, pituitary stalk and skull bones, especially the frontal bones [1]. He was treated with vemurafenib, but there was no improvement [1]. The study is excellent, but some points should be discussed.

The first is that we disagree with the statement made in the title that the index case is the first case of ECD with neurological involvement in Poland [1]. In 2022, Chrostowska et al. reported a 40-year-old man with ECD diagnosed after clinical presentation and the presence of the BRAF V600E mutation. He had marked infiltration of the extraocular eye muscles to such an extent that the optic nerves were compressed and clinical visual impairment occurred [2]. Since skeletal musculature is the responsibility of a neurologist, and the optic nerve is not actually a cranial nerve but an appendage of the brain, it must be assumed that this Polish patient suffered from ECD with neurological involvement.

Our second point is that the spectrum of CNS manifestations of ECD is much broader than that described in the study [1]. CNS involvement in ECD can affect the hypothalamic-pituitary axis, the meninges, the cerebral arteries and the brain parenchyma [3]. CNS involvement in ECD can manifest not only in the form of cognitive impairment, seizures, headaches, ataxia, nystagmus, dysmetria, cranial nerve dysfunction, gait disturbances, sensory deficits and psychiatric problems, but also in the form of visual disturbances, diabetes insipidus, short stature, secondary hydrocephalus, pyramidal signs, peripheral neuropathy, cerebral atrophy, demyelination and/or neurodegenerative diseases of the CNS [4]. Abnormalities due to involvement of the anterior pituitary include secondary adrenal insufficiency, secondary hypothyroidism, growth hormone deficiency, and hypogonadotropic hypogonadism [5]. Impairment of the posterior pituitary gland can lead to hyperprolactinemia or hypoprolactinemia [5]. The CNS may even be the only manifestation of ECD if no organs other than the brain are affected [6]. In a single ECD patient, a double subclavian steal syndrome has been reported as a vascular and neurological manifestation of the disease [7].

The final point is that ECD can also be complicated by secondary cerebral disease due to primary involvement of the heart, e.g. ischaemic stroke or cerebral haemorrhage. Hypoaldosteronism can be complicated by seizures.

In summary, the excellent study has some limitations that should be addressed before final conclusions can be drawn. Clarification of these weaknesses would strengthen those conclusions and improve the study. Since neurological involvement can occur in almost half of patients with ECD, and the average delay in ECD diagnosis is four years, neurologists should consider ECD in patients with inflammatory,

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infectious, or neoplastic-appearing white matter changes due to infiltration of CD68-positive histiocytes. It must also be considered that cerebral disease may be the first, or even the only, manifestation of ECD.

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DNAJC30 variants can also manifest phenotypically as Leigh/ /LHON overlap syndrome

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Keywords: DNAJC30, LHON, Leigh syndrome, dystonia, ataxia

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To the Editors

We were interested to read the article by Dzwilewski et al. about a 12-year-old boy who had been suffering from a progressive gait disorder, ataxia and dystonia of the limbs since the age of four, which was attributed to the homozygous variant c.152A > G (p.Tyr51Cys) in DNAJC30, the phenotype of which was classified as Leigh syndrome [1].

Despite oral treatment with idebenone (900 mg/d), the phenotype progressed and the patient developed dysarthria and dysphagia, quadruparesis and quadrudystonia, which is why idebenone was discontinued after 18 months [1]. The study is convincing, but some points should be discussed.

The first of these is that we disagree with the diagnosis of Leigh syndrome. Leigh syndrome is characterised on imaging by symmetrical lesions of the basal ganglia, thalamus, brainstem, cerebellum, or dorsal columns [2]. The index patient had only unilateral lesions in the midbrain, caudate nucleus and putamen [1]. As the presented cerebral MRI was not typical for Leigh syndrome, the patient might also have been diagnosed with non-syndromal mitochondrial disorder (MID). As the patient also exhibited optic atrophy, it is also conceivable to classify the phenotype as Leber's hereditary optic neuropathy (LHON) plus, rather than as Leigh syndrome. In addition to visual impairment, the index patient also had ataxia, left-sided hemiparesis and limb dystonia [1]. LHON plus with dystonia has been reported previously [3]. Ataxia has also been described as a manifestation of LHON plus [4].

Our second point is that it was not reported whether the patient had only optic atrophy or also features of LHON such as severe visual impairment, colour vision defects, central scotoma, loss of retinal nerve fibres, loss of macular retinal ganglion cells, microangiopathy, or telangiectasia [5]. The results of the ophthalmological examination, including optical coherence tomography (OCT), should be reported.

The third point is that Leigh syndrome is usually characterised by epilepsy [6]. The index patient had no history of epilepsy, nor was he taking antiepileptic drugs (ASD) regularly. Therefore, we should know whether the patient had ever had an electroencephalogram (EEG) recorded, and if so whether epileptiform discharges were ever seen on any of the EEGs.

The fourth point is that the design of a single case report is not suitable for assessing whether a particular drug is useful or not. To assess whether idebenone really helps in patients with DNAJC30 variants, a double-blind, placebo-controlled, multi-centre design would be desirable. However, due to the rarity of DNAJC30 variants, such an approach is challenging to achieve.

Our fifth and final point is that the cause of gait disturbance was not clarified. Was gait impairment due to ataxia or dystonia, or both? Did the patient also develop muscle weakness? Myopathy can be a feature of Leigh syndrome. There has also been one report of a DNAJC30 mutation carrier who presented with a neuromyelitis optica spectrum disorder (NMOSD)-like disease [7].

Overall, this interesting study has limitations that relativise the results and their interpretation. Addressing these limitations could strengthen the conclusions and support the study's message. DNAJC30 variants may phenotypically also manifest as Leigh/LHON overlap syndrome.

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Helping patients find their voice

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To the Editors

Patients with a functional neurological disorder (FND) are common in neurological practice, with an incidence in the general population of 10–15/100,000 [1]. Available studies show that 60–75% of patients with FND are female [2]. The most frequent presentations of FND are functional seizures and functional movement disorders (FMDs) [1].

Functional speech and voice disorders (FSVDs) are quite common among patients with FMD.

We present two cases of FSVD initially suspected as being laryngeal dystonia, and discuss the characteristics of FSVD.

Case 1: A 53-year-old female had developed acute difficulty in vocal expression. She experienced effort during speaking, and had needed to rest afterwards. She also complained of chronic generalised exertion.

Her past medical history revealed a brainstem stroke cured with alteplase, strumectomy complicated by right vocal cord paresis, and Hashimoto's thyroiditis treated with levothyroxine.

On neurological examination, prosodic disturbances and intervals of silent speech were found.

Standard blood investigations were normal. Brain and cervical MRI were normal. Electrophysiological recordings e.g. repetitive nerve stimulation and single fibre electromyography were normal.

Pulmonary diseases were ruled out. On ENT consultation, paresis of the right vocal cord was seen. Normal voice was recorded after disappearance of voice problems with distraction.

Neuropsychological testing showed periodic phonatory and articulatory impairment during spontaneous statements accompanied by shortness of breath, and sometimes the flow of speech was slowed down. It was noted that full remission was observed in distraction (up to 10 minutes). The subject presented a tendency to repress more difficult emotions, with the possibility of dissociation (conversion). The study indicated the functional-psychogenic nature of the symptoms.

Her psychosocial history revealed that the patient had had tertiary education and and had been very successful professionally. She was married with two grown-up children. For several years, the patient had experienced serious problems in her marriage including her husband's infidelity, and had considered leaving home because she felt like she was "suffocating" there. She decided to stay in the relationship and later engaged in psychotherapy. This somewhat alleviated her distress, but did not address the issues associated with her marriage. The patient withdrew from psychotherapy. Reflecting upon her marriage, the patient ambivalently reported that the relationship was now satisfactory but at the same time that the previous problems remained unresolved.

Functional voice and speech disorder were diagnosed. The patient was recommended for a psychiatric consultation and further management.

Case 2: A 46-year-old female was referred with dysphonia, of which the initial symptoms had appeared suddenly 10 years earlier. The patient felt paresthesia in the chest and general weakness during considerable voice impairment. A slight improvement was observed after speech therapy.

Her past medical history featured thymus hyperplasia without compressive symptoms or systemic symptoms (autoimmune diseases).

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Table 1. Characteristics of types of functional speech and voice disorders [4]

Type of FSVD	Clinical features
Psychogenic voice disorder	Sudden onset of aphonia or dysphonia; aphonia can present as a whisper, dysphonia may present as a breathy falsetto, hoarseness or vocal production of two separate tones
Muscle tension voice disorder	Gradual onset of dysphonia, secondary to excessive tension in para-laryngeal musculature, often mistaken for laryngeal dystonia, improves with speech therapy, may coexist with an underlying organic condition of vocal cords (secondary type)
Functional stuttering	Manifests as repetitions of sound, syllables or words, speech blocks, or extended pauses between sounds, may present as an accent on the wrong syllable, excessive variability, absence of dysarthria, aphasia, or apraxia of speech
Foreign accent syndrome	Type of prosodic disturbance, ability to imitate additional accent(s) with ease, may demonstrate stereotyped behavioural mannerisms, variability of accent, cases of organic aetiology (often linked to dominant hemisphere vascular or traumatic lesions)
Childlike prosody	Infantile speech ('baby talk'), sometimes accompanied by infantile gestures and facial expressions
Articulation abnormalities	Coexists with inconsistent lingual, jaw or facial weakness on tasks unrelated to speech

On neurological examination, a breathy falsetto was noted. Her symptom alters significantly with distraction and intervals of normal voice was heard.

Standard blood investigations, a brain MRI and electrophysiological recordings were all normal.

On ENT consultation, a minor abduction of the right vocal cord was seen. Psychogenic component influence was taken into consideration.

Neuropsychological testing revealed a significant impact of the functional component in the clinical picture. Analysis of the patient's psychological mechanisms indicated a tendency for repression of intense emotions and somatisation. Further assessment also showed that the patient had trouble in adjusting to new environments (e.g. when changing jobs) and in tolerating the distress related to day-to-day activities.

An eventual diagnosis of functional voice and speech disorder was made, and the patient was sent for psychotherapy.

Functional (previously psychogenic) neurological disorders are thought to be the results of psychological causes, although the pathophysiology is not fully understood.

FMDs include tremor, dystonia, myoclonus, and parkinsonism. Functional speech and voice disorders (FSVDs) represent 16.5–53% of FMDs, and are recognised as being challenging to diagnose, as they may resemble organic motor speech disorders [3].

To be diagnosed as an FSVD, at least five of the following seven criteria must be present: sudden onset, marked distractibility of speech disorder, temporal association with an FMD or another psychogenic phenomenon, the occurrence of periods of unexplained improvement, speech abnormalities inconsistent with developmental stuttering or neurological dysarthria, the absence of an organic neurological disorder that could explain abnormal speech or voice, and an improvement with suggestion or placebo [4].

Any aspect of speech or phonation can be affected, and various FSVDs are set out in Table 1.

Patients with an FSVD may demonstrate facial movements including grimacing, lip pursing, blinking, and contraction of the periorbital lower facial muscles or platysma during attempted speech [5]. The symptoms of an FSVD usually present in seemingly neutral situations and reflect an increased level of psychobiological activation in response to daily life stressors, but they can also occur in association with a sense of immediate threat.

All possible organic disorders should be ruled out following a detailed examination in order to make the diagnosis of an FSVD.

In patients with an FSVD, psychiatric disorders are usually identified, including anxiety, distress, depression, conversion reaction, personality disorders, and interpersonal conflicts within family and/or work environments. Nevertheless, diagnosis by DSM-5 no longer requires the identification of a precipitating stressor.

Neurologists have traditionally avoided taking responsibility for people with FMD, although they are actually the most appropriate specialist to engage upon a patient's treatment. Studies report that engaging in psychological contact is important to prevent a relapse in patients suffering from an FSVD, but only c.60% in fact visit a psychologist. Traditional voice therapy includes behavioural techniques which can be direct (i.e. vocal exercise and rehabilitation programmes) or indirect (i.e. vocal hygiene advice and education). However, this does not address the issues which are closely related to FSVD, i.e. psychosocial problems, personality traits predisposing to, precipitating and/or maintaining FSVD symptoms, and comorbid anxious or depressive disorders with FSVD burden. Cognitive behavioural therapy (CBT) is a more complex, evidence-based structured treatment method, which helps patients modify not only their behaviour but also aids their understanding of their own symptoms and helps them to develop alternative coping strategies and manage coexisting psychological distress.

Therefore, a combination of the traditional approach plus CBT offers better results than traditional behavioural intervention in terms of voice improvement, psychosocial wellbeing, and reduced risk of relapse [6]. Given the importance of psychological help for patients with FSVDs, neurologists may have a significant role to play in providing patients with adequate psychoeducation, referrals, and checking that they follow through on the consultations' recommendations. Alternatively, CBT can be provided by speech-language therapists provided that they have firstly received appropriate training [6].

In summary, the prognosis of FSVD remains poor. Speech therapy rarely improves patients. Psychotherapy seems necessary for most patients. Cognitive behavioural therapy is recommended, while physiotherapy and pharmacotherapy should also be considered.

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Uncommon localised form of axonal injury involving *pontes grisei caudatolenticulares*

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To the Editors,

Diffuse axonal injury (DAI) is a severe type of widespread neuronal injury due to rotational acceleration-deceleration forces encountered in trauma [1]. The majority of neuronal damage in DAI does not occur at the time of the trauma, but is rather caused by secondary injury processes [2, 3]. A dissociation between clinical findings and early head computed tomography (CT) is the hallmark of this entity. Magnetic resonance imaging (MRI) is the modality of choice when DAI is suspected, and should be done promptly.

Grading depends on the location of the lesions, and long white matter tracts are predominantly involved, particularly in grey-white matter interface. Localised injuries and the 'pure' involvement of grey matter are uncommon.

We present a case of traumatic axonal injury in an 18-year-old boy in an unusual location, the short and rarely mentioned grey matter bridges in the basal ganglia — *pontes grisei caudatolenticulares*.

An 18-year-old boy, with an unremarkable previous medical history, was admitted to the Accident & Emergency department after suffering an accident while riding a scooter with helmet resulting in head trauma, transient loss of consciousness, and loss of strength in the right limbs. On admission, the patient showed normal vital signs. He was conscious and aware, with a Glasgow Coma Scale score of 15 points. Neurological examination revealed mild dysarthria, right central facial palsy, and severe right-sided hemiparesis, with grade 2/5 muscle strength in the upper limb and grade 3/5 in the lower limb. The patient described a slight improvement in muscle strength since the moment of trauma. The remainder of the physical examination revealed ecchymotic swelling in the right clavicle area, with crepitus upon palpation. Chest radiography and CT confirmed a displaced middle third clavicle fracture, with no relation to the ipsilateral brachial plexus that could justify the hemiparesis. Head CT showed multiple linear hyperdensities in the left posterior corona radiata (Fig. 1A), and cervical CT excluded traumatic pathology, prompting further investigation. Brain MRI revealed T2 and T2 FLAIR high signal intensity (Figs. 1B–D) in the posterior left putamen and caudate nucleus with focal linear T1 hyperintense (Fig. 1E), low susceptibility weighted imaging (SWI) signal (Fig. 1F) and restricted diffusion (Figs. 1G and 1H), involving the caudolenticular grey bridges region. MR diffusion tensor imaging with tractography depicted focal decreased fractional anisotropy of the ipsilateral cortico-spinal tract fibres crossing the affected area (Figs. 1I and 1J). These MRI findings were highly suggestive of axonal injury due to shearing forces, comparable to the lesions found in DAI. A conservative approach was adopted, including physical rehabilitation. The patient showed progressive improvement of the neurological deficit over the following week. There was evidence of grade 4 right muscle strength on discharge, and he was able to walk unaided.

DAI, also known as traumatic axonal stretch injury, is a severe type of traumatic brain injury and a major cause of loss of consciousness after trauma. Pathophysiology includes a sudden acceleration-deceleration injury, as grey matter moves at a different speed from the underlying white matter, resulting in axonal stretching, particularly where brain tissues with different densities intersect [2]. Axons are stretched, causing

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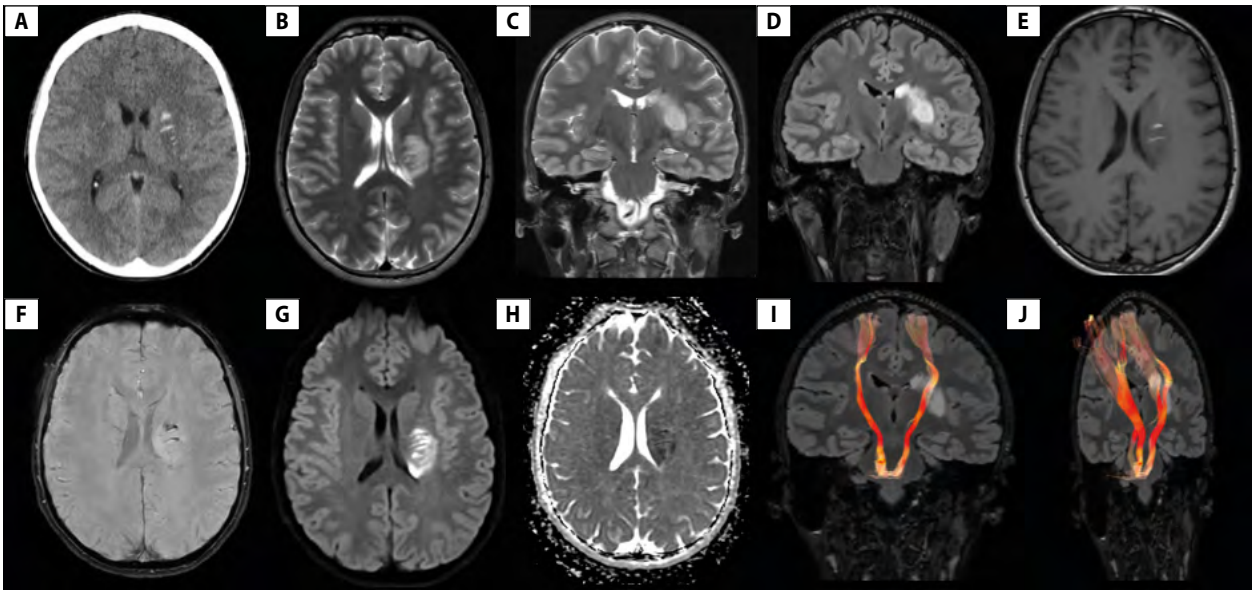

Figure 1. Brain image. Head CT (**A**) shows hypodense lesion associated with linear hyperdensities in region of left posterior corona radiate; brain MRI axial T2 (**B**) and coronal T2 (**C**) and T2 FLAIR (**D**) images depict a high signal intensity lesion in posterior left putamen and caudate nucleus, associated with focal linear haemorrhagic lesions hyperintense on T1 (**E**) and hypointense on SWI (**F**) corresponding to caudolenticular grey bridges and white matter interface regions; lesion shows areas of restricted diffusion evidenced by high signal on DWI (**G**) and low ADC (**H**); brain DTI tractography (**I** and **J**) demonstrates a focal loss of anisotropy in some corticospinal tract fibres crossing affected area

massive calcium influx, neuron depolarisation, biochemical and metabolic changes, impairment of axonal transport, degradation of axonal cytoskeleton, cytotoxic oedema, and eventual apoptosis [3]. This entity, when diffuse, is marked by a discrepancy between clinical and imaging findings.

Initial CT scan may be normal or show only small focal ovoid hyperdense haemorrhagic lesions, along with focal oedematous areas that become progressively more evident after a few days. MRI is the modality of choice and can show haemorrhages and oedema earlier, especially if using SWI MRI. Grading of DAI is done according to the location of lesions: in mild DAI, the grey-white matter interface is affected; in moderate DAI, there is additional corpus callosum involvement; while in severe DAI, brainstem lesions also occur [2].

During brain development, innumerable white matter fibres cross the striatal area on their way to and from the cerebral cortex, forming the internal capsule that divides the dorso-medial caudate nucleus from the ventrolateral putamen. The *pontes grisei caudatolenticulares* or caudolenticular (transcapsular) grey bridges represent the connections between the caudate nucleus and the putamen across the internal capsule, are on average 1 mm thick, and serve as the primary efferent gateway from the cortical premotor and supplementary motor area to the basal ganglia [4].

These anatomical structures have very rarely been mentioned in the literature, and there is limited knowledge regarding their functional role and microstructural properties. A recent study has made a pioneering effort to bridge this gap in our understanding by using advanced techniques such as diffusion weighted imaging (DWI) and tractography [5].

To the best of our knowledge, no previous report has described a traumatic lesion isolated in this specific location.

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John Cunningham virus as cause of progressive multifocal leukoencephalopathy

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To the Editors

The JC virus was first isolated in 1971 and named the John Cunningham polyomavirus (JCV) after the patient from whose brain this virus was isolated [1]. This polyomavirus infects about 60% of the adult population worldwide, and is an opportunistic pathogen.

In the initial infection, the virus undergoes gene rearrangement and replicates in infected cells, transforming into a neurotropic form. JC virus primarily damages the brains of patients with innate immunodeficiency or those taking immunomodulatory medications. It has also been reported in association with rheumatological diseases, lymphoreticular malignancies, and post-organ transplantation immunosuppression. JC virus has a tropism for oligodendrocytes but has also been observed in astrocytes, granule neurons of the cerebellum, and cortical pyramidal neurons [2, 3].

This polyomavirus is aetiologically linked with progressive multifocal leukoencephalopathy (PML). Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system with a multifocal process.

The classic clinical presentation of PML includes subacute-to-chronic focal neurological deficits, depending on the location of the lesions. Initially, the diagnosis of PML was based on neuropathological examination characterised by a classic triad: demyelination, bizarre astrocytes, and oligodendroglial nuclear inclusions. The enlarged nuclei are often described in the literature as 'ground-glass' [4]. In clinical diagnostics, standard MRI pulse sequences are used for screening and monitoring PML. The typical magnetic resonance imaging (MRI) findings of PML are white matter lesions in different brain areas. They are usually hyperintense in T2-weighted and FLAIR sequences, reflecting white matter involvement [2]. Cerebrospinal fluid (CSF) examination is very helpful in excluding other diagnoses. The demonstration of JC virus by PCR in CSF is also considered diagnostic [4]. The use of a diagnostic algorithm in diagnosing fatal PML may expedite the correct diagnosis, but does not exhaustively identify the brain changes caused by the JC virus.

A 70-year-old woman presented to the clinic with left-sided hemiparesis (symptoms had been worsening for two weeks), psychomotor retardation, depressed mood, balance disorders, and dizziness. She had a 10-year history of follicular lymphoma. Her medical history also included an aortofemoral transplant 10 years ago, depression, removal of squamous cell carcinoma five years ago, and a recent (three weeks prior) COVID-19 infection. Systemic connective tissue diseases, neuroborreliosis, onconeuronal antibodies, antibodies against surface receptors, antibodies against aquaporin, and anti-MOG were excluded. Cerebrospinal fluid analysis was

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normal: protein 24.0 mg/dL, glucose 60.2 mg/dL, and normal cell count and IgG levels. CSF was not tested for the presence of JCV-DNA. No antibodies against aquaporin 4, oligodendrocytes, or myelin proteins were detected in the cerebrospinal fluid, and no antibodies against surface antigens were found (NMDA, AMPA1, AMPA2, GABA B, CASPR2, LGI1, DPPX). CT of the head revealed a hypoattenuating lesion in the subcortical white matter (Fig. 1A). In MRI of the head, an extensive FLAIR/T2 hyperintense focus located in the white matter of the right frontal lobe caused a slight mass effect (Fig. 1B). MRI and CT scans showed asymmetrical pathological areas of hyperintense signal in T2-weighted images and hyperintense signal in T1-weighted images. These pathological areas were located in the white matter of both brain hemispheres, mainly subcortically, and in the deep temporal structures, corpus callosum, cerebellum, and pons. Mild periventricular leukoaraiosis was noted. The subcortical U-fibres were involved. These areas did not show contrast enhancement or mass effect, but exhibited peripheral ring and patchy diffusion restriction, particularly at their leading edge. Steroid therapy was initiated with methylprednisolone sodium succinate, followed by levetiracetam due to involuntary movements. Although there was a slight improvement in limb mobility and verbal contact, no clinically significant improvement was observed after completing steroid therapy. The patient fell asleep, and disturbances in consciousness increased. She was transferred to the ICU due to a sudden deterioration in her general condition, resulting in acute respiratory failure. Cardiac arrest occurred a few hours later.

A post mortem was performed, leading to the following diagnosis: extensive multifocal intrapulmonary infiltration of lymphoma, probably of B-cell origin; a scar from a previous myocardial infarction with moderate myocyte degeneration; passive congestion with an increased number of lymphocytes in the vessels; and blurred structure with signs of necrosis in the spleen and peripancreatic lymph node. Lymphatic infiltrates were found in the portal spaces of the liver. Colloid adenomas of the thyroid gland were also observed.

Brain samples from 10 different structures were fixed in 10% buffered formalin and embedded in paraffin. The specimens were stained with haematoxylin-eosin (H&E) and Klüver-Barrera (KB). Immunohistochemical studies were performed using antibodies GFAP, CD68, LCA, and CD45RO. For electron microscope evaluation, small fragments of brain tissue were taken from the paraffin blocks. After deparaffinisation, the material was fixed in 2.5% glutaraldehyde and post-fixed in 2% OsO4, then processed for Spurr resin embedding. Ultrathin sections were stained with uranyl acetate and lead citrate. The sections were examined with a transmission electron microscope (TEM), JEOL model 1400.

Light microscopic examination of the brain samples from the right frontal lobe revealed necrotic foci of demyelination with macrophage proliferation and opaque enlarged nuclei of oligodendrocytes. Numerous scattered partially confluent foci of demyelination were observed in the left frontal and parietal lobes, the right temporal lobe, the cerebellum, the pons, and the corpus callosum (Fig. 1C–E, G). These demyelinating lesions contained a large number of foamy macrophages, but only a few perivascular lymphocytes (Fig. 1F, H). Older demyelinating lesions contained large reactive astrocytes with bizarre pleomorphic hyperchromatic nuclei (Fig. 1I, J). Enlarged oligodendrocytes with glassy chromatin nuclei were filled with large inclusions resembling 'ground glass' (Fig. 1D). Electron microscopic examination of enlarged oligodendrocytes revealed granular intranuclear inclusions/virions of the JC polyomavirus (Fig. 1K, L).

In the differential diagnosis following ultrastructural identification of JC virions in the nucleus, the following disease entities were considered: progressive multifocal leukoencephalopathy (PML), PML-immune reconstitution inflammatory syndrome (PML-IRIS), fulminant JC encephalopathy involving cortical pyramidal neurons (JCE), JC granule cell neuronopathy (JC GCN), and JC meningitis [3–5].

The most frequently described entities in the medical literature are progressive multifocal leukoencephalopathy (PML) and PML-immune reconstitution inflammatory syndrome (PML-IRIS) [5]. In the classic form of PML, histopathological images show little or no inflammation. PML-IRIS is the same disease as PML, but with a high degree of inflammation. Neuroimaging findings in inflammatory forms of the disease include contrast enhancement, perilesional oedema, and mass effect on midline structures. Contrast enhancement suggests an inflammatory component, but the absence of enhancement does not exclude the diagnosis. In PML without signs of inflammation, MRI shows no contrast enhancement or mass effect. In PML-IRIS, demyelination may result from excessive brain tissue destruction by the host's immune system, whereas in PML demyelination is caused by JC virus-induced damage to infected oligodendrocytes [5].

Other disorders caused by the JC virus have also been described, including granule cell neuronopathy of the cerebellum (JCV GCN) and fulminant JC encephalopathy involving cortical pyramidal neurons (JCE) [3]. Dang and Koralnik (2009) suggested that JCV tropism for granule cells was associated with a 10-nucleotide deletion in the C-terminus of the VP1 gene. It is possible that other mutations in the JCV coding region may be associated with JC virus tropism for different types of neurons and neuroglial cells [6]. Cerebellar symptoms may occur in patients with JCV GCN. Neuropathological findings include cerebellar atrophy and cerebellar granule cell damage, but demyelination in the cerebellum is rarely observed. Patients with JC encephalopathy often present clinically with aphasia and global cognitive decline. Histologically, damage to cortical pyramidal neurons and astrocytes is observed in the cortex and subcortical grey matter [3].

In our case, the clinical symptoms, neuroimaging features, ultrastructural visualisation of intranuclear polyomavirus particles, and especially the neuropathological evaluation of fragments from 10 brain structures, allowed the diagnosis of

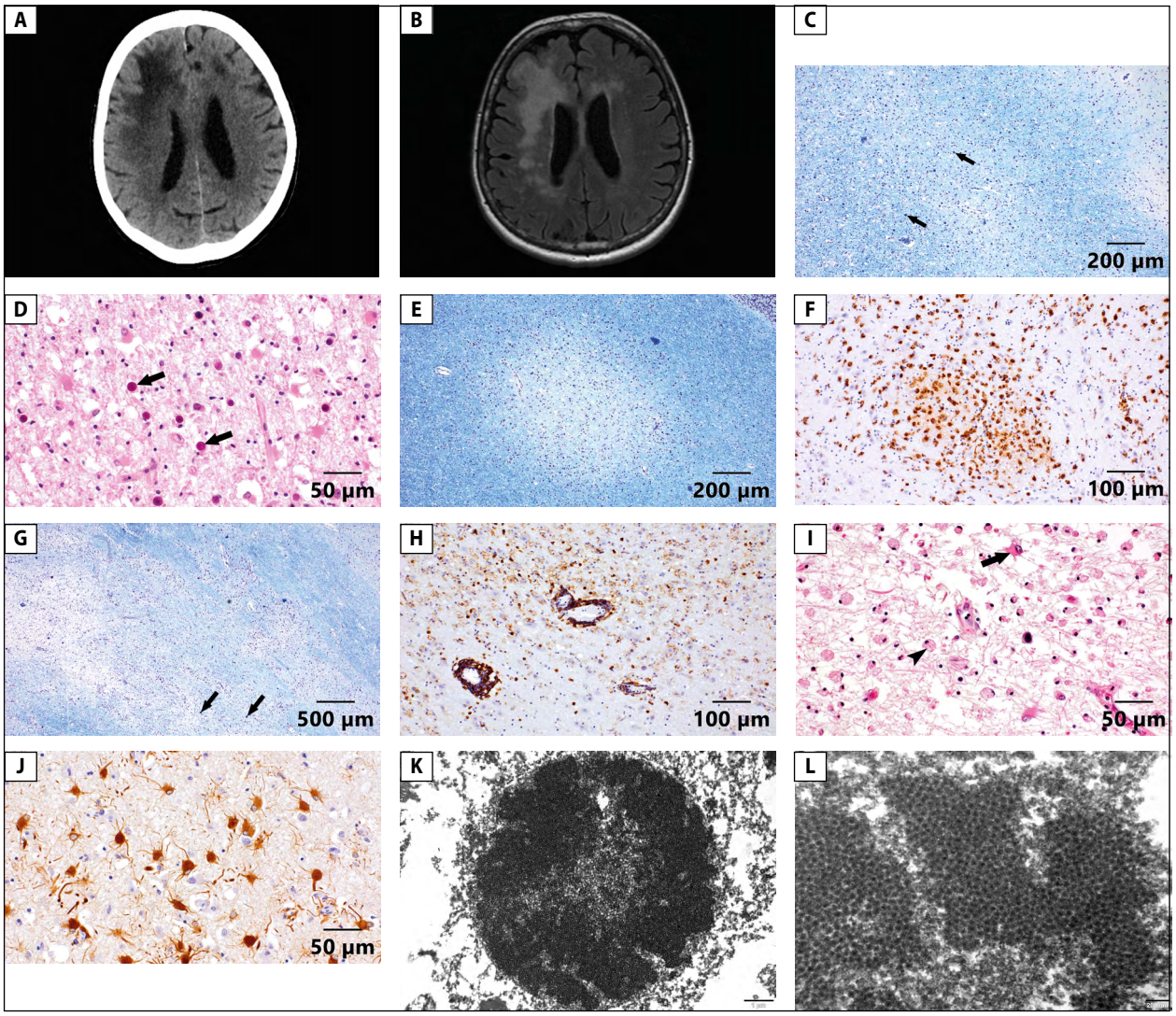

Figure 1. **A.** CT of head shows a hypoattenuating lesion in subcortical white matter. Note characteristic scalloped lateral margin; **B.** T2-weighted MRI shows a hyperintense lesion in right frontoparietal region within subcortical and periventricular white matter; **C.** Klüver-Barrera staining of frontal lobe shows areas of demyelination and enlarged oligodendrocytes (arrows); **D.** Haematoxylin and eosin staining of frontal lobe shows enlarged oligodendrocytes with 'ground glass' inclusions (arrows); **E.** Klüver-Barrera staining of cerebellum shows areas of demyelination and enlarged oligodendrocytes; **F.** Immunostaining of cerebellum with CD68 antibody shows macrophage proliferation in demyelination area; **G.** Klüver-Barrera staining of pons shows areas of demyelination and enlarged oligodendrocytes (arrows); **H.** Pons. Scanty perivascular lymphocytes. IHC CD45RO; **I.** Haematoxylin-eosin staining of frontal lobe shows macrophages (arrowhead) and atypical astrocytes (arrow); **J.** Immunostaining of frontal lobe with GFAP antibody shows large bizarre astrocytes; **K.** Electron micrograph showing granular large inclusions of JC virions in nucleus of an infected oligodendrocyte. Original magnification × 15,000; **L.** Electron micrograph showing intranuclear polyomavirus particles in PML. Original magnification × 60,000

PML. Brain biopsy, as proposed in the diagnostic algorithms for PML, seems to be helpful, but it may not be sufficient to diagnose other JC virus-related brain conditions [4].

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RESPONSE TO LETTER
TO THE EDITORS

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From rarity to reality: Poland's first case of neurological Erdheim-Chester Disease with cerebellar manifestations

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To the Editors

We thank Finsterer and Mehri [1] for their interest in our paper [2] and their constructive comments. We welcome this chance to clarify and expand upon the points they have raised.

In reply to the first statement on our report of the first case of ECD with neurological involvement in Poland, we hereby acknowledge the case described by Chrostowska et al. in 2022 [3]. Their patient showed a massive infiltration of the ocular adnexa of the eye with compression of the optic nerve and presented with severe limitation of eye motility and episodes of diplopia. While we were aware that the optic nerve is anatomically part of the CNS, we regret not citing this case, and thank Finsterer and Mehri for bringing it to our attention. We also acknowledge that we selected a somewhat provocative title to underline the importance of recognising ECD's neurological manifestations. Our aim was to raise awareness among neurologists that, in Poland (population 38 million) and other European countries, other cases are likely to exist. Our intention was to highlight a case involving cerebellar involvement, representing a different spectrum of CNS manifestations in ECD that required neurological assessment and management, thereby contributing to the neurological understanding of ECD in Poland.

Finsterer and Mehri also highlighted the endocrinological manifestations of ECD [1]. We fully agree that such symptoms are of interest and should be included. Due to journal limitations, and since our patient did not exhibit endocrine symptoms or abnormalities indicating endocrine disorders — and was indeed thoroughly examined in this regard — we did not emphasise this aspect of the disease in our paper.

However, we agree that in the discussion we should have included information that endocrine symptoms may occur within the spectrum of ECD manifestations. As delineated in the consensus recommendations by Goyal et al. [4], endocrine dysfunction is a common feature in ECD, and deserves a place in the comprehensive management of the disease. We shall keep this aspect in focus in future discussions, and work towards interdisciplinary cooperation to bring about the best outcomes for patients.

The authors of the letter also referenced neurological symptoms cited from the research by Jezierska et al. [5], which is linked to Langerhans cell histiocytosis (LCH) in the paediatric population. LCH and ECD are both histiocytoses, but they are very different in their clinical manifestations and demographic distributions. ECD is found predominantly in older males, and is comparatively rarely seen in the paediatric age group. It is important to distinguish between these entities so as to avoid inappropriate extrapolation of symptoms from LCH patients to ECD-diagnosed patients. LCH patients might present with more pronounced neurological symptoms than ECD individuals. However, this remains an unanswered question as it is also known that there might be a possible overlap between ECD and LCH, as underlined in the study by Pegoraro et al. [6], which could have consequences on the evolution and symptoms of ECD.

To conclude, we appreciate the chance to become part of this debate and believe that expert dialogues such as this will contribute substantially to better understanding regarding ECD. We hope that this response has clarified our position, and that we have emphasised the utmost importance of interdisciplinary approaches in the diagnosis and treatment of rare diseases like ECD.

Article information

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RESPONSE TO LETTER
TO THE EDITORS

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Response to: DNAJC30 variants can also manifest phenotypically as Leigh/LHON overlap syndrome

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To the Editors

We have read with interest dr. Finsterer's response to our letter to the editor, entitled 'Effects of Idebenone Treatment in a Patient with DNAJC30-Associated Leigh Syndrome', and appreciate his thoughtful comments, which we address below [1, 2].

Regarding the first point, the clinical and magnetic resonance imaging (MRI) features in our patient support the diagnosis of Leigh syndrome spectrum (LSS) based on current diagnostic guidelines. While we agree that symmetrical lesions are common in LSS, symmetry is not a strict diagnostic criterion [3]. As described in detail in the previous report, our patient exhibited bilateral lesions in basal ganglia, midbrain, and brainstem, albeit not simultaneously [4]. Moreover, symmetrical lesions in the thalamus were observed. The patient did not experience subacute visual failure, which is the core feature of Leber hereditary optic neuropathy (LHON). Although 'LHON-plus' can present with bilateral basal ganglia lesions, the severity of the lesions, and particularly the brainstem involvement, is more characteristic of LSS. Other clinical features such as early-childhood onset, elevated lactate levels in blood and cerebrospinal fluid, and developmental regression, also support the LSS diagnosis.

Regarding the second point, based on clinical, biochemical, and MRI findings, the diagnostic pathway prioritised LSS, and optical coherence tomography (OCT) was therefore not included in the initial workup. The patient exhibited chronic visual impairment, which had probably begun in early childhood. However, due to poor cooperation, the extent of visual acuity loss and retinal structural changes could not be thoroughly assessed. Ophthalmological examinations showed pale optic discs but no features characteristic of LHON, such as microangiopathy or telangiectasia.

Regarding the third point, it is important to note that according to the International League Against Epilepsy guidelines, epilepsy cannot be diagnosed solely based on electroencephalography (EEG) findings. Since the patient had never experienced any incidents suspected of being epileptic seizures, we did not find indications for an EEG study. While seizures are often observed in patients with a classical, neonatal-onset LSS, they are not part of its diagnostic criteria. Thus, the absence of epilepsy in our patient does not in fact preclude the diagnosis, because LSS encompasses a broad clinical spectrum.

Regarding the fourth point, we did not discourage the use of idebenone in patients with DNAJC30-associated LS or autosomal recessive LHON. On the contrary, we emphasised the need for further studies to evaluate idebenone's efficacy in similar cases. We fully acknowledge that robust conclusions require larger studies, ideally with a double-blind, placebo-controlled, multi-centre design.

Regarding the fifth point, the aetiology of gait impairment in our patient is challenging to determine due to overlapping and complex neurological symptoms. We have concluded that his gait disturbance results from a combination of pyramidal, extrapyramidal, and cerebellar features. There were no signs of myopathic or neurogenic degeneration in electromyography. We find the reported case of a DNAJC30 mutation associated with neuromyelitis optica spectrum disorder (NMOSD) intriguing. Nevertheless, our patient did not display any core clinical characteristics of NMOSD (with unknown AQP4-IgG status).

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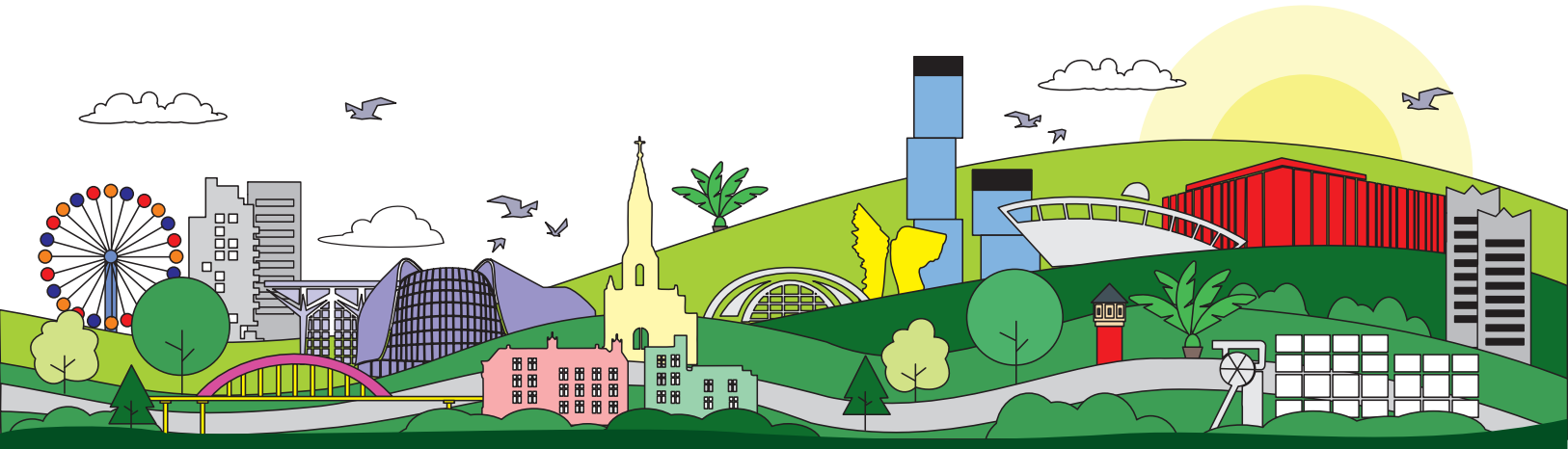

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