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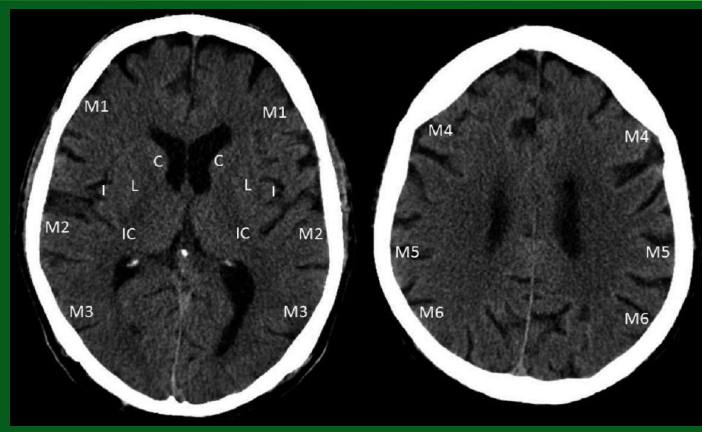

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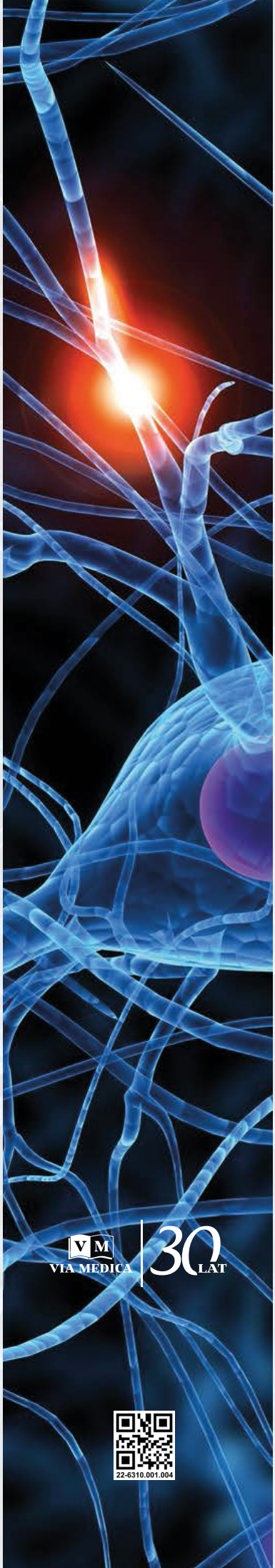

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Konferencja jest skierowana do wszystkich osób zainteresowanych tematyką. Sesje satelitarne firm farmaceutycznych, sesje firm farmaceutycznych oraz wystawy firm farmaceutycznych są skierowane tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (Dz. U. z 2017 r. poz. 2211., z późn. zm.).

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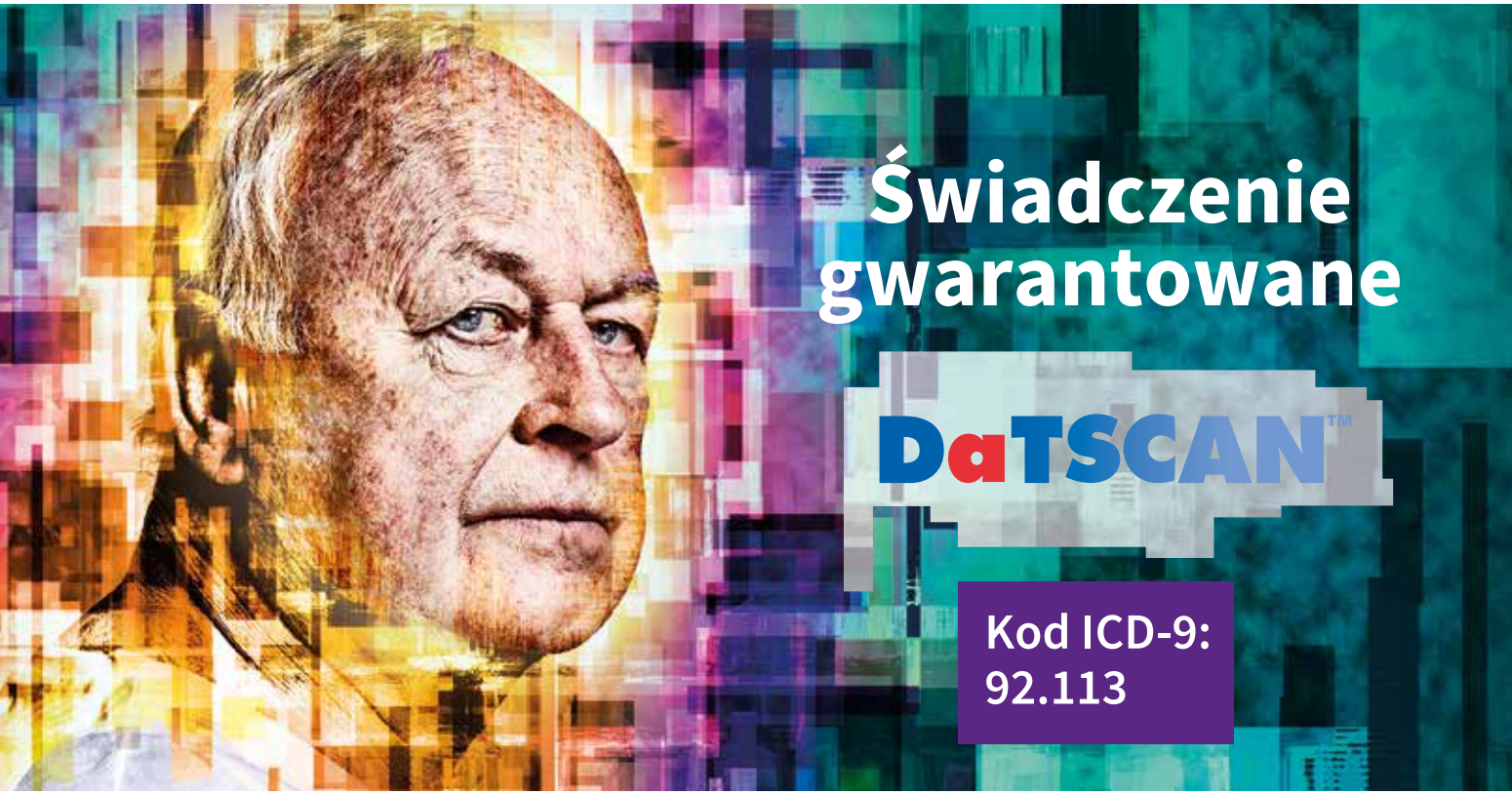
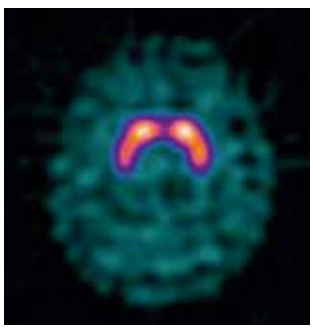


Dzięki wizualizacji DaT otrzymujemy zwiększenie jasności postawionej diagnozy

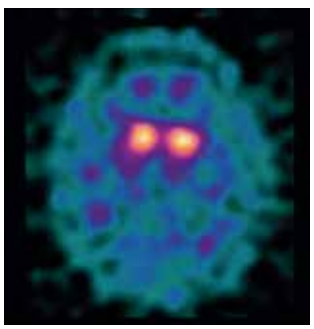
DaTSCAN odsłania funkcje mózgu leżące u podstaw patologii

Pozwalając dostrzec skalę utraty dopaminy, od 2000 roku DaTSCAN pomaga w stawianiu wczesnych, dokładnych diagnoz [1-4]

DaTSCAN jest analogiem kokainy z radioaktywnym izotopem I-123, który z dużym powinowactwem wiąże się z transporterami dopaminy na neuronach presynaptycznych [4]



W prawidłowym obrazie skanu DaTSCAN przyjmuje postać charakterystycznych „przecinków”



W nieprawidłowym obrazie skanu DaTSCAN przyjmuje postać „kropek”

Zalecenia:

- Dopaminergiczna tomografia emisyjna pojedynczych fotonów (single-photon emission computed tomography, SPECT) jest zalecana przez EFNS do stawiania diagnoz różnicowych degeneracyjnego parkinsonizmu oraz ET [5]
- Dopaminergiczna SPECT jest zalecana przez EFNS i konsorcjum DLB do stawiania diagnoz różnicowych degeneracyjnej AD oraz DLB [6,7]

Ilustracje pochodzą ze skanowania na potrzeby diagnozy różnicowej AD względem DLB.
Ilustracje uzyskano dzięki uprzejmości Szpitala w Birmingham City w Wielkiej Brytanii.
Uwaga: DaTSCAN nie umożliwia rozróżnienia pomiędzy PD, zanikiem wieloukładowym (multiple system atrophy, MSA) i postępującym porażeniem nadjądrowym (progressive supranuclear palsy, PSP). DaTSCAN nie umożliwia rozróżnienia pomiędzy DLB a demencją spowodowaną chorobą Parkinsona.

AD: Choroba Alzheimera; DaT: transporter dopaminy; DLB: otępienie z ciałami Lewy'ego; ET: drżenie samoistne; EFNS: European Federation of Neurological Sciences [Europejska Federeacja Nauk Neurologicznych]; MSA: zanik wieloukładowy; PD: choroba Parkinsona; PSP: postępujące porażenie nadjądrowe; SPECT: tomografia emisyjna pojedynczych fotonów

Piśmiennictwo:
1. Benamer HTS, Patterson J, Grosset DG. Mov Disord 2000; 15: 503-510.
2. McKeith IG i in. Lancet Neurol 2007; 6(4): 305-313.
3. Tinelli M i in. The value of early diagnosis and treatment in Parkinson's disease. Marzec 2016 r. Opracowanie dostępne pod adresem: http://www.braincouncil.eu/wp-content/uploads/2016/11/Parkinson-report-2016-1.pdf [Dostęp uzyskano dnia: 09/06/2017].
4. DaTSCAN Charakterystyka Produktu Leczniczego (PL), GE Healthcare, styczeń 2021 r.
5. Berardelli A i in. Eur J Neurol 2013; 20: 16-34.
6. Hort J i in. Eur J Neurol 2010; 17: 1236-1248.
7. McKeith IG et al. Neurol 2005; 65(16): 1863-1872.

Skrócona Charakterystyka Produktu Leczniczego DaTSCAN (*Ioflupanum 123I*)
Przed przepisaniem produktu leczniczego należy zawsze zapoznać się z Charakterystyką Produktu Leczniczego (ChPL). Dodatkowe informacje są dostępne na żądanie.
Skład jakościowy i ilościowy Każdy mililitr produktu zawiera 74 MBq joflupanu (123I) w czasie aktywności referencyjnej (0,07 do 0,13 µg/ml joflupanu).
Każda fiolka zawierająca pojedynczą dawkę 2,5 ml zawiera 185 MBq joflupanu (123I) (zakres aktywności 2,5 do 4,5 x 1014 Bq/mmol) w czasie aktywności referencyjnej. Każda 5 ml fiolka zawiera pojedynczą dawkę 370 MBq joflupanu (123I) (zakres aktywności 2,5 do 4,5 x 1014 Bq/mmol) w czasie aktywności referencyjnej.
Substancje pomocnicze o znanym działaniu Ten produkt leczniczy zawiera 39,5 g/l etanolu. Pełny wykaz substancji pomocniczych, patrz punkt 6.1.
Postać farmaceutyczna Roztwór do wstrzykiwań. Przejrzysty, klarowny roztwór.
Wskazania do stosowania Produkt leczniczy przeznaczony wyłącznie do diagnostyki. DaTSCAN przeznaczony jest do wykrywania zmniejszenia liczby funkcjonalnych dopaminergicznych zakończeń neuronalnych w prążkowiu: - u dorosłych pacjentów z klinicznie niejasnymi zespołami parkinsonowskimi, na przykład tych na wczesnym etapie, w celu odróżnienia drżenia samoistnego od zespołów parkinsonowskich powiązanych z idiopatyczną chorobą Parkinsona, zanikiem wieloukładowym i postępującym porażeniem nadjądrowym. DaTSCAN nie pozwala na rozróżnienie choroby Parkinsona, zaniku wieloukładowego oraz postępującego porażenia nadjądrowego; - u dorosłych pacjentów ułatwia różnicowanie prawdopodobnego rozpoznania demencji z obecnością ciałek Lewy'ego oraz choroby Alzheimera; DaTSCAN nie pozwala na różnicowanie demencji z obecnością ciałek Lewy'ego oraz demencji w przebiegu choroby Parkinsona.
Dawkowanie i sposób podawania Przed podaniem należy upewnić się, że dostępny jest zestaw reanimacyjny. Produkt DaTSCAN należy stosować wyłącznie u pacjentów skierowanych przez lekarzy doświadczonych w leczeniu zaburzeń ruchowych i (lub) demencji. Produkt DaTSCAN powinien być stosowany wyłącznie przez wykwalifikowany personel, posiadający odpowiednie uprawnienia do wykonywania badań z zastosowaniem produktów radiofarmaceutycznych, w wyznaczonej jednostce klinicznej.
Dawkowanie Skuteczność kliniczną udokumentowano w zakresie dawek od 111 MBq do 185 MBq. Nie należy stosować dawki większej niż 185 MBq ani stosować, jeżeli aktywność wynosi mniej niż 110 MBq. W celu zminimalizowania wychwytu radioaktywnego jodu przez tarczycę przed podaniem należy zastosować u pacjentów odpowiednie zablokowanie gruczołu tarczowego, np. poprzez doustne podanie 120 mg jodku potasu, od 1 do 4 godzin przed podaniem DaTSCAN. Populacje specjalne Zaburzenia czynności nerek i wątroby Nie przeprowadzono oficjalnych badań u pacjentów ze znacznymi zaburzeniami czynności wątroby lub nerek. Brak dostępnych danych (patrz punkt 4.4). Dzieci i młodzież Nie określono bezpieczeństwa stosowania i skuteczności produktu leczniczego DaTSCAN u dzieci w wieku od 0 do 18 lat. Brak dostępnych danych. Sposób podawania Do stosowania dożylnego. Produkt DaTSCAN powinien być stosowany bez rozcieńczania. Aby zminimalizować ryzyko wystąpienia bólu w miejscu iniekcji podczas podawania leku, zalecane jest podawanie w formie powolnej iniekcji dożylnej (w czasie co najmniej 15 do 20 sekund) do żyły kończyny górnej. Uzyskiwanie obrazu Obrazowanie metodą SPECT należy wykonać w okresie od trzech do sześciu godzin po iniekcji. Obrazy należy uzyskiwać za pomocą gammakamery wyposażonej w kolimator o wysokiej rozdzielczości, skalibrowany przy użyciu fotopiku 159keV oraz ± 10% okna energii. Korzystne jest, aby próbkowanie kątowe wynosiło nie mniej niż 120 projekcji na 360 stopni. Dla kolimatorów o wysokiej rozdzielczości promień rotacji powinien być zgodny i jak najmniejszy (zwykle 11-15 cm). Badania doświadczalne wykonane za pomocą fantomu prążkowia sugerują, że w przypadku obecnie używanych systemów, najlepsze obrazy uzyskuje się przy dobraniu rozmiaru macierzy oraz współczynnika zbliżenia tak, aby rozmiar piksela wynosił 3,5-4,5 mm. W celu uzyskania optymalnych obrazów należy uzyskać co najmniej 500 000 zliczeń.
Przeciwwskazania - Nadwrażliwość na substancję czynną lub którąkolwiek substancję pomocniczą wymienioną w punkcie 6.1 ChPL. - Ciąża (patrz punkt 4.6 ChPL).
Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania Jeżeli wystąpi reakcja nadwrażliwości, należy natychmiast przerwać podawanie produktu leczniczego i jeżeli jest to konieczne, rozpocząć leczenie dożylnie. Produkty lecznicze stosowane w reanimacji oraz wyposażenie reanimacyjne (np. rurka dotchawiczna i respirator) muszą być gotowe do użycia. Ten produkt radiofarmaceutyczny może być stosowany i podawany wyłącznie przez osoby upoważnione, w wyznaczonych do tego jednostkach klinicznych. Jego przyjmowanie na stan, przechowywanie, stosowanie, transport oraz niszczenie podlegają przepisom i wymagają posiadania licencji wydawanych przez upoważnione do tego instytucje. U każdego pacjenta narażenie na promieniowanie jonizujące powinno być uzasadnione spodziewanymi korzyściami. Podawana aktywność musi być taka, aby dawka promieniowania była możliwie najmniejsza, przy uzyskaniu zamierzonego wyniku diagnostycznego. Dotychczas nie przeprowadzono badań u pacjentów ze znaczną niewydolnością nerek lub wątroby. Wobec braku takich danych nie zaleca się stosowania DaTSCAN u pacjentów z umiarkowaną lub ciężką niewydolnością nerek lub wątroby. Ten produkt leczniczy zawiera 39,5 g/l (5% obj.) alkoholu etylowego. Jedna dawka zawiera 197 mg alkoholu, co odpowiada 5 ml piwa lub 2 ml wina. Preparat szkodliwy dla pacjentów z chorobą alkoholową. Należy to uwzględnić w przypadku pacjentów z grup wysokiego ryzyka na przykład z chorobami wątroby lub u chorych na padaczkę.
Interpretacja obrazów DaTSCAN Obrazy DaTSCAN są interpretowane wizualnie na podstawie wyglądu prążków. Optymalną prezentacją zrekonstruowanych obrazów do interpretacji wizualnej są przekroje poprzeczne równoległe do linii spoidła przedniego i tylnego (AC-PC). Analiza, czy obraz jest prawidłowy, czy nieprawidłowy, odbywa się poprzez ocenę zasięgu (na co wskazuje kształt) i intensywności (w stosunku do tła) sygnału prążkowia. Prawidłowe obrazy cechują się obecnością dwóch symetrycznych, sierpowatych obszarów o jednakowej intensywności.

GE Medical Systems Polska Sp. z o.o.
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02-583 Warszawa

04-2023 JB00493PL POLAND

Nieprawidłowe obrazy są albo asymetryczne, albo symetryczne o nierównej intensywności i(lub) nie mają kształtu sierpowatego. Wizualnej interpretacji może towarzyszyć dodatkowo półilościowa ocena z użyciem oprogramowania z oznakowaniem CE, jak np. DaTQUANT, gdzie absorpcja produktu DaTSCAN w prążkowiu jest porównywana z absorpcją w referencyjnym regionie, a wskaźniki te są porównywane z bazą danych zdrowych osób dostosowaną pod względem wieku. Ocena wskaźników takich jak absorpcja produktu DaTSCAN w lewym/prawym prążkowiu (symetrycznie) lub absorpcja skorupa/jądro ogoniaste prążkowia, może być dodatkową pomocą w ocenie obrazów.
Z stosowaniem metod półilościowych należy zachować następujące środki ostrożności: - Ocena półilościowa powinna być stosowana jedynie jako dodatek do oceny wizualnej
- Należy używać wyłącznie oprogramowania ze znakiem CE
- Użytkownicy powinni zostać przeszkoleni przez producenta w zakresie obsługi oprogramowania oznaczonego znakiem CE i postępować zgodnie z wytycznymi EANM dotyczącymi akwizycji, rekonstrukcji i oceny obrazu
- Osoby odczytujące powinny wizualnie zinterpretować skan, a następnie przeprowadzić analizę półilościową zgodnie z instrukcjami producenta, w tym kontrolę jakości procesu ilościowego
  - Techniki ROI/VOI powinny być używane do porównania absorpcji w prążkowiu z absorpcją w referencyjnym regionie.
  - Zalecane jest porównanie z bazą danych zdrowych osób dostosowaną pod względem wieku w celu uwzględnienia spodziewanego zmniejszenia się wiązania w prążkowiu
  - Zastosowane ustawienia rekonstrukcji i filtra (w tym korekta tła) mogą wpływać na wartości półilościowe. Należy przestrzegać ustawień rekonstrukcji i filtrów zalecanych przez producenta oprogramowania oznaczonego znakiem CE i powinny one odpowiadać tym stosowanym do półilościowego oznaczenia bazy danych osób zdrowych.
  - Intensywność sygnału prążkowia mierzona metodą SBR (stratial binding ratio, współczynnik wiązania prążkowia) oraz asymetria i stosunek jądra ogoniastego do skorupy dostarczają obiektywnych wartości liczbowych odpowiadających parametrom oceny wizualnej i mogą być pomocne w trudnych do odczytania przypadkach
  - Jeśli wyniki oceny półilościowej są niezgodne z interpretacją wizualną należy ocenić skan pod względem prawidłowości położenia ROI/VOI, poprawności orientacji obrazu, poprawności doboru parametrów do pozyskiwania obrazu i poprawności korekty tła.
  - Ostateczna ocena powinna zawsze uwzględniać zarówno interpretację wizualną, jak i wyniki oceny półilościowej

Działania niepożądane Dla produktu DaTSCAN zidentyfikowano następujące działania niepożądane: Podsumowanie dotyczące objawów niepożądanych w Tabeli Częstość występowania objawów niepożądanych została zdefiniowana w następujący sposób: bardzo często (≥1/10), często (≥1/100 do <1/10), niezbyt często (≥1/1 000 do <1/100), rzadko (≥1/10 000 do <1/1 000), bardzo rzadko (<1/10 000) oraz częstość nieznana (częstość nie może być określona na podstawie dostępnych danych). W obrębie każdej grupy o określonej częstości występowania objawy niepożądane są wymienione zgodnie ze zmniejszającym się nasileniem. Zaburzenia układu immunologicznego
Częstość nieznana: nadwrażliwość Zaburzenia metabolizmu i odżywiania Niezbyt często: zwiększony apetyt Zaburzenia układu nerwowego Często: ból głowy Niezbyt często: zawroty głowy, mrowienie (parestezje), zaburzenia smaku Zaburzenia ucha i błędnika Niezbyt często: zawroty głowy Zaburzenia skóry i tkanki podskórnej
Częstość nieznana: rumień, świąd, wysypka, pokrzywka, nadmierne pocenie się Zaburzenia układu oddechowego, klatki piersiowej i śródpiersia Częstość nieznana: duszność Zaburzenia żołądkowo-jelitowe Niezbyt często: nudności, suchość w ustach,
Częstość nieznana: wymioty Zaburzenia naczyniowe Częstość nieznana: obniżone ciśnienie krwi Zaburzenia ogólne i odczyny w miejscu podania Niezbyt często: ból w miejscu podania (silny ból lub uczucie pieczenia po podaniu do drobnych żył), Częstość nieznana: uczucie gorąca
Narażenie na promieniowanie jonizujące ma potencjalne działanie rakotwórcze i wiąże się z ryzykiem powstania wad genetycznych. Ponieważ dawka skuteczna wynikająca z podania maksymalnej zalecanej aktywności 185 MBq DaTSCAN wynosi 4,63 mSv, prawdopodobieństwo wystąpienia działań niepożądanych jest niewielkie.
Zgłaszanie podejrzewanych działań niepożądanych Po dopuszczeniu produktu leczniczego do obrotu istotne jest zgłaszanie podejrzewanych działań niepożądanych. Umożliwia to nieprzerwane monitorowanie stosunku korzyści do ryzyka stosowania produktu leczniczego. Osoby należące do fachowego personelu medycznego powinny zgłaszać wszelkie podejrzewane działania niepożądane za pośrednictwem Departamentu Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych.
Al. Jerozolimskie 181C, 02-222 Warszawa, Tel.: + 48 22 49 21 301, Faks: + 48 22 49 21 309, Strona internetowa: https://smz.ezdrowie.gov.pl
Podmiot odpowiedzialny posiadający pozwolenia na dopuszczenie do obrotu
GE Healthcare B.V. De Rondom 8, 5612 AP, Eindhoven, Holandia
Numery pozwoleń na dopuszczenie do obrotu EU/1/00/135/001 (2,5 ml)
EU/1/00/135/002 (5 ml)
Nazwa organu, który wydał pozwolenia na dopuszczenie do obrotu
Komisja Europejska
Kategoria dostępności Produkt leczniczy wydawany z przepisu lekarza do zastrzeżonego stosowania – Rpz.
Data zatwierdzenia lub częściowej zmiany tekstu Charakterystyki Produktu Leczniczego 28 stycznia 2021 r.
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Cover photo: Ewa Pilarska et al. Extent of MCA vascularisation on both sides (see figure on page 248)

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REVIEW ARTICLE

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Sleep disturbances in progressive supranuclear palsy syndrome (PSP) and corticobasal syndrome (CBS)

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Abstract

Introduction. Progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) are clinical manifestations of tauopathies. They are commonly associated with rapid motor and cognitive deterioration. Sleep disturbances are less frequently described as a feature of these diseases, though they are reported among 50–75% of PSP patients.

State of the art. Apart from various clinical manifestations, sleep abnormalities in PSP and CBS seem to be a factor enhancing pathogenesis as well its consequences. Multiple researchers have looked into the issue of whether the complexity of sleep disturbances in PSP and CBS could be linked to atrophic changes within structures crucial for daytime regulation, coexisting pathologies, or other less explored mechanisms.

Clinical significance. Among sleep abnormalities in PSP and CBS have been reported excessive daytime sleepiness, night-time insomnia, reduction of total sleep time, more pronounced sleep fragmentation, restless leg syndrome (RLS), agrypnia excitata, periodic limb movements, sleep respiratory disturbances, rapid-eye movement behaviour disorder, and others.

Future directions. The aim of this review was to elaborate upon the significance of sleep abnormalities in tauopathic parkinsonian syndromes, and to determine their usefulness in differential diagnosis with synucleinopathic parkinsonian syndromes. Extended analyses of sleep disturbances may provide a different perspective on atypical parkinsonisms.

Key words: progressive supranuclear palsy, corticobasal syndrome, CBS, PSP, sleep disturbances

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Introduction

Progressive supranuclear palsy syndrome (PSP) and corticobasal syndrome (CBS) are clinical manifestations of tauopathies. They are classified as atypical parkinsonisms. While PSP is most commonly associated with PSP pathology, CBS is observed among patients with various pathologies, among which could be mentioned what used to be known as corticobasal degeneration (CBD), PSP, frontotemporal degeneration (FTD), Alzheimer's disease (AD) and others. The pathogenesis of these diseases is not fully understood [1]. There has been growing interest in the non-motor symptoms of tauopathic parkinsonian syndromes [2], and more attention has recently been paid in the context of sleep disturbances in this group, a feature often omitted in clinical examination.

Clinical significance

The frequency of sleep disorders among patients diagnosed with parkinsonisms varies widely. An observational study

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released in 2010 evaluated 1,307 patients with parkinsonisms, among whom 34 patients had multiple system atrophy (MSA), 30 had PSP, 14 had dementia with Lewy bodies (DLB), and 11 had CBD. Sleep disturbances were observed in more than 75% of patients with PSP and DLB, in c.65% of those with MSA and PD, and only in 36.4% of CBS patients [3].

This discrepancy between PSP and CBD may suggest that the sleep disturbance in parkinsonian syndromes may not be directly associated with underlying pathology, as both entities are tauopathies.

Though sleep disorders are interpreted as a common feature of PSP, they are not indicated in the criteria of diagnosis [4]. The incidence of sleep abnormalities in CBS is less specified. The aim of this review was to present an overview of findings concerning sleep abnormalities in PSP and CBS.

Material and methods

Our search for articles related to sleep abnormalities in PSP and CBS was based on the use of the PubMed database. We used the phrases "Corticobasal Syndrome Sleep", "Corticobasal Syndrome Sleep Abnormalities", "Progressive Supranuclear Palsy Sleep", and "Progressive Supranuclear Palsy Sleep Abnormalities". Due to the rarity of the syndromes, we also acknowledged case reports and research studies based on groups of fewer than 10 patients examined. Additionally, due to the evolution of terminology, certain older works referring to "Corticobasal Syndrome" used to describe it as "Corticobasal Degeneration". The goal of our search was to obtain a perspective dedicated to these clinical entities.

Sleep disturbances

Sleep disturbances in development of neurodegeneration

Sleep disturbances have been evaluated as a factor in neurodegeneration. They may be a condition preceding the initiation of other symptoms of neurodegenerative disease. The exact relation between these processes is not verified. Growing interest is associated with dysfunction of the glymphatic system, which on the one hand is linked with slow-wave sleep, while on the other hand its abnormalities have been found to contribute to neurodegeneration [5]. The role of the glymphatic system has been evaluated in PD, where the extracellular accumulation of alpha-synuclein is a feature impacting upon the neuroinflammatory and glymphatic response [6]. Deficits of the glymphatic system, a deterioration in eliminating waste proteins, and the correlation between this and an increase of tau accumulation have also been studied in AD [7]. Abnormalities of the system have been interpreted as possibly modifiable points in the pathogenesis of dementia [7]. Sleep abnormalities have been indicated as parallel features correlated with this process, as the accumulation of tau may disrupt the wake-sleep cycle. To the best of our knowledge, no study presenting this issue in PSP and CBS has previously been published.

Sleep disturbances in progressive supranuclear palsy

The first report presenting PSP indicated that fatigue was a feature of the disease [8]. With the evolution of knowledge concerning this disease, sleep abnormalities and night-time behavioural deviations became associated with approximately half of PSP patients [9]. Interestingly, the abnormalities have been interpreted as moderate to severe among almost one out of four [9]. Among sleep disturbances associated with PSP can be mentioned excessive daytime sleepiness, night-time insomnia, reduction of total sleep time, more pronounced sleep fragmentation, rapid-eye movement behaviour disorder, restless leg syndrome (RLS), and sleep respiratory disturbances [10–13]. Insomnia and deviated sleep architecture are the most common sleep abnormalities in PSP [14]. Sleep disturbances are rarely observed at the time of diagnosis. However, they are reported by 50% of patients who have experienced three years or more of disease duration [15].

Sleep disturbance has been interpreted as a factor inducing up to a quadrupling in mortality in PSP [16]. Additionally, the pathogenesis of sleep abnormalities seems multifactorial, being on the one hand linked with neurodegenerative changes within the brainstem, and on the other hand being associated with cognitive, pseudobulbar and extrapyramidal disturbances [17]. The sleep disturbances in PSP may be also related to degeneration of the thalamus, as this has been interpreted as a milestone in the gating of sensory information, which induces different patterns of activity during sleep and wakefulness [18]. Abnormalities related to the thalamus have been reported in various works, although the issue of sleep disturbances associated with these deviations was not explored [19–21]. Hypothalamus, another structure impacted upon by PSP degeneration, is associated with decreased pre- or post-synaptic orexin neurotransmission [22]. In a work evaluating orexin levels in the cerebrospinal fluid in PD, DLB, PSP and CBD, it was revealed that its levels were significantly lower in tauopathic parkinsonian syndromes [23].

The disturbance of orexin regulation may cause abnormalities in the sleep-wake cycle [24]. Interestingly, disturbances of this cycle may be both a manifestation and a cause of neurodegenerative disorders [25]. PSP and CBS have also been examined in the context of wake-promoting neurons. It was found that the structure, though highly impacted upon by AD, is spared in both PSP and CBS [26].

Sleep abnormalities in PSP refer to different entities. The quality of sleep in PSP is interpreted as being more deteriorated partly due to its fragmentation, which can be observed in polysomnographic examination (PSG) [27]. Patients with PSP are considered as experiencing a longer duration of falling asleep [28]. The neurodegeneration and subsequent atrophic changes within the brainstem result in deviations affecting sleep regulating structure [16]. Due to the degeneration of the brainstem, insomnia in patients with PSP is more severe than the insomnia observed in Parkinson's Disease (PD) and AD. [29]. This deterioration within the brainstem has been

found to be correlated also with excessive daytime sleepiness and obstructive sleep apnoea [30]. The atrophies within the pedunculopontine tegmentum significantly decrease the percentage of REM sleep in PSP [31, 32]. Additionally, the durations of N2 and N3 sleep have been shown to be significantly decreased [28]. Vertical saccadic restriction was also found to decrease both sleep time and its efficiency [33]. In a work presenting two phenotypes of PSP-PSP Richardson Syndrome (PSP-RS) and PSP-speech and language subtype (PSP-SL) it was pointed out that sleep deviations are more frequent in probable PSP-RS than in PSP-SL. The work was based on a screening questionnaire evaluation of 90 patients with PSP-SL and 71 with PSP-RS.

Interestingly, the threshold of at least one sleep disturbance has been observed in almost twice the number of patients with PSP-RS compared to PSP-SL. Features such as using one's voice during sleep or acting out dreams, commonly associated with being an aspect of synucleinopathies, have been found to be often present in probable PSP-RS [34]. Excessive daytime sleepiness was not considered a differentiating feature of the examined entities. Fatigue in PSP patients has not been fully explored [35]. Its increased level correlates not only with severely disturbed sleep hygiene, but also a more pronounced tendency towards depression [36]. The EEG patterns of sleep in PSP have been considered to resemble those reported in presenile dementia [37].

Rapid Eye Movement Behaviour Disorder (RBD), a feature commonly associated with synucleinopathies, is one of the sleep abnormalities found in tauopathic parkinsonian syndromes [38–43]. Extended research has revealed that abnormalities such as RBD, which have been primarily described in synucleinopathies, have also been found to be present in PSP and CBS. In PSP, RBD is linked with recurrent dream enactment behaviour [11]. RBD is associated with 14–33% of patients with PSP compared to c.60% in PD [10, 11, 44]. A different study investigating the incidence of RBD showed significantly lower rates of RBD among patients afflicted by PSP — 36.7% and especially CBS — 5.5%, when compared to those afflicted by PD, DLB and MSA (58-81.9%) [45]. The authors, Smilowska et al., revealed that although RBD is not a common feature of PSP, it should be interpreted as a possible aspect of the disease, unlike CBS [40]. A different work presenting similar rates (11–14%) of RBD among PSP and CBD patients was affected by smaller groups — 35 with PSP and only seven with CBD [46].

The frequency of REM without atonia (RWA) in PSP has been evaluated in various works. In the study by Arnulf et al., evaluating 15 patients with PD, 15 with PSP and 15 controls, the incidence of RWA in both diseases was similar, ranging from 28% to 36% [47]. This study was based on sleep interviews, overnight polysomnography (PSG), and Multiple Sleep Latency Tests. In the work by Nomura et al. examining 20 patients with PSP and 93 with PD, RWA was more common in PD [48]. The authors verified interviews with patients and their caregivers, and subsequently assessed the clinical backgrounds and PSG parameters. None of the abovementioned works acknowledged any differentiation between phenotypes of PSP. The study highlighting the higher prevalence of RWA among PD patients was based on older PD and PSP patients than the work by Arnulf et al. (75 ± 7 years in PSP and 73.4 ± ± 7.9 in PD compared to 68 ± 8 in PSP and 67 ± 7 in PD) [47]. The percentage of males in the study indicating lower RWA incidence in PSP was three times higher than females. The disease duration of the PD group with similar to PSP. RWA incidence was more diverse. Comparing these works may suggest an additional impact of sex, age at onset, and disease duration on the prevalence of RBD in both diseases. Restless leg syndrome, RLS, though commonly linked with PD, is also frequently present in PSP, and has been correlated with deviated sleep efficiency and duration [30]. PSP rating scale (PSPRS), a common test evaluating PSP, is interpreted as feasible in the evaluation of sleep disturbances. In the section covering daily activities can be found a query regarding sleep difficulties. This part of the test is dedicated to insomnia in PSP and may be insufficient in other sleep abnormalities [49].

Sleep disturbances in corticobasal syndrome

The interpretation of sleep abnormalities in CBS is more difficult than in PSP, due to the more diverse underlying pathologies and the lower incidence of the disease. Recent advances have revealed that CBS should be interpreted as a group of diseases among which could be mentioned most commonly tauopathies, however the group also includes vascular changes, TDP-43 pathology and others [50–52]. The presence of TDP-43 pathology has been reported in up to 17%, while the incidence of vascular CBS is not yet fully evaluated [53]. Among sleep disturbances in CBS one can mention insomnia, RLS, agrypnia excitata, sleep respiratory disorders, inversion of sleep and vigilance pattern, periodic limb movements, and less commonly RBD [45, 46, 54–61]. Periodic limb movements in CBS may be unilateral. Their presence is linked with disrupted inhibitory pathways initiated in the cortex or basal ganglia [62].

A work highlighting Lewy body disease with clinical manifestation of CBS showed a lower incidence of RBD and a younger age at disease onset among these patients when compared to LBD [63]. The incidences of RBD in CBS are commonly based on a small number of patients or case reports [45, 46, 54, 55, 57]. Patients with CBS and RBD may experience symptoms of overlapping synucleinopathic and tauopathic parkinsonian syndromes. One of the patients with clinical manifestation of apraxia, rigidity, bradykinesia and right arm myoclonus, suffered due to hallucinations and RBD. Neuropathological evaluation revealed astrocytic plaques, and thorny astrocytes were disseminated within cortical, subcortical and limbic structures [51, 53]. Lewy bodies were found in the substantia nigra, locus ceruleus and nucleus of the solitary tract. The appearance of subclinical RBD in CBS is associated

Table 1. General overview on sleep disturbances in PSP and CBS

	Progressive supranuclear palsy syndrome	Corticobasal syndrome
Frequency*	75%	36.4%
Sleep disturbances — clinical features	**Most common:** — excessive sleepiness — insomnia — sleep fragmentation — night-time insomnia — reduction of total sleep time **Less common:** — rapid-eye movement behaviour disorder — restless leg syndrome — sleep respiratory disturbances	*insufficient data to determine frequency of disorders — insomnia — restless leg syndrome — agrypnia excitata — sleep respiratory disorders — inversion of sleep vigilance pattern — periodic limb movements
Sleep disturbances — related features	Decreased level of orexin	Decreased level of orexin

CBS — corticobasal syndrome; PSP — progressive supranuclear palsy syndrome

with simultaneous atrophic changes in the cortex, thalamus and brainstem [59]. Brainstem nuclei and pontomedullary pathways being affected is considered to be a possible cause of RBD in CBS [64].

Conclusions

Our review of sleep disturbances shows them to be an insufficiently explored aspect of PSP and CBS (Tab. 1). Undoubtedly, PSP and CBS show a significantly lower rate of RBD incidence than synucleinopathic parkinsonian syndromes. However, the presence of RBD should not be a factor leading to the exclusion of tauopathic parkinsonian syndromes in a differential diagnosis. On the other hand, the presence of factors such as insomnia, excessive daytime sleepiness and sleep fragmentation combined with parkinsonian syndrome may not necessarily be observed in PD or other synuclienopathies, however they can be also associated with possible tauopathic atypical parkinsonisms. There are several limitations which make interpretation of the studies more difficult. Chief among these is the lack of neuropathological verification in the majority of the presented works; also, the diverse pathology of CBS, the small groups rarely exceeding 20 patients in the research studies in the context of CBS, and the lack of indication regarding subtypes of PSP. Any of these could additionally impact upon the obtained results.

In the context of PSP and CBS, the features regarding the course of sleep disturbances are multifactorial. The evolution of the abnormalities is likely to be correlated with the stage of atrophic changes, and the dissemination of pathological proteins and other coexistent mechanisms. The presence of RBD may be additionally impacted upon by the coexistence of Lewy bodies in neuropathological examination.

Analysis of the combination of sleep deviations may be interpreted as an interesting feature of disease progress and may provide additional hints on the possible underlying pathology. Our review shows that patients with diagnoses of probable or possible PSP and CBS, or their caregivers, should undergo a detailed interview concerning sleep disturbances. The course of these abnormalities may be both a manifestation and a cause of the progress of the disease. Further research in this field is required.

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Targeting CD20 in multiple sclerosis — review of current treatment strategies

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ABSTRACT

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system (CNS) that mostly manifests as irreversible disability. The aetiopathogenesis of MS is still unclear, although it was initially thought to be primarily mediated by T-cells.

Research into the immune concepts of MS pathophysiology in recent years has led to a shift in the understanding of its origin i.e. from a T-cell-mediated to a B-cell-mediated molecular background. Thus, the use of B-cell-selective therapies, such as anti-CD20 antibody therapy, as expanded therapeutic options for MS is now strongly supported.

This review provides an up-to-date discussion on the use of anti-CD20 targeted therapy in MS treatment. We present a rationale for its use and summarise the results of the main clinical trials showing the efficacy and safety of rituximab, ocrelizumab, ofatumumab, and ublituximab. Future directions that show selectivity to a broader population of lymphocytes, such as the use of anti-CD19 targeted antibodies, as well as the concept of extended interval dosing (EID) of anti-CD20 drugs, are also discussed in this review.

Key words: multiple sclerosis, targeting CD20, ofatumumab, ocrelizumab, ublituximab, rituximab, extended interval dosing

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Introduction

Multiple sclerosis (MS) is one of the most common autoimmune inflammatory diseases of the central nervous system (CNS) and is characterised by the accumulation of irreversible disability. The most common form of the disease, relapsing-remitting multiple sclerosis (RRMS), is characterised by the appearance of new or worsening neurological symptoms (relapses), which last for at least 24 hours. In the early stages of the disease, complete resolution of neurological defects is observed; however, after some time, the symptoms can become permanent.

Gradually, MS symptoms become more severe, and patients suffer from serious neurological deficits, including physical, psychological, and cognitive deficits. Nevertheless, there is no specific course of the disease, as it can vary from patient to patient. Other forms of MS, including primary progressive MS (PPMS), secondary progressive (steady worsening after RRMS; SPMS), and progressive-relapsing MS (PRMS), are characterised by a particularly intensive accumulation of disability [1]. Therefore, effective early treatment is crucial to prevent disability progression and reduce relapse risk.

The aetiopathogenesis of MS is still not fully clear. Nevertheless, excessive activation of the immune system is known to be responsible for the destruction of myelin and, consequently, axonal (neuronal) failure. For many years, the essential component of the immune system attacking myelin was considered to be CD4+ lymphocytes. As a result, many drugs used in the treatment of MS, such as interferons, teriflunomide, or natalizumab, decrease the activity of CD4+ cells and reduce the risk of relapses and disease progression [2, 3]. However, a profound decrease in the immune response can increase the risk of serious infections or even anticancer responses.

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In recent years, a growing body of evidence has emerged showing that the picture of the abnormal immune response in MS is far more complicated. An important role in the process of neuronal and myelin damage is played by B lymphocytes, or B cells [4, 5]. The involvement of these cells in MS pathology is supported by the existence of oligoclonal bands in the cerebrospinal fluid, as well as by the detection of myelin-targeted antibodies, which are responsible for myelin damage and neuronal loss. Currently, in the treatment of MS, we have some CD20-targeted antibodies at our disposal, including rituximab, ocrelizumab, and ofatumumab. Some others are still under investigation e.g. ublituximab and inebilizumab (MEDI-551, an antibody that binds to CD19, which is a surface antigen expressed on a broader range of B cells than CD20).

In this review, our aims were to describe the role of B lymphocytes in MS pathology, to present the latest data regarding the efficacy and safety of the currently available CD20-targeted drugs, and to indicate the future perspective of the use of such drugs.

Our *modus operandi* involved searching the PubMed database from 1970 to the present. Clinical trial registries were also searched for appropriate data. Key words searched for were "CD20", "rituximab", "ocrelizumab", "ofatumumab", "ublituximab", "multiple sclerosis", "RMS", "RRMS", "SPMS", and "randomised clinical trial". Records were limited to those in the English language. The search was last updated on 5 January 2023.

B lymphocytes in MS

Research into the pathology associated with MS has been ongoing for many years. Initially, attention was focused on the role of T lymphocytes, including CD4+ and CD8+ lymphocytes, with consideration given to subtypes releasing IL-17 or granulocyte-macrophage colony-stimulating factor (GM-CSF) [6, 7]. These cells were believed to play a crucial role in demyelination and neuronal damage. In recent years, attention has been drawn to a shift in thinking regarding the pathogenesis of MS.

It now appears that CNS damage results from multiple types of immune cells, with a more significant than expected role played by B lymphocytes [8, 9]. In patients with MS, B lymphocytes have been shown to be an important component of inflammatory infiltrates, especially in active demyelinating lesions with predominantly perivascular localisation [10, 11]. The concept of B-cell-mediated pathogenesis of MS was prompted by the finding of impaired antibody production in the CNS (presence of anti-myelin antibodies), the presence of oligoclonal bands in the cerebrospinal fluid (CSF), the detection of antibodies in inflammatory lesions, and, above all, the clinical confirmation of the high clinical effectiveness of antibodies directed against CD20, the most reliable marker of B lymphocytes [12].

In MS, increased numbers of B cells and plasmablasts (PB) have been observed in the CSF. Most B lymphocytes present the phenotype of memory cells and short-lived PB [13]. It is worth noting that CSF PB numbers in MS patients are correlated with intrathecal IgG synthesis and inflammatory parenchymal disease activity as revealed by MRI, in other words, CNS inflammation.

It should be noted however, that antibodies directed against CD20 do not cover the entire population of B lymphocytes suspected to be involved in the pathogenesis of MS. Plasma cells, as well as plasmablasts, which are responsible for the production of antibodies and whose presence and number in inflammatory infiltrates correlate with the severity of inflammatory processes in the CNS, do not present CD20 antigens, i.e. they are not targeted by anti-CD20 antibodies [14].

B lymphocytes can contribute to MS in multiple ways. Subsets of B lymphocytes may produce cytokines with pro- (which secrete TNFα, GM-CSF, IL-6, IL-12, and IL-15) and anti-inflammatory (which secrete IL-10 and IL-35) properties [5]. Furthermore, they are antigen-presenting cells pivotal for T-cell activation. B cells can also express CD80 and CD86 antigens on their surface, which play a crucial role in the T-cell activation observed in MS [15].

The available data indicates that the initial step of the autoimmune reaction may be the attraction of Th cells into the CNS followed by secondary infiltration of the affected region by B lymphocytes. Finally, B lymphocytes undergo differentiation into plasma cells that are able to produce autoantibodies, thus directly contributing to the demyelination of neurons, which is strongly facilitated in conditions of increased inflammation. Antibodies produced by B lymphocytes in the CNS are directed against various structural, but also other functional, elements of neurons. Previous studies have identified antibodies directed against myelin basic protein (MBP), proteolipid protein (PLP), myelin oligodendrocyte glycoprotein (MOG), inwards rectifying potassium channel (Kir) 4.1, a calcium-activated chloride-channel protein called 'anoctamin 2' (ANO2), and many other antigens [16–19]. The role of B cells is also postulated to be linked with the trafficking of Th cells to demyelinating lesions. This action of B cells could form a 'vicious circle' of inflammation and lead to intense accumulation of different inflammatory mediators in the CNS.

Conversely, in MS, the pathophysiological role of individual antibody production needs to be clarified. Specifically, no clear correlation has been demonstrated between antibody titres and disease severity [20]. It is worth noting that among the isolated antibodies, none are strictly specific for MS. However, their occurrence correlates with disease activity e.g. the number of demyelinating foci lesions, indicating that in individual patients, a certain unique specificity may be expected. In addition, there is a lack of research into the nature of stimuli that trigger B-cell influx into the CNS and the mechanism of B-cell accumulation in specific CNS regions [21].

However, these doubts do not change the fact that inhibition of CD20+ cell activity will effectively slow disease progression, regardless of the antigenic spectrum of antibodies produced. Accordingly, the role of B lymphocytes as antigen-presenting cells and cells that induce overactivity of T cells is becoming increasingly important. Recent studies have shown that the involvement of B lymphocytes in CNS damage in the course of MS is not only limited to the production of antibodies directed against structural elements of myelin, glial cells, or neurons, but also involves the activation of T lymphocytes. This phenomenon is related to the activity of B lymphocytes as antigen-presenting cells, and their action includes the effective presentation of soluble and membrane-bound antigens [22].

The predominant mechanism by which CD20-blocking antibodies exert their therapeutic effect is still unclear. Protection against relapses is achieved within 1–2 months of administration depending on the agent used, which is faster than the effect on antibody production or plasma cell counts [23]. It is speculated that the reduced function of B lymphocytes as antigen-presenting cells, as well as a reduced influx of B lymphocytes across the blood–brain barrier, may lead to a local decrease in antibody production in the CNS [8]. In addition, B lymphocytes in MS have a disturbed cytokine production profile, with excessive production of proinflammatory cytokines such as IL-6, TNFα, or lymphotoxin alpha, and a concomitant deficiency in inhibitory cytokines, including TGFβ. The disturbed profile of cytokine production results in an excessive activation of Th1 or Th17 cells, leading to processes associated with myelin and neuronal damage [5]. An important element affecting the effectiveness of drugs targeting CD20 is the profile of B lymphocytes reconstituted after treatment. Reconstituted B lymphocytes produce fewer proinflammatory cytokines, such as TNFα, IL-6, or GM-CSF, and more IL-10. The change in the profile of B lymphocytes also appears to reduce the proinflammatory response of T lymphocytes [15, 24]. This phenomenon seems very important in terms of the long-term suppression of the pathological inflammatory response in MS.

CD20-targeted drugs in MS

Due to evidence of B lymphocyte involvement in MS-related pathology, a decision was made to use anti-CD20 monoclonal antibody medication for MS treatment. Currently used anti-CD20 agents include ocrelizumab, ofatumumab, and rituximab (off-label). The last of the CD20 ligands currently being assessed by the FDA and the EMA is ublituximab. CD20 is a surface antigen present on B lymphocytes at different stages of maturation, from pre-B cells to naïve and memory B cells, and is involved in the generation of T-cell-independent antibody responses [25]. The binding of anti-CD20 antibodies to the antigen leads to the activation of mechanisms that result in a profound decrease in the number of B lymphocytes. Usually, these mechanisms are antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). Available drugs targeting CD20 do not act identically in this regard. Ocrelizumab and ublituximab are drugs with a dominant ADCC effect involving NK cells (natural killer cells), whereas rituximab and ofatumumab have a dominant CDC effect with activation of the C1q component of the classical complement pathway [26, 27]. A decrease in CD20+ cell levels below 10% is considered to be therapeutic and correlates with clinical efficacy. However, in clinical practice and clinical trials, the reduction in B lymphocytes (measured as CD19+ cells) is usually more profound, reaching as low as less than 1% [28]. Current clinically used antibodies directed against CD20 have different structures and some differences in binding sites. However, their efficacy in reducing CD20+ cell levels appears to be similar.

Rituximab

Rituximab (RTX) is a chimeric (mouse–human) anti-CD20 antibody used in the off-label treatment of MS. As mentioned above, the drug's mechanism of action is mainly based on the activation of CDC. In addition to its use in MS, RTX is widely used in haematological disorders and autoimmune diseases such as B-cell lymphomas (e.g. non-Hodgkin's lymphoma, chronic lymphatic leukaemia, rheumatoid arthritis, and granulomatosis with polyangiitis) (SmPC Mabthera).

One of the first clinical trials to evaluate the efficacy and safety of RTX in MS was an open-label, 72-week clinical trial in which 1.0 g of RTX was administered on days 1 and 15 of treatment and then at 6-monthly intervals in adult patients with RRMS [29]. The use of RTX was shown to be associated with a reduction in the annualised relapse rate (ARR) from 1.27 at baseline to 0.18 at week 72 of treatment, with the proportion of patients without relapses exceeding 80% (80.8%). However, the high rate of infusion-related allergic reactions was noteworthy (65.4%).

Subsequent studies confirmed the initial observations. The double-blind, placebo-controlled HERMES study, which used RTX in 69 RRMS patients at a dose of 1.0 g on days 1 and 15 of treatment, showed that, starting at week 12 of follow-up, there was a significant reduction in both the number of Gadolinium-enhancing (Gd+) lesions (by more than 90%) and the risk of relapse [20.3% (RTX) *vs.* 40% (PBO)] at week 48 of follow-up [RR 1.9 (1.1–3.2), p = 0.04]. Infusion-related adverse events were common following the first infusion (in more than 90% of patients) and most likely reflected cytokine release syndrome. However, during the next dose, their frequency did not differ from the placebo [30]. In contrast, the OLYMPUS study, which was also a double-blind, placebo-controlled trial using RTX in 439 adult patients with PPMS, with a modified regimen (two infusions of RTX at a dose of 1.0 g every two weeks or placebo every 24 weeks until week 96) showed no significant difference in terms of confirmed disability progression (CDP12 — time

to confirmed disease progression sustained for 12 weeks; hazard ratio (HR) 0.77, 95% confidence interval (CI): 0.55–1.07, p = 0.1442). However, subgroup analysis indicated a significant effect in a population of younger patients (50 years or younger) with active disease [with active Gd+ lesions present; HR 0.33 (95% CI: 0.14–0.79, p = 0.0088)] [31].

Although the results of the study were disappointing to some extent, they did indicate a direction for further research on a subpopulation of younger patients with active disease (with active Gd+ lesions). As in previous studies, infusion-related side effects occurred primarily after the first dose of the drug. The tolerability of RTX treatment appears to be good. A retrospective analysis of MS patients adhering to treatment, based on data from a Swedish multiple sclerosis registry, showed much the lowest dropout rate to be from RTX therapy (3%) compared to other agents such as IFNsβ (53%), fingolimod (38%), dimethyl fumarate (32%), and natalizumab (29%) [32].

The long-term efficacy and safety of RTX use in patients with relapsing multiple sclerosis with active disease were evaluated in a double-blind, placebo-controlled, randomised, single-centre study. Participants were followed up for three years. The primary endpoint was the number of participants with no evidence of disease activity (NEDA). At the end of the study, 44% of RTX-treated patients showed NEDA, compared to 19.23% of the placebo-treated group (p = 0.049). More than two new lesions, relapses and/or sustained accumulation of disability, defined as treatment failure, was smaller in RTX--treated patients than in placebo-treated patients (37.04% *vs.* 69.23%, p = 0.019). Furthermore, the time to treatment failure was longer in RTX-treated patients than in placebo-treated patients (23.32 months *vs.* 11.29 months, p = 0.027). More infusion-related reactions were observed in the RTX-administered group than in the control group. No differences in serious adverse events between the groups were observed [33].

Ocrelizumab

Ocrelizumab (OCR) is the first anti-CD20 drug registered for the treatment of MS. The drug has received a positive recommendation from both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with RRMS as well as PPMS. Due to structural differences compared to RTX (i.e. slightly different target site, humanised antibody), OCR is a drug that exerts its effects primarily through an ADCC mechanism.

The two largest phase III trials using OCR in adult patients with RRMS were the two identical, double-blind OPERA I and OPERA II trials, in which more than 800 patients (in each trial) were randomised to receive OCR (300 mg on days 1 and 15 of therapy followed by 600 mg every 24 weeks) or the active comparator, IFNβ 1α, s.c. at a dose of 44 μg (three times weekly). After 96 weeks of treatment, there was a statistically significant difference in favour of OCR in terms of ARR (0.29 for IFN1β *vs.* 0.16 OCR, p < 0.001 for both studies). At the same time, almost complete protection was observed in terms of Gd+ lesions [OPERA I — 0.02 *vs.* 0.29 (= 94%), p < 0.001; OPERA II — 0.02 *vs.* 0.42; p < 0.001 — 95% reduction] and in terms of the number of new Gd+ lesions [OPERA I — 0.32 *vs.* 1.41 (= 77%), p < 0.001; OPERA II — 0.33 *vs.* 1.90 (= 83%), p < 0.001]. Additionally, the use of OCR was shown to be associated with a c.30–40% reduction in the risk of 24-week CDP [OPERA I — 5.9% *vs.* 9.5% (= 38%), p = 0.03; OPERA II — 7.9% *vs.* 11.5% (= 31%), p = 0.003].

These results clearly demonstrated the usefulness of OCR and its significant advantage over the active comparator (IFNβ 1a). An interesting observation was the weaker functional effect (progression of disability) compared to almost complete protection in the context of new demyelinating lesions. However, this phenomenon was not explained [34].

The long-term efficacy and safety of OCR in relapsing MS were assessed over the course of 6.5 years (336 weeks) in the double-blind period (DBP) and open-label extension (OLE) period of the OPERA I and OPERA II studies, wherein the influence of OCR administration (compared to IFN) on time to EDSS ≥ 6.0, confirmed for ≥ 24 and ≥ 48 weeks, was assessed [35]. The risk of requiring a walking aid confirmed for ≥ 24 weeks was 34% lower in patients who initiated OCR treatment over 6.5 years earlier [HR (DBP + OLE) 0.66, 95% CI: 0.45–0.95, p = 0.024]. Furthermore, over 6.5 years, the risk of requiring a walking aid at ≥ 48 weeks was 46% lower in patients who initiated OCR treatment earlier compared to those who started it later [HR (DBP + OLE) 0.54, 95% CI: 0.35–0.83, p = 0.004].

A continuation of the set of studies with OCR was a double-blind, placebo-controlled phase III study in 732 adult patients with PPMS (the ORATORIO trial). OCR was administered intravenously at a dose of 300 mg on days 1 and 15 and then repeated every 24 weeks. OCR was shown to result in a moderate but statistically significant reduction in the risk of disability progression (12-week CDP — 24% reduction, OCR — 32.9% *vs.* PBO — 39.3%, and 24-week CDP — 25% reduction, OCR — 29.6% *vs.* PBO — 35.7%). Similarly to RTX, the effect of OCR was most pronounced in the younger subpopulation (under 45 years) [36].

The safety profile of OCR is quite similar to that of RTX, and as in the case of RTX, the most common adverse reactions observed in clinical trials were drug-related reactions associated with cytokine release, especially after the first dose of OCR. Pruritus and redness of the skin and hot flushes were the most common. However, the incidence of these changes was significantly lower than with RTX, probably due to premedication, including antipyretics and antihistamines. It is worth mentioning that OCR has been discontinued in patients with rheumatoid arthritis due to an increased risk of opportunistic infections. The older age of patients and the concomitant use of other immunosuppressive drugs were the most likely causes of these infections [23, 28].

Ofatumumab

Another drug registered by the FDA (2020) and the EMA (2021) targeting CD20 is ofatumumab. This is a fully human IgG1 antibody suspected to have reduced immunogenicity compared to chimeric rituximab and ocrelizumab. It is postulated that the mechanism of action on B lymphocytes is mainly based on CDC. An additional advantage of ofatumumab is that it can be administered subcutaneously. In addition to MS, the drug is also registered for the treatment of chronic lymphocytic leukaemia.

The primary evidence for the efficacy of ofatumumab comes from two methodologically identical, double-blind, randomised trials (ASCLEPIOS I and II) comparing the efficacy and safety of ofatumumab (20 mg every four weeks after 20 mg loading doses on days 1, 7, and 14) *vs.* teriflunomide (14 mg daily) [37].

Both studies showed that, compared to teriflunomide, the use of ofatumumab was associated with a reduced risk of relapse (ARRs were 0.11 and 0.22, respectively, in ASCLEPIOS I [RR 0.49 (95% CI — 0.37 to 0.65), $p < 0.001$] and 0.10 and 0.25 in ASCLEPIOS II [RR 0.42 (0.31 to 0.56), $p < 0.001$)]. In addition, there was a significantly better inhibitory effect of ofatumumab on the progression of disability confirmed at six months [8.1% and 12.0%, respectively (HR 0.68 (95% CI — 0.50 to 0.92), $p = 0.01$]. A very strong effect of ofatumumab was also observed in terms of inflammatory parameters on MRI, in terms of the number of Gd+ lesions on T1-weighted MRI [ASCLEPIOS I — Rate ratio 0.03, (95% CI) (0.01 to 0.05) $p < 0.001$; ASCLEPIOS II — Rate ratio 0.06 (95% CI) (0.04 to 0.10), $p < 0.001$], as well as in terms of new or enlarging lesions on T2-weighted MRI [ASCLEPIOS I — Rate ratio 0.18 (95% CI) (0.15 to 0.22), $p < 0.001$; ASCLEPIOS II — Rate ratio 0.15 (95% CI) (0.13 to 0.19), $p < 0.001$]. The safety profile of ofatumumab was very favourable, with the most common changes associated with the first administration of the drug (e.g. headache, flushing) (14.4% and 7.5% ofatumumab *vs.* placebo injections, respectively). In both studies, other adverse effects, particularly those leading to treatment discontinuation, occurred in 5% of both the ofatumumab and teriflunomide groups.

Additional data pertaining to the long-term safety of ofatumumab comes from the ALTHIOS study, which was a phase IIIb, open-label, long-term safety study. Patients completing the ASCLEPIOS I/II, APLIOS, or APOLITOS trials could enter ALITHIOS [38]. The safety and tolerability of ofatumumab were assessed in RMS patients after extended treatment for up to 3.5 years. A total of 1,650 patients (83.8%) reported ≥ 1 adverse event, and 191 (9.7%) had ≥ 1 serious adverse event. No opportunistic infections or progressive multifocal leukoencephalopathy events were identified; the risk of malignancies was very low (0.55%, 11/1,969).

Ublituximab

The last of the CD20 ligands currently being evaluated by both the FDA and EMA is ublituximab. Unlike the recently registered ofatumumab, but similarly to ocrelizumab and rituximab, ublituximab is a chimeric antibody with different binding sites on CD20 and a mechanism based mainly on ADCC [39].

The main results regarding treatment efficacy have come from the ULTIMATE I and II studies. As with other CD20 ligands, these were double-blind, controlled phase III studies, with teriflunomide as an active comparator. The results were not published as full text but have been presented as conference reports. In both studies, ublituximab was administered as an intravenous infusion of 450 mg UTX via a one-hour *i.v.* infusion every 24 weeks (following a 150 mg UTX infusion on day 1) or 14 mg oral teriflunomide once a day.

Over a 96-week follow-up period, ublituximab was shown to be associated with no relapses in 86.7% (ULTIMATE I) and 87.5% (ULTIMATE II) of MS patients. In addition, ublituximab was associated with a significant reduction in the risk of developing a relapse compared to teriflunomide (ULTIMATE I: HR 0.50; 95% CI: 0.33–0.75; $p = 0.0007$; ULTIMATE II: HR 0.43, 95% CI: 0.28–0.65, $p < 0.0001$) [40].

The ULITMATE study showed an acceptable safety profile for the drug. Infusion-related adverse events occurred in 47.7% (ublituximab) and 12.2% (placebo) of patients and, as with ocrelizumab or rituximab, these adverse events were mostly associated with the first infusion. A severe anaphylactic reaction was observed in one patient [41].

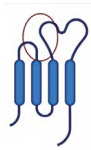
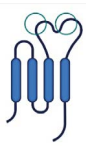
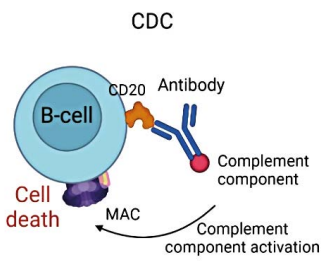
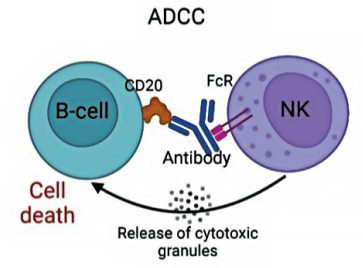
At the time of writing, full results have not yet been published, but the preliminary data indicates similar efficacy and safety profiles for ublituximab compared to other drugs belonging to the CD20 ligand group. Long-term data regarding efficacy and safety is not available for ublituximab. An OLE study of ublituximab in subjects with relapsing multiple sclerosis is ongoing. This study is planned to be completed in October 2023 (clinicaltrials.gov, NCT04130997) (Tab. 1).

Future directions

In clinical practice, in addition to the drugs used for the treatment of MS, other anti-CD20 molecules are available for the treatment of haematological diseases or treatment-resistant autoimmune conditions. These include veltuzumab, obinutuzumab, tositumomab, and ibritumomab; however, to date (based on ClinicalTrials.gov), there is no data regarding their efficacy in MS.

Another therapeutic option being considered for the treatment of MS is blocking the CD19 antigen. Similar to CD20, the CD19 antigen is localised on B lymphocytes but, unlike CD-20, CD19 is also localised on younger forms (early pro-B cells) and on plasmablasts and plasma cells, which are responsible for antibody production [42]. It is therefore postulated that antibodies

Table 1. Biological, pharmacological and clinical characteristics of anti-CD20 antibodies used in multiple sclerosis treatment

Antibody	Rituximab	Ofatumumab	Ocrelizumab	Ublituximab
Structure	Chimeric	Human	Humanised	Chimeric
Target epitope of CD20				
Primary mechanism of action				
Important clinical endpoints				
Symptomatic results	ARR reduction from 1.27 at baseline to 0.18 at week 72 in RRMS [29] ARR not reduced compared to PBO at week 48 in RRMS (0.37 *vs.* 0.72) [30]	ARR reduction compared to teriflunomide in RRMS at EOS (median 86 weeks) (0.11 *vs.* 0.22 — ASCLEPIOS I and 0.10 *vs.* 0.25 — ASCLEPIOS II) [37]	Reduction of CDP in PPMS (at week 24 CDP for OCR — 29.6% *vs.* PBO — 35.7%; OLYMPUS [36] Reduction compared to IFN-β1a in RRMS (0.16 *vs.* 0.29 at week 96 — OPERA I and II) [34]	Full data not available Nearly 86.7% of RMS patients free of relapse at week 96 (ULTIMATE I) and 87.5% (ULTIMATE II) [40]
MRI results	Reduction of T2 lesion volume compared to baseline (from 8,566.4 mm^3 at baseline by 272.7 mm^3 at week 72 in RRMS [29] Reduction of Gd+ lesions from 1.31 at baseline to 0 at week 72 in RRMS [29] Reduction of T2 compared to PBO (–175 mm^3 *vs.* +418 mm^3) at week 36 in RRMS [30] Reduction of Gd+ lesions compared to PBO at weeks 12, 16, 20, 24, and 48 in RRMS (0.5 *vs.* 5.5) [30]	Reduction of mean number of Gd+ lesions compared to teriflunomide at EOS (median 86 weeks) in RRMS (0.01 *vs.* 0.45) (ASCLEPIOS I and 0.03 *vs.* 0.51) (ASCLEPIOS II) [37] Reduction of new or lesions on T2 compared to teriflunomide at EOS (median 86 weeks) in RRMS (ASCLEPIOS I — 0.72 *vs.* 4.0; ASCLEPIOS II — 0.64 *vs.* 4.15) [37]	Reduction of mean percent change in total volume of lesions on T2 compared to placebo in PPMS (–3.37 *vs.* +7.43 from baseline to week 120; OLYMPUS) [36] Reduction of mean no. of Gd+ lesions compared to IFN-β1a in RRMS at week 96 (OPERA I — 0.02 *vs.* 0.29; OPERA II — 0.02 *vs.* 4.2) [34] Reduction of number of new Gd+ lesions compared to IFN-β1a in RRMS at week 96 (OPERA I — 0.32 *vs.* 1.41; OPERA II — 0.33 *vs.* 1.9) [34]	Full data not available Mean number of lesions per scan per participant: 0.282 for ublituximab + oral placebo *vs.* 2.831 for teriflunomide + IV placebo in RMS at week 96 (ULTIMATE I) [40, 41]

directed against CD19 may be more potent in modifying immune activity. Conversely, this effect may also be associated with a poorer safety profile than that of anti-CD20 antibodies due to its more potent suppression of the immune system.

The results of a phase I trial using inebilizumab (MEDI-551), a humanised IgG1κ monoclonal antibody directed against the CD19 antigen, for the treatment of MS are now available [43]. During a 24-week follow-up period, the use of inebilizumab was shown to lead to an effective reduction in B-lymphocyte counts, with an acceptable safety profile and a reduced risk of new Gd+ lesions. However, these results should be regarded as preliminary.

Extended interval dosing

The high efficacy of anti-CD20 drugs used in MS has led to increased consideration of the option of increasing the dosing interval for patients with good disease control achieved with standard dosing [44]. The concept of extended interval dosing (EID) is related to observations that the use of anti-CD20 drugs results in prolonged immunosuppression, which in turn is associated with maintaining clinical activity. Currently available data indicates that ocrelizumab can take more than six months to repopulate B lymphocytes and, in some cases, more than 12 months. Furthermore, no significant differences

in treatment efficacy have been found when comparing the effectiveness of standard dosing to EID. Similarly, encouraging findings were also obtained for another highly active drug (not acting on CD20), natalizumab [45]. However, the issue requires further study, especially since most of the available clinical data is from phase III trials with standard dosing, and there is relatively limited long-term data [46].

Conclusions

The importance of drugs directed against CD20 in the treatment of MS is not in doubt. Clinical evidence indicates that these agents are highly effective in various forms of MS. Although the full mechanism of their high clinical efficacy is not yet fully understood, it is mainly related to their effect on the number and function of B lymphocytes. Currently used agents include ocrelizumab, ofatumumab, and rituximab (off-label). In addition, promising data also exists for ublituximab, which is presently being evaluated by the registration agencies (FDA and EMA). Despite the relatively modest data supporting the long-term efficacy of anti-CD20 antibodies, they represent an important therapeutic option in the treatment of MS.

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Ocrevus® (okrelizumab). Skład i postać farmaceutyczna, dawka: 300 mg koncentrat do sporządzania roztworu do infuzji. **Wskazania:** leczenie dorosłych pacjentów z rzutowymi postaciami stwardnienia rozsianego, z aktywną chorobą, definiowaną na podstawie cech klinicznych lub radiologicznych (RMS); leczenie dorosłych pacjentów z wczesną, pierwotnie postępującą postacią stwardnienia rozsianego ocenianą na podstawie czasu trwania choroby i poziomu niesprawności oraz cechach radiologicznych charakterystycznych dla aktywności zapalnej (PPMS). **Dawkowanie i sposób podawania:** Dawkę początkową 600 mg podaje się w dwóch oddzielnych wlewach dożylnych 300 mg w odstępie 2 tygodni. Kolejne dawki podaje się jako pojedynczy wlew dożylny podawany co 6 miesięcy. Pierwszą kolejną dawkę 600 mg należy podać sześć miesięcy po pierwszym wlewie dawki początkowej. Pomiędzy kolejnymi dawkami należy zachować odstęp minimum 5 miesięcy. W przypadku pominięcia wlewu, należy go podać tak szybko, jak to możliwe. Pomiędzy dawkami należy zachować odstęp 6 miesięcy (minimum 5 miesięcy). Po rozcieńczeniu Ocrevus jest podawany we wlewie dożylnym przez oddzielną linię infuzyjną. Wlewu nie należy podawać w postaci wstrzyknięcia dożylnego lub bolusa. **Przeciwwskazania:** nadwrażliwość na substancję czynną lub na którąkolwiek substancję pomocniczą; trwające aktualnie, czynne zakażenie; pacjenci w stanie ciężkiego obniżenia odporności; znane, aktywne nowotwory złośliwe. **Specjalne ostrzeżenia i środki ostrożności:** w celu poprawy identyfikowalności biologicznych produktów leczniczych, nazwa handlowa oraz numer serii podanego produktu powinny być wyraźnie zapisane w dokumentacji pacjenta. Leczenie produktem leczniczym Ocrevus powinno być rozpoczynane i nadzorowane przez specjalistów mających doświadczenie w diagnozowaniu i leczeniu stanów neurologicznych, posiadających dostęp do odpowiednich środków medycznych niezbędnych w leczeniu ciężkich reakcji, takich jak ciężkie reakcje związane z wlewem, reakcje nadwrażliwości i (lub) reakcje anafilaktyczne. Przed każdym podaniem leku konieczne jest zastosowanie dwóch rodzajów premedykacji: 100 mg metyloprednizolonu (lub jego odpowiednika) dożylnie, około 30 minut przed każdym podaniem wlewu; lek antyhistaminowy na około 30-60 minut przed każdym podaniem wlewu. Dodatkowo można rozważyć premedykację lekiem przeciwgorączkowym (np. paracetamolem) na około 30-60 minut przed każdym podaniem wlewu. Pacjentów należy monitorować w trakcie podawania wlewu i przez co najmniej jedną godzinę po zakończeniu wlewu. Podawanie leku Ocrevus wiąże się z występowaniem reakcji związanych z wlewem, które mogą być związane z uwalnianiem cytokin i (lub) innych mediatorów reakcji chemicznych. Objawy reakcji związanych z wlewem mogą wystąpić w trakcie każdego podania wlewu, ale częściej zgłaszano je w trakcie pierwszego podania wlewu. Reakcje związane z wlewem mogą wystąpić w ciągu 24 godzin od podania. Reakcje tego typu mogą mieć postać świądu, wysypki, pokrzywki, rumienia, podrażnienia gardła, bólu jamy ustnej i gardła, duszności, obrzęku gardła lub krtani, zaczerwienienia twarzy, hipotensji, gorączki, zmęczenia, bólu głowy, zawrotów głowy, nudności, częstoskurczu i anafilaksji. Może wystąpić reakcja nadwrażliwości (ostra reakcja alergiczna na produkt leczniczy). Reakcja nadwrażliwości może rozwinąć się w trakcie każdego podania wlewu, chociaż zazwyczaj nie występuje w trakcie pierwszego podania wlewu. Jeżeli w trakcie kolejnych podań wystąpią objawy cięższe niż poprzednio lub jeśli wystąpią nowe ciężkie objawy, należy założyć podejrzenie wystąpienia reakcji nadwrażliwości. Nie należy stosować leczenia u pacjentów ze znaną nadwrażliwością IgE-zależną na okrelizumab. Podawanie leku Ocrevus musi być opóźnione u pacjentów z aktywnym zakażeniem do czasu ustąpienia tego zakażenia. Zaleca się ocenę stanu układu immunologicznego pacjenta przed podaniem produktu leczniczego, ponieważ pacjenci z ciężkim obniżeniem odporności (np. z limfopenią, neutropenią, hipogammaglobulinemią) nie powinni być leczeni. Leczenie produktem leczniczym Ocrevus prowadziło do spadku całkowitego stężenia immunoglobulin wynikającego głównie ze spadku miana IgM. Dane z badań klinicznych wykazały związek pomiędzy zmniejszonym stężeniem IgG (a w mniejszym stopniu także IgM lub IgA) a ciężkimi zakażeniami. W PPMS pacjenci z trudnościami w przełykaniu podlegają wyższemu ryzyku aspiracyjnego zapalenia płuc. Leczenie produktem Ocrevus może dodatkowo zwiększać ryzyko ciężkiego zapalenia płuc u tych pacjentów. Lekarze powinni podjąć niezwłoczne działania w przypadku pacjentów z objawami zapalenia płuc. Nie można wykluczyć ryzyka wystąpienia postępującej wieloogniskowej leukoencefalopatii (PML), ponieważ zakażenie wirusem JC powodującym PML obserwowano u pacjentów leczonych przeciwciałami anty-CD20 i innymi lekami stosowanymi w SM i było ono związane z czynnikami ryzyka (populacja pacjentów np. z limfopenią, w podeszłym wieku; politerapia lekami immunosupresyjnymi). Lekarze powinni zachować czujność wobec wczesnych przedmiotowych i podmiotowych objawów PML, do których należą wszelkie nowe objawy lub nasilenie już istniejących przedmiotowych i podmiotowych objawów neurologicznych, ponieważ mogą one przypominać stwardnienie rozsiane. W przypadku podejrzenia PML należy wstrzymać podawanie produktu leczniczego Ocrevus oraz należy rozważyć przeprowadzenie oceny, w tym wykonanie badania MRI, najlepiej z kontrastem (wynik należy porównać z wynikiem sprzed leczenia), badanie płynu mózgowo-rdzeniowego w kierunku DNA wirusa JC oraz powtarzane badania neurologiczne. Jeżeli rozpoznanie PML zostanie potwierdzone, leczenie należy przerwać i nie wznawiać. Przed rozpoczęciem leczenia produktem leczniczym Ocrevus u wszystkich pacjentów należy wykonać badania przesiewowe w kierunku zakażenia HBV, zgodnie z lokalnymi wytycznymi, w celu oceny ryzyka reaktywacji HBV. Pacjentów z czynnym wirusem HBV (tj. z dodatnimi wynikami HBsAg i przeciwciał anty-HB) nie należy leczyć produktem leczniczym Ocrevus. Pacjentów z ujemnym wynikiem HBsAg i dodatnim wynikiem przeciwciał HbcAg oraz pacjentów z HBsAg+ należy skonsultować przez specjalistów chorób wątroby przed rozpoczęciem leczenia oraz monitorować i leczyć zgodnie z lokalnymi standardami medycznymi, aby zapobiec reaktywacji wirusowego zapalenia wątroby typu B. Zgłaszano przypadki neutropenii o późnym początku. Większość przypadków była stopnia 1. lub 2. U pacjentów z przedmiotowymi i podmiotowymi objawami zakażenia zaleca się oznaczanie liczby granulocytów obojętnochłonnych we krwi. Należy dokonać indywidualnej oceny stosunku korzyści do ryzyka u pacjentów ze znanymi czynnikami ryzyka wystąpienia nowotworów złośliwych oraz u pacjentów, którzy są aktywnie monitorowani ze względu na ryzyko nawrotu nowotworu złośliwego. Pacjenci powinni poddać się standardowym badaniom przesiewowym w kierunku raka piersi, zgodnie z lokalnymi wytycznymi. Nie zaleca się stosowania innych leków immunosupresyjnych w skojarzeniu z produktem leczniczym Ocrevus, poza kortykosteroidami w objawowym leczeniu rzutów. Rozpoczynając podawanie leku Ocrevus po leczeniu immunosupresyjnym lub rozpoczynając leczenie immunosupresyjne po leczeniu produktem Ocrevus należy wziąć pod uwagę prawdopodobieństwo nakładania się efektów farmakodynamicznych. Podawanie szczepionek zawierających żywe lub żywe atenuowane wirusy nie jest rekomendowane w trakcie leczenia oraz do czasu odnowy limfocytów B. Lekarze powinni sprawdzać wynik szczepień pacjentów, u których rozważają leczenie produktem leczniczym Ocrevus. Zaleca się szczepienie pacjentów leczonych produktem Ocrevus inaktywowanymi szczepionkami przeciwko grypie sezonowej. Pacjenci, którzy wymagają podania szczepionek powinni ukończyć szczepienia przynajmniej 6 tygodni przed rozpoczęciem przyjmowania produktu leczniczego Ocrevus. Zaleca się, by wszystkie szczepienia inne niż szczepienia szczepionkami żywymi lub żywymi atenuowanymi były podawane zgodnie z lokalnie obowiązującym kalendarzem szczepień oraz należy rozważyć oznaczanie miana odpowiedzi na szczepienie, aby sprawdzić, czy u danej osoby wzrosła ochronna odpowiedź immunologiczna, ponieważ skuteczność szczepienia może być zmniejszona. Ze względu na potencjalną deplecję limfocytów B u niemowląt matek, które były narażone na działanie produktu leczniczego Ocrevus w okresie ciąży, zaleca się, by szczepienia szczepionkami żywymi lub żywymi atenuowanymi były opóźnione do czasu powrotu liczby limfocytów B do normy; z tego względu zaleca się pomiar liczby CD19-dodatnich limfocytów B u noworodków i niemowląt przed szczepieniem. Kobiety w wieku rozrodczym powinny stosować antykoncepcję w trakcie leczenia produktem leczniczym Ocrevus oraz przez 12 miesięcy od ostatniego podania wlewu produktu leczniczego Ocrevus. **Działania niepożądane:** Bardzo często: zakażenie górnych dróg oddechowych, zapalenie nosogardła, grypa, zmniejszone stężenie immunoglobuliny M we krwi, reakcja związana z wlewem. Często: zapalenie zatok, zapalenie oskrzeli, opryszczka jamy ustnej, zapalenie żołądka i jelit, zakażenie układu oddechowego, zakażenie wirusowe, półpasiec, zapalenie spojówek, zapalenie tkanki łącznej, kaszel, nieżyt błony śluzowej nosa, zmniejszone stężenie immunoglobuliny G we krwi, neutropenia. Częstość nieznana: neutropenia o późnym początku. **Numer pozwolenia na dopuszczenie do obrotu:** EU/1/17/1231/001-002 nadany przez Komisję Europejską. **Podmiot odpowiedzialny**: Roche Registration GmbH, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Niemcy. **Przedstawiciel podmiotu odpowiedzialnego:** Roche Polska Sp. z o.o., ul. Domaniewska 28, 02-672 Warszawa. Pełna informacja o leku dostępna na życzenie. **Kategoria dostępności:** Lek wydawany z przepisu lekarza do zastrzeżonego stosowania. Przed przepisaniem leku należy zapoznać się z aktualną charakterystyką produktu leczniczego, dostępną na życzenie oraz na www.roche.pl. *ApI wersja nr 7.1, z dnia 20.04.2021 r.*

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Polish recommendations for diagnosis and therapy of paediatric stroke

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ABSTRACT

Stroke remains one of the greatest health challenges worldwide, due to a high mortality rate and, despite great progress in its treatment, the significant disability that it causes. Studies conducted around the world show that the diagnosis of stroke in children is often significantly delayed.

Paediatric ischaemic arterial stroke (PAIS) is not only a problem that varies greatly in frequency compared to the adult population, it is also completely different in terms of its risk factors, clinical course and outcome.

The main reason for the lack of a rapid diagnosis of PAIS is a lack of access to neuroimaging under general anaesthesia. The insufficient knowledge regarding PAIS in society as a whole is also of great importance. Parents and carers of children should always bear in mind that paediatric age is not a factor that excludes a diagnosis of stroke.

The aim of this article was to develop recommendations for the management of children with acute neurological symptoms suspected of ischaemic stroke and further treatment after confirmation of the ischaemic aetiology of the problem. These recommendations are based on current global recommendations for the management of children with stroke, but our goal was also to match them as closely as possible to the needs and technical diagnostic and therapeutic possibilities encountered in Poland. Due to the multifactorial problem of stroke in children, not only paediatric neurologists but also a neurologist, a paediatric cardiologist, a paediatric haematologist and a radiologist took part in the preparation of these recommendations.

Key words: stroke, paediatric, risk factors, diagnosis, treatment

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Introduction

Stroke remains the third most common cause of death worldwide, after cardiovascular disease and cancer, despite tremendous progress in its treatment. Around the world, about 17 million people suffer a stroke each year, and about 90,000 of these are registered in Poland.

Paediatric arterial ischaemic stroke (PAIS) is not only a problem that is significantly different in its incidence compared to the adult population, but it has also completely

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different risk factors and prognosis. The PAIS incidence rate is estimated at c.3–13 new cases per 100,000 children per year. This frequency range is due to several reasons, i.e. the ages of patients recruited for the studies (including newborns or an extension of recruitment up to 21 years of age), the recruitment of children with any type of cerebral vascular disease including haemorrhagic stroke or cerebral venous thrombosis of the brain (CVT), and another factor that leads to differing incidences is geography, e.g. in the basin of the Mediterranean Sea and in sub-Saharan Africa, children with sickle cell disease (SCD) will be more often affected [1, 2].

Therefore, for practical and methodological reasons, it is necessary to define PAIS and the correct use of this term for confirmed cases.

PAIS is an acute neurological deficit of sudden onset in children aged between 29 days and 18 years, and the results of neuroimaging tests show acute ischaemic changes corresponding to the range of symptoms observed in the patient [3–5].

Late diagnosis of stroke in children is a worldwide problem, especially when contrasted with the diagnosis of adult patients. Frequently, the delay in making a correct diagnosis after the onset of symptoms of stroke can take several days. This means that the child is excluded from thrombolytic treatment, because the therapeutic window remains the same for children and adults.

The crucial reason for the delay in PAIS diagnosis is lack of access to neuroimaging under general anaesthesia. Moreover, in children with acute neurological symptoms, a large proportion of changes detected in radiological studies are pathologies different from ischaemic stroke (so-called 'stroke mimics') [6].

A lack of understanding in society in general, and among parents and caregivers in particular, about the fact that paediatric age does not exclude stroke is also very important. The consideration of stroke in differential diagnosis is likewise inadequate among medical staff and doctors. This means that training programmes for radiologists, as well as for paediatricians and paediatric neurologists, are necessary to improve the accuracy and promptness of PAIS diagnoses.

Bearing in mind the specificity of childhood stroke, special attention should be paid to risk factors for its occurrence in children. The most common are arteriopathies with pathologies of the arterial wall being a cause of acute cerebral ischaemia. Among arteriopathies, the most prevalent is so-called focal cerebral arteriopathy of childhood (FCA), affecting large arterial vessels such as the middle cerebral artery (MCA) with uni- or bilateral location. Upper respiratory tract infections are a predisposing factor for FCA, and its nature is often reversible. Dissection of extracerebral arteries in children and adolescents, usually due to trauma, accounts for c.20% of the arteriopathies associated with stroke in children.

The recommended diagnostic method in the case of suspected PAIS is magnetic resonance imaging. If however this technique is not available, then a computed tomography examination is acceptable [2, 7, 8]. The frequency and variable localisation of vascular lesions in PAIS contribute in turn to the scope of imaging diagnostics in a child with suspected ischaemic stroke. The current recommendations for the diagnostics of a child with sudden symptoms of central nervous system impairment indicate the need for head and neck imaging, taking into account angio mode. Otherwise, if cervical vessels and structures are not assessed in radiological scans, an important arteriopathy such as extracerebral dissection might be overlooked and not properly treated [2, 7, 8].

The current classification of paediatric stroke, CASCADE (Childhood AIS Standardised Classification and Diagnostic Evaluation), which includes seven categories, also places strokes in the course of various arteriopathies in items 1–4; indicating at the same time a possible variety of their aetiologies (i.e. genetic, metabolic, or infectious) and their course (stable, progressive, or reversible). A follow-up neuroimaging examination is required to determine the extent of the course of arteriopathy, and the recommended period is 3–6 months after disease onset. Category 5 in the CASCADE classification is a cardiac-embolic stroke, which in turn affects the youngest children with congenital heart defects, often requiring numerous surgeries.

Nearly 40% of all childhood strokes occur under the age of five years. This fact contradicts the popular belief that there is no stroke in children. Moreover, newborns are a group in which stroke occurs much more often than does AIS in children over 29 days of age; but due to specific risk factors and the course of neonatal stroke, this is excluded from the PAIS category [9].

Idiopathic aetiology of childhood stroke is another element that significantly distinguishes it from stroke in adults, when despite extensive laboratory and imaging diagnostics, none of the well known risk factors for acute cerebral ischaemia can be found.

Today, in the adult population with stroke, thrombolytic therapy is common, provided that a stroke is diagnosed and that contraindications have been ruled out within the therapeutic window, i.e. 4.5 hours from the onset of clinical symptoms. Australian and American recommendations indicate the possibility of using intravenous thrombolysis under these conditions in children aged 2–17 years. According to the Summary of Product Characteristics in Poland, this treatment can be considered in children aged 16 years or older. In turn, endovascular therapy can be performed in children with a stroke up to six hours after its onset. Uncertainty about the timing of a stroke is a contraindication to both of the above procedures.

For all children with PAIS, initial therapy with unfractionated heparin, low-molecular heparin or aspirin is recommended until a cardioembolism or a dissection has been excluded. Aspirin for another two years is recommended even after the exclusion of the two reasons mentioned; for cardioembolic aetiology or vascular dissection, low-molecular weight heparin

(LMWH) or vitamin K antagonists would be appropriate for 6–12 weeks after stroke onset [7].

The purpose of this paper was to develop recommendations on how to deal with a child with acute neurological symptoms being suspected of an ischaemic stroke, and for further treatment after confirming the ischaemic aetiology of the problem. These recommendations are based on the current global recommendations for the management of children with stroke, but our goal was also to match them as closely as possible to the needs and technical diagnostic and therapeutic possibilities encountered in Poland.

Obviously, although paediatric stroke, as has been repeatedly emphasised, is not a 'tracer' of adult stroke, the experience of 'adult' neurologists dealing with stroke contributes to the management of children. For this reason, the team developing our recommendations included 'adult' neurologists. On the other hand, due to the multifactorial and complex basis of stroke in children, the team also included a cardiologist, a haematologist and a radiologist because our goal was to not only set out theoretical assumptions, but above all to convey the experience and practical knowledge of a group of people experienced in dealing with paediatric stroke.

When preparing the guidelines, we used the tips contained in the work by Graham ID, Harrison MB, Brouwers M et al., 2002 [10].

Paediatric stroke recommendations — definitions, epidemiology and clinical presentation in acute phase

For a diagnosis of paediatric ischaemic stroke, several conditions must be met:

1. occurrence of a sudden neurological deficit with an acute onset;
2. results of radiological examinations, i.e. magnetic resonance imaging (MRI) or computed tomography (CT), showing the presence of a stroke/strokes of vascular origin and corresponding to known ranges of arterial vascularisation as well as clinical symptoms;
3. symptoms occurring in a child aged between 29 days and 18 years [11–14].

According to various researchers, the prevalence of ischaemic stroke in children is estimated at between 1.2 and 7.9 per 100,000 child population per year [15–16].

These differences in the estimated prevalence of AIS in children result from several factors, such as the age of the patients recruited for the study (e.g. just the neonatal period, or with an upper age limit ranging between 16 and 19 years), various ethnic origins, and thus various factors risk of AIS (e.g. moya moya disease and sickle cell disease), and whether or not to include patients with heart defects and patients diagnosed with TIA (transient ischaemic attack) or CVT.

Less than half of childhood strokes affect patients under 5 years of age, and it is largely determined by the number of cases of cerebral ischaemia in children with congenital heart defects. In the entire paediatric population, stroke occurs more often in boys than in girls; the neonatal population, especially preterm infants, is also characterised by a higher incidence of strokes due to risk factors specific to this age group [17–23].

Clinical symptoms of a child's stroke depend on three factors: the patient's age, and the location and the size of the brain ischaemia. In newborns and young infants, the symptoms of stroke are disturbances of consciousness and epileptic seizures, including so-called 'subtle seizures'.

Neurological symptoms associated with the occurrence of stroke in adult patients, can also concern older children. In the case of localisation of an ischaemic focus in the anterior circle of cerebral circulation (i.e. arteries: ICA, the Internal Carotid Artery, MCA, the Middle Cerebral Artery, and ACA, the Anterior Carotid Artery), the symptoms of a stroke will be paresis or hemiplegia, central paresis of the facial nerve on the side of limb paresis, semi-amblyopia, and aphasia (speech disorder) which may be motor, sensory or mixed, in the case of dominant hemisphere involvement. In some patients, these symptoms are accompanied by, or preceded by, symptoms such as headache, nausea, vomiting and/or convulsions, which are an expression of increased intracranial pressure syndrome.

On the other hand, if the stroke is located within the posterior part of the cerebral vascularisation, the clinical picture will be dominated by the features of the cerebellar syndrome.

In the paediatric population, anterior strokes occur much more frequently than those in the posterior part of brain circulation. The division of strokes into PACI (Partial Anterior Circulation Infarct), TACI (Total Anterior Circulation Infarct), LACI (Lacunar Infarct) and POCI (Posterior Circulation Infarct) was based on the location of vascular changes in stroke patients, and it concerns both adults and children with stroke [24–27].

The most important risk factors for death in the early phase of childhood stroke are the patient's young age, the presence of a heart defect, and the large size of the stroke [26]. Malignant middle cerebral artery syndrome is characterised by a dramatic course, with rapidly increasing cerebral oedema and deterioration of the patient's condition; in patients not qualified for decompressive craniectomy, the course of the stroke is usually fatal.

Paediatric stroke recommendations — risk factors

The factors predisposing towards paediatric arterial ischaemic stroke (PAIS) are numerous, and it is not uncommon for one patient to recognise several comorbid factors. Such coincidences make the ischaemia more likely to recur (see Table 1).

The first group of factors, cerebral arteriopathies, are any pathologies of the cerebral vessel wall, both congenital and acquired, of a transient, stable or progressive nature, which cause abnormal cerebral flow and, consequently, cerebral

Table 1. Risk factors of paediatric arterial ischaemic stroke (PAIS)

Cerebral arteriopathies	
FCA (focal cerebral arteriopathy of childhood)	
Moya moya disease and syndrome (e.g. in course of SCA, sickle cell anaemia)	
Vascular wall dissection	
PVA (post-varicella arteriopathy)	
Congenital blood wall defects, e.g. hypoplasia, fibro-muscular dysplasia	
Congenital and acquired heart diseases/defects	
Thrombophilia (prothrombotic state)	**Congenital**
	High lipoprotein(a)(lp(a) serum concentration
	Protein C (PC) deficiency
	Protein S (PS) deficiency
	Antithrombin III (ATIII) deficiency
	Activated protein C resistance (APCR)
	Genetic polymorphisms of genes of coagulation factors
	Factor V G1691A
	Factor II G20210A
	MTHFR C667T
	Factor XIII Val34Leu
	Fibrinogen A (FGA) Thr312Ala
	Fibrinogen B (FGB) G455A
	Acquired
	Antiphospholipid syndrome (APS)
URI (upper-respiratory infection), generalised infection (sepsis)	
Connective tissue diseases	
Traumas	
Intoxications (e.g. amphetamines, cocaine)	

Table 2. Recommended tests for thrombophilia screening

*It is necessary to refer the results to the norms for different age groups [70–74, 77, 83–84].
**A single finding of deviations in the results requires control (except for pathogenic mutations).
— coagulation tests:
APTT, PT, fibrinogen; thrombin time (TT)
— antithrombin (AT)
— protein C
— free protein S
— activated protein C resistance (APCR) → in more than 95% corresponds to factor V Leiden mutation
— factor V Leiden mutation
— prothrombin G20210A mutation
— homocysteine → in the case of abnormal result, testing for MTHFR gene polymorphism
— lipoprotein (a)
— antiphospholipid antibodies: anticardiolipin antibodies (aCL), anti-β2-glycoprotein I antibodies (anti-β2GPI); lupus anticoagulant (LA); activity of clotting factors: VIII, IX, XI
***To be considered:
— plasminogen
— tissue plasminogen activator (t-PA)
— tissue plasminogen activator inhibitor 1 (PAI-1) → in the case of abnormal PAI-1 results, testing for 4G/5G polymorphism in the PAI-1 gene

ischaemia. The most common in this group is FCA, which affects large cerebral vessels (e.g. the ICA or MCA), unilaterally or bilaterally, and the nature of which is often reversible.

Of the acquired arteriopathies, vascular wall dissection, most often associated with neck trauma, deserves attention; this problem accounts for c.20% of arteriopathies associated with the risk of childhood stroke. Indeed, this possibility is the reason why imaging of the vessels of the head and neck to the aortic arch is included in the recommendations for the methodology of neuroimaging in children with suspected stroke [3, 11, 28–30].

The second group of risk factors of acute cerebral ischaemia in the paediatric population is congenital, and less frequently acquired, heart disease [33–35].

Another group of factors contributing to the occurrence of PAIS are coagulation disorders, congenital or acquired, known as thrombophilia or prothrombotic state [12,31].

In the differential diagnosis of stroke risk factors in the pediatric population, infections should also be taken into account, among which is the presence of post-varicella arteriopathy (PVA) as a consequence of chickenpox. Upper respiratory tract infections deserve special attention (URIs, upper respiratory infections) as they are considered a predisposing factor for FCA. Moreover, the possibility of intoxication with amphetamines or cocaine as a risk factor for PAIS has been included in the set of laboratory tests [12, 31].

Despite the described imaging methods and laboratory diagnostics, in as many as one third of children with ischaemic stroke, it is not possible to determine the aetiology.

Paediatric stroke recommendations — acute phase management

The scheme for dealing with a child with acute CNS (central nervous system) symptoms/suspected acute cerebrovascular disease, is based on the 2017 recommendations of the RCPCH, the Royal College of Paediatrics and Child Health, as well as on the guidelines developed in 2019 by a team of specialists from the AHA, the American Heart Association/ /American Stroke Association [35–36].

For a quick assessment of symptoms in a patient, including a child, the simple FAST (Face Arm Speech Time) mnemonic is useful:

F — face asymmetry (i.e. sudden onset of paresis of facial muscles);

A — arm drift (i.e. sudden upper limb weakness);

S — speech disturbances (i.e. sudden onset of aphasia or dysarthria);
T — time (summon ambulance as soon as possible and transport patient to hospital to qualify for treatment of causal stroke).

Correctly collected history is of great importance in the diagnosis of a stroke. When a stroke is suspected, the timing of the first symptoms, the circumstances of the onset of the disease, the possibility of trauma to the skull, throat or neck, upper respiratory tract infections, and drug poisoning are important facts to gather. The course of symptoms (sudden, relapsing), the sequence of neurological symptoms, and the circumstances of their occurrence are all important. When taking an interview, account should be taken of previous diseases, the presence of heart disease, medications used, unexplained fever (systemic diseases), and psychomotor retardation. Family history, the presence of hypertension, diabetes, atherosclerosis, and genetically determined diseases are also important.

In a suspected childhood stroke, i.e. a sudden neurological deficit in a patient aged 29 days to 18 years, or in the neonatal period a neonatal stroke, the child should immediately be sent to the accident and emergency department of a hospital prepared for the treatment of children with stroke. A multidisciplinary stroke team including a paediatric neurologist, a neuroradiologist/radiologist, and an anaesthetist, should be available 24/7. A paediatric cardiologist, a paediatric haematologist, a physiotherapist, and a neurosurgeon should also be available in the hospital treating a child with stroke.

On the way to the hospital, it is necessary to secure the intravenous catheter, to monitor blood pressure, heart rate and respiration — oxygen therapy (goal sat > 92%), and to control and symptomatically treat hypoglycaemia, fever and convulsions.

Laboratory tests to be performed on admission to the hospital/A&E department:

- Blood tests: blood gas analysis, complete blood count with smear, CRP (C-reactive protein), blood coagulation parameters, glucose level, electrolytes: sodium, potassium, calcium, magnesium, phosphorus; creatinine, urea, transaminases, bilirubin, urine.
  Vital functions should be monitored constantly.
  - Evaluation of child's condition using Glasgow Coma Scale and PedNIHSS score.
  - Enclosed is a workflow, Glasgow Scale and PedNIHSS.
  - Every child suspected of having an acute stroke should have an urgent neuroimaging examination after going to the hospital — recommended for children are MRI or CT and/or with vascular examination (MR/ /CT angiography) — up to one hour after the child is admitted to hospital [7]. Further treatment depends on the diagnosis.
- In case of ischaemic stroke: ASA (acetylosalicylic acid) or LMWH/UFH (unfractionated heparin) treatment to be considered. If conditions are met: thrombolysis, thrombectomy or decompressive craniectomy if necessary.
- Haemorrhagic stroke:
  - Urgent contact with a neurosurgeon is necessary — surgical treatment to be considered
  - ICU care (intensive care unit) — anaesthetist
- Stroke mimic: further management is based on clinical symptoms, and the result of an imaging examination; a careful history should be taken into account.

Paediatric stroke recommendations — imaging diagnosis

The logistics of admitting a child with a suspected stroke to the paediatric accident and emergency department should aim at performing neuroimaging tests as soon as possible. In a child with suspected stroke, imaging of the brain should be performed immediately, and preferably within 60 minutes of arrival at hospital. Magnetic resonance imaging (MRI) diagnostics is the method of choice in children with suspected stroke, in the absence of contraindications to its performance.

The final decision to perform a specific imaging test, i.e. computed tomography (CT) or MRI, should be made depending on the availability of these methods, and on the centre's own procedures and experience in neuroradiological diagnostics in children.

MRI has higher sensitivity and an undoubted advantage over CT in detecting ischaemic changes in the acute and hyperacute phases, and their differentiation from other sudden states imitating a stroke (bearing in mind that in children stroke-mimics are more frequent than in adults) [35–38].

In the detection of a haemorrhagic stroke, both CT and MRI techniques are similarly effective, but it is easier to recognise the presence of blood in the subarachnoid space in a CT. CT imaging of the brain should not be delayed if MRI, general anaesthesia or staff are not available. If it is impossible to perform a CT or MRI scan in a given unit, the child should be immediately transported to a centre equipped with full diagnostic capabilities [40–44].

These are the recommended neuroimaging diagnostic guidelines in the case of a child suspected of stroke:

1. Every child suspected of having an acute stroke should immediately undergo a neuroimaging diagnosis (no later than 60 minutes after arriving at the hospital) in order to confirm or rule out the diagnosis of ischaemic stroke. This is very important when deciding to start thrombolytic treatment.
2. Magnetic resonance imaging or computed tomography should be performed, depending on the availability of these techniques and on the centre's own experience in paediatric neuroradiological diagnostics. Whether or not to perform the examination under general anaesthesia, especially in young children who are agitated or who are unable to remain motionless throughout the examination

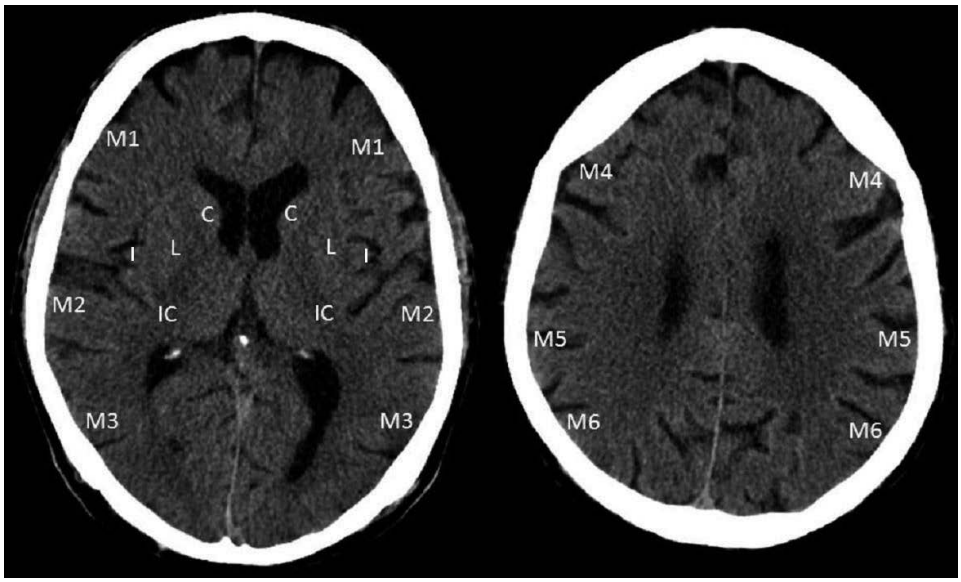

Figure 1. Extent of MCA vascularisation on both sides with marked areas, enabling assessment of ischaemic lesions on ASPECTS scale. Markings as follows: Alberta Stroke Programme Early CT Score (ASPECTS) — a scale used to quantify early ischaemic changes in CT, where C — caudate nucleus; L — lenticular nucleus; I — island; IC — inner capsule; M1 — anterior cortical area part frontal lobe; M2 — cortical area lateral to island ribbon; M3 — posterior cortical area temporal lobe; M4 — anterior area located above M1 area; M5 — central area located above M2 area; M6 — posterior area located above M3 area

period, should be taken into account (CT — 1–3 minutes, MRIc. 7–20 minutes). Some children who will require MRI anaesthesia will be able to have a CT scan without the need for anaesthesia.

3. Ischaemic stroke from onset until 7–10 days after acute symptoms can be diagnosed on the basis of DWI (diffusion-weighted imaging) sequence which is the most sensitive and specific tool for ischaemia detection in the first minutes.
4. MRI examination is the examination of choice in children suspected of having acute stroke.Due to the race against time, the MRI examination should be as short as possible.

The most important sequences are DWI, T2* or SWI (susceptibility-weighted imaging), FLAIR (fluid attenuated inversion recovery) and optionally T1 weighted images with TOF (time of flight) MRA (magnetic resonance angiography). The examination time must not exceed 15 minutes in the basic version without TOF MRA. It is recommended that this should be less than 10 minutes if the MRI machine is technically capable of doing it (e.g. automatic positioning of scans, fast diffusion scanning).

5. If ischaemic stroke is diagnosed, a follow-up CT examination is recommended to assess if haemorrhagic transformation was observed up to 48 hours [45–50].

Based on the distribution of ischaemic lesions, radiologists can identify the cause of a stroke in a child. Ischaemic strokes of cardiogenic aetiology are more often bilateral, occur in both the anterior and posterior circulations, and have an increased tendency for haemorrhagic transformation. Similarly, stroke caused by the herpes virus is multifocal but more frequently unilateral and related to limbic system and basal ganglia [51–54].

The radiological picture of ischaemic stroke depends mainly on its duration and the extent of ischaemia caused by the size of the occluded artery (e.g. internal cerebral artery *vs.* anterior cerebral artery) and the level of occlusion (e.g. occlusion of the first segment in the middle cerebral artery, so-called M1 *vs.* M4).

The time from the onset of clinical symptoms is the criterion for the division of the stroke into the following phases: hyperacute (0–6 hours; divided into the thrombolytic window: 0–4.5 hours and outside the thrombolytic window 4.5–6 hours), acute (6–24 hours), subacute (1–7 days), and chronic (8 days to 3 months).

In the first minutes of ischaemia, lactic acidosis develops and the cell membranes and the ion pump are damaged. This in turn leads to the redistribution of water from the extracellular to the intracellular space and the formation of cytotoxic oedema. Cytotoxic oedema in the infarction zone is visible as areas of restriction of free diffusion of water molecules in the extracellular space, i.e. high signal areas on DWI maps and low signal areas on apparent diffusion coefficient (ADC) maps.

Cytotoxic oedema lowers the brain tissue density in CT theoretically by 2 HU (Hounsfield units) within 2.5 hours, which can be difficult for the human eye to see and requires extensive experience in evaluating CT scans [55–56].

Paediatric stroke recommendations — qualification for mechanical thrombectomy [57–59]

This decision is made jointly by an interventional radiologist, a paediatric neurologist, and a neurologist from a centre experienced in treating patients with mechanical thrombectomy based on the following data: the age of the child, the time elapsed since the onset of clinical symptoms, the severity of clinical symptoms according to the MRS and NIHSS scales, the angio-CT examination/angio-MRI performed on the height of the aortic arch, and the advancement of ischaemic lesions on CT according to the ASPECTS scale (Alberta Stroke Programme Early Computed Tomography Score).

For MRI, the size of the lesion can be assessed using the approximate ASPECTS to DWI scale [60–70].

Standard considerations for qualifying adult ischaemic stroke patients for endovascular treatment with mechanical thrombectomy are as follows:

- up to 6 hours from the presentation of symptoms
- MRS = 0 or 1
- NIHSS = not less than 6
- ASPECTS = not less than 6
- occlusion or critical stenosis of a large arterial trunk documented in angio-CT or angio-MRI: ICA, MCA (M1, M2, ACA), BA, VA and changes at the junction of the above-mentioned arteries.

The ASPECTS scale used to quantify early ischaemic CT lesions identifies patients who will benefit from mechanical thrombectomy. According to this scale, the brain is divided into 10 areas of MCA supply, 1 point is scored for ischaemic changes in a single area. If there is ischaemia in several areas — the changes add up and the rating is weighted. In the case of a correct CT image in the MCA range, the brain CT image gets 10 points on the ASPECTS scale, when all 10 MCA territories are occupied — ASPECTS is 0 points, but when three areas are occupied — ASPECTS is 7. We only add up fresh ischaemic changes, ignoring the old ones. The MCA areas are set out in Figure 1.

In addition, an extended therapeutic window may be considered in children by considering the principles used in adults in the DEFUSE-3 and DAWN studies and in the absence of certain information at the time of onset according to the WAKE-UP protocol.

The DAWN study showed that adult patients with obstruction of the large cerebral artery and a small volume of infarcted area (reduced flow in CBF) and, at the same time, with a relatively large neurological deficit, may benefit from mechanical thrombectomy in the therapeutic window up to 24 hours after the onset of symptoms.

Similar conclusions can be drawn from the DEFUSE-3 study, in which the target mismatch profile on CT perfusion or MRI-mismatch between the volume of the penumbra area and ischaemic core volume was the basis for the qualification of patients for endovascular treatment of occlusion of the large arterial trunk 6–16 hours after the clinical manifestation of stroke. Volumetric assessment of an outbreak on DWI maps in the adult population in the DAWN study was used to qualify patients for endovascular therapy between six and 24 hours from the time they were last seen without clinical signs of stroke, outside the standard therapeutic window.

Patients with a relatively small volume of diffusion restriction and, at the same time, a significant neurological deficit, have been successfully treated with mechanical thrombectomy in an extended therapeutic window. Similar observations were made in the DEFUSE-3 study, where the decisive factor in endovascular restoration of the main arterial trunk 6–16 hours after the onset of the disease was a clear mismatch between the DWI and PWI sequences [27–36].

Although a fairly large number of randomised trials conducted in adults have found that they do benefit from mechanical thrombectomy, we cannot directly transfer these guidelines to children. Therefore, in each case, the assessment should be highly individualised, and we recommend thrombectomy therapies only in older children.

Summary

1. Neuroimaging on admission — CT or MRI in every child:
   a. CT of head without using contrast agent;
   b. Rapid MRI protocol including inversion and recovery sequences (FLAIR, fluid attenuated inversion recovery), MR diffusion-weighted imaging (DWI) with actual diffusion-weighted imaging (ADC, apparent diffusion coefficient) and T2 * or SWI;
2. In children with symptoms of ischaemic stroke on MRI/ /CT or with a normal CT image, it is recommended to perform angio-CT or angio-MRI of intracerebral arteries (from level of aortic arch);
3. Control neuroimaging of head (CT or MR) to exclude haemorrhagic transformation — usually performed 24 hours after start of thrombolytic treatment and/or mechanical thrombectomy, or performed earlier in event of significant deterioration of neurological condition.

An abbreviated method of neuroimaging diagnosis is presented in Figure 2.

Paediatric stroke recommendations — diagnostics of thrombophilia

The basic analysis includes blood group, complete blood count with microscopic smear and iron balance assessment, biochemical tests, and coagulation tests. Their implementation is also aimed at assessing the safety of anticoagulant/ /antiplatelet or thrombolytic therapy [70–72]. D-dimer is of limited importance in children, because the results are often false-positive (including infection, pre-laboratory errors), and a low concentration of D-dimer does not exclude a thromboembolic event, including ischaemic stroke [70–73].

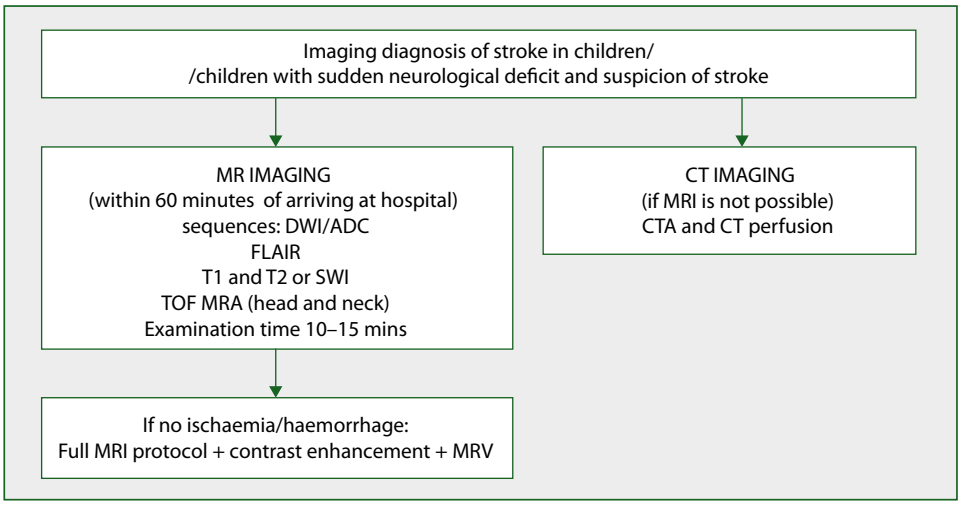

Figure 2. Imaging diagnosis of stroke in children/children with sudden neurological deficit and suspicion of stroke

In our opinion, laboratory tests for thrombophilia should be performed in every child diagnosed with ischaemic stroke, although experts in this field are not unanimous on this topic. The parameters set out in Table 2 are used in the differential diagnosis of hypercoagulability [71–77].

Important to consider

1. In the acute phase of stroke/thrombosis, the determination of proteins C, free S, antithrombin III, and activity of clotting factor VIII, can be inaccurate. If incorrect results are obtained, it is recommended to repeat them at least 6–8 weeks after the acute episode. Factor VIII is also an acute phase protein [74–76].
2. Determination of homocysteine level is recommended, and, only if elevated, polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene should be tested. Carriage of clinically insignificant MTHFR polymorphisms is common in the Caucasian race. Importantly, the increase in homocysteine concentration also occurs in vitamin deficiencies (folic acid, vitamins B6, B12) and in metabolic diseases such as homocystinuria or cobalamin C deficiency [75].
3. Antiphospholipid syndrome (APS) is the most severe acquired thrombophilia. It is most common in adolescents and young adults. The diagnosis and treatment of APS in children is based on the guidelines for adults (Tab. 2), and the criteria for paediatric patients are being drawn up [78–81]. Antiphospholipid syndrome comprises primary (isolated) and secondary (coexisting) APS, which is usually found in the course of rheumatological diseases (mainly systemic lupus erythematosus). After a bacterial or viral infection, as well as in patients with atopic dermatitis, antibodies typical for APS [anticardiolipin antibodies (aCL), anti-β2-glycoprotein I antibodies (anti- β2GPI); lupus anticoagulant (LA)] may be transient, and therefore it is necessary to repeat the tests after 12 weeks. It should be emphasised that in a group of 121 children from the Ped-APS Registry, ischaemic stroke was the first manifestation of APS in 31 children [80]. In the case of perinatal/ /neonatal stroke, the role of maternal antiphospholipid antibodies penetrating the placenta is ambiguous, and additional factors (including perinatal hypoxia, infection, and congenital thrombophilia) seem to play a role in the development of stroke [83].
4. Oral contraception, or increased activity of factor VIII, are associated with acquired activated protein C resistance (APCR) [70–75].
5. In the case of ischaemic stroke in a patient with sickle cell anaemia, the RCPCH 2017 recommendations discuss in detail the management and different treatment for this group of patients [15].

Tests for thrombophilia screening are set out in Table 3.

Diagnostic criteria for the antiphospholipid syndrome recommendations in Table 3 [78].

Paediatric stroke recommendations — other laboratory tests

An important element of the diagnosis of the aetiology of stroke, apart from neuroimaging tests, are laboratory tests that should take into account haematological disorders that predispose people, especially children, to the occurrence of a stroke. Additional tests should exclude the inflammatory process, systemic diseases, disorders of lipid and electrolyte metabolism, as well as mitochondrial diseases or infection [6, 37]. Most of these tests can be performed in the days following acute illness.

If an infection is suspected, a chest X-ray should be performed, and if an inflammatory aetiology of ischaemic stroke

Table 3. Diagnostic criteria for antiphospholipid syndrome [77]

Clinical criteria:
Venous or arterial thrombosis confirmed by imaging tests
Obstetric failures:
— death of a morphologically normal foetus > 10 weeks of gestation
— premature birth of a morphologically normal child < 34 weeks gestation due to eclampsia, severe pre-eclampsia or confirmed placental insufficiency
— three or more spontaneous abortions < 10 weeks gestation, other causes excluded
Laboratory criteria:
Lupus anticoagulant confirmed at least twice with an interval of ≥ 12 weeks
Anticardiolipin antibodies (IgG and/or IgM) in medium or high titre (> 40 GPL or MPL*, or > 99 percentile), confirmed at least twice at an interval of ≥ 12 weeks
Antibodies against β2-glycoprotein I (in IgG and/or IgM class), titre > 99th percentile, confirmed at least twice with an interval of ≥ 12 weeks)

*At least one clinical criterion and one laboratory criterion are required for diagnosis
*Symbols GPL and MPL denote standardised units used in measurement of anti-cardiolipin antibodies in IgG and IgM classes, respectively

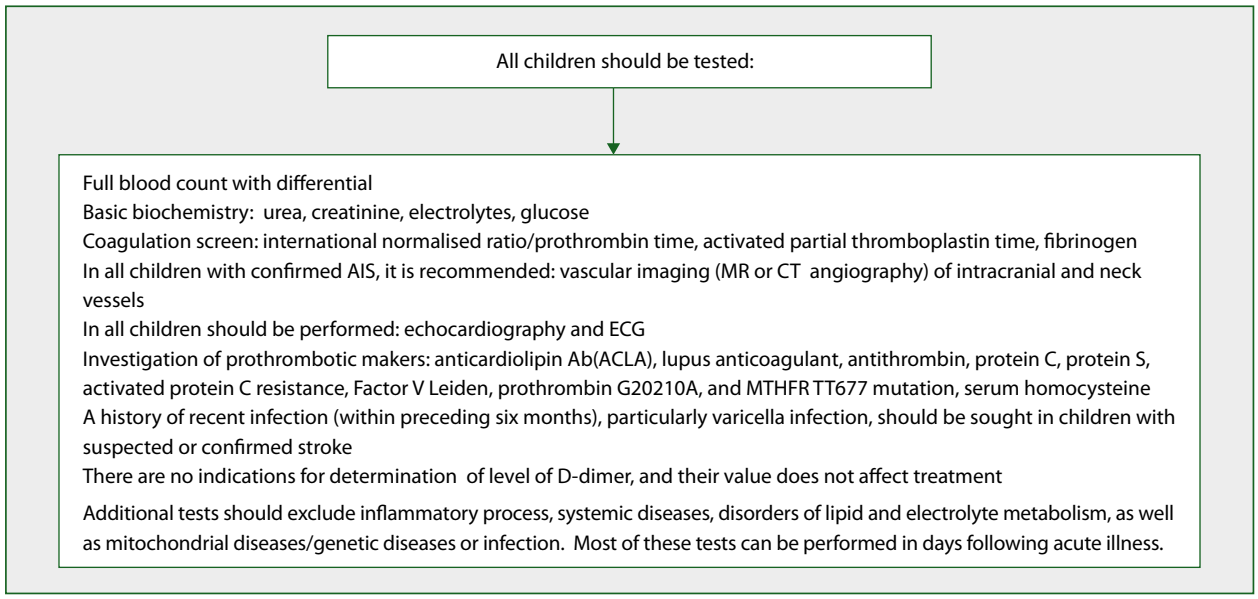

Figure 3. Investigations for suspected or confirmed childhood stroke

or subarachnoid haemorrhage is suspected, a cerebrospinal fluid test is performed if the CT image is abnormal.

If there are seizures or non-seizure status epilepticus, electroencephalography (EEG) should be performed. If possible, this should be performed in a child at the beginning of the disease, in order to be able to follow the dynamics of changes in subsequent tests, which may be a possible indicator of the development of epilepsy. Every child with suspected stroke should have the following test (Fig. 3).

Paediatric stroke recommendations — Doppler ultrasound of vessels in children

This test should be performed in all children who have had a stroke or transient ischaemic attack, regardless of other neuroimaging tests [86].

Probes used in ultrasound examinations

Examination of extracranial and intracerebral arteries should be performed with a duplex-Doppler apparatus, a 5–13 MHz linear probe, which enables the assessment of the vessel wall, as well as the assessment of flow in the form of colour-coded flow according to velocity or amplitude (the so-called 'power Doppler'), with an assessment of the flow direction and velocity graph (Doppler spectrum in visualisation of the spectrum shape and measurement of systolic and diastolic velocities as well as vascular resistance coefficients).

The transcranial examination can be performed using Transcranial Doppler ultrasonography (TCD), sometimes called 'blind Doppler', equipped with a 2 MHz pulse wave (PW) probe) or duplex-Doppler examination with a sector probe with a frequency of 2–3.5 MHz. The lower frequency

used in transcranial probes makes it impossible to assess the walls of intracranial vessels, so the most important thing is to assess the velocity, flow direction and shape of the Doppler spectrum.

In very young children with an open fontanelle, convex duplex probes with a small forehead area, broadband with a frequency of 5–11 MHz is used. The examination is routinely performed through the anterior fontanelle [87].

Paediatric stroke recommendations — cardiological diagnostics

A cardiogenic stroke is an ischaemic stroke caused by embolic material formed in the cavities or valves of the heart. In the general population, cardiogenic stroke accounts for 25–30% of all ischaemic strokes. With age, the proportion of cardiogenic strokes in the pathomechanism of ischaemic stroke increases, and it reaches 50% in the 45–80 age group. This is due to the increase in potential risk factors, such as: an increase in the percentage of cardiac arrhythmias (mainly atrial fibrillation), dilated and contractile disorders of the heart cavities, and valve prostheses as well as venous flow disorders, which can lead to the formation of embolic material and its subsequent migration into cerebral circulation in the mechanism of paradoxical (cross) embolism. Such a mechanism of stroke is favoured by impaired venous flow and inflammation of these vessels, which predisposes to the formation of embolic material in them. The incidence of these diseases increases significantly with age.

A large percentage of strokes are cryptogenic strokes with an undiagnosed cause. It depends, of course, on the scope and detail of the conducted diagnostics. The causes and pathomechanisms of cardiogenic stroke in the paediatric population are completely different. The disease entities that are the main causes of stroke in adults (atrial fibrillation and dilated cardiomyopathy) are almost entirely absent in the paediatric population. In an analysis of 667 children with ischaemic stroke, 30.6% were diagnosed with heart disease. Congenital heart defects were found in 59.3%, acquired cardiovascular abnormalities in 19.6%, and PFO (patent foramen ovale) in 15.2% [88].

There is an increased risk of cardiogenic stroke in children with congenital heart disease. Defects with a right-to-left leak (e.g. Fallot syndrome) allow the embolic material to pass from the venous system to the systemic circulation through the existing communication. The formation of embolic material is favoured by compensatory polyglobulia, which occurs in response to cyanosis accompanying the defect.

A similar situation occurs in patients with Eisenmenger's syndrome, in whom changes in the pulmonary vessels in the course of the defects with increased pulmonary flow leads to the development of pulmonary hypertension and right-left reversal of the intracardiac shunt. Also, children after cardiac surgery for heart defects have an increased risk of thrombotic material formation, which is facilitated by the presence of artificial materials used during the correction of the defect. This thrombotic material can be clots or bacterial vegetations.

Bacterial endocarditis, especially located on the valves or structures of the left heart, is associated with a high (25–50%) risk of stroke [89]. Compared to the general population, the risk of ischaemic stroke in young adults with a heart defect is 9–12 times higher, and in children up to 19 times higher [90–91]. Studies of more than 25,000 children and young adults with congenital heart disease have shown that the incidence of ischaemic stroke is 0.5%, which is 11 times higher than in the general population [92].

Heart defects predisposing to ischaemic stroke in the mechanism of paradoxical embolism include atrial septal defect (ASD II). This defect causes blood to flow from the left to the right heart. However, the pressure difference between the atria is small. In certain situations, the leak direction may be reversed temporarily. This can cause the transfer of embolic material to the systemic circulation. A history of ischaemic stroke in this mechanism is an indication for the closure of the interatrial defect, regardless of its size and haemodynamic significance. A similar mechanism of stroke may occur in the case of patent foramen ovale (PFO). This remnant of the foetal circulation remains patent in up to 20–30% of the population. It is not treated as a heart defect, and under no circumstances is there any indication for its prophylactic closure. Due to the anatomy of PFO, spontaneous leakage of blood between the atria is often not observed, or the flow is haemodynamically insignificant.

However, in situations such as pushing, sneezing, lifting heavy objects, or Valsalva's manoeuvre, right-left blood flow may occur, and with it, embolic material may enter the systemic circulation. In patients after ischaemic stroke and after excluding its other causes, patent foramen ovale may be considered as a potential site for the transition of the embolic material from the venous to the systemic circulation.

In people under 45 years, as many as half of ischaemic strokes may be caused by a paradoxical embolism. In this age group, percutaneous PFO closure can be considered as a secondary prophylaxis of stroke. However, in paediatric patients, this embolic mechanism is much less frequent. This is mainly due to the fact that venous thrombosis as a potential source of embolism occurs rarely in children, with a frequency of 0.05/1,000/year [93].

Data from the literature shows that in children after an ischaemic stroke of uncertain origin, the incidence of PFO is higher than in the adult population, and in many of them the decision has been made to percutaneously close the PFO [94–97]. Implantation of the device closing interatrial communication is a safe and effective method of treatment also in paediatric patients.

Arterio-venous fistulas located in the lungs may be another cause of ischaemic stroke in the mechanism of paradoxical embolism. The prevalence of arteriovenous fistulas in the lungs is estimated at 2–3/100,000. More than 80% of fistulas are congenital and often coexist with Rendu-Weber-Osler syndrome. Fistulas are abnormal connections between the artery and the pulmonary vein, bypassing the pulmonary capillaries, in which there is a constant flow of desaturated blood from the pulmonary bed directly into the pulmonary veins, bypassing the capillaries. Fistulas can cause desaturation (cyanosis), volume overload, or be asymptomatic. Ischaemic stroke in the mechanism of paradoxical embolism may be the first, and often the only, symptom. The frequency of strokes in pulmonary arteriovenous fistulas is estimated at 18–32%, and up to 60% in the case of multiple fistulas [98].

The risk of paradoxical embolism is increased by the fact that there is constant right-left blood flow. Percutaneous embolisation of abnormal connections is the method of choice for the treatment of these malformations. This allows for minimally invasive, precise closure of them while maintaining healthy lung tissue. Valsalva contrast echocardiography is standard in the diagnosis of leaks between the right and left hearts. During echocardiography, saline is administered intravenously with microbubbles in the air. During the Valsalva test, it is found that the micro air vesicles enter the systemic circulation.

Transoesophageal echocardiography is the most sensitive and specific. However, in children with good echocardiographic visualisation, a transthoracic examination is sufficient. Equally sensitive is the transcranial Doppler (TCD) test, also with agitated saline. During the Valsalva manoeuvre, the micro signals are detected in the cerebral circulation. This examination, although simpler and less invasive for the patient, does not allow for the indication of the leakage site, and only detects its presence. It can definitely be used as a screening test.

Paediatric stroke recommendations — anticoagulant treatment and secondary prevention of stroke in children, based on RCPCH 2017 and AHA 2019 guidelines

1. If patient is qualified for thrombolytic treatment according to scheme included in these recommendations, antiplatelet/ /anticoagulant treatment is postponed for 24 hours [35].
2. Patients who do not qualify for thrombolytic therapy should be urgently initiated on antiplatelet therapy (in absence of CNS bleeding and other contraindications) [36]. Recommended therapy is acetylsalicylic acid (ASA) at a dose of 5 mg/kg (up to a maximum of 300 mg daily) with dose reduction after 14 days (up to a maximum of 75 mg daily) [35, 71, 72].
3. Patients with a suspected cardiovascular or vascular embolism should be treated with anticoagulation (low molecular weight heparin/unfractionated heparin/vitamin K antagonist; in the absence of contraindications and intracranial bleeding) [35, 71–72]. Anticoagulation therapy should last at least six weeks (in the case of dissection of the arteries) or longer. A multi-specialist council and planning of further therapy, including procedures in the field of invasive cardiology, is necessary [36, 72, 98].

It must be emphasised that the main goal of antiplatelet or anticoagulant therapy is to prevent recurrence of stroke [35, 71–73].

Safety of therapy

Patients with a massive ischaemic stroke involving a significant area of the brain (> 2/3 of the vascular territory of middle cerebral artery), or with arterial hypertension, are at high risk of secondary haemorrhage. The decision whether to initiate anticoagulant/antiplatelet therapy should be postponed for up to 72 hours. Patients with middle cerebral artery involvement may develop a malignant cerebral oedema requiring urgent neurosurgical treatment (hemicraniectomy) and reversal of anticoagulant drugs [35, 71–73].

During antiplatelet therapy with ASA, in case of severe epistaxis or gastrointestinal intolerance, it is recommended to reduce the dose to 1–3 mg/kg/day. ASA therapy is advised to last at least two years, because the risk of recurrent stroke is highest during this period. ASA therapy is considered safe, and so far Reye's syndrome has not been reported in children receiving the drug in a prophylactic dose [99].

Based on the observation of large groups of patients, the risk of secondary haemorrhage in ischaemic lesions in children who have received or have not received antiplatelet/anticoagulant therapy is similar [100–102]. The same observations also apply to newborns treated with anticoagulants due to cardiogenic strokes [101].

Paediatric stroke recommendations — indications for use of chronic secondary anticoagulant prophylaxis after ischaemic stroke [103–105]:

- Recurrent ischaemic stroke
- Predisposing heart defect, arrhythmias, blood vessels abnormalities
- Antiphospholipid syndrome
- Severe thrombophilia: deficiency of antithrombin, protein C deficiency, free protein S deficiency, homozygous factor V Leiden mutation, homozygous G20210A mutation in prothrombin gene

- Complex thrombophilia (e.g. coexistence of heterozygous forms of factor V Leiden mutation and prothrombin gene G20210A and others)
- Current process/inflammation in body predisposing to relapse (e.g. active nephrotic syndrome, active ulcerative colitis, use of asparaginase).

Long-term anticoagulants in children are vitamin K antagonists (VKA) administered orally (e.g. warfarin, acenocoumarol) or subcutaneously injected low molecular weight heparin when the use of VKA is impossible (gastrointestinal malabsorption, in tablet form in young children). Therapy requires regular monitoring, including INR or anti-Xa determination, respectively. In 2022, the direct oral anticoagulant (DOAC) rivaroxaban was approved for use in children in Poland in the treatment of VTE and prevention of its recurrence, while other DOACs are yet to be registered in patients under 18.

Studies in adults have shown that DOACs should not be used in patients with antiphospholipid syndrome or in patients undergoing heart valve replacement (due to the increased frequency of recurrence of thrombosis) [105].

The risk of recurrent ischaemic stroke and, on the other hand, the risk of bleeding, the chronicity and the burden of secondary anticoagulation in children raise many doubts. To make therapeutic decisions, specialist consultations and the active participation of the patient and his or her family are necessary.

Paediatric stroke recommendations — intravenous thrombolytic therapy

Intravenous thrombolytic therapy of ischaemic stroke (*i.v.* cerebral thrombolysis) with tissue plasminogen activator (rt-Pa *i.v.*) has been approved for the treatment of adult patients since 1996, initially in the USA based on results from the National Institute of Neurological Diseases and Stroke (NINDS), and then since 2002 in Europe, following the results of randomised clinical trials and the European Cooperative Acute Stroke Study (ECASS) [106].

In Poland, cerebral thrombolysis, implemented incidentally since the beginning of the 21st century, has been admitted into routine clinical practice since 2003 and is currently used in an average of 17%, and in the best patient centres more than 33%, of ischaemic stroke patients. Even though access to endovascular methods is increasingly common, rt-Pa *i.v.* remains a standard method of treatment of stroke patients [107].

The insufficient data on safety and long-term effects can probably be explained by the fact that the US Food and Drug Administration and Health Canada do not recommend thrombolytic therapy for ischaemic stroke in children and adolescents. Also, the American Heart Association, the American Stroke Association, and the American College of Chest Physicians do not recommend routine use of thrombolytic therapy for stroke before the age of 18 [36].

The opinion of the American Heart Association/American Stroke Association on the management of stroke in newborns and children, published in 2019, states that it remains controversial, without providing clear indications/contraindications for the use of thrombosis brain due to the absence of clinical trial results on the treatment of acute phase of stroke. The AHA/ASA recall only the protocol elements used in the TIPS (Thrombolysis in Paediatric Stroke) study (classic rt-PA dosing at a dose of 0.9 mg/kg body weight: 10% by bolus in the first 5 minutes, the remaining amount in the infusion pump within 55 min) [108].

Currently, the most detailed practical guidance is provided by the algorithm proposed by the Boston Children's Hospital Neurological Department, prepared on the basis of the TIPS study protocol (Tab. 2) [8]. Similarly, the Australian Clinical Consensus Guidelines for diagnosis and acute management appropriate in specific children proposes the use of criteria based on the TIPS study consensus, pointing to "weak" evidence of the benefits of thrombolytic therapy in children [7].

In a small group of patients, it is additionally helpful to use the premises contained in the summary of product characteristics of actilyse/alteplase, indicating: "in children ≥ 16 years of age, the individual benefit-risk ratio should be carefully assessed. Children aged ≥ 16 years should be treated according to the guidelines for adults after confirmation of arterial ischaemic thromboembolism (exclusion of a disease imitating stroke)" [108].

In light of the above facts, thrombolytic therapy in children and adolescents < 16 years of age can still be performed outside the registration indications (only off-label), and therefore should be considered individually and after a detailed consideration of the benefit-risk ratio. Its conduct should be carried out in a centre equipped with an interdisciplinary team of specialists experienced in the diagnosis and treatment of stroke in children and adolescents.

Indications and contraindications for cerebral thrombolysis in children and adolescents proposed in TIPS study [109]

Indications

- Age: 2–17 years
- Symptoms of acute ischaemic stroke defined as sudden onset of focal deficit
- NIH Stroke Scale (PedNIHSS) ≥ 4 and ≤ 24 points (Annex 1) [110]
- Duration of symptoms < 270 minutes
- Features of acute ischaemia confirmed by neuroimaging:
  - MRI with diffusion-weighted sequences and MRA showing at same time signs of partial or complete occlusion of cerebral arterial vessel in location corresponding to symptoms,

- CT examination showing correct image of brain structures or minimal early ischaemic changes and CT-angio examination showing partial or complete obstruction of cerebral arterial vessel in location corresponding to symptoms,
- Exclusion of haemorrhagic foci.

Contraindications*

- Unknown time of onset
- Pregnancy
- Clinical symptoms suggesting a subarachnoid haemorrhage even with a normal CT imaging
- Patients in whom consent has not been obtained for a potential blood transfusion
- Previous intracranial haemorrhage
- Known arteriovenous malformation, aneurysm or brain tumour
- Systolic blood pressure in lying or sitting position > 15% higher than 95th percentile value for patient's age
- Blood glucose < 50 mg/dL (2.78 mmol/L) or > 400 mg/dL (22.22 mmol/L)
- Platelet count < 100,000, PT > 15 sec, INR > 1.4, PTT > laboratory norm
- Symptoms of myocardial infarction or pericarditis that require a cardiac evaluation
- Stroke, major head injury, or intracranial surgery in previous three months
- Major surgery or biopsy within previous 10 days (relative contraindication)
- Bleeding from gastrointestinal tract or urinary tract during previous 10 days (relative contraindication)
- Puncture of artery in a place inaccessible to pressure or lumbar puncture in period of seven preceding symptoms (relative contraindication) (patients with a catheter inserted into pressure artery are not excluded)
- Patients with active neoplastic disease or within one month after end of treatment
- Patients with known significant coagulation deficits (patients with mild platelet dysfunction, mild von Willebrand's disease, or other mild coagulation deficits are not excluded)
- Mild neurological deficit (PedNIHSS < 4) at initiation of rt-PA infusion or prior to initiation of sedation for neuroimaging (if applicable)
- Significant neurological deficit suggesting extensive territorial stroke (PedNIHSS > 24 points), regardless of size of ischaemic focus seen in neuroimaging
- Symptoms of stroke in course of bacterial endocarditis, moya moya disease, sickle cell anaemia, meningitis, myeloid, air or fat embolism
- Previously diagnosed primary central nervous system vasculitis (PACNS) or secondary central nervous system vasculitis (childhood focal cerebral arteriopathy (FCA) is a contraindication)
- Intracranial haemorrhage (HI-1, HI-2, PH-1 or PH-2) demonstrated by MRI or CT of head
- Dissection of intracranial arteries (above exit of eye artery)
- Significant volume of infarct on MRI, covering > one third of MCA supply area
- Known allergy to recombinant plasminogen activator
- INR > 1.4
- APTT in laboratory standard for heparin treatment up to 4 hours
- LMWH treatment in previous 24 hours (aPTT and INR do not reflect LMWH effect).

*The occurrence of an epileptic seizure upon onset is not a contraindication if the other inclusion criteria are met and if the exclusion criteria are absent.

Paediatric stroke recommendations — malignant MCA syndrome

Malignant middle cerebral artery syndrome (MMCAI) is a situation where the ischaemic area is large and covers over 33% of the MCA vascularisation range, which is associated with large swelling of the brain and rapid deterioration of the patient's condition. MMCAI risk factors include seizures lasting more than 5 minutes as a manifestation of trauma, and a severe neurological condition at the beginning. For adult patients with MMCAI, the recommended management is to perform a decompressive craniectomy; this improves the survival rate of the stroke and the neurological outcome of patients in long-term follow-up; in the case of children, there is no reliable research [8, 36]

In summary, we propose a scheme illustrating in a simplified way the diagnostic procedure in the case of a child with suspected stroke (Fig. 4).

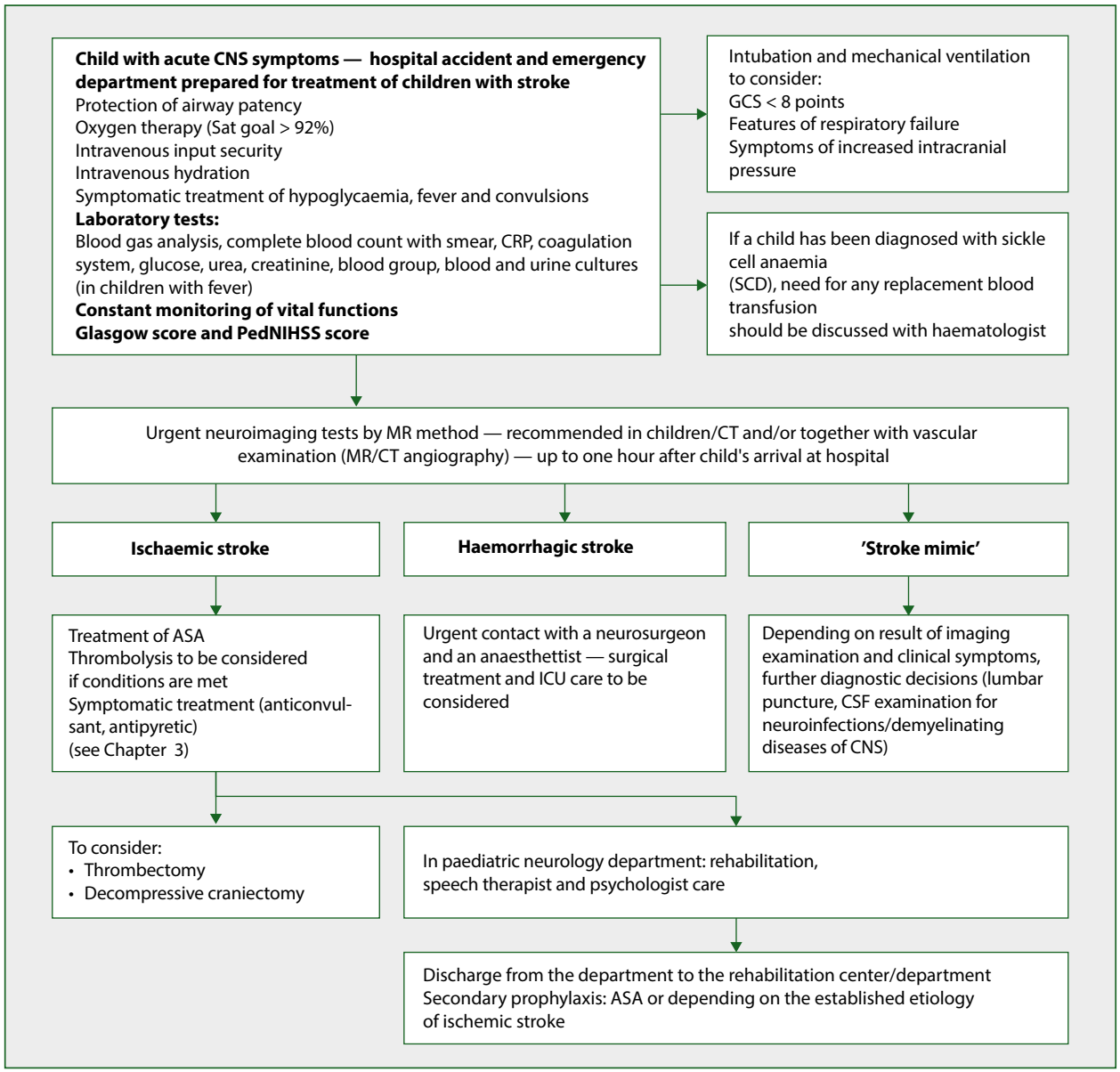

Figure 4. Scheme of management of child with acute symptoms of central nervous system/suspected acute cerebrovascular disease — from appearance of symptoms through diagnosis and treatment of acute phase to secondary prophylaxis (according to Royal College of Paediatrics and Child Health recommendations in 2016, 2019 [8, 36], modified by the authors)

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Heart rate variability in evaluation of autonomic dysfunction in idiopathic REM-sleep behaviour disorder

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ABSTRACT

Introduction. Nearly 80% of people diagnosed with idiopathic REM sleep behaviour disorder (iRBD) via video-polysomnography (v-PSG) are expected to be in the prodromal stage of an alpha-synucleinopathy. Signs of autonomic dysfunction can appear earlier than motor or cognitive alpha-synucleinopathy symptoms. Heart rate variability (HRV) can potentially be an objective measurement of autonomic dysfunction, and furthermore can be obtained directly from v-PSG.

Objectives. The aim of this study was to evaluate dysautonomia in iRBD subjects using HRV obtained during different sleep stages and wakefulness from v-PSG.

Material and methods. Subjects positively screened by an RBD screening questionnaire (RBD-SQ) underwent v-PSG to diagnose RBD. HRV obtained from v-PSG recordings was correlated to dysautonomia evaluated from a Non-Motor Symptoms Scale (NMSS) questionnaire. Optimal cut-off values of HRV parameters to predict dysautonomia were calculated using receiver operating characteristics (ROC) — area under the curve (AUC) analysis. The effect of confounder variables was predicted with binomial logistic regression and multiple regression analyses.

Results. Out of 72 positively screened subjects, 29 subjects were diagnosed as iRBD (mean age 66 ± 7.7 years) by v-PSG. Eighty-three per cent of the iRBD subjects in our cohort were at the time of diagnosis classified as having possible or probable prodromal Parkinson's disease (pPD) compared to zero subjects being positively screened in the control group. The iRBD-positive subjects showed significant inverse correlations of NMSS score, particularly to log low-frequency (LF) component of HRV during wakefulness: $r = -0.59$ ($p = 0.001$). Based on ROC analysis and correlation between NMSS score, log LF during wakefulness (AUC 0.74, cut-off 4.69, sensitivity 91.7%, specificity 64.7%, $p = 0.028$) was considered as the most accurate predictor of dysautonomia in the iRBD group. Apnoea-hypopnoea index (AHI) negatively predicted dysautonomia in the iRBD group. None of the HRV components was able to predict the presence of iRBD in the full cohort. Age, gender, and PSG variables were significant confounders of HRV prediction.

Conclusions. The presented study did not confirm the possibility of using HRV from v-PSG records of patients with iRBD to predict dysautonomia expressed by questionnaire methods. This is probably due to several confounding factors capable of influencing HRV in such a cohort.

Key words: idiopathic REM sleep behaviour disorder, dysautonomia, heart rate variability, RBD Screening Questionnaire

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Introduction

Consistent evidence indicates that RBD is the most specific clinical prodromal marker of alpha-synucleinopathies — neurodegenerative disorders characterised by the pathological accumulation of alpha-synuclein, such as Parkinson's disease (PD), dementia with Lewy bodies and multiple system atrophy [1, 2]. The presence of RBD is also currently being studied in tauopathies, such as progressive supranuclear palsy [3] and Alzheimer's disease [4]. Several studies have demonstrated that c.80% of v-PSG proven RBD patients eventually develop alpha-synuclein-induced neurodegeneration [2, 5, 6], with a nearly 6.3% phenoconversion rate per year [7], and thus it can be effectively used as a substitute for pPD in research studies of other potential biomarkers [1].

Such a predictor is dysfunction of the autonomic nervous system (ANS). Signs of autonomic dysfunction are estimated to start developing as much as 15 years before the diagnosis of PD [8]. Orthostatic hypotension in PD involves a combination of sympathetic denervation and baroreflex failure, and occurs in 20–50% of patients with PD, according to the different diagnostic criteria used [9]. Other signs of dysautonomia are constipation, with a prevalence ranging from 24.6–63% [10], and lower urinary tract dysfunction, mostly characterised by overactivity of the detrusor muscle leading to an overactive bladder, occurring in 27–80% of PD patients [11].

It has been recognised that the presence of RBD identifies a specific PD subtype characterised by a higher prevalence of autonomic dysfunction [12]. A recent proposal [13] divides PD into two subtypes, according to the phenotypes seen in the prodromal stage. One is the 'body-first' subtype, clearly associated with the presence of RBD, appearing during the prodromal stage and with significant damage to the ANS preceding measurable damage to the nigrostriatal dopamine system. The other subtype is designated 'brain-first', which in its prodromal stage is without RBD or quantifiable dysfunction of the ANS, but already with evident damage to the nigrostriatal dopamine system [13].

Questionnaires and rating scales are currently the gold standard for assessing most aspects of autonomic dysfunction; however, these are subjective, and few objective measures are available, e.g. HRV. HRV measures the fluctuation of the time intervals between consecutive heartbeats, revealing the dynamic interactions between the sympathetic and parasympathetic functions. HRV has been suggested as a possible biomarker for dysautonomia in conditions such as diabetes mellitus type 2 [14] and ischaemic stroke [15]. Having the advantage of being directly obtained from diagnostic v-PSG, HRV is an inexpensive measure of cardiac dysautonomia compared to examinations such as 123 I-MIBG-scintigraphy [16], and could potentially be an objective measure of autonomic dysfunction in subjects at risk of developing an alpha-synucleinopathy. In this study, we tested the hypothesis that HRV can predict subjective autonomic dysfunction in iRBD patients.

Material and methods

Study participants were recruited in a single Movement Disorder Centre in Kosice, Slovakia, between 2018 and 2021 after a nationwide media campaign, followed by a multistage screening described previously [17]. Patients were screened using the REM Sleep Behaviour Disorder Single-Question Screening [18], followed in the case of positive findings by the RBD-SQ [19]. Patients with ≥ 5 points on the RBD-SQ underwent v-PSG. All involved subjects signed informed consent forms prior to their enrolment. The investigation protocol was approved by the local ethics committee, and the work was carried out in accordance with the Declaration of Helsinki.

A full night v-PSG examination was performed over the course of one or two nights using Sleepware G3 version 3.9.5. software to guarantee an appropriate amount of REM sleep for the evaluation. The v-PSG scoring used was according to the American Academy of Sleep Medicine's recommendation [20]. REM sleep muscle tone was recorded and scored according to the SINBAR group's recommendations [21]. Subjects were considered as RBD-positive patients in the presence of REM-sleep without atonia (RWA) in PSG and complex motor behaviour in the REM phase based on the synchronised v-PSG recording or patient history, according to the International Classification of Sleep Disorders — 3rd edition [22].

All patients were evaluated by a movement disorder specialist to exclude the presence of clinically established parkinsonism and also by a level 2 neuropsychological assessment to exclude the presence of cognitive dysfunction [23]. Patients presenting with severe autonomic dysfunction and age below 50 were also excluded in the initial visit [24]. After performing v-PSG analysis, those patients who were observed to have severe OSA (apnoea-hypopnea index (AHI) over 30 per hour of total sleep time), and those with cardiac arrhythmia or artefacts affecting ECG signal were excluded from the study as well. Subjects included in the study were then divided into an iRBD group and an RBD-negative group based on the presence of RBD (Fig. 1).

The likelihood ratio (LR) of a given subject being in pPD at the time of examination was also calculated based on the updated Movement Disorder Society (MDS) Research Criteria for prodromal Parkinson's disease [24], using all risk factors and prodromal markers, excluding genetic testing, plasma urate levels in men, and physical inactivity, as described previously [17].

HRV analysis came from a 5-min interval with stable ECG taken from v-PSG in three distinct sleep and wake stages: pre-sleep relaxed wakefulness, NREM (especially stage N2 but occasionally also N1 and optimally from the first sleep cycle), and REM. Intervals did not contain arousals, motor or respiratory events. For each interval, HRV was analysed in the frequency domains using Kubios HRV Premium software version 3.5.0 (University of Eastern Finland, Kuopio, Finland).

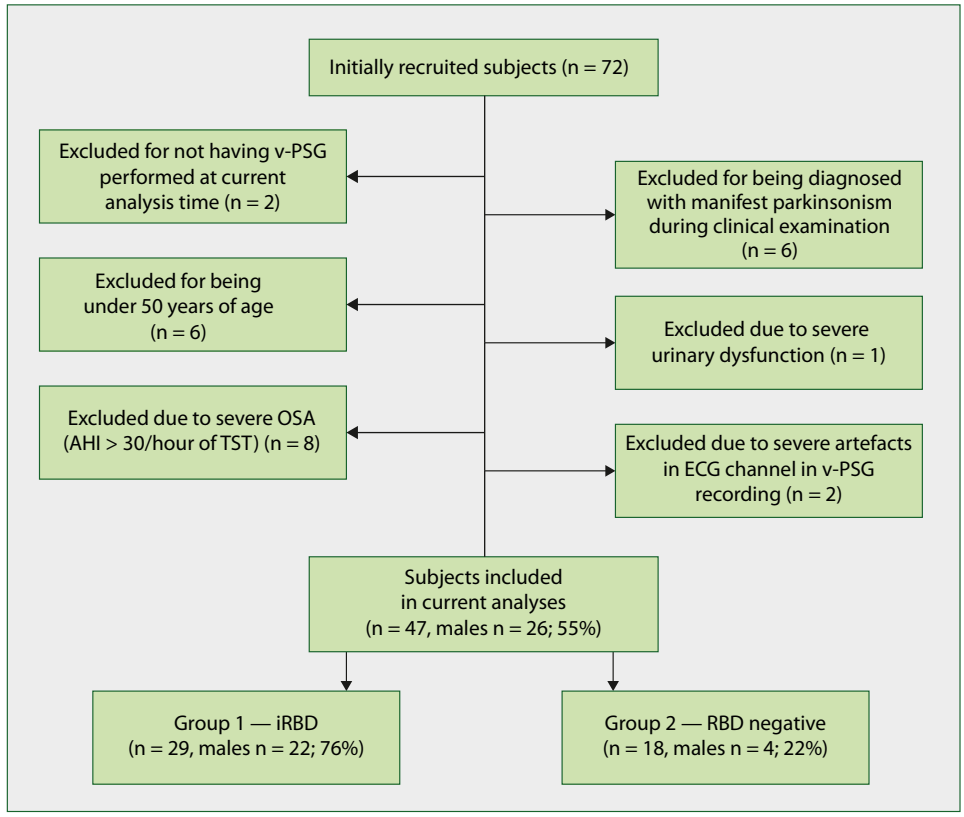

Figure 1. Flow chart of study population. AHI — Apnoea-Hypopnoea Index; iRBD — idiopathic rapid eye movement (REM) sleep behaviour disorder; n — number; OSA — obstructive sleep apnoea; v-PSG — video-polysomnography; TST — total sleep time

HRV analysis provided several different metrics: the frequency-domain metric LF is a measure of the low-frequency band (0.04–0.15 Hz) traditionally associated with both sympathetic and vagal influence and reflects baroreflex sensitivity [25]. Parasympathetic activity is considered to be a major contributor to the high-frequency (HF) band (0.15–0.4 Hz). The LF/HF ratio is used to estimate the relation between the influence of the sympathetic and parasympathetic systems under controlled conditions, also known as the sympathovagal balance [26]. In our analysis, the following frequency-domain spectral components of HRV were obtained, as quantified by a fast Fourier transform decomposition algorithm available in the software: absolute power of LF — LF ms^2, natural logarithm of LF — log LF, absolute power of HF — HF ms^2, natural logarithm of HF — log HF, and the LF/HF ratio.

Lastly, the Non-Motor Symptoms Severity Scale (NMSS) questionnaire was selected in this study based on MDS recommendations [27] to reflect multidomain autonomic dysfunction due to its cross-validity with other scales [28]. Items regarding autonomic function were selected (Nos. 1, 2, 19–24 and 30) [29]. Each item is evaluated based on the severity of the symptoms (0–3 points) and frequency (1–4 points). The final score for each NMSS item is the result of the severity multiplied by the frequency.

The NMSS total in the study represents the sum of the scores for the items concerning autonomic function, and the separate domains of autonomic dysfunction — the cardiovascular (CVS), gastrointestinal (GIT), urinary domains or sweating, were quantified by a set of NMSS items regarding specific domain.

We defined significant dysautonomia if the subject scored at least one severity score of 2 or 3 points that represents symptoms which were a moderate or major source of disturbance for the patient.

Data analysis

Statistical analysis was performed using IBM SPSS Statistics 22 and managed by spreadsheet software. The one-tail unequal variance t-test (Welch's t-test) was used when assessing the differences in demographic, v-PSG and autonomic parameters between the two study groups.

Correlations between the values of NMSS total, as well as of separate autonomic dysfunction in the CVS, GIT, urinary and sweating domains, with the LF (ms^2), log LF, HF (ms^2), log HF and the LF/HF ratio components of HRV obtained separately during wakefulness, NREM and REM sleep, were calculated using Pearson's correlation coefficient (r) in the full cohort and in iRBD subjects. The correlations were considered to be significant if $r > 0.5$ or $r < -0.5$.

Table 1. Description of study groups. Values are expressed as averages followed by standard deviations (in brackets)

	All individuals n = 47, age [years] = 63.8 (7.7)		
	Group 1 (iRBD) n = 29	Group 2 (RBD negative) n = 18	Statistical significance – p-value
Age [years]	66 (7.7)	60.4 (6.6)	0.006
MDS-UPDRS-III total evaluation score	7.1 (6)	6.5 (6.1)	0.379
TST —total sleep time [min]	375.7 (106.4)	407.8 (62.3)	0.1
Sleep efficiency [%]	76.7 (13.5)	82.4 (7.8)	0.039
AHI index (/h TST)	11.9 (8.1)	9.8 (7.3)	0.19
PLMS index (/h TST)	20.7 (19)	12.1 (12.9)	0.035
Arousal index (/h TST)	9.6 (5.5)	10.7 (8.6)	0.311
NMSS total autonomic score	11.1 (10.2)	10.2 (15.8)	0.416

AHI — Apnoea-Hypopnoea Index; MDS-UPDRS-III — Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III; N — number; NMSS — Non-Motor Symptoms Severity Scale; PLMS — periodic Limb movements of sleep; TST — total sleep time

We performed ROC analysis, from which the AUC (values 0–1) was calculated, using HRV components as the diagnostic test and significant dysautonomia as the outcome.

The ROC analysis was performed to obtain a cut-off value for different components of HRV that predict whether or not a given subject has a significant autonomic dysfunction, with a given sensitivity and specificity. Using the AUC calculation, we obtained a cut-off value for each of the studied HRV components, predicting if a given subject had a significant autonomic dysfunction.

Binomial logistic regressions were performed to ascertain the effects of independent variables — age, gender, AHI index and PLMS index on the prediction of HRV changes, having iRBD, and the presence of significant autonomic dysfunction. The Nagelkerke r^2 coefficients and correct prediction — overall percentage of the final binary regression model for the prediction of the dependent variables were calculated. The magnitude of association between the dependent and the independent variables was measured by the odds ratio (OR). A 95% confidence interval (CI), was used in the study, with a p-value of under 0.05 considered statistically significant.

Results

Demographic, v-PSG, autonomic parameters and HRV components

Seventy-two initially recruited patients with positive RBD-SQ (average age 62.6 ± 9 years, 29 females and 43 males) were eventually included in the study (Fig. 1). Due to technical problems, two of the 72 subjects did not undergo v-PSG. Six patients were excluded because of the presence of parkinsonism. From the remaining 64 subjects, six were excluded from further analysis due to age under 50 years, plus one because of severe urinary dysfunction (associated with a complication of surgery), plus 10 due to severe OSA or severe artefacts in ECG (Fig. 1). For the further analysis of HRV, we used 47 patients (average age 63.8 ± 7.7 years, 21 females and 26 males), 29 of them diagnosed with iRBD (Tab. 1). Thirty-five (50%) positively RBDSQ-screened subjects out of the 70 were confirmed as RBD.

The diagnosis of RBD was based on the presence of RWA and dream-enacting complex behaviour on v-PSG or patient history. On average, 7.53% of the REM epochs presented with RWA in the RBD positive group.Of the 29 RBD positive subjects, 12 manifested dream-enacting behaviour on v-PSG.

The LR for pPD was calculated for each subject. The iRBD group consisted of 22 (76%) subjects with an LR of probable pPD; two (7%) subjects met the criteria for possible pPD, and five were classified as negative for pPD. All 18 subjects in the RBD negative group – the control group — were classified as negative for pPD.

Table 1 presents a description of the demographic, v-PSG, and autonomic parameters of the two studied groups according to the presence of RBD. Significant statistical differences were found between the groups in terms of age, sleep efficiency, and periodic limb movements in sleep (PLMS) indices. IRBD subjects were older, had decreased sleep efficiency, and had more PLMS.

Relationship between HRV components and questionnaire-assessed autonomic parameters in iRBD patients

In iRBD subjects, we found significant inverse correlations of NMSS total to the natural logarithm of the LF and HF components of HRV during wakefulness: log LF: r = –0.59 (p = 0.001), log HF r = –0.54 (p = 0.003). Significant correlations were also observed between the urinary domain of autonomic function and log LF (r = –0.58; p = 0.001), as well as log HF (r = –0.54; p = 0.003) during wakefulness (Tab. 2). In the control group, we did not find any significant correlations. Also when considering the full cohort, there were no significant correlations.

By performing the ROC analysis, we obtained values of AUC for each of the HRV components. Only three HRV components had statistically significant AUC values. Of these three

Table 2. Correlations between HRV components and autonomic parameters in iRBD group

		Relaxed wakefulness				NREM				REM			
		LF (ms^2)	logLF	HF (ms^2)	logHF	LF/HF rat.	LF (ms^2)	logLF	HF (ms^2)	logHF	LF/HF rat.	LF (ms^2)	logLF	HF (ms^2)	logHF	LF/HF rat.
NMSS total	Pearson's r	–0.43*	**–0.59****	–0.35	**–0.54****	0.05	–0.18	–0.24	–0.18	–0.28	–0.06	–0.18	–0.45*	–0.16	–0.25	–0.14
	p-value	0.02	.001	0.06	0.003	0.814	0.346	0.22	0.353	0.146	0.759		0.014	0.405	0.198	
CVS	Pearson's r	–0.02	–0.17	0.06	–0.02	–0.16	0.03	0.01	0.12	0.07	–0.13	–0.09	–0.04	–0.06	0.02	–0.13
	p-value	0.921	0.375	0.76	0.907	0.415	0.874	0.976	0.543	0.733	0.51		0.836	0.77	0.907	
GIT	Pearson's r	–0.31	–0.27	–0.19	–0.11	–0.13	–0.19	–0.29	–0.03	–0.09	–0.19	0.02	0.01	0.09	0.03	–0.07
	p-value	0.099	0.15	0.32	0.559	0.519	0.326	0.125	0.879	0.645	0.337		0.975	0.634	0.895	
Urinary	Pearson's r	–0.41*	**–0.58****	–0.27	**–0.54****	0.05	–0.28	–0.24	–0.19	–0.32	–0.08	–0.17	–0.45*	–0.13	–0.22	–0.11
	p-value	0.026	0.001	0.153	0.003	0.813	0.137	0.213	0.315	0.096	0.671		0.015	0.511	0.245	
Sweating	Pearson's r	–0.09	–0.2	–0.3	–0.37*	0.23	0.22	0.1	–0.15	–0.11	0.23	–0.19	–0.41*	–0.29	–0.31	–0.07
	p-value	0.643	0.29	0.115	0.048	0.23	0.247	0.601	0.449	0.581	0.225		0.026	0.123	0.105	

*Correlation is significant at < 0.05 level (2-tailed). **Correlation is significant at < 0.01 level (2-tailed). In **bold** are marked correlations with a Pearson's correlation coefficient of either < –0.5 or > 0.5, considered significant correlations
CVS — cardiovascular system; GIT — gastrointestinal system; HF — high-frequency HRV component; HRV — heart rate variability; iRBD — idiopathic REM sleep behaviour disorder; LF — low-frequency HRV component; log — natural logarithm; ms^2 — absolute power of HRV component; NMSS — Non-Motor Symptoms Scale for Parkinson'sDisease; NMSS total — sum of scores of items in NMSS regarding autonomic function; Pearson's r — Pearson's correlation coefficient

HRV components, one of them had been described previously as also having a significant correlation to the total NMSS score in the correlation analysis: log LF during wakefulness; therefore, this HRV component was finally selected to be the HRV component that could more accurately predict significant dysautonomia. We further selected an optimal cut-off level for predicting significant dysautonomia, together with sensitivity and specificity values: log LF during wakefulness has an AUC of 0.74 and an optimal cut-off of 4.69 (sensitivity 91.7% and specificity 64.7%, p = 0.028) (Suppl. Material A).

Using binomial logistic regression, we described that the influence of age, gender and PSG variables is 44.1% (Nagelkerke r_2) on the prediction of significant dysautonomia in the group of iRBD subjects. The only variable that can significantly impact the prediction of significant dysautonomia was the AHI index, where an increase of 1 point in the AHI index decreases the chance of having significant dysautonomia by 19% (p = 0.017) (Suppl. Material B).

Differences in HRV between iRBD patients and controls

The subjects in the cohort did not show any statistically significant differences between the HRV components during wakefulness or NREM, and REM sleep, when comparing the iRBD group to the RBD negative group (Suppl. Material C).

A ROC curve was performed in the full cohort to predict iRBD based only on HRV values during wakefulness and sleep. No HRV component was able to independently predict the diagnosis of iRBD, which is reflected in the values of AUC without statistical significance (Suppl. Material D).

Using binomial logistic regression, we described that the influence of age, gender and PSG variables on the prediction of iRBD in the full cohort was 83%. The Nagelkerke r_2 indicated approximately 43% of the variance in the iRBD prediction was accounted for by independent factors. The only variable that could significantly impact the prediction of iRBD was gender: females were 88.1% less likely to have iRBD than males (p = 0.005) in the presented cohort.

Multiple regressions were used to predict how much of the variance of each HRV component in sleep and wake stages was accounted for by age, gender, AHI and PLMS indices, in the full cohort (Suppl. Material E). The HRV component which was most influenced by these variables was log LF in wakefulness (R^2 = 0.22).

Discussion

The presented study revealed that 50% of subjects after a questionnaire screening process were v-PSG proven as RBD--positive, which was lower than in a previous study [19]. Eighty--three per cent of the iRBD subjects in our cohort were at the time of diagnosis classified as possible or probable pPD, compared to zero subjects being positively screened in the control group, which was in accordance with previous observations [30, 31].

For the first time, changes in HRV were correlated with the questionnaire-assessed autonomic dysfunction. The study revealed correlations between NMSS questionnaire-assessed autonomic function scores and HRV indices in the iRBD group, especially with the low-frequency (LF) components of HRV in wakefulness, which mainly represent the sympathetic nervous system function.

In contrast, in the study we observed that although HRV is strongly correlated with general autonomic dysfunction in iRBD subjects (based on the total score for the questions regarding autonomic function in the NMSS), it is only weakly correlated with the separate domain of CVS function. The explanation for this could be that HRV is closely related to cardiac autonomic function, while the CVS domain in the NMSS questionnaire mostly concerns orthostasis, which more accurately represents peripheral vascular autonomic function, or it could be that the subjective nature of questionnaire--assessed dysautonomia in NMSS does not reflect all of the aspects of CVS function. However, Sumi et al. demonstrated that the decrease in HRV indices during the supine position can predict orthostatic hypotension, providing an alternative to the orthostatic challenge test [32]. While using the head-up tilt test, Rocchi et al. [33] described LF and LF/HF ratio as significantly higher in controls compared to iRBD, while we did not find statistically significant differences between both groups.

The other issue could be the reliability of subjective NMSS domains for orthostasis and objective head-up tilt test. Unfortunately, the presented study was set before the MDS updates for pPD evaluation, and such data was not available for the first patients included. A question that remains unanswered in the presented study is that while log LF was significantly correlated with autonomic questionnaires, the absolute power of LF was not. In practice, this finding means that it can only be a random statistical phenomenon, and not a relationship between quantities. Moreover, log LF in wakefulness was the HRV component which was the most affected by confounders. The assessment of HRV in the studied iRBD patients during any stage of sleep and wake is not able to identify the presence of subjectively reported dysautonomia.

In previous studies that only looked at HRV changes in patients with RBD, the findings were inconsistent as for the main impact on LF or HF component or distribution during sleep and wakefulness: Attenuated sympathetic nervous system activity has been observed in RBD patients (11 iRBD, 14 PD patients with RBD) when compared to controls, and being more pronounced in patients with PD [34]. Decreased HRV (both the sympathetic and parasympathetic components) in iRBD has been described when analysing 5-minute pre-sleep ECG segments [35]. Another study however reported reduced HF in RBD (47 individuals) compared to age- and gender-matched controls (26 individuals), along with reduced time-domain HRV components (RMSSD and SDRR). The latter study also observed that tonic activity in RWA was inversely correlated with LF and LF/HF ratio, and positively correlated with HF [36].

The other studies found reduced HRV during sleep in iRBD and RBD associated with neurodegenerative disorders [37]. Significant differences in HRV between iRBD and healthy control subjects were found in the very LF and LF components of HRV during wakefulness, independent of whether or not the iRBD subjects would eventually develop neurodegeneration [38]. The presented study failed to show significant changes in HRV between iRBD patients and controls in any sleep-wake stage.

It has been demonstrated that HRV can be easily influenced by other variables, such as age, gender, OSA, and PLMS [39–43]. There is a high interindividual variability in HRV, so there are no ranges of normative values for a given individual [44]. There were no significant differences between the study groups regarding comorbidities that may affect HRV evaluation (heart arrhythmia, diabetes mellitus type 2, arterial hypertension, thyroid disorder, neuropathy, myocardial infarction, and ischaemic heart disease) no regarding medication (antidepressants, beta-blockers, alpha-blockers, ACE inhibitors and sartans, calcium-channel blockers, diuretics, statins and antiaggregants). Lower HF, reflecting deficient vagal inhibition, has been correlated with stress, anxiety, and increased morbidity [45]. It was reported that LF power was lower in healthy individuals who developed type 2 diabetes mellitus over an average follow-up period of 8.3 years, with no differences in HF power [46].

Since, in the presented study, iRBD patients differed from controls in terms of age, gender and PSG variables, we considered that confounding factors were involved in HRV changes. We demonstrated that gender could have significantly influenced the prediction of iRBD using HRV. Despite the fact that there were men and women in a ratio of 1:1.2 in the entire cohort obtained by the questionnaire survey, the gender distribution in the iRBD (male 76%) group and the non-RBD group (male 22%) was clearly uneven. The higher representation of the male gender in the iRBD group is also in accordance with previous findings, which led to the expression of a 1.5-fold increased risk for pPD in males [27]. The high ratio of women in the iRBD-negative group could indicate that the questionnaire survey in women fails to differentiate the motor and dream activity in women associated with other sleep and mental disorders, especially the abuse of psychoactive substances. No other independent variable (age, AHI and PLMS indexes) had a significant effect on this prediction. In the group of iRBD subjects, we observed that AHI may be a significant confounder (even if patients with severe OSA were excluded from the study).

Limitations

This study has several limitations. Firstly, the limited number of the studied subjects, due to iRBD rarity, should be followed by studies on larger patient cohorts. The nature

of our study did not allow for having age- and gender-matched subjects. In addition, while our study evaluated autonomic symptoms based on subjective patient reports correlated to objective HRV components, other multimodal objective autonomic examinations, such as orthostatic and/or head-up tilt test, the quantitative sudomotor axon reflex test, thermoregulatory sweat test, urodynamic investigations, as well as emerging GIT autonomic tests [47], should be included in future studies.

Conclusions

Questionnaire screening for RBD positively predicted the disease in 50% of subjects. HRV changes failed to differentiate iRBD patients from controls, as HRV changes were affected by age, sex, and AHI. The presented study did not confirm the possibility of using HRV from v-PSG records of patients with iRBD to predict dysautonomia expressed by the NMSS questionnaire.

Conflict of interest: *None.*

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Children with corpus callosum anomalies: clinical characteristics and developmental outcomes

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Abstract

Introduction. Corpus callosum abnormalities are complex, aetiologically diverse, and clinically heterogeneous conditions. Counselling parents regarding their causes and associated syndromes, and predicting the neurodevelopmental and seizure risk prognosis, is challenging.

Material and methods. We describe the clinical characteristics, associated anomalies, and neurodevelopmental outcomes of children with agenesis of corpus callosum (ACC). Fifty-one neonates with ACC/hypoplasia of the corpus callosum were identified over a 17-year period, and their medical records were retrospectively reviewed.

Results. Patients were classified into two groups depending on the presence or absence of associated abnormalities. The first group (17 patients, 33.4%) presented with isolated callosal anomalies. The second group included 34 patients (66.6%) with associated cerebral and extracerebral anomalies. We achieved an identifiable genetic aetiology in 23.5% of our cohort. Magnetic resonance imaging was performed in 28 patients (55%), and of these 39.3% had additional brain anomalies. During the study period, five patients died early in the neonatal period and four were lost to follow up. Of the 42 followed patients, 13 (31%) showed normal neurodevelopment, 13 (31%) showed mild delay, and 16 (38%) had a severe delay. Fifteen (35.7%) had epilepsy.

Conclusions and clinical implications. We have confirmed that callosal defects are frequently accompanied by brain and somatic anomalies. Additional abnormalities were shown to be significantly associated with developmental delay and increased risk of epilepsy.

We have highlighted essential clinical features that may provide diagnostic clues to physicians and we have given examples of underlying genetic disorders. We have provided recommendations about extended neuroimaging diagnostics and widespread genetic testing that may impact upon daily clinical practice. Paediatric neurologists may therefore use our findings to help base their decisions regarding this matter.

Key words: agenesis of corpus callosum, developmental delay, somatic anomalies, brain malformation, genetic anomalies

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Introduction

The corpus callosum (CC) is the largest connective structure of the brain, joining the two cerebral hemispheres [1, 2].

Development of the ACC comprises variable mechanisms of neurogenesis and neuronal migration in which multiple genes are involved. Agenesis of the corpus callosum (ACC) can result from disruption of its formation at numerous developmental stages, leading to a total or partial absence of the CC, when one of its components (rostrum, genu, body, isthmus, or splenium) is missing. It may also present as hypoplasia of the CC (HCC), when the CC is fully formed, but thinner. ACC can

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occur as an isolated condition, or in association with various brain and extracranial malformations, as well as with a broad range of genetic disorders [3–8].

ACC can result from antenatal infections, vascular or toxic factors. Foetal alcohol spectrum disorders (FASD) and inborn errors of metabolism are also considered as causes of ACC [6, 8–10]. The reported prevalence of callosal anomalies ranges between 1.47–2.05 per 10,000 live births to 2.49 per 10,000 births [10–13].

Prenatal diagnosis of ACC is possible on the mid-trimester ultrasound, when there is a failure in visualisation of CC in mid-sagittal plan [14–16]. Callosal anomalies can also be detected based on the presence of indirect ultrasound signs, such as the absence of the cavum septi pellucidi (CSP), colpocephaly (dilatation of the occipital horns of the lateral ventricles), increased separation of the hemispheres, abnormally elevated third ventricle, and lack of pericallosal arteries [15, 17].

The clinical course of ACC varies remarkably widely, ranging from asymptomatic cases to severe developmental delays. A lack of CC affects intelligence and behaviour, leading to motor and intellectual disability, epilepsy, and social and language deficits [3, 6, 18]. Parental counselling as to its causes and associated syndromes, and predicting the prognosis for neurodevelopment and seizures is difficult. Asymptomatic neonates without an antenatal diagnosis of ACC can be discharged without a congenital callosal defect being recognised. Thus, early diagnosis and prediction of long-term complications can help towards earlier intervention and better outcomes.

Objective

The clinical and diagnostic features of a group of children with CC anomalies born in a single tertiary perinatal care centre were analysed to show the possible diagnostic difficulties encountered in paediatric practice. Isolated and non-isolated cases were compared to show the impact of extracallosal abnormalities on long-term outcomes. We focused on the key steps in the diagnosis, assessment, investigation, and management of neonates and children presenting with ACC. We wanted to highlight any essential clinical features that could provide diagnostic clues to physicians.

Materials and methods

This study was conducted at the Department of Neonatology of the University Clinical Centre in Gdansk associated with the Medical University of Gdansk, Poland.

We evaluated prenatal findings and postnatal outcomes of neonates who presented with a congenital anomaly diagnosis during hospitalisation in our centre from 1 January, 2001 to 31 December, 2017.

Fifty-seven neonates demonstrating CC anomalies were found during this 17-year study period. Of these, we eliminated six infants in whom the CC was missing due to the presence of severe destructive central nervous system (CNS) lesions (two cases of holoprosencephaly, two neonates with bilateral schizencephaly, one with schizencephaly and hemisphere atrophy, and one with hemisphere atrophy coexisting with hypoplasia of the CC after intracranial haemorrhage following prematurity).

This left a total of 51 cases with callosal anomalies included in the study. Of these, 43 (84.3%) underwent postnatal head ultrasound following prenatal suspicion of congenital defects, including callosal anomalies and other brain or organ defects. The remaining eight (15.7%) cases underwent ultrasound due to prematurity (one case), intrauterine growth restriction (one case), the presence of dysmorphic features (four cases), being a neonate of a diabetic mother (one case), and coexisting prematurity, dysmorphic features and other anomalies, namely congenital heart defect and cleft lip and palate (one case).

Children with anomalies of the CC were initially identified during their stay in the Neonatal Department. The following data was assessed: gestational age (GA) at birth, birth weight (BW), gender, prenatal and postnatal diagnoses, brain magnetic resonance imaging (MRI) if carried out, genetic test results (if available), and the presence of additional cerebral and extracerebral malformations. Mothers were asked to complete a questionnaire regarding pregnancy course, parity, comorbidities and place of residence. Prenatal diagnoses were also taken into consideration. After assigning an identification number and anonymisation, data was transferred to the hospital database. Written informed consent was obtained from parents or authorised representatives of all the subjects included in this study. Informed consent to collect subsequent patient observations and patient information to be published was also provided. Clinical records of the selected patients were retrospectively reviewed for additional examinations (e.g. brain neuroimaging, genetic tests), developmental course, and neurological status by researching the hospital database.

Patients showing callosal anomalies were classified into two groups depending on the presence or absence of accompanying anomalies.

Group 1

Isolated callosal anomalies; no other malformations identified. Patients with an interhemispheric cyst, a lipoma, or colpocephaly were included in this group, as we considered these findings to be a part of callosal anomalies [1, 2, 7, 11, 12].

Group 2

Callosal anomalies associated with both CNS and other organ anomalies, including genetic disorders.

The main characteristics and developmental outcomes of each group were compared.

The extent of the defects in each baby was defined based on head ultrasound; MRI was performed in 28 patients (55% of the 51 studied). In cases of neonatal death, post mortem reports were available. Callosal defects were classified as

either agenesis of the CC, complete — ACC, or agenesis of the ACC, partial — pACC, or HCC, according to the description provided by the radiologist or pathologist. The assessment of neurological development was conducted by paediatricians or paediatric neurologists during hospitalisations or follow-up visits. The patient's age at the time of the last examination was taken into consideration. We relied on clinical descriptions of neurological conditions from children's medical records, as this was a retrospective study. The phrase "children with motor delay" is a description of patients who were not diagnosed with an intellectual disability, but who did show delayed motor milestones. Intellectual disability, social problems, and speech delay were defined by hospital psychologists without providing the type of tools used for the diagnosis.

Statistical analysis

Data was analyzed using Statistica 13.3 software (TIBCO, Palo Alto, CA, USA). Descriptive statistics were calculated separately for groups of patients with callosal defects. Analysis of variance (ANOVA) and Chi-square test were used to compare data between groups of children with ACC depending on the ACC pattern. Contrast analysis and Fisher's LSD test were used to evaluate the differences between these groups. A P-value < < 0.05 was considered statistically significant.

Ethical approval

This study is consistent with the Helsinki Declaration, and was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdańsk, Poland, approval number NKBBN/65/2014.

Results

Over the study period, 36,145 neonates were born at our centre. Congenital malformations were identified in 1,163 (3.2%) infants. CNS anomalies were found in 217 cases (18.7% of all inborn defects and 0.6% of the general population). Of them, 51 infants had ACC/HCC diagnosed, resulting in a prevalence of 14.1 per 10,000 births.

In patients with ACC, the mean GA at birth was 37.1 weeks (range 24–41) and the mean BW was 2,891.4 g (range 600––4,730). Newborns with an isolated ACC/HCC had a significantly higher BW (3,433.8 g) than those presenting with additional somatic and CNS defects (2,614.0 g, p = 0.027). Similarly, they had a significantly higher GA at birth (38.6 weeks), than the remaining patients (36.3 weeks, p = 0.018). There were 30 (58.8%) males and 21 (41.2%) females. Twenty-eight (55%) neonates had complete ACC, 14 (27.4%) had pACC, and nine (17.6%) had HCC.

A prenatal diagnosis was made in 11 (21.5%) foetuses. Mean GA at diagnosis was 25 weeks (range 21–30). Finding one of the indirect signs of failed commissuration was strongly associated with a prenatal diagnosis of ACC (Table 1). Ventriculomegaly (VM) was found in five (45.5%) of 11 foetuses with a correct diagnosis of ACC and in 33 (82.5%) of 40 cases without antenatal diagnosis (p = 0.102). There were 40 (78.5%) cases in which CC anomalies were not suspected during pregnancy despite other abnormalities being diagnosed. In this group, the most common abnormality was hydrocephalus in 17 foetuses, VM in seven, Dandy Walker Syndrome in four, cardiac defects in three (Hypoplastic Left Heart Syndrome, Ebstein anomaly, dextrocardia), chromosomal aberration in one, and arm and leg deformations in two foetuses.

Table 1. Correlation between presence of indirect symptoms and prenatal diagnosis of agenesis of corpus callosum

Prenatal diagnosis of colpocephaly	Prenatal diagnosis of ACC		
	Not diagnosed (%)	Diagnosed (%)	Row (%)
Not diagnosed	38 (95.0)	5 (45.5)	43
Diagnosed	2 (5.0)	6 (54.5)	8
Totals	40 (100.0)	11	51
p = 0.00059			
Prenatal finding of interhemispheric cyst or widening of interhemispheric fissure	**Prenatal diagnosis of ACC**		
	Not diagnosed (%)	**Diagnosed (%)**	**Row (%)**
Not diagnosed	39 (97.5)	8 (72.7)	47
Diagnosed	1 (2.5)	3 (27.3)	4
Totals	40 (100)	11 (100)	51
p = 0.028			
Non-visualisation of cavum septi pellucidi	**Prenatal diagnosis of ACC**		
	Not diagnosed (%)	**Diagnosed (%)**	**Row (%)**
Not diagnosed	40 (100)	7 (63.6)	47
Diagnosed	0	4 (36.4)	4
Totals	40 (100)	11 (100)	51
p = 0.00132			

ACC — agenesis of corpus callosum

In total, 29 (57%) neonates were born by caesarean delivery (CD) and 22 (43%) by vaginal delivery (VD). Newborns with a prenatal diagnosis of CNS anomalies were more likely to be born by CD, either planned or emergency (p = 0.060). Prenatal diagnosis of ACC did not affect the plan of delivery (Tab. 2).

There was no difference in the level of care received by neonates born by CD and VD (p = 0.466). Six (20.7%) neonates born by CD and five (22.7%) born by VD received normal neonatal care, and 18 (62.0%) born by CD and 13 (59.1%) by VD required special care in the Neonatal Intermediate Care Unit. Five (13.7%) born by CD and two (9.1%) born by VD required admission to the Neonatal Intensive Care Unit, and two (9.1%) born by VD received palliative care.

Table 2. Impact of prenatal diagnosis on mode of delivery

	Mode of delivery			Row n (%)	p-value
	Elective CD n (%)	Emergency CD n (%)	VD n (%)		
Prenatally diagnosed ACC	4 (36.5)	2 (18.0)	5 (45.5)	11 (100)	0.525
Prenatally diagnosed CNS anomalies	14 (52.0)	4 (15.0)	9 (33.0)	27 (100)	0.060
Prenatally diagnosed other organ anomalies	1 (20.0)	2 (40.0)	2 (40.0)	5 (100)	0.817
Cases without prenatal diagnosis	1 (12.5)	1 (12.5)	6 (75.0%)	8 (100)	0.042
	20 (39.2)	9 (17.8)	22 (43.0)	51 (100)	

ACC — agenesis of corpus callosum; CD — caesarean delivery; CNS — central nervous system; VD — vaginal delivery

Patients were classified into two groups on the basis of accompanying anomalies. Group 1 included 17 (33.4%) patients who presented with isolated callosal anomalies. In one child, a congenital cytomegalovirus infection was diagnosed postnatally; this baby died at the age of one year. Three cases were lost to follow-up. The characteristics of this group are set out in Table 3.

Group 2 comprised 34 (66.6%) patients who presented with CC anomalies associated with extracallosal CNS anomalies and/or other organ anomalies or genetic syndromes. The characteristics of this group are set out in Tables 4–6. The most frequent extracallosal brain anomalies were agenesis of the septum pellucidum (9/51; 17.6%) and hydrocephalus (8/51; 15.6%).

Of the 28 (55%) patients who underwent MRI, 11 (39.3%) had additional brain abnormalities, including cortical malformations (seven cases), and septo-optic dysplasia, Chiari syndrome, lack of other cerebral commissures, and stenosis of aqueduct of Sylvius (one case each, see Tab. 4–6).

Genetic testing was conducted in 43% (22/51) of cases, including karyotype analysis, fluorescence in situ hybridisation, and array comparative genomic hybridisation (aCGH). Two of our patients were screened for FRAS1 and EPG5 mutations. An underlying diagnosis was found in 12 of the 51 patients (23.5%). Chromosomal disorders were confirmed in seven patients (13.7%), with one case each of mosaic trisomy chromosome 8, sex chromosome aneuploidy (47, XYY), trisomy 13/trisomy 18 mosaicism, 22q11.2 deletion syndrome, 5p deletion syndrome, and Vici syndrome. The last of these newborns had a disorder of sex development, in which the female phenotype did not correspond to the genetic sex (46, XY). In five (9.8%) cases, the genetic analysis did not reveal any abnormalities, although specific dysmorphic features were present. The following genetic syndromes were recognised: Fraser syndrome (one case), Smith-Lemli-Opitz syndrome (one case), Rubinstein-Taybi syndrome (one case), and Apert syndrome (two cases). The main features of these patients are set out in Table 6. In eight (15.6%) patients demonstrating unspecific dysmorphic features, the genetic basis remained unknown.

Neurodevelopmental outcomes were available for 42 (82.3%) of our patients. Four children were lost to follow-up, and five died early in the neonatal period. The mean age at the last neurological assessment was 4.7 years (range 4 months to 18 years).

Development at the last follow-up was normal in 31% (13/42) of patients. Of these, nine were in the isolated ACC group, while four were in the other group (p = 0.001, Tab. 7).

Of 14 patients who presented with isolated ACC, five had transient hypotonia, two had speech delay in early childhood, one had learning difficulties at school age, one demonstrated cognitive and social problems, and one developed epilepsy (see Tab. 3).

All of the 12 infants with chromosomal disorders or known genetic syndromes had mild to severe developmental delay (see Tab. 6).

Epilepsy occurred in 35.7% (15/42) of children. The risk of seizures was almost 13-fold higher for babies with additional abnormalities (OR = 12.99; 95% confidence interval (CI): 1.49–111.11), compared to cases with isolated callosal defects. Of 28 patients with callosal defects accompanied by other abnormalities, 14 (50%) developed epilepsy, while in the 14 patients with isolated callosal anomalies, only one (7.1%) had epilepsy (p = 0.008).

In a total of 51 ACC cases, nine deaths occurred (15.6%). The presence of extracallosal anomalies significantly affected mortality. Infants with ACC/HCC accompanied by additional defects were 10 times more likely to die compared to those with an isolated ACC/HCC (OR = 10.70; 95% CI: 1.20–95.23).

Discussion

The detection of callosal anomalies in infants always raises concerns among parents and healthcare professionals. The diagnosis of ACC is possible antenatally, which could allow for medical care for the mother and her child to be optimised after birth [10, 15, 19]. Postnatal detection of ACC may be limited, as ACC can be asymptomatic, especially if not associated with other anomalies. Head ultrasound in neonates is usually undertaken following prenatal suspicion of congenital anomalies, or as a neuroimaging investigation in newborns who have neurological abnormalities or risk factors for intracranial lesions [20].

The current study confirmed a relatively high frequency of clinical indications for brain imaging in the context of

Table 3. Characteristics of patients with isolated anomalies of corpus callosum

Sex GA at birth/ /weeks	Mode of delivery	Neonatal care	GA at diagnosis (weeks); Reason for referral (Initial antenatal findings ID); Antenatal diagnosis (AD)	Postnatal findings; Postnatal MRI (pMRI) results	Age at last exam	Neurodevelopmental outcome; Epilepsy	Death
F 40	VD	Normal	GA 22: ID: non-visualisation of CC; AD: IHF widening, fMRI: IHF widening, 46XX, Isolated ACC	ACC pMRI: confirmed diagnosis	3 years	Normal development; Epi (–)	(–)
M 41	VD	NIMCU admission	GA 25: ID: VM; AD: colpocephaly OH 17–18 mm, CSP absence, fMRI: colpocephaly OH 18 mm, Isolated ACC	ACC Colpocephaly: right OH 17 mm, left OH 20 mm pMRI: confirmed diagnosis	2 years	1st year of life — hypotonic, mild speech delay; Epi (–)	(–)
M 35	CD emerg	NIMCU admission	GA 28: ID: IHF widening, ACC; AD: IHF widening, Isolated pACC	pACC pMRI: (–)	3 years	Normal development; Epi (–)	(–)
M 41	VD	NIMCU admission	GA 30: ID: VM; AD: CSP absence, colpocephaly OH 16.2 mm, Isolated ACC	HCC Colpocephaly OH 8 mm pMRI: (–)	6 years	1st year of life — hypotonic. Mild speech delay, dyspraxia, cognitive problems, speech delay, social problems; Epi (–)	(–)
M 38	CD elect	NIMCU admission	AD: GA 24: VM OH 16 mm, GA 30: hydrocephalus OH 20 mm	ACC pMRI: (–)	Lost	(–)	(–)
F 40	VD	NIMCU admission	(–)	ACC pMRI: confirmed diagnosis	1 year	Mild developmental delay, hypotonic; Epi (–)	(–)
F 38	VD	Normal	AD: GA 33: hydrocephalus OH 22 mm	ACC; 46, XX pMRI: confirmed diagnosis	3 years	3 months of age — hypotonic; Normal development; Epi (–)	(–)
M 39	CD elect	Normal	AD: GA 23: VM ventricle width 10 mm	ACC Colpocephaly pMRI: (–)	2 years	Normal development; Epi (–)	(–)
F 37	CD elect	NIMCU admission	AD: GA 20: hydrocephalus OH 20 mm	ACC pMRI: midline cyst	12 years	Normal development, Learning difficulties; Epi (–)	(–)
F 38	VD	Normal	AD: GA 18: VM ventricle width 15 mm	ACC Colpocephaly pMRI: lipoma	5 years	Normal development; Epi — Yes	(–)
M 40	VD	NIMCU admission	AD: GA 39: VM, colpocephaly OH 18 mm	ACC pMRI: (–)	5 months	Severe developmental delay; Congenital cytomegalovirus infection; Epi (–)	1st year
F 40	CD elect	NIMCU admission	AD: GA 20: hydrocephalus OH 30 mm	pACC pMRI: (–)	3 years	Normal development; Epi (–)	(–)

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Table 3 cont. Characteristics of patients with isolated anomalies of corpus callosum

Sex GA at birth/ /weeks	Mode of delivery	Neonatal care	GA at diagnosis (weeks); Reason for referral (Initial antenatal findings ID); Antenatal diagnosis (AD)	Postnatal findings; Postnatal MRI (pMRI) results	Age at last exam	Neurodevelopmental outcome; Epilepsy	Death
M 37	VD	NIMCU admission	AD: GA 36: VM ventricle width 10 mm	pACC pMRI: (–)	4 years	Normal development; Epi (–)	(–)
F 38	VD	Normal	(–)	pACC pMRI: (–)	2 years	Normal development; Epi (–)	(–)
F 38	VD	NIMCU admission	(–)	pACC pMRI: (–)	Lost	(–)	(–)
M 39	CD elect	NIMCU admission	AD: GA30: VM ventricle width 18 mm	HCC pMRI: (–)	Lost	(–)	(–)
M 38	CD elect	NIMCU admission	(–)	HCC pMRI: (–)	3 years	Mild developmental delay, hypotonia; Epi (–)	(–)
N = 17			(–)				

ACC — agenesis of corpus callosum; ASP — agenesis of septum pellucidum; CD — caesarean delivery; CD elect — elective caesarean delivery; CD emerg — emergency caesarean delivery; CSP — cavum septi pellucidi; Epi — epilepsy; F — female; fMRI — foetal magnetic resonance imaging; GA — gestational age; HCC — hypoplasia of corpus callosum; IACC — isolated agenesis of corpus callosum; IHF — interhemispheric fissure; M — male; NIMCU — Neonatal Intermediate Care Unit; pMRI — postnatal magnetic resonance imaging; OH — occipital horn; pACC — partial agenesis of corpus callosum; VD — vaginal delivery; VM — ventriculomegaly

Table 4. Characteristics of patients with corpus callosum anomalies in association with extracallosal brain and extra-brain malformations

Sex, GA at birth weeks	Mode of delivery	Neonatal care	GA at antenatal diagnosis (weeks); Antenatal diagnosis AD	Postnatal findings: Other brain and other organ anomalies; Genetic test results	Age at last exam	Neurodevelopmental outcome	
						Epilepsy	Development; Death
M 34	CD elect	NIMCU admission	AD: GA 23; hydrocephalus, HPE, Schizencephaly	ACC; hydrocephalus, ASP 46,XY	3 years	Yes	Severe developmental delay
M 40	VD	Normal	AD: GA 28; VM, ventricle width 12 mm, CSP absence, Isolated ACC	ACC; ASP	7 years	Yes	Mild developmental delay
M 32	VD	NIMCU admission	AD: GA 25; VM colpocephaly OH 18 mm	ACC; ASP	2 years	No	First year of life — hypotonia, Normal development
F 36	CD elect	NIMCU admission	AD: GA 30; hydrocephalus	ACC; microcephaly, optic nerve atrophy	3 years	Yes	Severe developmental delay
M 39	CD elect	NICU admission	AD: GA 24; hydrocephalus, HLHS;	ACC; DWS HLHS	(–)	(–)	Neonatal death
M 36	CD elect	NIMCU admission	AD: GA 22; hydrocephalus	ACC; ASP Dysmorphism, genitourinary anomalies, musculoskeletal defects	4 months	No	Severe developmental delay

→

Table 4 cont. Characteristics of patients with corpus callosum anomalies in association with extracallosal brain and extra-brain malformations

Sex, GA at birth weeks	Mode of delivery	Neonatal care	GA at antenatal diagnosis (weeks); Antenatal diagnosis AD	Postnatal findings: Other brain and other organ anomalies; Genetic test results	Age at last exam	Neurodevelopmental outcome	
						Epilepsy	Development; Death
M 37	CD emerg	NIMCU admission	AD: GA 33; hydrocephalus, shortened foetal limbs	ACC; Hydrocephalus, midline cyst; Dysmorphism, genitourinary anomalies, musculoskeletal defects, 46, XY	9 months	No	Severe developmental delay
M 29	VD	NICU admission	(–)	ACC dysmorphism	(–)	(–)	Neonatal death
F 24	VD	Palliative care	AD: GA 22; fMRI: colpocephaly OH: 10–11 mm, TAC, hydronephrosis, 46, XX, complex ACC	ACC; TAC, hydronephrosis	(–)	(–)	TOP
F 37	VD	NIMCU admission	AD: GA 22; DWS, cardiac disease suspicion, mother refused further investigation	HCC; DWS; dysmorphism, VSD; 46, XX, aCGH — no abnormalities	1 year	No	Mild global developmental delay, hypotonia
M 40	CD emerg	NIMCU admission	AD: GA 16; hydrocephalus, DWS	pACC; DWS; 46,XY	3 years	No	Severe developmental delay
F 38	CD elect	Normal	AD: GA 24; midline cyst	pACC; genitourinary anomalies; 46,XX	(–)	(–)	Lost
F 38	VD	Normal	AD: GA 21; VM, fMRI: colpocephaly OH: 14 mm, Interthalamic adhesion, 46, XX, Isolated ACC	pACC, colpocephaly 12/15 mm; VSD, 46,XX	3 years	No	Normal development
N = 13				(–)			

ACC — agenesis of corpus callosum; aCGH — array comparative genomic hybridisation; ASP — agenesis of septum pellucidum; CSP — cavum septi pellucidi; CD — caesarean delivery; CD elect — elective caesarean delivery; CD emerg — emergency caesarean delivery; DWS — Dandy-Walker syndrome; F — female; fMRI — foetal MRI, GA — gestational age, HCC — hypoplasia of corpus callosum; HLHS — hypoplastic left heart syndrome; HPE — holoprosencephaly; IACC — isolated agenesis of corpus callosum; M — male; MRI — magnetic resonance imaging; NICU — Neonatal Intensive Care Unit; NIMCU — Neonatal Intermediate Care Unit; OH — occipital horn; pACC — partial agenesis of corpus callosum; TAC — truncus arteriosus communis; TOP — termination of pregnancy; VD — vaginal delivery; VM — ventriculomegaly; VSD — ventricular septal defect

Table 5. Characteristics of patients with corpus callosum anomalies in association with extracallosal brain and extra-brain malformations; additional brain anomalies found on MRI

Sex, GA at birth/ /weeks	Mode of delivery; Neonatal care	GA at diagnosis (weeks); Antenatal diagnosis AD	Postnatal findings		Age at last exam	Epilepsy	Neurodevelopmental outcome
			Brain anomalies	Other organ anomalies; Genetic tests results			Development; Death
M 36	CD elect; NIMCU admission	AD: GA 23; Hydrocephalus	ACC; hydrocephalus, Chiari syndrome	(–)	17 years	Yes	Mild developmental delay: mild intellectual deficit, learning difficulties, social problems
M 38	CD emerg; Normal	AD: GA 38; Hydrocephalus	ACC; midline cyst, gyration abnormalities	(–)	11 years	Yes	First year of life — hypotonia; normal development
F 35	VD; NIMCU admission	(–)	ACC; microcephaly, heterotopy	Dysmorphism, cleft lip, musculoskeletal defects, ToF, 46,XX	2 years	No	Severe developmental delay
M 41	CD emerg; NIMCU admission	(–)	ACC; microcephaly, heterotopy	Cleft lip, genitourinary anomalies, 46,XY	3 years	Yes	Severe developmental delay
M 35	VD; NICU admission	AD: GA 24; Hydrocephalus 25 mm	HCC; ASP, Cortical dysplasia	(–)	3 years	Yes	First year of life — hypotonia, mild developmental delay, speech delay
F 29	CD elect; NICU admission	AD: GA 20; VM ventricle width 15 mm	HCC; hydrocephalus, midline cyst, cerebellum hypoplasia, ASP, focal cortical dysplasia	46,XX	8 years	Yes	First year of life — hypotonia, mild developmental delay, learning difficulties
F 38	VD; NIMCU admission	AD: GA 24; DWS, CoA	HCC; widening of Sylvian fissures	Dysmorphism, musculoskeletal defects, renal anomalies, 46,XX	7 years	Yes	Severe encephalopathy, severe developmental delay. Able to stand up with a walker, special needs school
M 39	CD elect; Normal	AD: GA 25; Colpocephaly OH: 12 mm, IACC	pACC; ASP, colpocephaly, midline cyst, cortical dysplasia, heterotopy, gyration abnormality	Dysmorphism, ASD	18 years	Yes	Mild global developmental delay: able to walk, selfdependent, learning difficulties, choreoathetosis
M 38	CD emerg; NIMCU admission	AD: GA 22; fMRI excluded ACC,Dextrocardia	pACC; ASP, septo-optic dysplasia	(–)	5 years	No	Normal development; visual impairment, strabismus
N = 9	N = 9			(–)			

ACC — agenesis of corpus callosum; ASD — atrial septal defect; ASP — agenesis of septum pellucidum; CD — caesarean delivery; CD elect — elective caesarean delivery; CD emerg — emergency caesarean delivery; CoA — coarctation of aorta; DWS — Dandy-Walker syndrome; F — female; fMRI — foetal magnetic resonance imaging; GA — gestational age; HCC — hypoplasia of corpus callosum; IACC — isolated agenesis of corpus callosum; M — male; MRI — magnetic resonance imaging; NICU — Neonatal Intensive Care Unit; NIMCU — Neonatal Intermediate Care Unit; OH — occipital horn; pACC — partial agenesis of corpus callosum; ToF — tetralogy of Fallot; VD — vaginal delivery; VM — ventriculomegaly

Table 6. Characteristics of patients with corpus callosum anomalies in association with extracallosal brain and extra-brain malformations; patients with a determined underlying cause

Sex, GA at birth/ /weeks	Mode of delivery; Neonatal care	GA at diagnosis (weeks); Antenatal diagnosis AD	Postnatal findings		Age at last exam	Neurodevelopmental outcome	
			Associated brain and other organ anomalies	Chromosomal diagnoses and known genetic syndromes		Epilepsy	Development; Death
F32	VD; palliative care	AD: GA 29; hydrocephalus	ACC, hydrocephalus	Dysmorphism, DSD, eyeballs hypoplasia, renal anomalies, 46, XY	(–)	(–)	Neonatal death
M38	CD elect; NIMCU admission	AD: GA 32; Hydrocephalus, ventriculoam niotic shunt	ACC, hydrocephalus, absence of fornix and anterior commissure	Rubinstein-Taybi syndrome; 46, XY, aCGH — no abnormalities	3 years	Yes	Severe developmental delay
M39	CD elect; NIMCU admission	AD: GA 30; Strawberry shaped skull, CSP absence, bilateral anophtalmos, nose bone agenesis, 46, XY, complex ACC	ACC, hydrocephalus, midline cyst, cerebellum agenesis; bilateral anophtalmos, cleft lip/palate, genitourinary anomalies	Clinically suspected Fraser syndrome, 46, XY	2 years	Yes	Severe global developmental delay, drug-resistant epilepsy, GTDeath aged 2 years
F31	CD elect; NICU admission	AD: GA 28; choroid plexus cyst, colpocephaly OH: 10 mm; isolated ACC	ACC, cerebellum hypoplasia, PA, TAC type IV	DiGeorge syndrome:46, XX, ish22q11.2	1 year	No	Severe developmental delay Death: first year
F38	CD emerg; NIMCU admission	AD: GA 27; Ebstein anomaly	ACC, Ebstein anomaly	Vici syndrome,EPG5 gene mutation	(–)	Yes	Severe encephalopathy, Severe global developmental delay; ventilation at night, GT, Neurogenic bladder
M39	CD elect; Normal	AD: GA 13; hydrocephalus	ACC, renal and genitourinary anomalies	Trisomy 8 mosaicism: 47, XY, +8 [22] 46, XY [1]	12 years	No	Mild developmental delay: 1st year of life — hypotonia, mild intellectual deficit
F37	VD; NIMCU admission	AD: GA 13; 47,XX,+18	pACC, cleft lip/palate, renal anomalies, ASD	Trisomy 13/trisomy 18 mosaicism	12 years	No	Severe developmental delay Death: 12 years
M40	VD; NIMCU admission	(–)	pACC;	5p deletion syndrome: 46, XY del(5)(p14,2)(11)	3 years	No	Severe developmental delay
M38	CD elect; NICU admission	AD: GA 25; dolichocephaly, HPE, HCC, unilateral renal agenesis, TAC, 46, XY	pACC, renal and genitourinary anomalies, AVSD	SLOS, 46, XY	(–)	(–)	Neonatal death
M36	CD elect; NICU admission	AD: GA 23; legs, arms and facial abnormalities	pACC	Apert syndrome	1 year	No	Mild psychomotor delay
F39	VD; NIMCU admission	AD: GA 23; legs, arms and facial abnormalities	HCC	Apert syndrome	9 years	No	Mild intellectual delay
M39	CD emerg; NIMCU admission	AD: GA 31; hydrocephalus, DWS, HPE semilobaris	ASP, DWS, hydrocephalus, stenosis of aqueduct of Sylvius	47, XYY	6 months	Yes	Severe developmental delay
N = 12				(–)			

ACC — agenesis of corpus callosum; aCGH — array comparative genomic hybridisation; ASD — atrial septal defect; ASP — agenesis of septum pellucidum; AVSD — atrioventricular septal defect; CD — caesarean delivery; CD elect — elective caesarean delivery; CD emerg — emergency caesarean delivery; DSD — disorders of sex development; DWS — Dandy-Walker syndrome; F — female; GA — gestational age; GT — gastrostomy tube; HCC — hypoplasia of corpus callosum; HPE — holoprosencephaly; M — male; NICU — Neonatal Intensive Care Unit; NIMCU — Neonatal Intermediate Care Unit; PA — pulmonary atresia; pACC — partial agenesis of corpus callosum; SLOS — Smith Lemli Opitz syndrome; ToF — tetralogy of Fallot; TAC — truncus arteriosus communis; VD — vaginal delivery; VSD — ventricular septal defect

Table 7. Neurodevelopmental outcomes in all patients with corpus callosum anomalies: isolated callosal anomalies versus callosal anomalies associated with other abnormalities

Group	Development			Sum
	Normal	Mild delay	Severe delay	
Isolated ACC	9 (64.3%)	4 (28.6%)	1 (7.1%)	14 (100%)
ACC + other brain defects + other organ defects	4 (14.3%)	9 (32.1%)	15 (53.6%)	28 (100%)
Sum	13 (31%)	13 (31%)	16 (38%)	42 (100%)
p = 0.001			(–)	

ACC — agenesis of corpus callosum

postdelivery ACC diagnosis. In more than three-quarters of patients from our series, a neonatal head ultrasound and a subsequent diagnosis of ACC resulted from a prenatal suspicion of CNS defects [1].

Neonatal head ultrasound is usually the first step in the diagnosis of ACC; however, it has some limitations; it does not provide enough information to determine whether the lesion is isolated or not. Including MRI in the diagnostic pathway helps to confirm the diagnosis and to identify associated brain anomalies, especially cortical malformations previously undiagnosed during the prenatal and postnatal ultrasound [10, 21, 22].

Some clinicians value the reliability and reproducibility of a neonatal ultrasound in an accurate diagnosis of callosal anomalies, and this can lead them to abstain from performing MRI. MRI is typically undertaken in the context of evaluation for either developmental delay or epilepsy, and is not considered to be a standard procedure for a detailed diagnosis of callosal abnormalities. We noticed a similar trend in our study. MRI was performed most often in the group of patients presenting with additional defects and displaying neurological symptoms. In those cases in which an MRI was carried out, previously undiagnosed brain defects were revealed.

Like most previous series, we confirmed that callosal defects are frequently accompanied by a large number of brain and somatic anomalies [11, 13, 21, 23]. Isolated cases comprised only one-third of our cohort, while the remaining cases were accompanied by other defects. Most of these associated defects were found after birth, as has been shown in previous studies [24, 25]. Malformations of cortical development and heterotopia have been identified as the most common concomitant brain abnormalities, and their presence dramatically alters the prognosis [11, 13, 21, 22, 24, 25].

Chromosomal aberrations or gene mutations have been reported as common underlying factors of ACC. However, due to the presence of unknown causative genes and technical problems, approximately half of all ACC cases cannot be identified [3–5, 8, 13].

Although trisomy 18 and trisomy 13 have been previously shown as the genetic basis of ACC, the rare reported cases of their mosaicism did not include callosal defects [26].

To the best of our knowledge, this is the first study to describe a patient presenting with trisomy 13/trisomy 18 mosaicism accompanied by pACC. Other chromosomal disorders may impact upon CC morphogenesis [27–29]. Our study found DiGeorge and 5p deletion syndromes as an underlying aetiology of ACC. ACC accompanied by these syndromes has been previously presented in case reports [30, 31].

The challenge of identifying the underlying disorder of patients with ACC is significant. Patients should be offered paediatric genetic testing following a diagnosis of ACC. Genetic investigation usually starts with karyotyping. Molecular diagnostics with aCGH may be a valuable method, allowing re-investigation of cases in which conventional cytogenetic techniques reached no conclusion. Although the implementation and availability of molecular gene analysis is increasing, it is still not performed as a routine diagnostic protocol. It is more often undertaken in children with developmental delay, epilepsy or multiorgan manifestations, than in patients with normal or slightly delayed neurodevelopment. We observed a similar trend in our survey.

There are numerous conditions in which ACC may be a feature, as in Vici or Fraser syndromes. All previously reported cases of Vici syndrome featured ACC. In our patient suffering from this condition, ACC was also found. Vici syndrome is caused by mutations in the EPG5 (ectopic P granules protein 5) gene, while Fraser syndrome is caused by mutations in the FRAS1 and FREM2 gens. Fraser syndrome is rare, without clear genotype-phenotype correlations, and FRAS1 gene has many exons, which impedes the investigation of mutations in affected patients. For Vici syndrome, almost 40 EPG mutations have been already detected, making it difficult to identify the mutation in some patients [9, 32, 33]. Two of our patients were screened for FRAS1 and EPG5 mutations. Unfortunately, in a patient who met the clinical diagnostic criteria for Fraser syndrome, genetic testing did not prove this diagnosis. Patients with Fraser syndrome described so far have presented with several brain abnormalities, but, callosal anomalies have not been among those reported [32].

The differential diagnosis of ACC is wide. Subsets of callosal anomalies, dysmorphic features, other anatomical malformations and neurological impairment can be encountered in different syndromes, which can result in difficulties in choosing the relevant molecular screening test.

Apert, Aicardi, Smith-Lemli-Opitz, and Rubinstein-Taybi syndromes are among the known genetic syndromes that

could manifest with ACC [3, 8, 10]. Our results are in line with these findings, although we did not include any patients with Aicardi syndrome.

Defects of the CC, neurodevelopmental delay, epilepsy, and dysmorphism are frequently reported in patients presenting with various types of dystonia and other hereditary movement disorders with childhood onset. Results of the latest gene analyses have revealed varied molecular bases of these disorders [34, 35]. In neurodegenerative diseases with onset in the 4th and 5th decades of life, in which brain macrophages known as microglia play an important role in their formation, defects of the CC may also be present. Microglia proliferation and development requires the activation of a Colony Stimulating Factor 1 Receptor (CSF1R), the gene previously associated with adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP). However, the role played by brain microglia in nervous system development has been recently noted. Individuals with homozygous CSF1R mutations who presented paediatric phenotypes distinct from ALSP have been described. This mutation has been found in infants with ACC and in adolescents with severe developmental regression, epilepsy and leukodystrophy [36, 37]. It has also been described in paediatric patients as BANDDOS, a syndrome consisting of brain abnormalities including ACC, neurodegeneration and dysosteosclerosis [34, 35].

A CSF1R mutation was identified in a Polish patient with a diagnosis of ALSP accompanied by thin CC [38]. The clinical features of CSF1R-related leukoencephalopathy occupy a broad spectrum, encompassing seizures, movement disorders and psychiatric features, seen also in individuals with ACC [39].

Therefore, in patients with callosal abnormalities, genetic testing should also include this gene mutation.

The clinical course in children with callosal anomalies is unpredictable and varies from asymptomatic cases to a wide range of neurodevelopmental impairments [21–23]. Establishing the prognosis for further neurodevelopment of affected individuals remains difficult, as these infants may not show symptoms during the neonatal period, especially if they have no other associated malformations. Poor outcomes have often been reported when ACC has been associated with extracallosal anomalies, while patients without other associated malformations or chromosomal abnormalities have been shown to be more likely to obtain better neurological outcomes [6, 19, 25, 40–42]. Our results are consistent with these findings. The majority of children with normal development in our study were patients with isolated ACC. However, even in isolated cases, the prognosis remains unclear, and the neurodevelopmental outcome can range from normal development in 75% of patients, to differing levels of intellectual disability. Some clinical features may become more apparent during infancy and childhood, including seizures, abnormal muscle tone, poor coordination, cognitive impairment, and language developmental delay [24, 40, 41]. Similarly to previous works, a third of our isolated ACC cases showed (mostly mild) developmental disabilities. Hypotonia and slight motor delay occurred in the first six months of life, while cognitive disabilities manifested at school age.

The presence of extracallosal CNS and extra-CNS malformation, together with the detection of a genetic aetiology, have been linked to abnormal developmental outcomes [3, 6, 19].

Our study confirmed these findings: delayed neurodevelopment and intellectual disability were evident in all patients displaying chromosomal disorders and known genetic syndromes. Unfavourable neurological findings were also seen in the majority of children with additional serious CNS and non-CNS abnormalities.

Like most earlier studies, the present paper confirms that the coexistence of other defects significantly increases the risk of epilepsy [42].

Limitations of study

Firstly, as this was a retrospective study, some data may be missing or not fully reported (e.g. genetic testing reported for 43%, MRI imaging available for 55% of patients). MRI data was reported mostly in patients with poor neurological outcomes. It remains unknown how many patients with normal intelligence, mild behavioural problems, or assessed as having isolated ACC, actually had additional brain abnormalities. Secondly, intellectual disability, social problems, and speech delay were defined by hospital psychologists without providing the type of tools used for the diagnosis. Moreover, the assessment of neurological impairments relied on our review of medical records. However, our diverse cohort was a strength of this study; based on our hospital database, we obtained a diverse sample of ACC cases which were not limited to patients with neurodevelopmental delays. With respect to developmental outcomes, the results in our cohort may reflect those to be expected for the overall population of children with callosal defects.

Conclusions

Callosal defects are frequently accompanied by a large number of brain and somatic anomalies. Therefore, both children with additional malformations, and those with apparently isolated callosal anomalies, should undergo a detailed brain and cardiac examination. Thorough neuroimaging should also be carefully planned at a later date to confirm partial or complete agenesis and other accompanying abnormalities.

Since several chromosomal aberrations may be an underlying cause of callosal anomalies, genetic testing should be offered to all ACC patients. Patients presenting with ACC may exhibit different degrees of neurodevelopmental impairment. The coexistence of extracallosal abnormalities significantly worsens the neurological prognosis and increases the risk of epilepsy. Individuals with isolated ACC show better neurodevelopmental outcomes.

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Brain volume loss in multiple sclerosis is independent of disease activity and might be prevented by early disease-modifying therapy

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ABSTRACT

Introduction. Neurodegeneration is likely to be present from the earliest stages of multiple sclerosis (MS). MS responds poorly to disease-modifying treatments (DMTs) and leads to irreversible brain volume loss (BVL), which is a reliable predictor of future physical and cognitive disability. Our study aimed to discover the relationship between BVL, disease activity, and DMTs in a cohort of patients with MS.

Material and methods. A total of 147 patients fulfilled our inclusion criteria. Relevant demographic and clinical data (age, gender, time of MS onset, time of treatment initiation, DMT characteristics, Expanded Disability Status Scale (EDSS), number of relapses in the last two years prior to MRI examination) were correlated with MRI findings.

Results. Patients with progressive MS had significantly lower total brain and grey matter volumes ($p = 0.003$; $p < 0.001$), and higher EDSS scores ($p < 0.001$), compared to relapsing-remitting patients matched by disease duration and age. There was no association between MRI atrophy and MRI activity ($c2 = 0.013$, $p = 0.910$). Total EDSS negatively correlated with the whole brain ($r_s = -0.368$, $p < 0.001$) and grey matter volumes ($r_s = -0.308$, $p < 0.001$), but was not associated with the number of relapses in the last two years ($p = 0.278$). Delay in DMT negatively correlated with whole brain ($r_s = -0.387$, $p < 0.001$) and grey matter volumes ($r_s = -0.377$, $p < 0.001$). Treatment delay was connected with a higher risk for lower brain volume ($b = -3.973$, $p < 0.001$), and also predicted a higher EDSS score ($b = 0.067$, $p < 0.001$).

Conclusions. Brain volume loss is a major contributor to disability progression, independent of disease activity. Delay in DMT leads to higher BVL and increased disability. Brain atrophy assessment should be translated into daily clinical practice to monitor disease course and response to DMTs. The assessment of BVL itself should be considered a suitable marker for treatment escalation.

Key words: multiple sclerosis, brain volume loss, atrophy, neurodegeneration, disability

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Introduction

Multiple sclerosis (MS) is an inflammatory and degenerative disorder of the central nervous system (CNS) with complex and not yet fully-understood disease mechanisms [1, 2]. In addition, MS has a heterogeneous presentation and a wide range of onset age. This diversity can lead to a delayed diagnosis and result in more complicated management. Although the clinical course of MS is variable, in the vast majority of cases it starts with reversible episodes of neurological

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disability — as the relapsing-remitting (RR) form with dominant inflammatory pathogenesis. Later in the course of the disease, continuous and irreversible neurological decline due to neurodegeneration prevails (this is secondary progressive MS — SPMS) [3]. When exactly the progressive phase of MS begins is still the subject of debate. A minority (10–15%) of patients have primary progressive MS (PPMS), in which the progression of disability is present from the very onset [4]. Whether the clinical subtypes of MS are pathologically distinct from each other — or possibly even different disease entities — is still open for discussion. Some authors consider MS *per se* (all types) to be an asynchronously progressive disease from the very beginning [5]. Nevertheless, MS classification is still based on the clinical phenotype [6].

In the context of reserve capacity, progression occurs in all patients, but remains unrecognised by clinicians. Numerous magnetic resonance imaging (MRI) features — i.e. brain volume, spinal cord atrophy, and T2 lesion volume — are predictive of disability worsening and are variably present in both the relapsing and the progressive forms of MS [7, 8]. Brain volume loss (BVL) is relatively independent of lesion load, and, as a predictor of the evolution of disability, has become a critical biomarker of neurodegeneration [9]. Irreversible brain atrophy is clinically relevant, correlating with future physical and cognitive disability in MS patients [10]. Brain volume loss, reflecting the real tissue damage in MS patients, occurs from the preclinical stage of the disease and progresses up to five times faster than natural ageing [11]. Axonal damage accounting for brain atrophy may be acute due to inflammation or chronic due to pathogenic mechanisms primed by the preceding inflammation and later perpetuated with disease progression [12]. Brain atrophy assessment is substantial in MS, making BVL a relevant marker to diffuse CNS damage, leading to clinical disease progression, and serving as a useful parameter in evaluating the effects of MS therapies [13].

The definition for efficacy of MS treatment has become more comprehensive over the last decade. With the introduction of more effective types of disease-modifying therapies (DMTs), the disease-free period or "no evidence of disease activity" (NEDA) became a new measured outcome. Although NEDA status may strongly predict favourable long-term outcomes, its absence is not necessarily a poor prognostic sign. Daily clinical practice indicates that patients may experience a new relapse and/or new MRI lesion, and yet remain stable from a long-term point of view [14].

Three basic components — an absence of clinical relapses, no progression measured by expanded disability status scale (EDSS), and a lack of new T2 and/or enhancing lesions on brain MRI — represent NEDA-3. Cognitive state assessment and monitoring of neuroaxonal damage (measuring BVL or plasmatic levels of neurofilament chain) became the basis for NEDA-4 [15]. The concept of NEDA-4 has the potential to capture the impact of therapies on both inflammation and neurodegeneration. NEDA-4 deserves further evaluation across different compounds and long-term studies [16].

Clinical rationale for study

Our study aimed to analyse the clinical relevance of brain atrophy in a cohort of patients with MS. According to observations from clinical practice and our preliminary data [17], we postulated the following hypotheses:

- Brain atrophy is independent of MRI activity.
- Disability is more affected by brain volume loss than by disease activity (number of relapses and/or new T2 lesions on brain MRI).
- Delay in DMT initiation leads to worse outcomes in MS patients.

Material and methods

Patients

Inclusion criteria for study enrollment were:

- diagnosis of MS according to the 2017 McDonald criteria,
- minimum age of 18 years,
- having valid results from brain MRI and volumetry exams at the MRI Centre, Dr. Magnet Ltd, Bratislava, Slovakia.

Data collection was carried out between April 2017 and December 2020. We collected data from 150 patients; three of them were excluded due to incomplete information.

Methods

This was a retrospective, cross-sectional, single-centre study approved by the Ethical committee of Derer University Hospital, Comenius University, Bratislava, Slovakia under approval number 03/2017.

All MRI examinations were performed using the same hardware and software throughout the whole study duration. Data was assessed by neuroradiologists trained in MS. Visual evaluation of the brain focused on detecting lesions (Flair/T2 hyperintensities, T1 hypointensities) and distribution in space, the detection of new Flair/T2 lesions, and contrast-enhancing T1 hyperintensities to evaluate disease activity — distribution in time, according to the 2017 McDonald criteria. Description of atrophic changes was assessed using visual rating scales. Simultaneously, MRI scans (3D Flair, 3D T1) were analysed by Icobrain MS software (Icometrix, Leuven, Belgium). Icobrain MS software can detect, quantify and track the evolution of MS lesions (Flair, T1) and distribution in space and time. The software provides metrics that can assess the volume of the whole brain and grey matter, tracking annualised brain volume changes to evaluate disease progression. Additionally, the software compares brain volume and volume changes to age — and sex — having matched a normative reference population. The calculated volumes can be used to interpret the subjects' measurements concerning a normative population.

Table 1. Relevant demographic and clinical data of all included patients

	Mean	Median	SD	IQR	Min	Max
Age (years)	42.13	42.00	11.03	15.50	20.00	71.00
MS duration (years)	10.70	8.500	7.458	9.850	0.3000	46.70
Treatment duration (years)	6.128	5.700	4.263	5.600	0.000	20.90
Number of DMTs	2.007	2.000	1.089	2.000	0.000	5.000
EDSS	3.500	3.000	1.417	2.250	1.000	7.000

MS — multiple sclerosis; DMT — disease-modifying therapy; EDSS — expanded disability status scale; SD — standard deviation; IQR — interquartile range

Relevant demographic and clinical data was collected from the information system at the Centre for MS Treatment at the Second Department of Neurology, Faculty of Medicine, Comenius University in Bratislava. Data was obtained at the timepoint corresponding with the date of the brain MRI examination, and included:

- age,
- gender,
- time of MS onset,
- time of treatment initiation,
- DMT characteristics (escalation versus induction; 1st line versus 2nd line),
- Expanded Disability Status Scale (EDSS),
- number of relapses in the two years prior to MRI examination.

Statistical analysis

We determined the required minimum sample size based on a *a priori* power analysis [18] using the G*Power 3 program [19]. The data was analysed by JASP Team (2021) JASP (Version 0.16) software. Statistics were used to evaluate demographic and clinical data. For normality evaluation, individual variables were first tested with the Lilliefors modification of the Kolmogorov-Smirnov test. Continuous parametric data satisfying normal distribution were described as mean ± standard deviation. If the data was non-normally distributed, it was described as median values with corresponding interquartiles. Categorical parametric data was presented as percentages. Parametric data was compared by the Student T-test, non-parametric data by the Mann-Whitney U-test; the chi-square test was used for categorical variables. Using the Bonferroni approach to control Type I errors, a p-value ≤ 0.008 was required for statistical significance. Correlation analysis of the data was conducted with the Spearman correlation test and linear regression. In cross-sectional analysis, a binary logistic or linear regression model was used to estimate probability and 95% confidence intervals (CI) for the risk factors.

Results

Description of patients

We collected complete data from 147 patients with MS, of whom 68.7% were female. The mean age was 42.13 ± 11.03 years and mean disease duration was 10.70 ± 7.46 years. By far the most common MS subtype in our group was relapsing-remitting (n = 123; 83.7%), followed by the secondary progressive (n = 21; 14.3%) and then the primary progressive subtypes (n = 3; 2.0%). The median of EDSS was 3.0 (IQR 2.250, min 1.0, max 7.0). The mean duration of MS treatment was 6.13 ± 4.26 years; 36.7% patients were treated by their first DMT (n = 54), 34.0% (n = 50) by the second DMT, 17.0% by the third (n = 25), 6.8% (n = 10) by the fourth, and 3.4% (n = 5) by the fifth DMT in their medical history. Only three patients (2%) did not take any DMT. Demographic and clinical data is summarised in Table 1.

Both whole brain volume ($r_s = -0.409$, $p < 0.001$) and grey matter volume ($r_s = -0.747$, $p < 0.001$) negatively correlated with age; there were no significant differences between genders.

According to age, whole brain volume negatively correlated with MS duration ($r_s = -0.270$, $p < 0.001$). Progressive MS (both primary and secondary) patients had significantly lower whole brain and grey matter volumes ($p = 0.003$ and $p < 0.001$, respectively) compared to RRMS patients matched by disease duration and age.

Whole brain volume also negatively correlated with treatment duration ($r_s = -0.177$, $p = 0.037$).

There was no significant difference in whole brain volume when comparing patients treated by different treatment lines ($p = 0.384$), different therapy modes (induction versus escalation, $p = 0.552$), or the number of previous treatments ($p = 0.228$). We did not find any significant correlation with grey matter volume in these specific parameters (data available upon request).

MRI atrophy and MRI activity

There was no association between MRI atrophy and MRI activity ($\chi^2 = 0.013$, $p = 0.910$).

Comparing patients with and without MRI activity, there was a significant difference in age ($p = 0.006$) and the number of relapses in the last two years ($p = 0.008$). There was no significant difference in either MS or therapy duration ($p = 0.533$, and $p = 0.113$, respectively) or total brain and grey matter volume ($p = 0.533$, and $p = 0.113$, respectively).

Comparing patients with and without MRI atrophy, there was a significant difference in both whole brain volume ($p < 0.001$) and grey matter volume ($p < 0.001$), and in MS duration

Table 2. Comparison of patients with and without MRI activity, or MRI atrophy, respectively

		MRI activity			MRI atrophy		
	Group	Mean	SD	p-value	Mean	SD	p-value
Age (years)	No	43.577	10.889	0.006	40.527	9.923	0.027
	Yes	37.667	10.398		44.732	12.285	
MS duration (years)	No	10.639	6.833	0.533	9.291	6.501	0.005
	Yes	10.872	9.232		12.979	8.362	
Treatment duration (years)	No	6.356	4.017	0.113	5.384	4.019	0.004
	Yes	5.425	4.943		7.338	4.406	
Relapses in last two years (n)	No	0.360	0.569	0.008	0.429	0.635	0.680
	Yes	0.722	0.815		0.482	0.687	
Whole brain volume (mL)	No	1,509.586	75.779	0.314	1,548.132	64.039	< 0.001
	Yes	1,510.972	89.679		1,447.839	59.607	
Grey matter volume (mL)	No	904.135	48.802	0.038	927.297	46.476	< 0.001
	Yes	925.806	58.206		880.429	47.245	

MRI — magnetic resonance imaging; SD — standard deviation; MS — multiple sclerosis

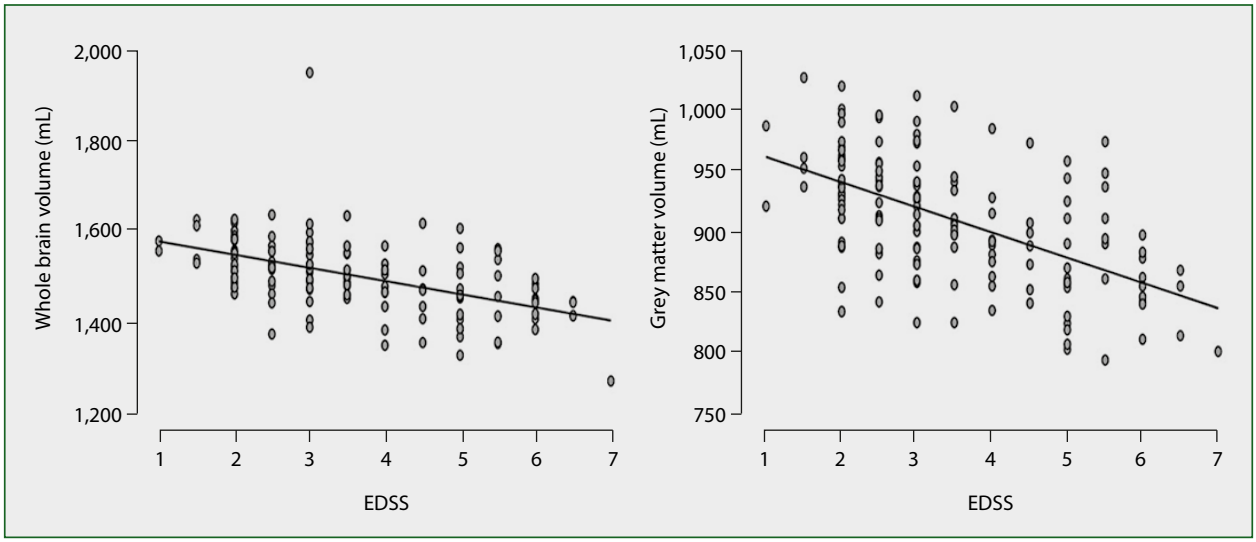

Figure 1. Negative correlation between expanded disability status scale (EDSS) and both whole brain volume (r_s = –0.368, p < 0.001) and grey matter volume (r_s = –0.308, p < 0.001)

(p = 0.005) and treatment duration (p = 0.004). All data is set out in Table 2.

Disability

Total EDSS score correlated positively with MS duration (r_s = 0.457, p < 0.001) and treatment duration (r_s = 0.329, p < 0.001), but was not associated with the number of relapses in the last two years (p = 0.278). Comparing patients with and without MRI activity, there was no significant difference in EDSS (p = 0.01). Comparing patients with and without MRI atrophy, patients with atrophy had higher EDSS scores (p < 0.001). EDSS negatively correlated with whole brain volume (r_s = –0.368, p < 0.001) and grey matter volume (r_s = –0.308, p < 0.001) as shown in Figure 1. Progressive MS patients had significantly higher EDSS scores (p < 0.001) compared to RRMS patients matched by MS duration and age.

Treatment delay

The number of years from MS onset to DMT initiation (treatment delay) negatively correlated with whole brain volume (r_s = –0.387, p < 0.001) and grey matter volume (r_s = –0.377, p < 0,001). Treatment delay was connected with a higher risk for lower brain volume (b = –102, p < 0.001).

There was no significant correlation between treatment delay and MRI activity or the number of relapses (p = 0.943, and p = 0.591, respectively).

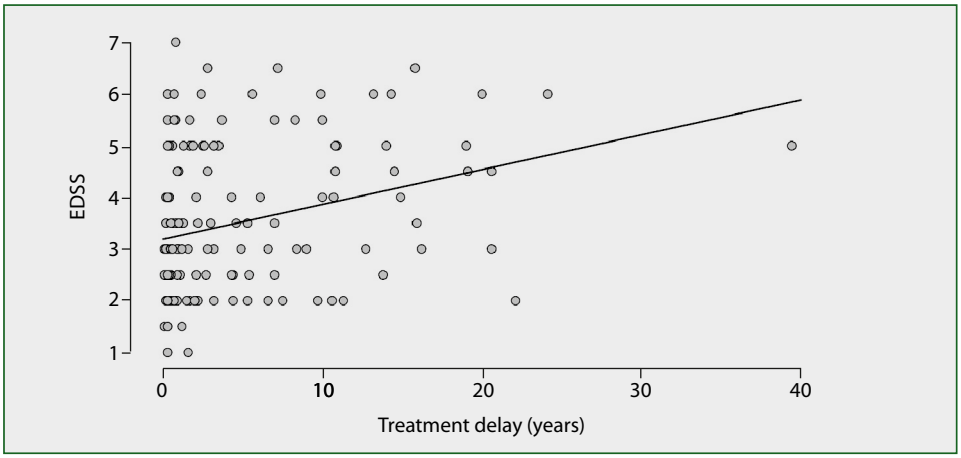

Figure 2. Positive correlation between treatment delay and expanded disability status scale (EDSS) score (r_s = 0.322, p < 0.001)

Discussion

Neuroimaging is of the utmost importance in both the diagnosis and the differential diagnosis of MS — especially in borderline, undetermined and atypical cases [20]. Multiple sclerosis used to be considered a white matter inflammatory disease, whereas brain volume loss was previously regarded as being present in more severe or advanced stages of the disease. This belief has been refuted in the last decade by numerous studies demonstrating that brain atrophy begins to occur from the preclinical stage of MS, and continues (at least partially) independently of inflammation [21]. This has been proved not only by volumetric studies; progressive neurodegeneration was recently confirmed by measuring the peripapillary retinal nerve fibre layer (pRNFL) by optical coherence tomography (OCT) [22].

MRI activity versus MRI atrophy and brain volume loss

Our results confirm that total brain volume is negatively correlated with MS duration. In addition, patients with progressive forms have significantly lower whole brain volume and grey matter volume compared to patients with RRMS (matched by disease duration and age). Previously published data showed that grey matter volume is lower in secondary-progressive disease compared to relapsing-remitting disease [10].

Regarding DMT, brain volume is negatively correlated with treatment duration, but it is not affected by current therapeutic approaches (i.e. the first versus the second line, escalation versus induction scheme). This supports the above-mentioned hypothesis that the neurodegenerative process is not significantly influenced by inflammation and/or immunomodulatory medication.

We found no association between MRI activity and brain volume changes on MRI (atrophy, total brain volume or grey matter volume). We proved that patients with confirmed activity on brain MRI — compared to patients with stable MRI findings — were significantly younger and had a higher number of relapses in the past two years — very probably being still in the inflammatory-predominant stage of MS. Here, MRI activity can predict the effects of immunomodulatory treatment on relapses of over two years [23]. This is important for clinicians' decisions about the escalation of DMT in a patient without manifest clinical worsening, as the predictive value of a new T2 MRI lesion counting as a predictor of longer-term effects on relapses has been assessed [24].

On the other hand, we found that the presence of brain atrophy on MRI did not correlate with disease activity (neither the number of relapses, nor new lesions on MRI). These patients had longer MS duration, as well as longer duration of DMT, compared to patients with no atrophy. All these findings underline that atrophy and activity are independent of each other.

Assessment of atrophy helps to distinguish between clinically and cognitively deteriorating patients and predicts those who will have a less favourable clinical outcome in the long term. Atrophy can be measured from brain MRI scans due to the many technological improvements made over the last few years. Despite this, measuring brain atrophy is not yet established as a routine clinical practice [12]. Early identification of patients with MS — accumulating future irreversible clinical disability in the long term — could help with therapeutic decision-making and patient management [25].

Impact of MRI findings on disability

In our study, EDSS score positively correlated with MS duration. However, it was not associated with disease activity assessed by the number of relapses in the last two years.

In addition, the difference in EDDS scores between patients with and without MRI activity was not significantly different. On the other hand, patients with brain atrophy had significantly higher EDSS scores, and this disability indicator negatively correlated with both whole brain and grey matter volume. An association between brain volume loss and

disability progression has been recently confirmed [12, 25]. These findings support previous research revealing that grey matter atrophy and T2 lesion volume are independent and mirror distinct pathological processes in a specific stage of MS [10].

Progressive MS patients had significantly higher EDSS scores, and lower total brain and grey matter volumes, than RRMS patients matched by disease duration and age.

Grey matter volume loss explains physical disability (as measured by the EDSS) better than white matter volume loss and/or T2 lesion volume [26]. Recent reports have confirmed that the rate of BVL is relatively stable throughout the course of RRMS. Accelerated BVL is weakly associated with concurrent higher disease activity [27]. Brain atrophy might also have a higher predictive value than conventional MRI findings in preventing physical disability progression (T2 lesion load) [21]. Our results are in agreement with the hypothesis that the neurodegenerative components of the progressive aspects of MS pathology, characterised by worsening disability, are independent of relapses [28].

Effect of treatment delay on outcomes

We found no significant correlation between treatment delay and MRI activity or the number of relapses in the last two years. This is not surprising, as the role of effective DMT is to decrease the activity of MS. On the other hand, a higher number of years from MS onset to DMT initiation was associated with lower brain volumes and higher EDSS scores. This has been referred to as the 'therapeutic window': if anti-inflammatory drugs are started late, too much damage has already accrued to prevent the consequences of previous focal inflammatory activity. Patients with SPMS show sustained accumulation of disability due to uncontrolled progression attributable to brain volume loss. The rate of cerebral atrophy is most significant in patients with established cerebral atrophy and a higher inflammatory lesion burden before DMTs [29]. Available DMTs are of only marginal benefit for patients already in the progressive stage of the disease [3]. Therefore, preventing patients from converting from the relapse-remitting to the progressive form of MS might be the only way of slowing down the irreversible neurological deterioration caused by axonal loss. Uher et al. [7] found that early initiation of adequate treatment helps halt the rate of BVL [27]. Randomised controlled trials and recent observational studies suggest that the initiation of early-intensive therapy is associated with decreased accumulation of overall disability. Understanding risk factors associated with disability progression is helpful in enhancing the clinician's availability to provide optimal treatment recommendations. There is clear evidence that a higher reduction in brain atrophy leads to a reduction of disability amelioration, but disease-modifying therapies (DMTs) can only partially slow down the rate of brain atrophy progression in MS patients [11, 21, 24]. Over the past decade, new DMTs with various secondary neuroprotective properties impacting on axonal survival have been implemented. Moreover, treatment delay is now shorter. All this might have contributed to the changes in the course of multiple sclerosis — which is apparently milder nowadays.

Our study has some limitations. The vast majority of our patients were treated with DMTs; therefore, the effect of pseudo-atrophy may have been present [30]. In our study, we did not assess the volume of T2 lesions, which, together with magnetisation transfer ratio (MTR) lesions, correlate with mean grey matter volume loss [31–33].

We did not include healthy controls; nevertheless, our data was statistically analysed, controlling for age and gender. We are aware that EDSS is not sensitive to signs of progression such as cognitive impairment, severe fatigue etc., but despite its limitations, this scoring system for disability evaluation is still the gold standard [6, 12, 28, 33]. Various volumetric software has been used in different reviewed studies compared to ours. However, the majority of results are still consistent [10, 27, 31–33].

Clinical implications / future directions

Our results have validated that brain atrophy manifests progressively in MS patients, and independently of clinical and MRI activity. Brain volume loss is a major contributor to disability progression, and we found that delay in DMT leads to higher BVL and increased disability. With the advent of easily accessible neuroimaging software, brain atrophy assessment should be translated into daily clinical practice to monitor disease course and responses to DMTs. Volumetric assessment should be implemented into routine MRI protocol for patients with MS. In addition, plenty of new, more promising DMTs are already being tested in progressive MS types, and the assessment of BVL itself should be considered a sufficient marker for treatment escalation. Further studies are required to confirm these promising results.

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RESEARCH PAPER

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Prevalence and prognostic value of prodromal symptoms in relapsing-remitting multiple sclerosis

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ABSTRACT

Introduction. Several studies have suggested the possibility that disease prodromes might occur months or even years before a multiple sclerosis diagnosis.

Objectives. To describe the profile of prodromal symptoms and the possible relationship between the occurrence of individual symptoms and clinical course characteristics in patients with relapsing-remitting multiple sclerosis (RRMS), and to assess their role as predictors of further disease course.

Material and methods. The cohort included 564 patients with RRMS. Patients were stratified based on their current EDSS score, and the annual EDSS growth rate was calculated. Logistic Regression Analysis was used to study the relationship between prodromal symptoms and disease progression.

Results. The most commonly reported prodromal symptom was fatigue (42%). The following symptoms were significantly more common in women than in men: headache (39.7% *vs.* 26.5%, $p < 0.05$), excessive sleepiness (19.1% *vs.* 11.1%, $p < 0.05$) and constipation (18.0% *vs.* 11.1%, $p < 0.05$).
Prodromal urinary and cognitive disturbances, fatigue and pain complaints were significantly more common in patients with the highest annual EDSS increase ($p < 0.05$).
Multivariate analysis revealed some potential predictors of long-term disability progression: hesitancy in starting urination predicted EDSS increase by 0.6 point ($p < 0.05$), while deterioration in everyday functioning because of cognitive disturbances, and pain complaints, were associated with an EDSS increase of 0.5 ($p < 0.05$), and 0.4 ($p < 0.05$), respectively.

Conclusions. Prodromal pain, urinary and cognitive complaints (especially when these lead to deterioration of everyday functioning) were associated with a higher EDSS increase rate, and may thus be regarded as possible predictors of worse clinical outcomes in RRMS patients.

Key words: multiple sclerosis, prodromes, disease predictors, RIS, preclinical phase

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Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of inflammatory and neurodegenerative aetiology, which mainly affects young adults [1]. Currently, MS diagnosis can only be made at the onset of clinical symptoms typical for MS, when the patient meets the criteria for dissemination in time and space [2]. However, it is vital to diagnose the disease at a very early stage, since starting treatment without delay allows patients to achieve better outcomes [3–6].

Radiologically isolated syndrome (RIS), first described by Okuda in 2009 [7], is a condition wherein the patient has brain

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magnetic resonance imaging (MRI) abnormalities suggestive of MS, but with no apparent signs or symptoms of the disease. Approximately 50% of subjects with RIS go on to develop MS within 10 years [8]. Therefore, describing RIS was one of the first arguments to suggest that there was a preclinical phase of MS. If such a phase does in fact exist, then it would be extremely important to be able to identify patients who are still in this very phase, possibly by careful screening for disease prodromes.

A prodrome is defined as a sign or symptom preceding the classical course of a specific disease [9]. One of the best examples of diseases with an evident prodromal phase is Parkinson's disease [10] but it is also features in Alzheimer's disease, depression, rheumatoid arthritis, and Crohn's disease [1, 11, 12].

Clinical rationale for study

Several studies have suggested the possibility that disease prodromes might occur even 5–10 years before MS diagnosis. Such a possibility is implied by a higher number of hospitalisations and visits to psychiatrists and dermatologists, and more frequent recognition of sleep and bowel disturbances, fatigue, pain, migraines or cognitive impairment [1, 13–18].

In this study we aimed to: (I) analyse the profile of prodromal symptoms based on information obtained directly from MS patients; (II) compare this profile to previously published data obtained from healthcare and insurers' registries; (III) analyse the profile of patient-reported prodromal symptoms with regards to gender and age at disease onset; and (IV) finally to assess the possible role of different prodromal symptoms as predictors of the subsequent disease course.

Material and methods

Participants were recruited from the single MS centre at the Department of Neurology, Poznan University of Medical Sciences, Poznan, Poland. Adult patients with relapsing remitting MS (RRMS) were enrolled to take part in the study between November 2021 and April 2022. The data was obtained by neurologists using an original questionnaire called 'ProdroMuS' (see Appendix 1) during the patients' visits to the clinic. In the questionnaire, patients were asked about any symptoms that preceded the onset of their first relapse for up to five years, but were not typical MS relapses. In the questionnaire, we listed the prodromal symptoms mentioned in previously published studies. Additionally, we asked patients about their subjective feelings about their cognitive functions during the time preceding their first MS relapse. The patients were asked to mark the time frame in which they developed symptoms. When asking about fatigue and upper respiratory tract infections, we asked about the increased number of symptoms or severity in comparison with their peers.

Patients were also assessed by their treating neurologists with Expanded Disability Status Scale (EDSS) at the time of enrollment into the study. Clinical data concerning the onset of first MS symptoms, MS diagnosis and all annual EDSS assessments since treatment onset were obtained from patient records, and verified with the data entered by treating neurologists to the central nationwide register under the Polish public healthcare system (the National Health Fund electronic database).

Patients who did not consent to participate in the study were excluded.

This study was approved by the Internal Review Board at Poznan University of Medical Sciences, Poznan, Poland.

Demographics and clinical characteristic of study group

We enrolled 564 patients with relapsing-remitting MS, consisting of 383 women (67.9%) and 181 men (32.1%). The study flow diagram is presented in Figure 1. The mean age (years) was 39.3 ± 10.4; median 39 (range 19–71); IQR 14.8. The mean EDSS at enrollment was 2.0 ± 2.8, median 2.0 (range 0–6.5), IQR 1.5.

The mean age at MS diagnosis (years) was 30.9 ± 9.2; median 29.5 (range 13–66); IQR 12.8.

The mean time from experiencing first MS symptoms to enrollment (years) was 9.9 ± 6.3, median 9.0 (range 0–39), IQR 9. The majority of patients were treated with disease-modifying therapies (N = 562; 99.6%), including 70 (12.4%) on high-efficacy therapies (natalizumab, alemtuzumab, ocrelizumab, cladribine, fingolimod) and 494 (87.6%) on platform therapies (injectables) i.e. teriflunomide or dimethyl fumarate. The relatively small percentage of patients treated with high-efficacy therapies in our centre is a result of the provisions of the National Health Fund that require meeting the appropriate (relatively high) criteria for receiving high-efficacy therapies [19].

Statistical analysis

The results were reported as counts (percentage) for the categorical variables, mean with standard deviation, and median with quartiles for the continuous variables. As appropriate, categorical variables were compared using Chi-square tests (with Yates correction for 2 × 2 tables) or Fisher's exact tests.

Continuous variables were compared between two groups using a Mann–Whitney test. The comparison of variables in three or more groups was performed using a Kruskal-Wallis test. After detecting statistically significant differences, *post-hoc* analysis with Dunn's test was conducted to determine which groups differed from each other.

A multiple linear regression model was used to investigate the combined effect of all prodrome variables on EDSS value.

A p-value of 0.05 or lower was considered statistically significant. All statistical analyses were performed using R software [R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/].

Results

Frequencies and timing of prodromal symptoms prior to first relapse

Four hundred and sixty-five out of 564 patients (82.4%) had at least one prodromal symptom, and 99 patients (17.6%) had no such symptoms. The mean number of prodromal symptoms per patient was 4.8 ± 4.4, median 4 (IQR = 7), and ranged from 0 to 22.

The period in which patients noticed prodromes was mostly reported as being difficult to assess (N = 142, 25.2%), followed by 2–3 years (N = 120, 21.3%), then within one year (N = 102, 18.1%), then within 4–5 years (N = 99, 17.6%) before the onset of classical MS symptoms (Tab. 1).

Two hundred and thirty-seven patients (42%) experienced fatigue and this was the most commonly reported prodrome. As the definition of fatigue can be vague, we asked specifically about fatigue which hindered everyday functioning and was more pronounced than in their peers.

A total of 65 (11.5%) patients observed new dermatological diseases, such as atopic dermatitis, psoriasis, rash, tinea versicolor or photodermatosis, in the years preceding MS onset. In addition to the symptoms mentioned in the questionnaire, we also asked an open question about any bothersome symptoms occurring in the years preceding the MS onset. Patients typically reported: paresthesia (N = 62, 11%), non-specific visual disturbances (N = 27, 4.7%), or Lhermitte sign (N = 12, 2.1%). Fewer than five patients mentioned other symptoms, such as syncope, Bell's palsy, hearing disturbances, sexual dysfunction, excessive sweating, tinnitus, stammering, or involuntary movements of the upper limbs.

Table 1. Prodromal symptoms reported by RRMS cohort in 'ProdroMuS' questionnaire

Symptom	N	%
Fatigue	237	42%
Headache	200	35.5%
Vertigo	173	30.7%
Sleep disturbances	165	29.3%
Bowel disturbances	146	25.9%
Cognitive difficulties at school/work	130	23.1%
Concentration disturbances	123	21.8%
Limb tremor	119	21.1%
Dizziness	112	19.9%
Urinary disturbances	104	18.4%
Spinning	101	17.9%
Excessive sleepiness	93	16.5%
Increased frequency of URTIs	89	15.8%
Constipation	89	15.8%
Insomnia	83	14.7%
Deterioration in everyday functioning due to cognitive difficulties	83	14.7%
Anxiety and depressive disorders	82	14.5%
Dermatological disorders	65	11.5%
Abdominal pain	61	10.8%
Urgent need to urinate	58	10.3%
Diarrhoea	46	8.2%
Incontinence	44	7.8%
Use of antidepressant drugs before diagnosis	36	6.4%
Hesitancy in starting urination	32	5.7%

URTIs — upper respiratory tract infections

Differences between women and men

A total of 318 women (83%) and 147 men (81.2%) reported prodromal symptoms, which was not significantly different ($p = 0.682$) However, women reported more symptoms than men (mean 5.1 *vs.* 4.3, $p < 0.05$).

The following symptoms were significantly more common in women than in men: headache (39.7% *vs.* 26.5%, $p < 0.05$), excessive sleepiness (19.1% *vs.* 11.1%, $p < 0.05$), and constipation (18% *vs.* 11.1%, $p < 0.05$). Gender-related differences were not statistically significant for other symptoms (see Tab. 2).

Prodromal symptoms and age at disease onset

We divided patients into five groups depending on their age when experiencing their first MS symptoms. The largest group constituted patients with a typical age at MS onset, namely 21 to 30 years of age (N = 231, 41%). The frequency of prodromal symptoms was not significantly different between the groups. However, the mean number of the reported prodromal symptoms was higher in the groups of middle age at disease onset (mean 5.3 and 6.1 for 31–40-years and 41–50-years onset respectively) compared to younger patients (mean 4.3 for onset ≤ 20 years and 4.2 for onset at 21–30 years) and to the late onset group (mean 4.8 for disease onset > 50 years), $p < 0.05$.

We also analysed whether the occurrence of specific prodromes was associated with age at MS onset. Pain complaints, sleep disturbances, vertigo, and fatigue were most common in the group that was diagnosed with MS between the ages of 41 and 50. Nightmares prevailed in the group with disease onset before age 20. Dizziness, urinary incontinence, or urgent need to urinate dominated in the group with late MS onset (after 50 years of age). All the above-mentioned relationships were statistically significant ($p < 0.05$, see Supplemental Tab. 1).

Prodromal symptoms and EDSS

To assess how and which of the prodromal symptoms were associated with future neurological status, we stratified patients into two groups according to their current EDSS (EDSS < 3 and ≥ 3).

The group with the higher EDSS reported more prodromal symptoms (a mean of 6.1 ± 5 *vs.* 4.4 ± 4.1, $p < 0.05$), see Figure 1.

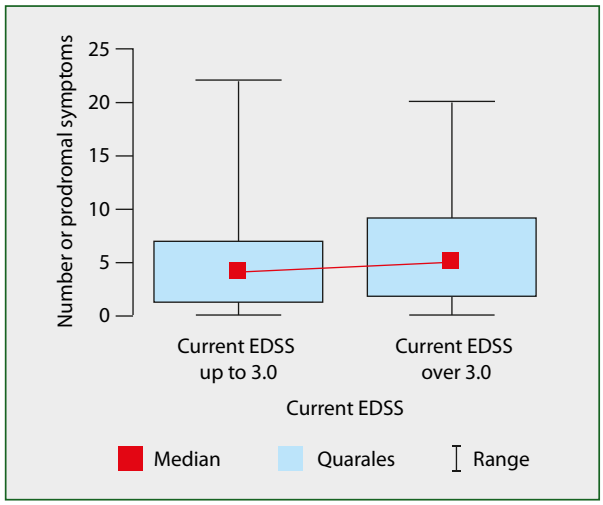

Figure 1. Number of the reported symptoms by the current EDSS score ($p < 0.05$)

The following prodromes were significantly more frequent in the higher EDSS group: pain complaints, headache, vertigo, dizziness, limbs tremor, diarrhoea, urinary disturbances (incontinence, urgency, hesitancy in starting urination) and deterioration in everyday functioning due to cognitive issues, see Supplemental Table 2.

In multivariate analysis, the following prodromes correlated significantly with the future EDSS score: hesitancy in starting urination (raised EDSS by 0.6, $p < 0.05$), deterioration in everyday functioning because of cognitive difficulties (raised EDSS by 0.5, $p < 0.05$), and pain complaints (raised EDSS by 0.4, $p < 0.05$). The R^2 coefficient for this model was 14.13% ($p < 0.05$).

Prodromal symptoms and subsequent increase in disability

We adopted the index EDSS increase per year to assess whether and which prodromal symptoms occurred in patients

Table 2. Prevalence of reported prodromal symptoms by gender

Symptom	Sex		p-value
	Women (N = 383)	Men (N = 181)	
Pain complaints	88 (23%)	38 (21%)	0.68
Headache	152 (39.7%)	48 (26.5%)	0.003*
Sleep disturbances	122 (31.9%)	43 (23.8%)	0.06
Insomnia	60 (15.7%)	23 (12.7%)	0.43
Excessive sleepiness	73 (19.1%)	20 (11.1%)	0.02*
Vertigo	128 (33.4%)	45 (24.9%)	0.005*
Spinning	71 (18.5%)	30 (16.6%)	0.65
Dizziness	80 (20.9%)	32 (17.7%)	0.44
Anxiety and depressive disorders	57 (14.9%)	25 (13.8%)	0.84
Limb tremor	78 (20.4%)	41 (22.7%)	0.61
Bowel disturbances	105 (27.4%)	41 (22.7%)	0.27
Diarrhoea	25 (6.5%)	21 (11.6%)	0.06
Constipation	69 (18%)	20 (11.1%)	0.046*
Abdominal pain	42 (11%)	19 (10.5%)	0.98
Urinary disturbances	76 (19.8%)	28 (15.5%)	0.26
Incontinence	34 (8.9%)	10 (5.5%)	0.22
Urgent need to urinate	41 (10.7%)	17 (9.4%)	0.74
Hesitancy in starting urination	21 (5.5%)	11 (6.1%)	0.93
Use of antidepressant drugs before dg	23 (6%)	13 (7.2%)	0.73
Fatigue	168 (43.9%)	69 (38.1%)	0.23
Cognitive difficulties at school/work	94 (24.5%)	36 (19.9%)	0.26
Concentration disturbances	86 (22.5%)	37 (20.4%)	0.67
Deterioration in everyday functioning due to cognitive difficulties	59 (15.4%)	24 (13.3%)	0.59
Increased frequency of URTIs	60 (15.7%)	29 (16%)	1.0

*statistically significant. URTIs — upper respiratory tract infections

with a more aggressive course of the disease. Patients with disease duration of less than one year were excluded from this analysis. Subjects were divided into four numerically similar subgroups (see Suppl. Tab. 3).

The presence and number of prodromal symptoms correlated significantly with a higher increase in index EDSS per year during the course of the disease (see Suppl. Tab. 3).

For several of the analysed prodromal symptoms, we showed statistically significant differences between the groups, with the following prodromes occurring more often in the two groups with the highest annual EDSS increase: urinary disturbances, cognitive complaints, fatigue, and pain (see Suppl. Tab. 4).

Pain complaints, headache, sleep disturbances, cognitive difficulties at school/work and deterioration in everyday functioning due to cognitive complaints were all significantly more frequent in the group with the fastest rate of disability accrual of ≥ 0.35 EDSS per year ($p < 0.05$ for all correlations).

Discussion

In this study, a great majority of our RRMS cohort (82.5%) presented with at least one prodromal symptom. The following characteristics correlated significantly with the number of reported prodromal symptoms: female sex, disease onset between ages 31 and 50, EDSS score ≥ 3.0 at enrollment into the study, and higher annual EDSS increase. We stratified patients into two groups using a cut-off of EDSS 3.0. This was selected as a generally accepted essential milestone in the course of the disease [20].

The occurrence of individual prodromes differed significantly depending on gender; specifically, headache, excessive sleepiness and constipation were significantly more common among women. The differences between the groups stratified by age at MS onset did not reach statistical significance. Therefore, it seems that the occurrence of the prodromal phase is independent of age at disease onset.

Fatigue, which is common among MS patients, has also been described in subjects with RIS [21], and was the most commonly reported symptom in our population (42%). In a study by Berger et al. [22], 28.9% of MS patients were labelled with chronic fatigue syndrome, malaise or fatigue in the three years preceding the MS diagnosis. In another study, fatigue was significantly more frequent in MS subjects up to five years before their diagnosis, compared to a healthy population [23].

Cognitive impairment in MS tends to progress over time, but might be detected as early as in clinically isolated syndrome [24] and even in up to 27.6% subjects with radiologically isolated syndrome [25]. Notably, almost a quarter of our patients reported that they had noticed problems with concentration and learning even several years before their first relapse. These cognitive disturbances resulted in difficulties at school or work [26] and in almost 15%, these symptoms had affected their everyday life months or even years before MS onset.

Similarly, according to a Norwegian study, impaired cognitive performance was found up to two years prior to the first MS event [27]. In an Argentinean population, it was shown that patients with subsequent MS diagnosis performed worse in their math exams at school compared to the healthy control group, even many years before disease onset [13].

In the current study, we were able to show that the prodromal cognitive complaints were most frequently reported by the group with the fastest rate of disability accrual.

Also, patients with EDSS ≥ 3 at enrollment were more likely to report that prodromal cognitive impairment and fatigue led to deterioration in everyday functioning even before their first MS relapse.

We acknowledge that fatigue could affect cognitive impairment. Importantly, our study participants were specifically asked whether their memory and concentration problems or difficulties in acquiring new information were more severe than in their peers and whether they made it difficult to cope with work or school duties. It was the deterioration in everyday functioning due to cognitive impairment that was a predictor of higher EDSS increase rate. This finding underlines the importance of patients' subjective judgements and patient-reported outcomes in clinical reasoning.

Another clinically significant complaint is pain, which is more prevalent in MS subjects, even as much as 10 years before their first MS relapse [15, 23, 28]. In our study group, pain complaints (usually muscles, joints or back) were a predictor of higher disability (raised EDSS by 0.4 point, $p < 0.05$) and were reported more commonly in the higher EDSS subgroup (33.6% *vs.* 18.7%, $p < 0.05$) and in the subgroup with the highest annual EDSS increase (33.8% in ≥ 0.35 EDSS/y group *vs.* 12.1% in ≤ 0.10 EDSS/y group, $p < 0.05$). However, pain might be more elusive as a potential outcome predictor than cognitive impairment, given that the latter allows for a more reliable quantification.

Interestingly, 6.4% of our patients were treated with antidepressant drugs before their first MS relapse, which is consistent with the data reported for Polish (7%) and European (7.2%) populations [29]. This points to the fact that in the years preceding the disease, future MS patients do not use antidepressant drugs more frequently than the general population, something which has been implied by some studies [14, 15]. Importantly, the number of patients on antidepressants doubled after the diagnosis was made, rising from 6.4% to 12.4%. The frequency of anxiety and depressive disorders did not statistically differ between groups divided based on EDSS outcome or age at onset of disease.

Vertigo was reported by 30.7% of our patients, which is consistent with studies revealing that patients with MS had more prescriptions made out for anti-vertigo drugs in the five years preceding the diagnosis [30]. This was reported more frequently in groups with a higher EDSS score and higher accrual of EDSS per year.

In our study population, gastrointestinal disturbances were observed in 29.1% of patients, which is higher than the numbers reported in Portuguese (17%) [15] and Swiss studies (11.6%) [23]. On the other hand, Almeida et al. [31] revealed that 31.6% of patients with RRMS reported bowel symptoms before the occurrence of clinically isolated syndrome, mostly constipation (50%) and diarrhoea (29.5%). In a Lithuanian population, 36.7% of patients experienced gastrointestinal disorders as prodromes [28]. The differences in the reported numbers may represent regional differences (dietary habits, environmental exposures) or may result from different group size effects.

Urological symptoms are rarely the first presentation of MS (3–10%), but in the course of the disease almost 65% of patients report moderate to severe urinary complaints [32]. Importantly, in our group 18.4% of patients reported them as prodromal signs, mostly in the groups with a higher disability increase rate. We must emphasise that studies based on International Classification of Diseases-10 (ICD-10) codes have also revealed that patients with MS have a significantly higher risk of presenting urinary dysfunction before their MS onset [14] and have a higher hospitalisation rate related to bladder disorders or higher number of prescriptions for urinary anti-spasmodics in the five years before typical MS onset [30, 33].

In the current study, hesitancy in starting urination as a prodromal sign correlated significantly with a higher EDSS at enrollment into the study.

The strengths of our study include its access to a relatively large RRMS population with well-documented disease onset and follow-up EDSS scores, as recorded in the clinical database by the treating neurologists.

So far, the majority of studies concerning the prodromal MS phase have been based on electronic healthcare databases, which does ensure large groups of patients. However, in such databases, MS onset would be reported as the date of the first MS clinic visit [15, 22, 23, 33]. Such an approach could easily be flawed as some of the earlier visits could already be related to MS and not constitute a prodrome. Additionally, symptoms were identified from records by ICD-10 classification, and not reported directly by patients, which we believe to be a limitation. Some complaints, such as fatigue, are rarely coded in ICD-10, especially if they accompany sleep or mood disorders.

Limitations of retrospective approach

Recall bias needs to be addressed as an important limitation of this study. Firstly, our questionnaire was designed to screen a period of only five years before MS onset, which is limiting but reliable (given the fact that it is self-reported). In fact, in most of the available studies on MS prodromes, a 5-year period has been analysed [14–16, 18, 30].

Another limitation is the lack of a control group. However, the aim of our study was rather to assess whether the symptoms were consistent with data available from studies based on ICD-10 databases, and not to compare MS to the general population. Importantly, we attempted to select symptoms that could be predictors of a more severe disease course.

Notably, most patients found it difficult to answer the open-ended questions about the other antecedent symptoms they noticed. This indicates the potential difficulties in accurately estimating prodromal symptoms. Due to their non-specific nature, relatively low intensity as compared to the symptoms of a relapse, and their chronicity, prodromes may sometimes simply be ignored by patients.

It is well established that radiologically isolated syndrome may precede the appearance of clinical symptoms of MS by up to several years [34–36], with levels of serum neurofilament light chain showing increases as much as six years before clinically definite MS [37].

Based on the pattern of radiological abnormalities in RIS and the presence of oligoclonal bands, we can estimate the risk of conversion from RIS to MS [34–36]. It is likely that considering prodromal symptoms would allow physicians a better selection of subjects requiring disease modifying therapies promptly in their care. As we nowadays have a wide range of therapies available, it seems that the biggest problem is still that we introduce them too late [4]. Also, in this specific population, neuroprotective strategies would be especially needed.

In this paper, we have shown that patients with higher EDSS scores reported more prodromal symptoms. Cognitive impairment and urinary disturbances were significantly correlated with a higher rate of EDSS increase in the future. This obviously necessitates further research.

This might be the right moment to change the generally dismissive approach to non-specific, 'mild' symptoms that do not affect a patient's life. This approach is clearly contraindicated by the high percentage of our study population who did experience a significant deterioration in their quality of life years before their first MS relapse.

Clinical implications and future directions

The inclusion of prodromes into the clinical course of MS may change the diagnostic criteria in future, although the use of additional tests/biomarkers, e.g. neurofilament light chain measurements, could be helpful in terms of minimising the risk of misdiagnosis [38]. We suggest that patients with RIS should receive routine assessments on Fatigue Severity Scale, neuropsychological tests, and a detailed history of urinary disturbances.

Since pain and fatigue can be difficult to objectify, we suggest focusing on complaints regarding cognitive impairment, especially since a large group of patients noticed that these deficits worsened their daily functioning, even before manifestation of the typical MS symptoms.

Our study may have important implications for newly diagnosed patients. Specifically, it suggests that screening this population for previous prodromal symptoms could be a factor in considering highly effective therapies (HET) earlier

on, if patients were identified as high-risk for early disability. Interestingly, in a Polish population, it has recently been shown that HET have been used less frequently than anticipated [19].

In the future, we plan to compare the results obtained from the MS population to those of additional comparative study cohorts of patients with other immune-mediated diseases, such as ulcerative colitis.

We conclude that a broader appreciation and deeper understanding of the phenomenon of prodromes will allow us to better apprehend the early stages of multiple sclerosis.

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Predictors of falls in Parkinson's disease, progressive supranuclear palsy, and multiple system atrophy: a retrospective study

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ABSTRACT

Introduction. Recurrent falling is a major clinical milestone in Parkinsonian syndromes. It has a detrimental impact on quality of life, further prognosis, and life expectancy.

Aim of the study. To improve fall management and prevention, we aimed at identifying clinical parameters predicting fall frequency. To this end, we retrospectively analysed records of fall events of patients with Parkinson's disease (PD), or progressive supranuclear palsy (PSP), or multiple system atrophy (MSA), during their two-week inpatient stay at the Parkinson-Klinik Ortenau, Wolfach, Germany. This data served as an objective proxy for patients' fall frequency and allowed us to estimate the impact of several demographic and clinical variables on the occurrence of falling.

Material and methods. Of 2,111 patients admitted to our hospital, 1,810 presented with PD, 191 with PSP, and 110 with MSA. We employed a multiple (quasi-) poisson regression analysis to model the fall frequency as a function of various demographic variables (age at diagnosis, gender) and clinical variables (disease duration and sub-type, motor and cognitive impairment, autonomic dysfunction).

Results. Statistically significant predictors for falls in PD were cognitive impairment, motor impairment, and autonomic dysfunction. In PSP, significant predictors for falls were motor and autonomic dysfunction, while in MSA only disease duration predicted falls, but with only marginal statistical significance.

Conclusions. Our results stress the importance of different factors in predicting falls in the different types of Parkinsonian syndrome. Preventive interventions should address these disease-specific targets for optimal success.

Key words: autonomic dysfunction, cognitive impairment, falls, multiple system atrophy, Parkinson's disease, progressive supranuclear palsy

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Introduction

The occurrence of falling is a major clinical milestone in the progression of Parkinsonian syndromes [1]. While in progressive supranuclear palsy (PSP) falling occurs early and is a diagnostic feature [2], falls occur later in the course of Parkinson's disease (PD). Specifically, the median time to the first fall has been reported to be 1.4 years in PSP, but 9 years in PD [3]. In multiple system atrophy (MSA), the first fall has been estimated to occur at a median of 3.5 years after diagnosis.

Alongside the occurrence of dementia [4], falling has been described as a major detrimental factor in patients with Parkinsonian syndromes, affecting their quality of life negatively [5]. A survey among Parkinsonian patients, including

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Table 1. Patient demographics and clinical characteristics

Variable	PSP	MSA	PD
N	191	110	1,810
Gender (female:male)	77:114	65:45	673:1,137
	40.3:59.7%	59.1:40.9%	37.2:62.8%
Age at diagnosis in years; mean ± SD (range)	68.7 ± 7.0 (47–86)	63.1 ± 9.4 (37–84)	64.0 ± 10.5 (30–89)
Disease duration in years; mean ± SD (range)	2.6 ± 2.5 (0–20)	3.2 ± 2.9 (0–17)	7.8 ± 5.9 (0–46)

PD and atypical Parkinsonian syndromes, has found that after falling, 65% of patients sustained injuries. Of these, 33% sustained fractures [6]. Falling, and in particular recurrent falls and their resulting injuries, are a major risk factor for nursing home admissions [7]. The early occurrence of falls has been described as being predictive of shorter survival in both MSA and PSP [8].

Previous studies have usually relied on retrospective chart reviews [3], post-hoc rating scales and questionnaires [9–11], or self-report diaries [12] to estimate fall rates in Parkinsonian syndromes. A major disadvantage of post-hoc self-reports is the possibility for recall bias. The occurrence of falls is likely to be underreported, patients and their caretakers might downplay fall events, and might only recall those falls resulting in injuries as being genuine falls.

Recording fall events of inpatients in a clinical setting has the advantage of standardised criteria as to what constitutes a fall event, and should thus provide an objective estimate of fall frequency.

In order to understand the occurrence of falls in Parkinsonian syndromes and to obtain possible insights into the mechanisms of falling, we retrospectively analysed data of 2,111 patients with PSP, MSA, or PD who were admitted as inpatients to the Parkinson-Klinik Ortenau, Wolfach, Germany between 2015 and 2020. As a part of standard clinical routine, we obtained various clinical parameters, describing the disease progression and its effects on motor, cognitive, and autonomic function. On average, patients stayed for about two weeks at our hospital, and many of them experienced fall events during that time. The aim of our data analysis was to identify predictors by modelling the fall rate at our hospital with regression analysis as a function of various demographic and clinical parameters. The fall rate observed at our hospital was thus used as an objective proxy measure for fall probability in general.

Material and methods

Participants

We retrospectively surveyed data of inpatients admitted to the Parkinson-Klinik Ortenau, Wolfach, Germany in 2015–2020. Inpatients were included in this study if they had been diagnosed with a) PSP, or b) MSA, or c) PD. PSP was diagnosed according to the criteria given in the National Institute for Neurological Disorders and Society for PSP [13] and the criteria devised by Höglinger et al. [14]. The diagnostic criteria for MSA were those of Gilman et al. [15]. The level of diagnostic certainty for PSP was "probable PSP" according to Höglinger et al. [14] and "probable MSA" following the guidelines described in Gilman et al. [15]. Diagnoses were supported by neuroimaging (magnetic-resonance imaging and positron-emission tomography), but neuropathological evidence was not available. Diagnosis of PD relied on the UK Brain Bank criteria [16] and the criteria published by Postuma et al. [17] and were sub-classified, with PSP being distinguished into PSP-Richardson's syndrome (PSP-RS), PSP with predominant parkinsonism (PSP-P), or others (see Höglinger et al. [14] for sub-type definitions).

MSA was sub-typed according to the guidelines described by Gilman et al. [15] into MSA with predominant cerebellar ataxia (MSA-C), or MSA with predominant Parkinson motor features (MSA-P).

PD patients were classified into tremor-dominant, akinetic-rigid, or mixed motor phenotypes (see [17]).

We identified 2,111 patients fulfilling the requirements (see Table 1 for patient characteristics). All patients received medication and various therapies (physical, speech, and occupational therapy; psychosocial counselling) according to best practice. Detailed information on prescribed medication was not collected for this study sample. See the supplementary material of Altmann et al. [19] for typical prescriptions of anti-Parkinson, anti-dementia, anti-psychotic, and anti-depressant drugs in a sample of PD patients at the same clinic. The procedures used in this study were in accordance with the ethical guidelines laid down in the Declaration of Helsinki 1964, and were approved by the local ethics committee of the State Medical Chamber of Baden-Württemberg, Germany (F-2021-151).

Assessment and procedure

Data on demographics was obtained from medical records. Disease severity was assessed with the Unified PD Rating Scale (UPDRS, [20]). As measures of motor function, we analysed part III of the UPDRS and the Berg Balance Scale (BBS, Berg et al., 1989 [21]; Scherfer et al. [22]). Global cognitive function was assessed with the Montreal Cognitive Assessment (MoCA, [23]), a diagnostic tool widely used in screening for cognitive impairment in PD [24]. Frontal lobe functions were tested with the Frontal Assessment Battery (FAB; Dubois et al., 2002 [25]).

To measure autonomic function, orthostatic hypotension (OH) was tested with the modified Schellong test [26]. The UPDRS was performed by neurologists, the BBS by physical therapists, the cognitive test by neuropsychologists, and the Schellong test by medical technical assistants. All examiners were experienced in applying the tests to patients with Parkinsonian syndromes. Fall events were recorded as part of clinical routine by any staff member who witnessed the event or its outcome, and were confirmed by a neurologist. Falls were defined as "an unexpected event in which the person comes to rest on the ground, floor or lower level" [27].

Statistical analysis

Fall frequency was computed by dividing the number of falls of a patient during his or her inpatient treatment by the number of days he or she was an inpatient. In the first analysis, the distribution of fall frequencies was calculated as a function of disease duration (in years). To assess correlations among clinical parameters, Pearson's correlation coefficients were computed and tested for significance computing a test statistic t and comparing to Student's t distribution (degrees of freedom: n-2). An $\alpha = 0.05$ was defined as a critical value for statistical significance.

An analysis of predictive factors was performed with multiple Poisson regression models, which are the canonical statistical model used for count data such as falls (see e.g. [12]). Calculation of these models was conducted in R (www.r-project.org, version 3.5.2) employing the glm function. For model selection, we followed a formal model-building procedure [28], as follows:

1. We started with a Poisson regression model to explain the number of falls during the inpatient residency as a function of various variables, including the demographic factors: age at first diagnosis and gender; disease duration and sub-type (sub-types being for PSP: PSP-RS, PSP-P, and PSP-others; for MSA: MSA-C and MSA-P; and for PD: akinetic-rigid, mixed, and tremor-dominant); motor parameters: UPDRS (part III), the BBS; cognitive parameters (MoCA and FAB scores); and autonomic dysfunction: OH.
2. We then tested the Poisson model for over-dispersion (i.e. for empirical variance not equal to the mean of the data) and the necessity for an additional parameter accounting for this. We tested for over-dispersion with a χ^2-test, with $\alpha = 0.05$ as the critical value. Over-dispersion was evident in all cases and therefore quasi-Poisson models were employed that entailed an additional coefficient by which the variance in the model is greater than the mean, as described in Ver Hoef and Boveng [29].
3. We then employed backward stepwise deletion and removed all predictors from the resulting model that did not reach significance in a t-test on the regression coefficients ($\alpha = 0.05$). Overall performance of the final models was evaluated with an Omnibus test and an R^2 value describing the explained variance [28].

Results

Data from 2,111 patients was analysed for this study. The patients' clinical characteristics are set out in Table 1. Frequencies of the different sub-types of Parkinsonian syndromes are shown in Supplementary Table 1. Figure 1 depicts the fall rate as a function of disease duration. Fall rates were highest early for PSP, increased with disease duration, and showed a slight decrease in advanced disease stages (4+ years). For MSA, fall rates were higher than for PD, and for both MSA and PD fall rates increased monotonically with disease duration for the disease stages observed in this study.

We obtained several clinical parameters as potential predictors for falls. Table 2 sets out correlations among these predictors. High correlations were observed between the two cognitive parameters, i.e. between the test scores of MoCA and FAB, and for the motor parameters, i.e. between the UPDRS (part III) and the BBS. To avoid collinearity in the regression model, only one of the cognitive parameters (the MoCA test score) was considered for further analysis. Results of the regression model including the FAB instead of the MoCA are set out separately in Supplementary Table 2. The strongest correlation with disease duration was observed for the UPDRS (part III)-score, in particular for MSA patients.

We analysed factors predicting fall rates separately for the different types of Parkinsonian syndrome (PSP, MSA, and PD). Statistically significant coefficients for the final multiple (quasi)-poisson regression models are set out in Table 3. Cognitive, motor, and autonomic factors were predictive for falls in PD, whereas for PSP, only the motor and autonomic factors predicted falls significantly. Sub-types of Parkinsonian syndromes were not significantly predictive for falls in this study. However, for PSP, the factor sub-type reached marginal significance ($p = 0.059$), with a tendency towards a higher fall rate in Richardson's Syndrome. The omnibus tests for the full models were significant for PSP and PD, but revealed only a marginally significant result for MSA, with disease duration as the only significant predictor for fall rate.

Our analysis was mainly focused on modelling fall frequency during the hospital stay as an inpatient. However, many previous studies have differentiated between frequent fallers and less frequent fallers [9, 11] or between fallers and non-fallers [12, 29] and have therefore represented falls as binary data. To allow for comparability with these previous reports, we show demographic and clinical parameters for fallers and non-fallers in Table 4.

Discussion

We analysed fall rates of patients with Parkinsonian syndromes based on objectively recorded fall events during hospitalisation as inpatients. While fall rates in PD were predicted by cognitive (MoCA), motor (UPDRS-III, BBS), and an autonomic parameter (OH), falls in PSP were significantly predicted by a motor (UPDRS-III) and an autonomic (OH)

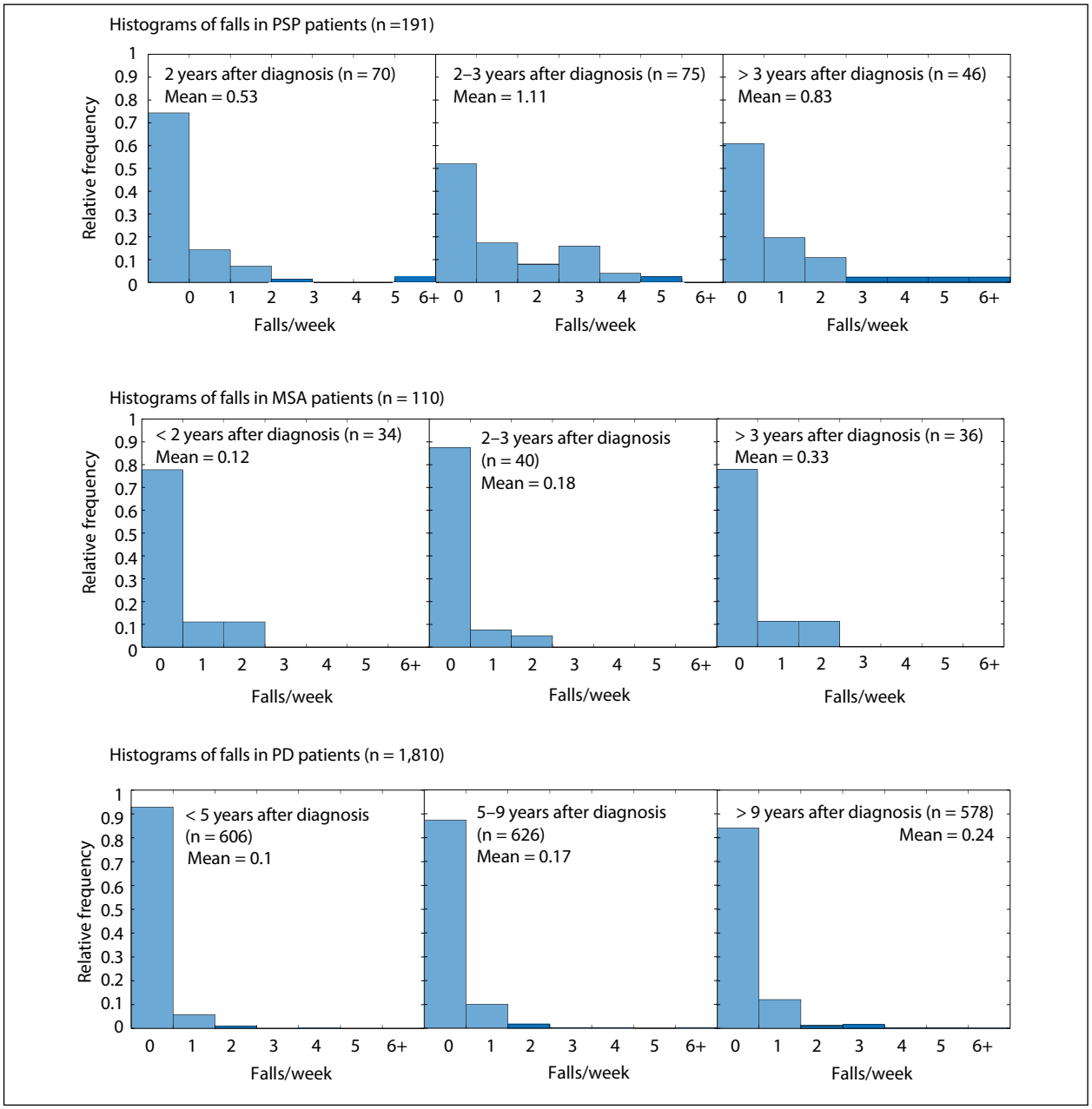

Figure 1. Histogram of falls during hospital stay as a function of disease duration for PSP, MSA, and PD patients, measured in years since diagnosis

Table 2. Pearson's correlation coefficients between parameters

Parameter pair	PSP	MSA	PD
MoCA ~ FAB	0.74***	0.79***	0.83***
UPDRS-III ~ BBS	–0.58***	–0.66***	–0.60***
MoCA ~ disease duration	–0.003	–0.08	–0.13***
FAB ~ disease duration	0.005	–0.16	–0.14***
UPDRS-III ~ disease duration	0.30***	0.39***	0.29***
BBS ~ disease duration	–0.23**	–0.24*	–0.22***
OH ~ disease duration	0.14	–0.02	0.13***

* — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$

Table 3. Multiple quasi-Poisson regression models

Parameter	PSP	MSA	PD
N	146	110	1540
MoCA	—	—	–0.059****
BBS	—	—	–0.028****
UPDRS-III	0.027***	—	0.012*
OH	0.018*	—	0.012***
Gender	—	—	—
Sub-type	—	—	—
Age at diagnosis	—	—	—
Disease duration	—	0.112*	—
Intercept	–4.328***	–3.828***	–2.81***
Dispersion parameter	3.17	2.26	2.10

* — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$. Omnibus test p-values and R^2: PSP $p < 0.0001$, $R^2 = 0.114$; MSA $p = 0.055$, $R^2 = 0.061$; PD $p < 0.0001$, $R^2 = 0.060$; dispersion parameters > 1 indicate overdispersion. Please note that sample sizes (N) can deviate from those in Table 1, because not all patients received all clinical tests (e.g. some patients had no MoCA or OH score)

Table 4. Comparison of demographic and clinical parameters between non-fallers (0 falls during hospital stay) and fallers (≥ 1 fall during hospital stay)

	PSP		MSA		PD	
	Falls = 0	Falls ≥ 1	Falls = 0	Falls ≥ 1	Falls = 0	Falls ≥ 1
N	99	92	84	26	1,529	281
Gender (f:m)	32:67	45:47	53:31	12:14	565:964	108:173
	32:68%	49:51%	63:37%	46:54%	37:63%	38:62%
Sub-type*	21:54:24	46:28:18	17:67	6:20	923:546:60	198:79:4
	21:55:24%	50:30:20%	20:80%	23:77%	60:36:4%	70:28:2%
Age at diagnosis [years]	69.3 ± 6.8	68.1 ± 7.2	63.1 ± 8.7	63.2 ± 11.6	63.6 ± 10.5	65.8 ± 9.9
Disease duration [years]	2.4 ± 2.2	2.8 ± 2.7	2.9 ± 2.5	4.0 ± 3.8	7.5 ± 5.7	9.6 ± 6.5
UPDRS-III	37.3 ± 14.7	42.2 ± 10.7	47.9 ± 14.6	46.8 ± 12	35.3 ± 12	42.4 ± 11.2
BBS	34.8 ± 16.4	28.3 ± 11.9	27.8 ± 17.2	22.9 ± 12.8	42.8 ± 13	31.8 ± 14.8
MoCA	20.9 ± 4.7	18.9 ± 5.9	24.2 ± 4.1	24.4 ± 5.5	22 ± 5.8	17.6 ± 6.5
FAB	12.1 ± 3.4	11.9 ± 3.5	15.2 ± 3	14.8 ± 3.6	14.3 ± 3.7	11.7 ± 4.2
OH [ΔmmHG]	10.5 ± 12.1	13.3 ± 15.1	31.9 ± 21.9	32.0 ± 21.2	17.8 ± 17	26.5 ± 21.8

*Sub-types for PSP: PSP-RS, PSP-P, and PSP-others; for MSA: MSA-C and MSA-P; for PD: akinetic-rigid, mixed, and tremor-dominant

parameter. Falls in MSA were significantly predicted by disease duration. Gender or age at diagnosis had no predictive value in any Parkinsonian syndrome.

The occurrence of falls and associated injuries follows different time-courses and is mediated by different risk factors, depending on the syndrome [3]. Our data showed that cognitive, motor, and autonomic factors predict fall rate in PD. This is in line with previous retrospective [3], but also prospective, studies [12]. The latter study has stressed the importance of tandem gait and global cognitive performance (mini-mental state examination) as predictors for short and long-term (6 months and 3.5 years, respectively) fall frequencies. Some studies have also proposed that gender (a higher risk for females) and age at disease onset (a higher risk for older age) contribute to fall frequency [3, 6], but this was not replicated in the current study.

The peak in fall frequency for intermediate disease durations in PSP, with fewer falls in later stages of the disease, is in line with descriptions of a single patient in Brown et al. [10] who suggested that advanced immobilisation and the use of a wheelchair in the later stages of the disease might lead to fewer falls. For PSP patients, falls in our study were predicted by motor and autonomic factors, but not by cognitive status. This finding is in line with previous studies reporting motor factors such as oculomotor parameters, modified turning, bradykinesia, axial rigidity, neck dystonia, and postural stability as being predictive of fall risk [9].

Interestingly, our analysis revealed an association between orthostatic hypotension (OH) and fall risk in PSP patients. However, OH values were lowest for the PSP group (only 40/191, i.e. 20.9% of PSP patients had OH ≥ 20). A recent study has even suggested that there is no association between neurogenic OH and PSP based on data from post mortem-confirmed cases [31]. Thus, even though clinically relevant OH is rare in PSP, it might still contribute to falls as a risk factor, possibly

due to mechanisms similar to those in the elderly in general [32]. The role of cognitive status as a risk factor in PSP is under debate. While some studies indicate a role of cognition in falls [3, 11], others point toward deficits of dual-tasking as a risk factor for falls [33]. A recent study with 339 patients did not find a significant association between cognitive parameters and fall risk in PSP [9].

As for MSA, only disease duration proved to be a predictor for falls in this study. While autonomic dysfunction was more severe in MSA than for PD and PSP, the OH was similar for fallers and non-fallers. This is in line with findings reported in a recent review [34] suggesting that dysautonomia does not predict falls, while motor parameters, in particular axial symptoms and early pyramidal tract signs, are associated with falls [3].

However, due to low sample sizes for MSA and PSP, we cannot rule out that in these cases statistical power was insufficient to detect subtle potential effects of cognitive or motor/autonomic parameters on fall rate. In contrast, since PD is comparatively more prevalent in the population, the sample size for PD was also larger in our study, resulting in better statistical power. Thus, for direct comparisons between the Parkinsonian syndromes, sample sizes of the atypical syndromes were possibly insufficient.

Other than that, four further factors might limit the generalisability of this study's results:

1. In this study, fall events were only counted when they occurred during an inpatient stay (of c.14 days). That means that patients with fall rates of less than one fall per two-week period were unlikely to fall during their inpatient stay, and were thus recorded as non-fallers. Therefore, a fall rate of once per six months [12] or two falls per 12 months [11] was likely not to be covered in our study. Thus, the fall rates covered in our study were in the 'very frequent' range.
2. Recording fall events in a hospital setting has the advantage of the presence of an objective witness, very often a trained member of nursing staff, and is thus not subject to bias due to delayed recall. Nevertheless, the possibility of under-reporting still exists. In particular, patients with high fall rates might not report some actual fall events, because they perceived them to be 'near-falls', e.g. when no injury occurred. Moreover, PSP patients very often lack insight into their postural disorder due to cognitive impairment [35] and may therefore also underreport fall events in the absence of witnesses.
3. Another factor that might distort fall rate estimates is that during a patient's stay in a hospital, the environment is very different from that at home and might therefore lack ecological validity (e.g. see Fasano et al. [36]). Specifically, patients might experience more mobilisation and increased activity in the less familiar hospital environment, resulting in an increase of fall frequency. Then again, the hospital might be a more controlled environment with aids such as handrails and wheeled walker, possibly resulting in a lower fall frequency. Furthermore, the presence of professional staff might result in avoiding many near falls from becoming actual fall events.
4. Another possible limitation of this study was the reduced variance in disease severity: patients seeking medical help as inpatients are commonly those who are already advanced enough in their disease to suffer significantly, so only a few PD patients in Hoehn & Yahr stages I–II are expected to be treated as inpatients. On the other hand, patients with a severely advanced Parkinsonian syndrome are also rarely present at a specialised Parkinson clinic, where most of the patients are in Hoehn & Yahr stages III–IV.

Interventions to prevent falls in PD have mainly focused on exercise and medication [36]. The targets for exercise-based interventions are mainly poor balance and decreased mobility as risk factors for falls. Interestingly, combining exercise targeted at both physical and cognitive factors using a virtual reality setting has been shown to positively affect the long-term (6-month follow-up) risk of falls [37]. Pharmacological interventions with an effect of reducing fall rates (besides anti-parkinsonian medication) include acetylcholinesterase inhibitors (rivastigmine), but also drugs (droxidopa) ameliorating neurogenic orthostatic hypotension [36].

Due to the retrospective nature of our study, we have not investigated the effect of prescribed medication as a risk factor for falls. However, polypharmacy, sedative, anticholinergic, and other drugs are known to affect the risk of falling for PD patients, and the elderly in general [36, 38]. Other potentially important variables, such as eye disease, sarcopenia or BMI were not investigated either, limiting the scope of the study, considering the effect of obesity on fall frequency demonstrated in previous studies on healthy elderly people [39].

Overall, the described targets to reduce falls in PD are in line with the risk factors predicting fall rate in PD in the current study. Compared to PD, interventions to reduce falls are much less established in PSP, owing to a scarcity of data [10]. Promising approaches have aimed at preventing falls with physical therapy employing treadmill or robot-assisted training [40], or reducing risk by targeting cognition and the impulsiveness typical of PSP [41]. However, the existing data is insufficient to draw valid conclusions as to the efficacy of these approaches. Similarly, therapeutic interventions specifically targeting fall risk reduction in MSA are rare; possibly, some of the strategies developed for PD may prove applicable for MSA as well [34]. Retrospective epidemiological studies can provide rough indications towards plausible targets for interventions.

Nevertheless, to develop effective and individualised therapies for Parkinsonian syndromes, detailed analysis of falls, their mechanisms and possible triggers is necessary. For instance, dual tasking during walking has been suggested as resulting in increased fall probability in PD due to cognitive-motor interaction [42]. Understanding the mechanisms of falling therefore allows for the development of targeted

therapies taking into account cognitive, motor, and autonomic factors.

Conclusion

Our study evaluated the rate of falling in a sample of patients with Parkinsonian syndromes. Rather than relying on self-report, we counted falls during a two-week stay as inpatients. We identified different predictors for falls depending on the particular type of syndrome. While for PD, cognitive, motor, and autonomic factors best predicted falls, for MSA the main variable predicting falls was the duration of the disease. For PSP, both motor and autonomic dysfunction predicted falls. Thus, optimal management and prevention of falls should consider these predictors in the different types of Parkinsonian syndrome.

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Endovascular embolisation as minimally-invasive treatment for spinal dural arteriovenous fistulas — evaluation of long-term results

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ABSTRACT

Aim of study. Spinal dural arteriovenous fistulas (sDAVF) are rare spinal cord lesions formed between a radicular artery and medullary vein leading to venous hypertension resulting in neurological impairment. Endovascular embolisation is a minimally-invasive method aiming to interrupt the shunt between the artery and vein. We report our experience with sDAVF treated endovascularly.

Material and methods. Clinical and procedural data of 16 consecutive patients diagnosed with sDAVF was reviewed. Pre- and post-operative neurological condition was evaluated using both the Aminoff and Logue disability scale and the VAS scale. Rates of complete occlusions, technical difficulties, and procedural complications were noted.

Results. Four of the patients were female and 12 were male; mean age was 62.4 years. Mean interval between symptom onset and treatment was 13.3 months. Complete occlusion was achieved in 88% (14/16 patients). Significant or moderate clinical improvement in long-term follow-up was observed in eight patients (50%). Recurrence was observed in two cases (13%).

Conclusions and clinical implications. While endovascular methods are being refined and thus achieving an increasing percentage of successful occlusions, patients should be closely monitored since this condition is recurrent and the clinical consequences of myelopathy can persist despite complete occlusion of the shunt.

Key words: spinal dural arteriovenous fistulas, endovascular, embolisation, outcome

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Introduction

Spinal dural arteriovenous fistulas (sDAVF) are rare spinal cord lesions formed between a radicular artery and medullary vein leading to venous hypertension with subsequent radicular pain and extremity weakness (paresis), as well as loss of bowel and bladder function [1]. They are also the most common vascular malformations found within the spinal canal [2]. Because of the manifold clinical presentations, which resemble much more common diseases such as degenerative disc disease or polyneuropathies, the diagnosis is often delayed [3].

However, due to the fact that sDAVF can result in permanent spinal cord injury if left untreated, prompt and accurate diagnosis is crucial. Initial diagnosis is based on magnetic resonance (MR) findings, with special attention to MR angiography (MRA), but digital subtraction angiography (DSA) is necessary for a thorough understanding of the anatomical condition and planning of the therapeutic strategy [4, 5]. Current medical treatment includes both microsurgical and endovascular methods [6–8]. A recent multicentre study aimed at comparing these two techniques did not find significant differences in overall clinical outcomes, but concluded that patients undergoing embolisation have a higher risk of late

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Table 1. Aminoff and Logue scale of disability

Grade	Characteristics
Gait disturbance	
1	Leg weakness or abnormal gait, no restricted activity
2	Grade 1 with restricted activity
3	Requiring one stick/crutch for walking
4	Requiring two sticks/crutches/walker for walking
5	Unable to stand, confined to bed/wheelchair
Micturition	
1	Hesitancy, frequency, urgency
2	Occasional urinary incontinence or retention
3	Total urinary incontinence or retention

recurrence [9]. However, with constant technological improvements the rate of successful embolisation has been rising and due to the additional advantages of minimally-invasive embolisation (i.e. shorter hospitalisation and a less painful postoperative course), some centres now consider this as the treatment of choice in selected patients [10].

The aim of this study was to report the clinical outcomes, as well as the failure and recurrence rates, of 16 patients with sDAVF treated with endovascular means.

Material and methods

In this single-centre retrospective study, we evaluated the clinical and procedural data of 16 consecutive patients diagnosed with sDAVF and treated with endovascular embolisation between January 2014 and December 2020. All sDAVF were initially diagnosed with MR and MRA and subsequently confirmed with DSA examination. All cases were then reviewed by a multidisciplinary board which consisted of a neurosurgeon and a neuroradiologist. All cases amenable to endovascular treatment were referred for embolisation. Baseline clinical condition was evaluated using both the Aminoff and Logue disability scale and the VAS scale [11]. All patients gave informed consent prior to the procedure (Tab. 1).

All endovascular interventions were performed under biplane angiography unit with 3D rotational angiography and with patients under general anaesthesia. After selective catheterisation of the feeding artery with a microcatheter, definitive embolisation was attempted with N-butyl cyanoacrylate (NBCA; Cordis Microvascular Inc.) or ethylene vinyl alcohol (Onyx, Covidien) depending on the vascular condition of the fistula. Control angiography was performed afterwards.

All patients underwent at least one control DSA and/ /or MR examination as well as a neurological examination 3–6 months after the procedure. In cases of recanalisation/ /incomplete occlusion and no clinical improvement, the possibility of secondary embolisation or surgical intervention was discussed with the patient.

Results

In total, 16 patients met the inclusion criteria. The majority of patients were male (12, 75%) and the mean age on admission was 62.4 years (range 28 to 70). Average time from symptoms onset to endovascular procedure was 13.3 months. In terms of fistulas localisation, the most common on spinal angiography was at the level of T7 (four cases), with 13 fistulas located at the thoracic level and three at the lumbar level. All the malformations were dural spinal arteriovenous fistulas (pathological arteriovenous shunting between the leaflets of the dura), with draining vein on the dorsal surface of the spinal cord, and were classified as type 1 according to the Spetlzer et al. classification [12]. Complete and super-selective occlusion was achieved in 10 patients (63%). Five patients required secondary intervention due to late recurrence (four cases) or the presence of multiple feeders (one case). As far as post-procedural complications were concerned, in one case a transient paralysis of the lower extremities was noted, which resolved within three months of the procedure.

Imaging examination performed at the long-term follow-up (mean duration = 28 months, range 7 to 58) disclosed that complete occlusion of the fistula was achieved in 14 patients (88%). In the two cases in which complete occlusion could not be obtained, one patient was referred for further microsurgical operation and one is being followed-up with incomplete occlusion of the fistula.

In the long term, clinical improvement was observed in eight patients (50%) and stable clinical condition in a further five patients (31%). Deterioration of the patient despite treatment was observed in three cases (19%). Among the patients with clinical improvement or stable neurological condition, average improvement was 1.25 points in the Aminoff and Logue disability scale and 2.1 points in the VAS scale (Fig. 1, Tab. 2).

Discussion

Due to variable clinical presentations, spinal dural arteriovenous fistulas (sDAVF) remain a diagnostic challenge. They are usually diagnosed in middle-aged male patients in the thoracic and lumbar spine, and this was reflected in the findings of our study. Although they might present with a variety of symptoms ranging from mild to severe neurological impairment, accurate diagnosis and effective treatment is crucial as the disease is progressive and leads to disability [13]. Fortunately, recent advances in diagnostic imaging modalities and endovascular treatment techniques have greatly increased the options regarding these lesions.

Magnetic resonance imaging is currently the best tool in the diagnosis of sDAVF. The diagnosis is confirmed by a triad of findings on routine MRI that is present in > 95% of cases: 1) spinal cord oedema (hyperintense signal on T2-weighted images); 2) enlarged veins around the spinal cord (flow voids on T2-weighted images); and 3) disruption of the blood-brain

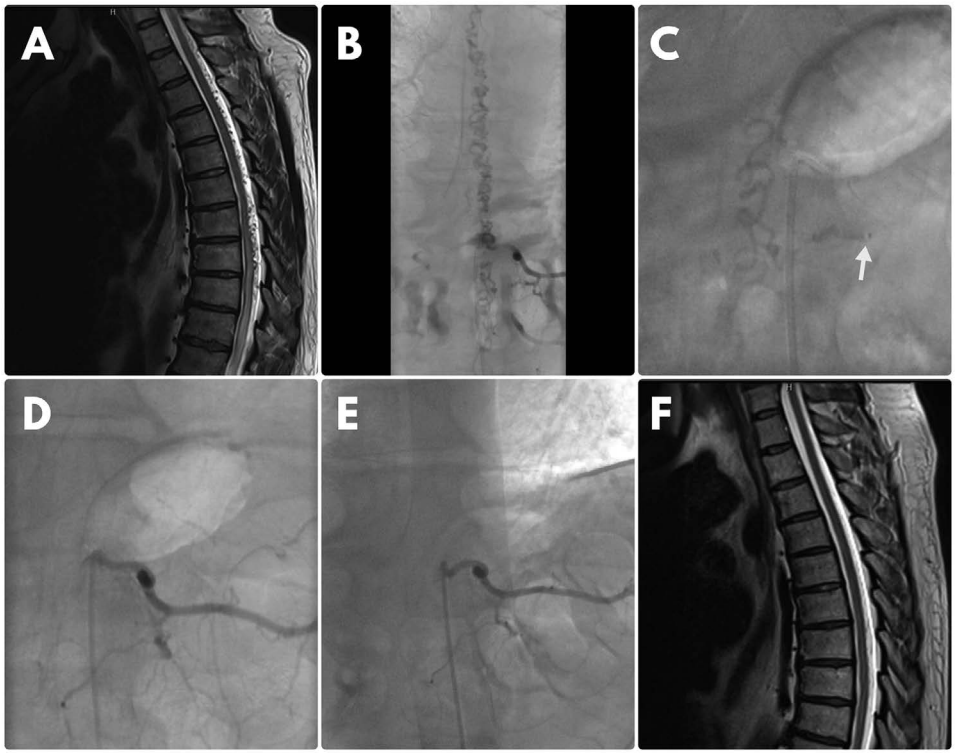

Figure 1. Successful embolisation of a thoracic sDAVF in a 53-year-old male patient who presented with increasing weakness in lower extremities. Initial diagnosis of sDAVF was made after MR examination (**A**) and confirmed in DSA afterwards (**B**). Super-selective catheterisation of feeding artery was performed (**C**), tip of a micro-catheter is pointed with white arrow. Embolisation of fistula was performed with N-butyl cyanoacrylate. Control angiography confirmed successful occlusion (**D**). Control imaging examinations performed six months after procedure (DSA — **E**) and two years after procedure (MR — **F**) showed no signs of recurrence

Table 2. Clinical data of patients and procedural outcomes

Clinical data	
Patients (n)	16
Male/female (n, %)	12 (75%), 4 (25%)
Mean age (years, range)	62.4 (28–70)
Mean time from onset to procedure (months, range)	13.3 (1–39)
Localisation of sDAVF (n, %)	
Thoracic	13 (81%)
Lumbar	3 (19%)
Procedural details	
Occlusion of fistula (n, %)	
Complete	10 (63%)
Incomplete	6 (37%)
Secondary treatment (n, %)	
Endovascular	4 (25%)
Microsurgical	1 (6%)
Complications (n, %)	
Transient paralysis	1 (6%)
Long-term outcome	
Duration of follow-up (months, range)	28 (7–58)
Occlusion of sDAVF (n, %)	
Complete	14 (88%)
Incomplete	2 (12%)
Clinical outcome (n, %)	
Improvement	8 (50%)
Stable condition	5 (31%)
Deterioration	3 (19%)

barrier (cord enhancement on T1-weighted images after contrast injection) [14]. The location of the sDAVF is determined by magnetic resonance angiography (MRA) and/or digital subtraction angiography [5].

The traditional treatment of sDAVF consisted of microsurgical occlusion of the fistulous connection. This involves a hemilaminectomy, opening the dura and coagulation or clipping of the vein [15]. A recent review of the literature published by Maimon et al. [14] described a reported success rate of this surgery ranging from 85–100%. However, being an open surgery, it is associated with several procedural complications including epidural haematoma, CSF leak, wound infection etc. [6, 16].

For this reason, some centres are implementing novel technologies (e.g. microscope-assisted endoscopic techniques in order to reduce the risk of complications) [17].

Minimally invasive endovascular embolisation is an alternative therapeutic approach for patients presenting with sDAVF. During this procedure, liquid embolic material is injected from a microcatheter placed in the proximity of the shunt aiming to permanently occlude the venous side of the fistula [14].

Although the initial experience was less satisfactory compared to the surgery, today with the introduction of modern microcatheters and liquid embolic materials, especially Onyx, the role of minimally invasive endovascular embolisation in

Table 3. Overview of literature on treatment and outcomes of patients with sDAVF

Study	Patients (n)	Treatment	Initial technical success (%)	Complications rate (%)	Overall clinical success (%)
Qi et al. [8]	52	Surgery — 40 Embolisation —12	Surgery — 100% Embolisation — 60%	4%	Improvement to some degree — 100%
Bretonnier et al. [9]	63	Surgery — 23 Embolisation — 40	Surgery — 91% Embolisation — 70%	Surgery — 9% Embolisation — 2%	N/i
Park et al. [10]	18	Embolisation	82%	6%	83%
Saladino et al. [16]	154	Surgery	95%	9%	Improvement — 82% Stability — 14%
Kirsch et al. [18]	78	Surgery — 17 Embolisation — 61	Surgery — 100% Embolisation — 77%	Surgery — 0% Embolisation — 5%	> 75%
Gemmete et al. [19]	33	Surgery — 4 Embolisation — 29	Surgery — 100% Embolisation — 76%	Surgery — 0% Embolisation — 3%	Improvement — 45% Stability — 55%
Sasamori et al. [20]	50	Surgery — 19 Embolisation — 31	Surgery — 95% Embolisation — 71%	Surgery — 11% Embolisation — 13%	Improvement — 66%
Present study	16	Embolisation	63%	6%	Improvement — 50% Stability — 31%

the management of spinal vascular malformations has expanded [8, 10, 14, 19]. In our series, compete occlusion of the fistula in long-term follow-up was achieved in 88% of patients, comparable to the outcomes reported by other authors [19, 20]. Similarly, the rate of complications remains within the range of reported procedural complications described in the above-mentioned articles.

As far as the clinical outcome is concerned, the observed clinical improvement rate was 50%. Similar results have been described in surgical studies [16, 21]. In addition to this, clinical stable condition was achieved in further 31% of monitored patients.

An overview of presented literature on treatment and outcomes of patients with sDAVF is set out in Table 3.

Considering the minimally-invasive nature of endovascular embolisation, and its high success rate combined with low rate of procedural complications, is seems reasonable to refer all sDAVF patients for multidisciplinary board evaluation consisting of a neurosurgeon and a neuroradiologist and to consider embolisation in all amenable patients.

We are aware that our study has some limitations. First and foremost, our small sample size of unrandomised patients limits the validity of the data. Secondly, the absence of a control group treated with surgical methods might be perceived as a potential drawback. Perhaps patients more suitable for microsurgical treatment were referred to other neurosurgical centres, and this preselection bias may have impacted upon the final outcome of our study. Finally, the heterogeneity of the location and morphology of the fistulas might have affected the results. Nonetheless, these drawbacks might be attributed to the rarity of the entity.

In conclusion, the results of this preliminary study suggest that long-term clinical outcomes in patients with sDAVF treated with endovascular embolisation are comparable to those reported in surgical studies, even if the initial success rate is significantly lower compared to microsurgical intervention. Similarly, the rate of procedural complication is comparable with microsurgery.

Clinical implications

Even if microsurgery remains the primary treatment modality for patients with spinal dural arteriovenous fistulas, modern endovascular methods offer a safe and reliable alternative, and should therefore be considered during multidisciplinary evaluation of these patients.

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First families with spinocerebellar ataxia type 7 in Poland

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ABSTRACT

Introduction. We present the first two Polish families diagnosed with spinocerebellar ataxia type 7 (SCA7) and draw attention to cardiac involvement as a new potential manifestation of this disease.

Material and methods. Two well-documented kindreds are presented.

Results. The proband from Family 1 presented aged 54 years with vision worsening followed by progressive imbalance. Brain MRI demonstrated cerebellar atrophy. Genetic testing confirmed CAG repeat expansion (42/10) in *ATXN7* gene. The proband from Family 2 developed imbalance at age 20, followed by progressive deterioration of vision. Brain MRI revealed cerebellar atrophy. Additionally, she developed chronic congestive heart failure and, at age 38, had cardiomyopathy with an ejection fraction of 20% and significant mitral and tricuspid regurgitation. Genetic analysis found abnormal CAG expansion in the *ATXN7* (46/10).

Conclusions and clinical implications. Vision loss due to pigmentary retinal degeneration is the distinguishing feature of SCA7 and often the initial manifestation. Although SCA7 is one of the most common SCAs in Sweden, it has never been reported in neighbouring Poland. Until now, cardiac abnormalities have only been described in infantile-onset SCA7 with large CAG repeats. The observed cardiac involvement in Family 2 may be coincidental, albeit a new possible manifestation of SCA7 cannot be excluded.

Key words: SCA7, hereditary, retinal degeneration, neurodegenerative

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Introduction

Spinocerebellar ataxia type 7 (SCA7) is a rare autosomal-dominant neurodegenerative disorder caused by abnormal CAG expansion (typically above 36 repeats) in the *ATXN7* gene encoding Ataxin-7 protein [1, 2]. SCA7 is very rare, with an estimated prevalence of less than 1:100,000 and accounting for 2% of all SCA cases worldwide [1, 2]. However, its prevalence is higher in Scandinavians, indigenous South Africans, and Mexicans, constituting approximately 50%, 22%, and 7% of all SCAs in those countries and regions, respectively [2]. Interestingly, until now, only one isolated case from Eastern Europe (Czechia) has ever been reported [3].

In this work, we present the first two Polish families diagnosed with SCA7 and draw attention to cardiac involvement as a new potential manifestation of the disease.

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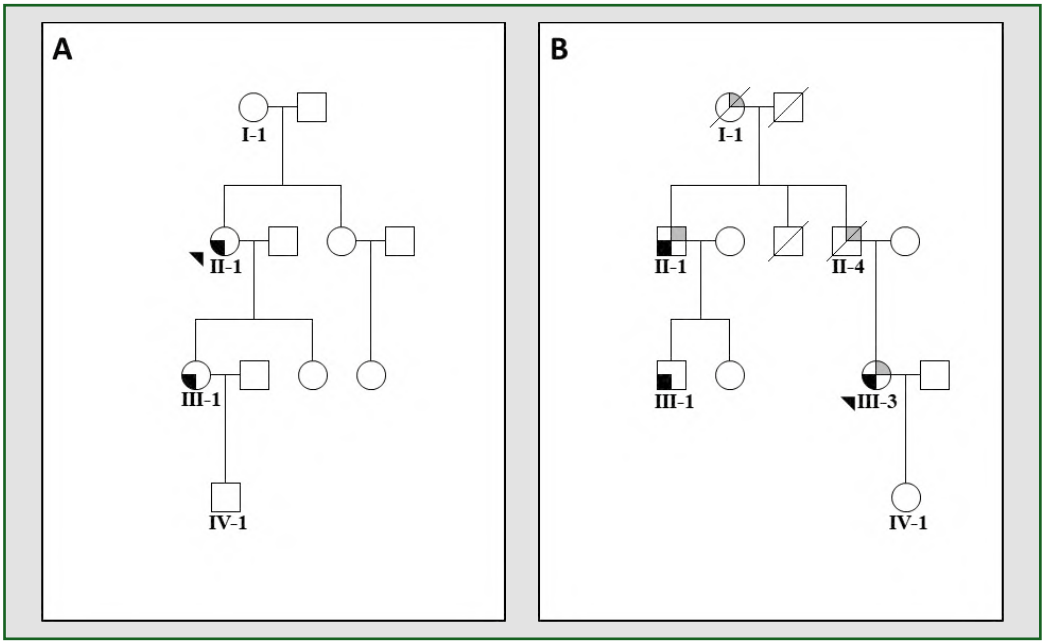

Figure 1. Pedigrees of Family 1 (**A**) and Family 2 (**B**). For family pedigrees, standard pedigree symbols are used: arrowhead indicates proband; circle indicates female; square indicates male; slash through symbol indicates diseased individual; left lower quadrant black symbol indicates affected individual with ataxia; right upper quadrant grey symbol indicates affected individual with cardiac disease

Material and methods

Family 1 (Fig. 1A)

A 54-year-old female (II-1) noticed a blurring of vision, and optical coherence tomography revealed degeneration of the optic nerve. Brain magnetic resonance imaging (MRI) demonstrated cerebellar atrophy. Subsequently, her vision deteriorated, and she developed imbalance. Neurological examination at age 57 showed dysarthria, vision loss, four-limb ataxia, and wide-based gait. Genetic testing confirmed CAG repeat expansion (42/10) in *ATXN7*. Her symptoms slowly worsened over time. During a follow-up evaluation at age 67, she had dysarthria, severe vision deficiency, impaired vertical gaze, four-limb ataxia, increased muscle tension of the mixed rigid-spastic type, brisk tendon reflexes, bilateral ankle clonus, and Babinski sign on the left side. She could stand only with intermittent support and walk with the strong support of an accompanying person. Her follow-up brain MRI showed progression of the cerebellar atrophy.

Her daughter (III-1) presented aged 32 with slurring of speech and difficulties with word retrieval. She was diagnosed with oligoastrocytoma WHO grade III in the left temporal lobe and underwent surgical excision, chemo- and radiotherapy. Despite recovering from the brain tumour, she experienced worsening of speech and imbalance. Genetic testing found abnormal CAG repeat expansion in *ATXN7* (43/10). On neurological examination aged 43, she had dysarthria, horizontal nystagmus during lateral gaze, four-limb ataxia, spasticity, exaggerated tendon reflexes, and Babinski sign on the left side. She could walk unsupported but occasionally staggered, was unable to walk in tandem, and had reduced right arm swing.

A second daughter, a 41-year-old (III-2), is asymptomatic, with genetic testing revealing abnormal CAG repeat expansion in *ATXN7* (42/10). The family history for similar symptoms in other family members was negative. Based on the genealogical information going three generations back, the family originated from the Greater Poland region.

Family 2 (Fig. 1B)

A 20-year-old female (III-3) developed imbalance and gait difficulty, followed by progressive vision loss. On neurological examination aged 28, she had dysarthria, vision deficiency, impaired vertical and horizontal gaze, spasticity in the lower limbs, exaggerated tendon reflexes, and four-limb ataxia. She needed an accompanying person or a walker to ambulate. Brain MRI revealed cerebellar atrophy. Genetic analysis found abnormal CAG expansion in the *ATXN7* (46/10). In subsequent years, her symptoms progressed, and she developed chronic congestive heart failure and was diagnosed with cardiomyopathy. Transthoracic echocardiography at 38 showed global hypokinesia with an ejection fraction of 20% and significant mitral and tricuspid regurgitation. Neurological examination at 39 revealed severe dysarthria, ophthalmoplegia with complete vision loss, four-limb ataxia, spasticity in the lower limbs, and bilateral Babinski sign. She could only walk a short distance with a walker or the strong assistance of an accompanying person. She depended on a caregiver for all her daily activities, and remained recumbent for most of the day.

The family history was positive for similar symptoms. Her father (II-4) did not suffer from a visual deficiency or gait difficulty, but developed cardiomyopathy at 50 and died suddenly while asleep at 60. However, the patient's uncle (II-1) noticed imbalance and gait difficulty at 54, and slowly progressed over the years. He also suffered from a cardiac disorder (atrial fibrillation). His son (III-1) presented gait and balance problems at 40. They both had genetic testing, which confirmed abnormal repeat expansion in the *ATXN7*. Of note, the proband's paternal grandmother (I-1) died suddenly at 57, of suspected cardiac arrest. The paternal side of the proband's family descended from central Poland, which they had inhabited for at least three generations.

Discussion

Normal *ATXN7* encodes a protein involved in the regulation of transcription and stabilisation of microtubules; however, the mutation results in an aberrant polyglutamine protein with a propensity to accumulate in the cerebellum, spinal cord, brainstem, and retina [1, 2]. Therefore, the disease usually manifests with progressive cerebellar ataxia, dysarthria, oculomotor disturbances, motor neuron symptoms, and vision deficiency due to pigmentary retinal degeneration [1, 2]. The latter feature distinguishes SCA7 from other hereditary ataxias and often is the first manifestation.

SCA7 has been reported in North and South America, Africa, Asia, Oceania, Europe, and the Caribbean [1, 2, 4]. It is one of the most common SCAs in Sweden, but interestingly, it has never been reported in neighbouring Poland [4, 5]. Although the two countries are separated by the Baltic Sea, they have a rich history of bilateral relations and migration in both directions. Previous studies on haplotyping suggested a common founder in a few populations with SCA7, including the Swedish one [4]. On the other hand, many cases, including the one from Czechia, were sporadic [3]. This may be due to the high intergenerational instability of CAG repeat length in the *ATXN7* gene, which may increase from low to pathogenic range even over one generation [6]. In particular, paternal transmission poses a risk of expanding CAG repeat length [3]. As the age of onset and severity of the phenotype is inversely proportional to the extent of CAG expansion, the next generation can present decades earlier [3]. In everyday clinical settings, most cases of ataxia are due to causes other than genetic ones [7, 8]; however, as many of the reported SCA7 cases were isolated, the disease should be included in the differential diagnosis of sporadic ataxia.

Interestingly, cardiac involvement has only been reported in infantile-onset SCA7 [9, 10]. It has been postulated that large (above 180 CAG repeats) *ATXN7* expansions may damage cardiac tissue and lead to congestive heart failure [9, 10]. In light of this, the relatively small size of the CAG expansion may suggest another aetiology of heart failure, including a genetic one, which cannot be precluded based on the available data regarding Family 2. However, the number of reported SCA7s is limited, and new data on its and other SCAs' possible symptomatology, including urinary dysfunction, is emerging [11]. Therefore cardiac involvement as a new manifestation of adult-onset SCA7 cannot be excluded.

At present, there is no approved specific therapy for SCA7, and the management remains symptomatic and supportive [2]. Physiotherapy has been shown to improve motor coordination and mobility in patients with other types of SCA, and these effects persisted beyond one year of follow-up [2, 12]. Although there is no consensus as to the optimal regimen of physiotherapy, its beneficial effects were shown by many previous studies with variable protocols used [2, 13–16]. Therefore, we suggest tailoring the form and intensity of physiotherapy to the needs of the individual patient. Occupational and speech therapy should also be considered [1, 2]. Diplopia may be alleviated with prism correction. Patients with spasticity may benefit from botulinum toxin injections [17–19]. Neuropathic pain and paresthesia may be mitigated with pregabalin and gabapentin; however, caution should be used as these medications can aggravate dizziness and imbalance. Therefore, acupuncture may also be considered in patients' neuropathic symptoms [2]. Neuropsychiatric symptoms (depression, behavioural abnormalities) should be managed in the first place with selective serotonin reuptake inhibitors [2].

Clinical implications/future directions

In this short communication, we present the first two Polish families with SCA7 and highlight the need to include this disease in the differential diagnosis. We draw attention to cardiac abnormalities in SCA7, which may be other possible disease manifestations. Further research is needed to investigate the genotype-phenotype correlations in SCA7 and to better our understanding of the disease's pathomechanism.

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Ethical approval: *All aspects of the research were approved by the Institutional Review Boards of Mayo Clinic and the Medical University of Gdansk. Written informed consent was collected from all patients.*

Availability of data and materials: *Additional data that supports the findings of this study is available from the corresponding author, ZKW, upon reasonable request.*

Conflict of interest: *None.*

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Giant cranial plasmacytoma: case report and discussion of a potential relationship with sex hormones

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Key words: multiple myeloma, cranial plasmacytoma, frontal bone, head bump, surgery, skull involvement, scalp swelling

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To the Editors

Cranial solitary plasmacytoma is a very rare clinical manifestation of multiple myeloma (MM) [1–3]. Moreover, cranial plasmacytomas presenting as visibly prominent swellings on the head are extremely rare, and their management poses a challenge for neurosurgeons. It remains unclear which patients are most likely to develop this type of large, solitary, protruding cranial plasmacytoma. Age and gender are the two main non-modifiable factors in an individual's risk of being diagnosed with cancer. [4] Various biological and behavioural factors have been proposed to explain how age and gender significantly modulate the incidence of cancer at the population level. Exploring common features of such cranial plasmacytomas may shed light on their pathophysiology.

A 90-year-old female patient was admitted to our hospital complaining of a soft, painless, rapidly swelling mass that had developed within a month on the left frontal region of her scalp. The skin overlying the lesion was hyperaemic because of enlarged vessels. The patient did not have any complaints about the bump, such as a headache, other than its cosmetic appearance, and no neurological deficit was detected during the examination. Her medical history revealed that not only had she been diagnosed with MM eight years before (which was treated with chemotherapy), but also that she had been diagnosed with basal cell carcinoma in the sacral region four years before presenting on this occasion. The patient was in remission, but had disrupted her treatment for the preceding two years because of the COVID-19 pandemic. The patient's blood and urine analyses were consistent with the diagnosis of MM, including increased monoclonal immunoglobulins, anaemia, and hypercalcaemia.

Cranial magnetic resonance imaging revealed a giant left frontal extra-axial lesion adjacent to the superior sagittal sinus (Fig. 1a). The lesion had compressed the cerebral tissues, causing a left ventricular collapse and subfalcine herniation. The lesion was isointense and showed homogeneous contrast enhancement on the T1-weighted sequences. Dural boundaries were indistinguishable. Magnetic resonance angiography showed that the mass was being fed from the distal branches of the external carotid artery (Fig. 1b). It was observed that the tumour had destroyed both the inner and outer tables of the skull in an area approximately 3 cm in diameter.

The patient was operated on with a bifrontal incision under general anaesthesia (Fig. 1c). There was a cleavage line between the skin and the tumour. The galea was taut but intact. Although the tumour was vascular in nature, no excessive bleeding was observed. The tumour had completely eroded the

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calvarial bone in a small area. The parts of the tumour extending outward from the bone surface were completely removed up to the bone surface. The grey-brown and slightly hard intracranial component of the tumour was also completely resected using a cleavage line plane between the tumour and the brain (Fig. 1d). The dura was closed using a galeal graft. In this elderly patient, cranioplasty was not performed, not only because of the small calvarial defect, but also to shorten the operation time and prevent the risk of infection. The patient woke from anaesthesia with a Glasgow Coma Scale (GCS) score of 15 without any problems and was extubated in the operating room. She was then taken as routine to the intensive care unit and transferred to a ward bed a day later. Diffuse plasma cell infiltration was observed histologically; the results were positive for kappa light chain and negative for lambda light chain (Fig. 1e). Plasma cells, which were kappa monoclonal, displayed strong and diffuse expressions of CD138, CD38 and CD56.

The patient did well postoperatively. She was transferred to the haematology ward on the seventh postoperative day, and after three weeks of chemotherapy, she was discharged. A postoperative MRI scan showed total removal of the tumour (Fig. 1f). Four months later, the patient developed sudden mild hemiparesis due to a cerebrovascular ischaemic event, but recovered after treatment.

In this article, we present a case of solitary cranial plasmacytoma presenting as a giant swelling on the head of a 90-year-old female patient with a history of sacral basal cell carcinoma and an eight-year history of MM in remission. Although MM is more common in men, cranial plasmacytomas tend to be more common in women. Similarly, basal cell carcinomas are more common in women under the age of 40 than in men [4]. To the best of our knowledge, the potential relationship between sex hormones and cranial plasmacytomas has not been explicitly researched.

Osteoclasts are important cells involved in the bone lysis of MM. Osteoclast formation during bone remodelling is affected by a protein from the tumour necrosis factor family called the receptor activator of nuclear factor-κB ligand (RANKL) [5]. RANKL increases osteoclast activation, which results in augmented bone resorption, leading to the release of IGF1 and TGF-β. This process then leads to immune suppression and the further proliferation of MM cells. An increase in serous RANKL has been found to increase the risk of sex hormone-induced breast cancer associated with a familial BRCA1 mutation. Females with BRCA1 mutations have an increased risk of developing breast and ovarian cancers. Although no laboratory examination for either RANKL or BRCA1 mutations could be performed on our patient, increased RANKL activation and/or a BRCA1 mutation may underlie the effects of aggressive bone lysis in females with giant, rapidly growing, bone-destroying plasmacytomas. With the excessive shift of the osteoclastic-osteoblastic balance in favour of osteoclastic activity, rapid destruction of the bone and rapid growth of the

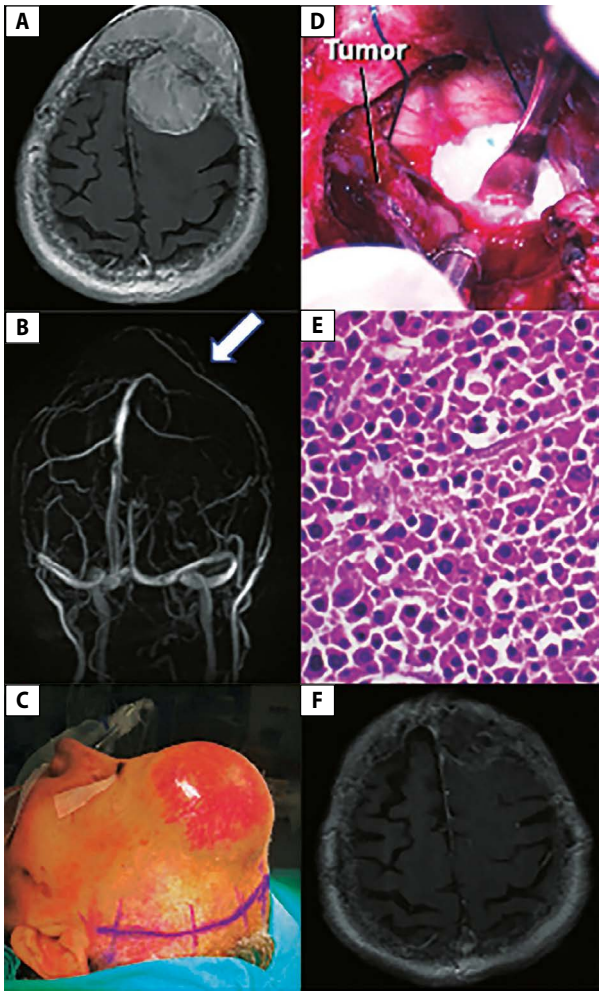

Figure 1. A. Cranial magnetic resonance image showing giant left frontal extra-axial lesion adjacent to superior sagittal sinus; **B.** Magnetic resonance angiographic scan showing that mass was being fed from distal branches of external carotid artery (arrow); **C.** Patient was operated on with a bifrontal incision under general anaesthesia. Skin overlying the lesion was hyperaemic because of enlarged vessels; **D.** Grey-brown and slightly hard intracranial component of tumour was also completely resected using a cleavage line plane between tumour and brain; **E.** Diffuse plasma cell infiltration was observed histologically; **F.** Postoperative MRI scan showing total removal of tumour

plasmacytoma from the bone surface towards a weak barrier, such as the skin, may be possible. Under the influence of sex hormones, excessive osteoclastic activity may cause the appearance of giant cranial solitary plasmacytomas in women more than in men. Another observation that supports this hypothesis is that Paget's disease, which is known to be more common in women, can be seen frequently with MM.

Although preoperative superselective tumour embolisation was recommended to prevent excessive blood loss during the operation, embolisation was not attempted in this case in order not to cause additional morbidity for the patient with advanced age and comorbidities. There was no uncontrollable

bleeding in the surgery. The primary surgical goal should be radical tumour resection, but radiotherapy may be preferred for small tumours or when resection is not possible because the tumour is extremely radiosensitive. Since the tumour was completely resected in the presented case, radiotherapy was planned to be considered only in case of recurrence.

Since cranial plasmacytomas can present in many different forms, many pathological lesions, such as glioblastomas, subdural haematomas, metastases, meningiomas, sarcomas, and giant cell tumours, should be considered during differential diagnosis [1, 2].

This case demonstrates the complexity of the pathophysiology of giant cranial solitary plasmacytomas. A potential relationship between sex hormones and giant cranial plasmacytoma may exist. Notably, this case featured the oldest patient to have been successfully surgically treated and documented in the medical literature.

Ethical issues: *The ethical issues for this study have been carefully considered in line with the Declaration of Helsinki and its amendments. Written informed consent and permission to reproduce copyrighted materials were obtained from the patient.*

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Perspectives on cortical connectivity in ischaemic stroke

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To the Editors

The neurological deficit of a stroke is not only the consequence of the focal lesion, but also the result of the disruption in connections with other areas. The analysis of brain connectivity provides new insights into post-stroke recovery mechanisms, as well as means of assessing the extent of the damage [1, 2].

Post-stroke electroencephalography (EEG) studies have demonstrated a reduction in intrahemispheric functional connectivity in various networks of the lesioned hemisphere after stroke, and this pattern has been shown to be associated with poor function. More pronounced low-frequency activity (delta or theta frequency activity) in the lesioned hemisphere and higher frequency activity (alpha or beta activity) in the contralesional hemisphere may create a higher interhemispheric imbalance. This may be associated with poor function and the restoration of balance may be associated with improved recovery after stroke [3].

Stroke leads to an early reduction of connectivity in the motor network. With recovery time, connectivity increases and can reach the same levels as in healthy participants. The increase in connectivity is correlated with functional motor gains. The analysis of changes in connectivity patterns may lead to a better understanding of these compensatory mechanisms in the brain after stroke [4].

EEG functional connectivity analysis can be performed using sLORETA (standardised low resolution electromagnetic tomography software). This is a linear inverse solution for EEG signals that have no localisation bias in the presence of measurement and biological noise. The electric potential differences from EEG can estimate the current density vector field on the cortex in LORETA [5].

We report below some observations regarding network reorganisation in two cases of ischaemic stroke with an early good outcome. Informed consent was acquired from both patients.

We firstly report the case of a 74-year-old man who was admitted to the neurological department for sudden onset of weakness in his left limbs of two days' duration. He had a history of alcohol drinking, but there were no known additional vascular risk factors.

Neurological examination revealed left hemiparesis (Muscle Strength Rating Scale 4.5/5 upper limb and 4/5 lower limb, left Babinski sign) and mild dysarthria with an NIHSS (National Institutes of Health Stroke Scale) score of 5 points. A CT (computed tomography) scan performed in the accident and emergency department revealed an ischaemic acute stroke in the right anterior cerebral artery territory (Fig. 1 A).

Routine blood exam was unremarkable, and cardiovascular investigations revealed atrial fibrillation.

We performed an EEG in a resting state condition, in an isolated room, with closed eyes for 20 minutes on the fifth day after symptoms onset. Electroencephalographic signals were measured from 32 electrodes positioned according to the augmented International 10–20 system. The data was analyzed with MATLAB software, using scripts based on the EEGLAB toolbox. Detection and rejection of the artifacts were completed through ICA (independent component analysis). We selected the components that had brain source (Fig. 1 B).

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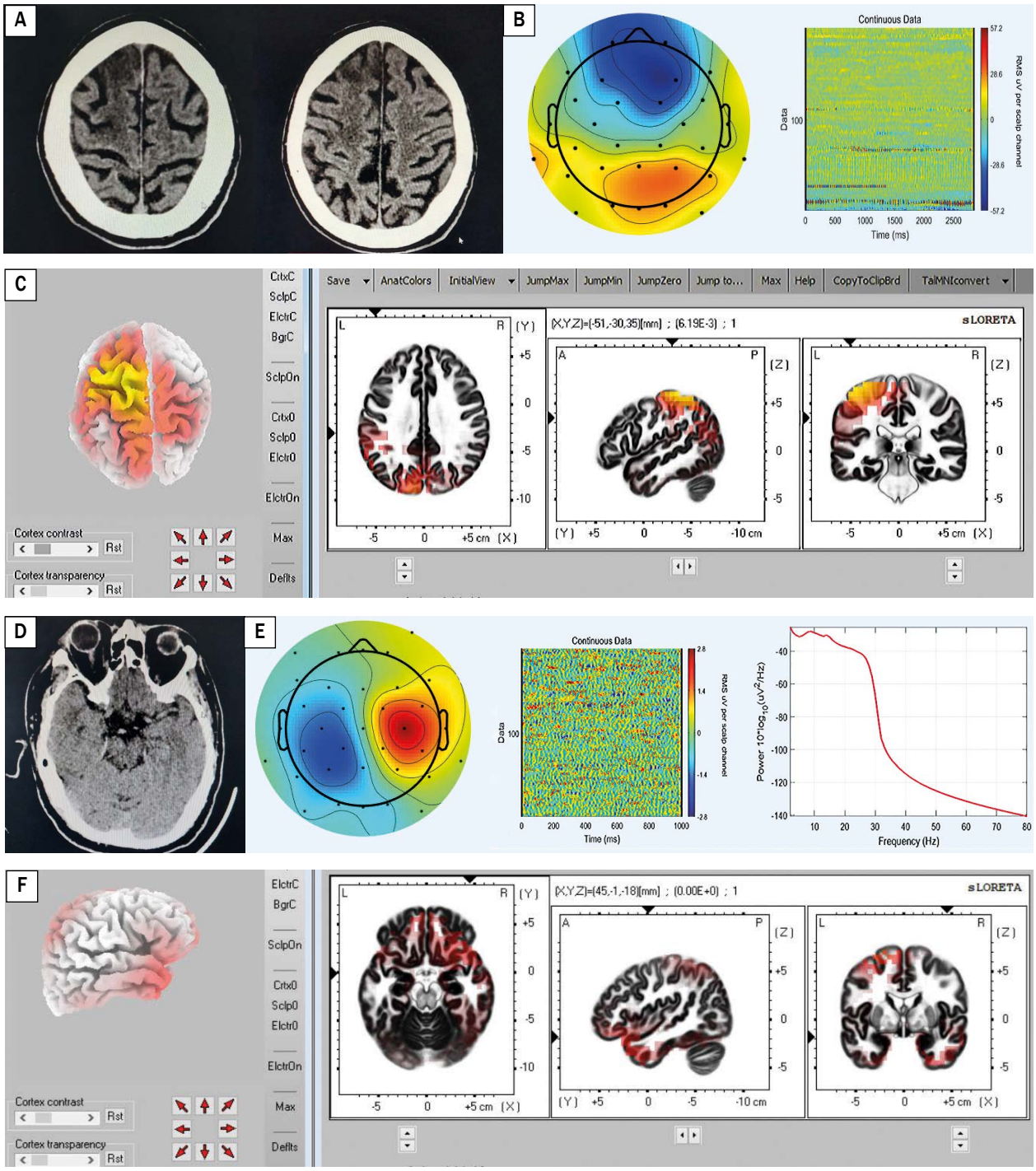

Figure 1. **A.** Axial CT reveals acute hypodensity in right anterior cerebral artery; **B.** Independent component analysis in MATLAB-EEGLAB for Patient 1; **C.** sLORETA algorithm for independent component chosen for Patient 1; **D.** Axial CT reveals acute hyperdense thrombus in M2 segment of left middle cerebral artery; **E.** Independent component analysis in MATLAB-EEGLAB for Patient 2; **F.** sLORETA algorithm for independent component chosen for Patient 2. CT — computed tomography; sLORETA — standardised low resolution electromagnetic tomography software

We used sLORETA to compute the cortical electrical distribution from the scalp potentials measured at the electrode sites (Fig. 1 C). We detected an increased distribution of electrical sources in the contralateral hemisphere (non-lesioned hemisphere — frontoparietal area).

We now report the second case: a 51-year-old man was admitted to the neurological department for sudden onset of weakness in his right limbs and expressive aphasia, of four hours' duration. He had a history of cigarette smoking, hypertension and dyslipidemia.

The neurological examination revealed right hemiparesis (strength was 4+ out of 5 on the right hand and 4+ out of 5 on the right foot, right Babinski sign) and motor aphasia with an NIHSS score of 6 points. A CT scan performed in the accident and emergency department revealed an acute hyperdense thrombus in the M2 segment of the left middle cerebral artery (Fig. 1 D). The ASPECTS (Alberta Stroke Program Early CT Score) was 10 points. The routine blood exam was unremarkable. During hospitalisation, the NIHSS score decreased to 1 point after intravenous (IV) thrombolysis. The cerebral CT performed one day after IV thrombolysis confirmed a small recent hypodense parietal area. Cardiovascular investigations during hospitalisation detected atrial fibrillation.

We performed a resting state EEG of 20 minutes' duration on the fifth day of hospitalisation, and we analysed the signals in MATLAB-EEGLAB (Fig. 1 E). We removed the artifacts and we selected the components corresponding to brain electrical dipoles.

We further investigated the cortical electrical distribution of scalp potentials in sLORETA and we detected an increased distribution of electrical sources in the contralateral temporal area (non-lesioned hemisphere) and the ipsilateral frontal area (Fig. 1 F).

These two clinical cases raise questions regarding the ability of the brain to reorganise its connections and the utility of assessing early clinical outcomes in acute stroke patients.

Recent studies have focused on connectivity after stroke in order to find predictive biomarkers in stroke recovery. This represents an active research area in neuroscience and this could be a new insight in the domain of rehabilitation. In the context of incomplete knowledge of network reorganisation after stroke and its importance in clinics, further research studies are required to validate the importance of connectomics in this disabling disorder.

Analysing recovery studies of resting state functional connectivity of stroke participants and comparing them to a control group, functional connectivity measures have shown decreases in at least some nodes or networks. When recovery occurs spontaneously, or is supported by therapy or training, connectivity increases over time [4]. Rehabilitative training (e.g. virtual reality as a therapeutic strategy can engage certain sensory and motor circuits) that indirectly affects the flow of information through brain connectomes and circuit-level plasticity may have a positive impact on stroke patients [1]. Studying functional connectivity in acute stroke, and finding early predictive biomarkers that are reliable enough in clinical practice to guide individualised rehabilitative training, represents a promising direction for future research.

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

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Impact of left ventricular noncompaction on brain

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Key words: noncompaction, stroke, complication, arrhythmias, heart failure, embolism

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To the Editors

We read with interest the article by Bistriceanu et al. [1] describing a 47-year-old male with ischaemic stroke in the territory of the right middle cerebral artery, which was classified as cardioembolic due to intracardiac thrombus formation in the context of left ventricular hyper-trabeculation (LVHT), also known as non-compaction. Their study is excellent, but has limitations that cause us concerns and which we would like to discuss.

We disagree with the statement that LVHT is congenital in each case [1]. Though rarely reported, several cases of LVHT have been reported in which LVHT was not present at birth, and therefore not congenital, but developed during post-partum life [2]. Acquired LVHT has been particularly reported in patients with neuromuscular disorders, in pregnant females, and in professional athletes [2]. There are also indications that acquired LVHT in pregnant females can disappear again after delivery or after cardiac surgery [3].

We also disagree with the statement that LVHT is a genetic disorder [1]. Though commonly associated with genetic disease, particularly chromosomal defects, LVHT and hereditary neuromuscular disorders, and although rare familial cases have been reported [4], a causal relation between any of these genetic defects and the intra- or extrauterine development of LVHT has not been proven.

The complications of LVHT not considered in the discussion of the index case are ventricular arrhythmias and sudden cardiac death (SCD). Ventricular arrhythmias can have neurological implications as they can be associated with heart failure or thrombus formation. Thrombus formation can occur either within the recessus between the trabeculations or within the left ventricular cavity. Because of the risk of ventricular arrhythmias, LVHT patients are recommended to undergo either repeated Holter monitoring or implantation of a loop recorder to detect malignant ventricular arrhythmias.

Detection of ventricular arrhythmias has therapeutic implications, because implantation of an implantable cardioverter defibrillator (ICD) should be considered in LVHT patients with recurrent syncopes or documented ventricular arrhythmias on long-term ECG recordings.

Neurological complications of LVHT not only include cardio-embolic stroke but also syncope, transitory ischaemic attack, or cerebral hypoxia in the case of heart failure, prolonged malignant ventricular arrhythmias, or insufficient resuscitation in the context of asymptomatic ventricular arrhythmias.

Because LVHT is most commonly associated with neuromuscular disorders [5], all patients with LVHT should be systematically investigated for myopathy. Accordingly, we would like to establish whether the index patient, who was seen by a neurologist because of the stroke, had any indications for peripheral nervous system disease.

Because LVHT is commonly associated with the phenomenon of late gadolinium enhancement (LGE) of the left ventricular myocardium [6], we would also like to ask whether the index patient underwent cardiac MRI, and if this phenomenon could be documented in his case as well. The pathophysiological consequences of this phenomenon are not fully understood, but it has been postulated that it represents intraventricular fibrosis. LGE is associated with the occurrence of major adverse cardiovascular events (MACE) [6].

To sum up, this interesting study has limitations that call the results and their interpretation into question. Addressing these issues would strengthen the conclusions and could improve the status of the study. LVHT has to be regarded as a risk

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factor of cardioembolic stroke, but before attributing stroke to LVHT, alternative aetiologies need to be thoroughly ruled out.

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Funding: *None.*

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Post-COVID 'brain fog' will clear up only through neuropsychological examination

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Key words: COVID-19, SARS-CoV-2, long-COVID syndrome, brain fog, neuropsychological deficits

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To the Editors

We read with interest the article by Chatys-Bogacka et al. on a cross-sectional study on the differences between the sexes in post-COVID 'brain fog' [1]. Data collection took place between April 2021 and August 2021 using previously published electronic questionnaires which were delivered via bulk email, Facebook, and a post-COVID outpatient unit [1]. It was found that females compared to males were more likely to report problems with writing, reading, counting, and thought communication at > 12 weeks post infection [1]. At > 12 weeks, no gender differences were found in multitasking, remembering past information, determining the current date, or field orientation [1]. We feel that the study is excellent, but has limitations and raise concerns that should be discussed.

The main limitation of the study is the definition of 'brain fog', a vague term that means different things to different people. There is no single, universally accepted definition of brain fog. Therefore, if neuropsychological deficits are recognised as a post-COVID complication, they should be described in detail after appropriate testing by a neuropsychologist, and not reported by the patient him or herself. When using electronic questionnaires in particular, there is a risk that different patients will understand the term 'brain fog' differently, which is why we suggest the term should be abandoned. The ambiguity of the term is supported by the different definitions in the article. In the introduction, the authors define brain fog firstly as "poor memory and concentration", then later as "poor concentration, intellectual ambiguity, mental fatigue, and anxiety", and thirdly as "disorders of concentration and memory, sleep and speech disorders" [1]. Even the investigators themselves seem to be unsure about a precise definition of the term 'brain fog' [1].

Another limitation is that electronic questionnaires were used for data collection [1]. Electronic questionnaires have several disadvantages. There is no guarantee that the patient will provide truthful answers; it is not verified that the patient addressed will in fact answer the questionnaire themselves rather than leave it to a relative or caregiver; and there is no certainty that the patient is physically and/or mentally able to fill out the form. There is also the disadvantage that only patients who are able to use a computer can respond. Individuals in a hospital, individuals without access to electronic media, and individuals unfamiliar with using electronic media will probably not be included in such a study. Individuals with severe complications resulting from COVID-19 may not be included because they simply cannot be reached for the investigation.

Another limitation is that no distinction was made between people with and without a SARS-CoV-vaccination. Vaccinated patients may have a different type, intensity, and frequency of symptoms compared to unvaccinated patients.

Another limitation is that it remains unclear how causes other than COVID-19 were ruled out in order to explain symptoms described by the patient. Since the latency period between the onset of COVID-19 and the completion of the questionnaire was 208 days on average [1], it is conceivable that some of the included patients suffered another disease

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that was responsible for the symptoms during this period. How was depression ruled out, and what scores were used to assess depression?

Furthermore, the results and conclusions drawn may be unreliable because the sex ratio was 5:1, meaning that five times more females than males were included in the study. This inequity is a strong bias, meaning that the results must be interpreted with caution.

Overall, this interesting study has several limitations that call the results and their interpretations into question. Clarifying these weaknesses would strengthen the conclusions and so improve the study. Before identifying a gender difference regarding post-COVID 'brain fog', we feel that the requirements for such a study must be met.

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

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Response to Letter to the Editors regarding article entitled 'Left ventricular non-compaction cardiomyopathy and ischaemic stroke'

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Key words: left ventricular non-compaction cardiomyopathy (LVNC), ischaemic stroke

(*Neurol Neurochir Pol 2023; 57 (3): 324–325*)

To the Editors

We thank Finsterer and Stöllberger for their valuable feedback [1], and we would like to respond to it.

A study from 2018 that involved a molecular analysis of 107 genes in 95 adult patients with LVNC in order to characterise the genetic spectrum of this disorder found that TTN, HCN4, MYH7 and RYR2 were the most common mutations among these patients.

The results of this study give substance to the idea that LVNC is basically a genetic disease. However, according to the European Society of Cardiology, LVNC is listed among unclassified cardiomyopathies, and according to the American Heart Association it is among the genetic cardiomyopathies [2].

Another interesting research field in this area is the association and overlapping with other conditions.

Several decades ago, the association of the phenotype with congenital heart diseases was first acknowledged and attributed to the additional burden imposed by the congenital defects on the LV [3].

Other associations between non-compaction cardiomyopathy and neuromuscular disorders can be found, i.e. Duchene muscular dystrophy, Becker muscular dystrophy, myotonic dystrophy, metabolic myopathy, and Leber's hereditary optic neuropathy [4].

No such neuromuscular pathology was detected in our patient, nor any other peripheral nervous system disorder.

We discussed in our article some complications such as cardiac arrhythmias, cardiac failure and sudden death. Cardiac monitoring is important because the treatment is related to cardiac failure management or an implantable defibrillator in ventricular arythmias [5]. In our patient, ECG monitoring did not reveal atrial fibrillation or any other cardiac arrhythmia at that moment. Further cardiac investigations did not reveal any thrombus between the trabeculations or within the left ventricular cavity. The phenomenon of late gadolinium enhancement (LGE) was not described on cardiac MRI.

However, we analysed the brain DWI-MRI imaging, and this revealed acute stroke in the right superficial MCA territory and left PCA territory. This is known as MACI (multiple acute cerebral infarcts in multiple arterial territories) and is radiologically defined as more than one acute ischaemic lesion in at least two cerebral territories. Several studies have emphasised cardiogenic embolism to be the primary aetiology for this group.

Further investigations in our case did not reveal a cervical or intracranial atherosclerosis that could have explained successive embolisation and affected clinical assessment or MRI timing. A cardio-embolic mechanism was hypothesised and

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the treatment with DOACs was started (the EF was < 20% and this represents another criterion according to other studies) [5, 6].

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

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RESPONSE TO LETTER
TO THE EDITORS

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Response to Letter to the Editors regarding article entitled 'Sex-related patient-reported brain fog symptoms in non-hospitalised COVID-19 patients'

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Key words: COVID-19, brain fog, sex, course of COVID-19, long COVID

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To the Editors

We are grateful to Finsterer and Mehri for their valuable comments [1] on our article entitled 'Sex-related patient-reported brain fog symptoms in non-hospitalised COVID-19 patients' that was recently published in the Polish Journal of Neurology and Neurosurgery [2].

However, we believe that all the points raised in their recent Letter to the Editors were in fact covered in detail within the 'limitations' section of our paper [2].

Firstly, we admit that the ambiguity exists regarding what is perceived as a 'brain fog' in COVID-19 research. However, for the purposes of the current study, we used the meaning proposed by the National Institute for Health and Care Excellence and the Centres for Disease Control and Prevention that underlined difficulty in thinking [3] and other cognitive problems, including loss of concentration and memory [4]. All of these aspects were covered by our detailed questionnaire that was created based on the experience of 70 healthcare professionals who were afflicted by SARS-CoV-2 infection [5]. Furthermore, the development and validation process of the BF-COVID questionnaire included a standardised methodology, i.e. item generation, validation of content, face validation, and psychometric analysis [6]. Noteworthy, exploratory factor analysis with varimax rotation and reliability testing showed good content validity and acceptable internal consistency (Kaiser-Meyer-Olkin value 0.796, Bartlett's test of sphericity $Chi^2 = 943$; df = 36, p-value < 0.001, and Cronbach's alpha of 0.740) [6].

Secondly, as we mentioned in the limitations section of our article, our research was based on patient-reported data only and, given that the anonymous questionnaires were completed retrospectively, our results inherently reflect largely subjective aspects of brain fog. However, we did not rely solely on electronic versions of questionnaires, because individuals who attended the ambulatory clinic for

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post-COVID patients in the University Hospital in Krakow were also asked to participate in the study [2]. It is also noteworthy that patient-reported outcomes are increasingly being used among COVID-19 survivors [7]. Furthermore, although neuropsychological examination remains an important and valuable assessment tool, it may actually be less sensitive in detecting subtle cognitive changes during recovery after SARS-CoV-2 infection [8].

Thirdly, only 19% of participants were vaccinated against COVID-19; however, most of them underwent this procedure after their diagnosis of SARS-CoV-2 infection [2]. Indeed, as the authors of the Letter to the Editors suggest, although vaccination against COVID-19 might reduce the risk of persistent problems after initial infection, nonetheless, in individuals with existing long COVID symptoms, including brain fog, the role played by subsequent vaccination remains uncertain, as some studies have suggested improvement while others have not [9].

Fourthly, as specifically stated in the limitations section of our paper, no data on comorbidities, including neurological and psychiatric conditions such as depression, were collected during the course of our study [2]. Therefore, their influence on the responses given by the patients cannot be excluded. On the other hand, using self-reported screening questionnaires might not be helpful in depression, and can even result in its overestimation [10]. Thus, face-to-face interviews would be the preferable method for both brain fog and depression assessment, but this would require studies with diverse methodologies and designs.

Finally, we are aware of the uneven sex distribution in our cohort [2]. However, post hoc power calculation remained satisfactory [2].

In summary, the limitations of our study are important when interpreting the results. Nevertheless, the use of a previously validated questionnaire allowed us to show significant differences in the course of brain fog between women and men [2]. Although consistent with previous research regarding the role of female sex in the risk of developing post-COVID brain fog, future studies are essential to confirm the results and conclusions set out in our paper.

Conflicts of interest: *None.*

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