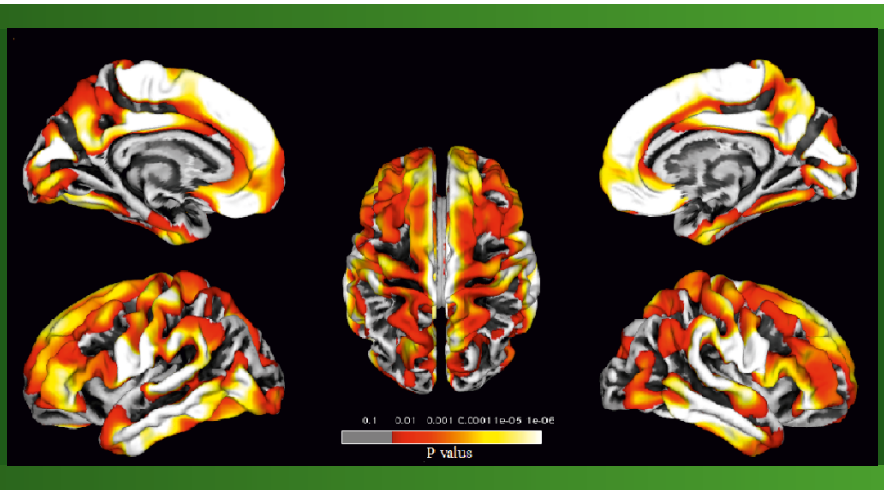
Neurologia i Neurochirurgia Polska, 2021, vol. 55, no. 4

NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF NEUROLOGY AND NEUROSURGERY

The Official Journal of Polish Neurological Society

2021, vol. 55, no. 4



Established: 1938

VIA MEDICA

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

www.journals.viamedica.pl/neurologia_neurochirurgia_polska

NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF NEUROLOGY AND NEUROSURGERY

The Official Journal of Polish Neurological Society
www.journals.viamedica.pl/neurologia_neurochirurgia_polska

Published by: VM Media sp. z o.o. VM Group sp. komandytowa. Via Medica Group

NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF NEUROLOGY AND NEUROSURGERY

The Official Journal of Polish Neurological Society
www.journals.viamedica.pl/neurologia_neurochirurgia_polska

Neurologia i Neurochirurgia Polska also known under the name of *Polish Journal of Neurology and Neurosurgery (PJNNS)* is a premier research and educational platform of the Polish Neurological Society and Polish Society of Neurosurgeons. It has a long and accomplished history dating back to earlier days of the XX Century. The journal publishes the results of basic and clinical research contributing to the understanding, diagnosis, and treatment of neurological and neurosurgical disorders.

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

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

Journal has an international indexation in Directory of Open Access Journals (DOAJ); Chemical Abstracts; EMBASE; Index Copernicus; MEDLINE; OpenMED; MEDLINE; Polish Scientific Bibliography / Pol-index; Polish Medical Bibliography (GBL); Science Citation Index Expanded

Current Impact Factor of Neurologia i Neurochirurgia Polska (2020) is 1.621

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

Cover photo: Li Z. et al., VBM and SBM analysis between healthy group and left-TLE patients (see figure on page 273).

Published by: VM Media sp. z o.o. VM Group sp. komandytowa. Via Medica Group

VIA MEDICA

20-0824.004.001

NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF
NEUROLOGY
AND NEUROSURGERY

The Official Journal of Polish Neurological Society

2021, vol. 55, no. 4

Table of Contents

RESEARCH PAPERS

LETTERS TO THE EDITORS

EDITORIAL NOTE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4, pages: 329–330
DOI: 10.5603/PJNNS.2021.0059

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

Latest bibliometric factors for the Polish Journal of Neurology and Neurosurgery

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

[1]Co-Editor-in-Chief, Department of Neurology, Mayo Clinic Florida, Jacksonville, Florida, United States
[2]Journal Administrator, Via Medica™, Gdansk, Poland
[3]Department of Neurology and Psychiatry, Medical University of Gdansk, Poland

The latest bibliometric measurements of the Polish Journal of Neurology and Neurosurgery (PJNNS, Neurologia i Neurochirurgia Polska) have recently become available.

The Clarivate Analytics' Impact Factor of the PJNNS increased from 1.025 in 2019 to 1.621 in 2020, and the Elsevier's Cite Score™ increased from 1.70 in 2019 to 2.30 in 2020 (Fig. 1). The editors of the Journal thank all authors for submitting their work to the PJNNS, and our reviewers for their critical assessment of the submitted manuscripts that led to this substantial improvement in the Journal's standing. We anticipate a further increase in these bibliometric measures in the next year because a number of our COVID-19 papers published in 2020 and 2021 are getting significant attention and are already frequently downloaded and referenced.

Here, we would like to thank the authors of the five most cited articles from the last pre-COVID-19 year of 2019. In that year, the first year in which our Journal was published by Via Medica™, our new publishing house, the most cited manuscript was an Invited Review paper on the role of vitamin D in multiple sclerosis authored by Dr. Halina Bartosik-Psujek and Dr. Marek Psujek from the University of Rzeszow, Poland [1]. The remaining four articles were all Research Papers.

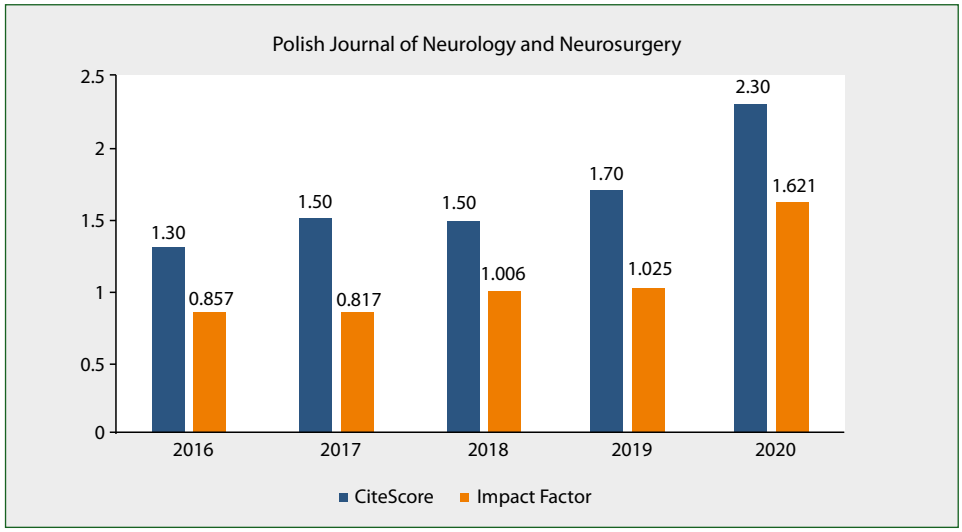


Figure 1. Gradual increases of both CiteScore and Impact Factor, the two most important bibliometric indicators used by Scopus database and Web of Science, respectively. CiteScore 2020 counted the citations received in 2017–2020 to all elements published in the Journal in 2017–2020 and divided this by the number of publications published in 2017–2020. Impact Factor 2020 was calculated by taking the number of citations in 2020 of all items published in 2018 and 2019 in the Journal and dividing that number by the total number of articles and reviews published in 2018 and 2019. An Impact Factor of 1.0 means that, on average, the article published has been cited once in the past two years. An Impact Factor of 2.0 means that, on average, these articles have been cited twice

Address for correspondence: Zbigniew K. Wszolek, M.D., Department of Neurology, Mayo Clinic Florida, 4500 San Pablo Rd, Jacksonville, FL 32224, USA; e-mail: wszolek.zbigniew@mayo.edu

Among them, the most cited article was an assessment of the relationship between C-reactive protein and albumin ratio on mortality in acute ischaemic stroke patients written by Dr. Mehtap Kocatürk and Dr. Özcan Kocatürk from the Harran University in Sanliurfa, Turkey [2]. The third most cited article, written by Dr. Michał J. Schinwelski, Dr. Emilia J. Sitek, Dr. Piotr Wąż, and Dr. Jarosław Sławek from St. Adalbert Hospital and the Medical University of Gdansk, Poland and from the Neurology Clinic in Tczew, Poland, discussed the prevalence and predictors of post-stroke spasticity and its impact on daily living and quality of life [3]. The fourth manuscript, written by Dr. Gabriela Rusin, Dr. Ewa Wypasek, Dr. Elżbieta Papuga-Szela, Dr. Joanna Żuk, and Dr. Anetta Undas from Jagiellonian University Medical College in Krakow, Poland, provided data on oral anticoagulants in the treatment of cerebral venous sinus thrombosis [4]. The fifth and final manuscript, written by Dr. Edyta Krajczy, Dr. Marcin Krajczy, Dr. Jacek Luniewski, Dr. Katarzyna Bogacz, and Dr. Jan Szczegielniak from the Municipal Hospital in Nysa, Poland, and from the Opole University of Technology in Opole, Poland, assessed the effects of dysphagia therapy in patients in the early post-stroke period [5].

The Editors congratulate all of the authors whose manuscripts were published in PJNNS for their important contributions to science.

References

1. Bartosik-Psujek H, Psujek M. Vitamin D as an immune modulator in multiple sclerosis. Neurol Neurochir Pol. 2019; 53(2): 113–122, doi: 10.5603/pjnns.a2019.0015.
2. Kocatürk M, Kocatürk Ö. Assessment of relationship between C-reactive protein to albumin ratio and 90-day mortality in patients with acute ischaemic stroke. Neurol Neurochir Pol 2019;53(3):205–211, doi: 10.5603/PJNNS.a2019.0020.
3. Schinwelski M, Sitek E, Wąż P, et al. Prevalence and predictors of post-stroke spasticity and its impact on daily living and quality of life. Neurol Neurochir Pol. 2019; 53(6): 449–457, doi: 10.5603/pjnns.a2019.0067.
4. Rusin G, Wypasek E, Papuga-Szela E, et al. Direct oral anticoagulants in the treatment of cerebral venous sinus thrombosis: a single institution's experience. Neurol Neurochir Pol. 2019; 53(5): 384–387, doi: 10.5603/PJNNS.a2019.0037.
5. Krajczy E, Krajczy M, Luniewski J, et al. Assessment of the effects of dysphagia therapy in patients in the early post-stroke period: a randomised controlled trial. Neurol Neurochir Pol. 2019; 53(6): 428–434, doi: 10.5603/pjnns.a2019.0053.

INVITED EDITORIAL

This Invited Editorial accompanies a Research Paper, see page 380

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4, pages: 331–332
DOI: 10.5603/PJNNS.a2021.0046

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

Underdiagnosis and undertreatment of migraine in Poland

Olga P. Fermo

Department of Neurology, Mayo Clinic, Jacksonville, Florida, USA

(*Neurol Neurochir Pol 2021; 55 (4): 331–332*)

'Migraine without aura' is defined as recurrent long-lasting (4–72 hours) headache attacks which display at least two of the following four characteristics: unilateral location, a pulsating quality, moderate or severe pain intensity, and/or aggravation by routine activity. This must be accompanied by additional symptoms during the attack, specifically nausea and/or vomiting or photophobia and phonophobia [1].

'Migraine with aura' is diagnosed when a migraine headache is accompanied by stereotypical attacks of gradual, fully reversible, visual, sensory, language, motor, brainstem or retinal symptoms typically lasting between five minutes and one hour [1].

An individual is said to have 'chronic migraine' when headaches occur on at least 15 days a month for more than three months, and when the headache displays the previously defined features of migraine on at least eight days each month [1].

The term 'episodic migraine' is used when headaches occur on 14 or fewer days per month.

Migraine is one of the most common disorders, estimated to affect 1.04 billion people worldwide, with a global prevalence of 14.4% in adults [2]. Lifetime prevalence in Poland has been reported to be 10% [3]. Migraine not only limits activity during the ictal phase but also causes disability between attacks, for example by causing anticipatory anxiety. This disability, when taken together with the particularly high prevalence during the working-age decades of life, and the inherent, lifelong nature of the disorder, accounts for migraine being the second leading cause of years lived with disability [4].

Given the high disability associated with migraine attacks, all patients should be offered acute (as-needed) treatment [5]. Optimal acute treatment should provide pain freedom at 2 hours without the need for rescue medication, and should sustain that response over the next 46 hours. These are the currently used benchmarks in migraine drug development, and the same goals should translate into clinical practice [5, 6]. The American Headache Society published an evidence-based assessment of acute treatments in 2015, with all six available triptans and ergots (termed migraine-specific treatments because of their action on the trigeminovascular calcitonin gene-related peptide (CGRP) pathway) demonstrating Level A evidence [5, 7].

Since late 2019, three additional migraine-specific acute treatments have joined the commercial market: lasmiditan, ubrogepant and rimegepant, further expanding the armoury of efficacious, safe, well-tolerated treatments [8–10]. The choice of specific agent depends on the attack characteristics. It is recommended to tailor the formulation (oral, intranasal, or subcutaneous), onset of action and duration of action of the drug to the time of migraine attack (morning attacks being typically more severe), time to peak headache intensity, degree of associated nausea and vomiting, typical duration of attack, and frequency of recurrence [5]. An inappropriately or incompletely treated attack risks increasing the number of attacks over time or making the attacks more severe [11].

The American Migraine Prevalence and Prevention Study, a large epidemiological summary of the US prevalence, burden, and treatment patterns of migraine, found that nearly 40% of migraineurs were candidates to receive prevention therapy for migraine, but only 12.4% were currently using a preventive treatment. Since the chances of developing chronic migraine greatly increase with escalating episodic migraine frequency, patients with frequent migraine should be offered preventive treatment to keep attack frequency low [12, 13]. Prevention is not necessary when attack frequency is low (i.e. three or fewer days per month) and disability is low. Prevention should be offered when attack frequency is 6+ days per month, regardless of associated disability, and should be considered when the frequency is lower but some level of impairment is present [12]. There are numerous available treatments with established efficacy for prevention, in particular since the commercial arrival in 2018 of CGRP monoclonal antibodies [14, 15].

Migraine-specific acute treatment, and preventive treatment, can only be offered when migraine is clinically recognised. Despite its high prevalence, migraine is significantly under-recognised by both patients and physicians in Europe [16].

Address for correspondence: Olga P. Fermo, Department of Neurology, Mayo Clinic, Jacksonville, Florida, USA, e-mail: fermo.olga@mayo.edu

Received: 22.03.2021 Accepted: 23.03.2021 Early publication date: 16.06.2021

In this issue of PJNNS, Domitrz et al. have conducted a survey of general practitioners (GPs) in Poland to assess their treatment habits. They found that only 10% of GPs could correctly define migraine without aura according to the fully published criteria, and only 18% correctly distinguished episodic from chronic migraine [17]. This gap in knowledge implies that a sizeable proportion of Polish migraineurs are not being offered migraine-specific acute or preventive treatment. Indeed, most GPs in this group did not prescribe prevention for episodic migraine, and only 18% were aware that monoclonal antibodies were available for use in Poland [17].

Moreover, these results highlight only part of the problem, given the recent demonstration that the majority of surveyed neurologists in Poland also could not provide the exact diagnostic criteria for migraine [18].

The study by Domitrz et al. is another demonstration of all-too-common gaps in the understanding and treatment of migraine, a frequently encountered debilitating lifelong disorder. This should serve as a wake-up call for educational and awareness campaigns.

References

1. Olesen J. The International Classification of Headache Disorders, 3rd edition. Cephalagia. 2013; 33(9): 629–808.
2. Stovner LJ, Nichols E, Steiner TJ, et al. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018; 17(11): 954–976, doi: 10.1016/S1474-4422(18)30322-3, indexed in Pubmed: 30353868.
3. Stępień A, Prusiński A, Suwa A, Klinika Neurologii Uniwersytetu Medycznego K, Pfizer Polska. Wybrane Dane Epidemiologiczne Występowania Migreny w Polsce (Selected Epidemiological Data on Migraine Prevalence in Poland).
4. Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, Burden, and Comorbidity. Neurol Clin. 2019; 37(4): 631–649, doi: 10.1016/j.ncl.2019.06.001, indexed in Pubmed: 31563224.
5. Tepper SJ. Acute Treatment of Migraine. Neurol Clin. 2019; 37(4): 727–742, doi: 10.1016/j.ncl.2019.07.006, indexed in Pubmed: 31563229.
6. Tfelt-Hansen P, Pascual J, Ramadan N, et al. International Headache Society Clinical Trials Subcommittee. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. Cephalalgia. 2012; 32(1): 6–38, doi: 10.1177/0333102411417901, indexed in Pubmed: 22384463.
7. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the american headache society evidence assessment of migraine pharmacotherapies. Headache. 2015; 55(1): 3–20, doi: 10.1111/head.12499, indexed in Pubmed: 25600718.
8. Kuca B, Silberstein SD, Wietecha L, et al. COL MIG-301 Study Group. Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study. Neurology. 2018; 91(24): e2222–e2232, doi: 10.1212/WNL.0000000000006641, indexed in Pubmed: 30446595.
9. Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the Treatment of Migraine. N Engl J Med. 2019; 381(23): 2230–2241, doi: 10.1056/NEJMoa1813049, indexed in Pubmed: 31800988.
10. Croop R, Lipton RB, Kudrow D, et al. Rimegepant, an Oral Calcitonin Gene-Related Peptide Receptor Antagonist, for Migraine. N Engl J Med. 2019; 381(2): 142–149, doi: 10.1056/NEJMoa1811090, indexed in Pubmed: 31291516.
11. Lipton RB, Fanning KM, Serrano D, et al. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. Neurology. 2015; 84(7): 688–695, doi: 10.1212/WNL.0000000000001256, indexed in Pubmed: 25609757.
12. Lipton RB. Bigal ; M E, Diamond ; M, Freitag ; F, Reed ML, Stewart WF. Migraine Prevalence, Disease Burden, and the Need for Preventive Therapy. ; 2007.
13. Katsarava Z, Schneeweiss S, Kurth T, et al. Incidence and predictors for chronicity of headache in patients with episodic migraine. Neurology. 2004; 62(5): 788–790, doi: 10.1212/01.wnl.0000113747.18760.d2, indexed in Pubmed: 15007133.
14. Silberstein SD, Holland S, Freitag F, et al. Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012; 78(17): 1337–1345, doi: 10.1212/WNL.0b013e3182535d20, indexed in Pubmed: 22529202.
15. Parikh SK, Silberstein SD. Preventive Treatment for Episodic Migraine. Neurol Clin. 2019; 37(4): 753–770, doi: 10.1016/j.ncl.2019.07.004, indexed in Pubmed: 31563231.
16. Katsarava Z, Mania M, Lampl C, et al. Poor medical care for people with migraine in Europe - evidence from the Eurolight study. J Headache Pain. 2018; 19(1): 10, doi: 10.1186/s10194-018-0839-1, indexed in Pubmed: 29392600.
17. Domitrz I, Lipa A, Rożniecki JJ, et al. Migraine diagnosis and treatment in Poland: survey of primary care practitioners. Neurol Neurochir Pol. 2021, doi: 10.5603/PJNNS.a2021.0045.
18. Domitrz I, Lipa A, Rożniecki J, et al. Treatment and management of migraine in neurological ambulatory practice in Poland by indicating therapy with monoclonal anti-CGRP antibodies. Neurol Neurochir Pol. 2020; 54(4): 337–343, doi: 10.5603/PJNNS.a2020.0054, indexed in Pubmed: 32687594.

INVITED REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4, pages: 333–345
DOI: 10.5603/PJNNS.a2021.0035

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

The assessment of cognitive and behavioural disturbances in vascular cognitive impairment (VCI) — recommendations of an expert working group

Pasquale Calabrese[1,2], Emilia J. Sitek[3,4], Amos D. Korczyn[5], Yanhong Dong[6], Raquel Manso-Calderón[7,8], Manuel Sierra-Beltrán[9], Agnieszka Skrzypkowska[10], Elka Stefanova[11,12]

[1]Neuropsychology and Behavioural Neurology Unit, Division of Molecular and Cognitive Neuroscience, University of Basel, Basel, Switzerland
[2]Department of Neurology, University Clinic of Basel, Basel, Switzerland
[3]Division of Neurological and Psychiatric Nursing, Faculty of Health Sciences, Medical University of Gdansk, Poland
[4]Department of Neurology, St. Adalbert Hospital, Copernicus PL, Gdansk, Poland
[5]Department of Neurology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[6]Centre for Studies of Psychological Application, School of Psychology, South China Normal University, Guangzhou, China
[7]Department of Neurology, Complejo Asistencial Universitario de Salamanca (CAUSA), Salamanca, Spain
[8]Instituto de Investigación Biomédica de Salamanca (IBSAL), University of Salamanca, Salamanca, Spain
[9]Instituto Nacional de Cardiologia Ignacio Chavez, Tlalpan, Mexico
[10]Faculty of Health Sciences, Medical University of Gdansk, Poland
[11]Faculty of Medicine, University of Belgrade, Serbia
[12]Neurology Clinic, Clinical Centre Serbia

ABSTRACT

With newer research-based classification systems, the term Vascular Cognitive Impairment (VCI) is now preferred to vascular dementia. VCI is an umbrella term that includes all forms of cognitive deficits ranging from mild cognitive impairment of vascular origin (VaMCI) to vascular dementia (VaD).

The new VCI construct takes into account the fact that in addition to single strategic infarcts, multiple infarcts, and leukoaraiosis, there are other mechanisms of cerebrovascular disease such as chronic hypoperfusion that might account for the pattern of cognitive deficits associated with vascular dementia. The key to defining the spectrum of VCI is neuropsychological testing, bedside or office-based clinical examination, and neuroimaging. The lack of specific cognitive tools that are sufficiently sensitive to detect subtle deficits makes the assessment of cognitive impairment difficult. Prospective cross-sectional and longitudinal studies of VCI from different settings are therefore required.

Although there have been few published reports, behavioural and psychological symptoms (BPS) are inherently present in VCI from the onset and during the course of the disease. Besides the type of population (i.e. clinical, community or nursing-home settings), the definition of VCI/VaD and the instruments used, and differences in the prevalence and pattern of BPS between various studies, could be due to other, often unconsidered, factors such as gender, age, education, use of medication and VCI/VaD severity.

Key words: vascular dementia, mild cognitive impairment, stroke, cerebrovascular disorders, cognition, behaviour, dementia, multi-infarct, mixed dementia

(*Neurol Neurochir Pol 2021; 55 (4): 333–345*)

Address for correspondence: Emilia J. Sitek, Department of Neurology, St. Adalbert Hospital Copernicus PL Ltd., Al. Jana Pawła II 50, 80–462 Gdansk, Poland, e-mail: emilia.sitek@gumed.edu.pl

Received: 24.01.2021 Accepted: 15.03.2021 Early publication date: 21.04.2021

Introduction

The construct 'vascular cognitive impairment' (VCI) was introduced to comprise a heterogeneous group of cognitive disorders that share a presumed vascular cause; this includes both dementia and cognitive impairment without dementia. The most severe form of VCI is vascular dementia (VaD), and new subtypes with milder cognitive symptoms such as vascular mild cognitive impairment (i.e. VaMCI) are gradually being defined. The new VCI construct takes into account the fact that in addition to single strategic infarcts, multiple infarcts, and leukoaraiosis, also chronic hypoperfusion might account for the pattern of cognitive deficits associated with VaD. Hence, VCI is an umbrella term that includes all forms of cognitive deficits ranging from VaMCI to VaD [1, 2]. Different magnetic resonance imaging techniques remain crucial for the determination of vascular pathology using both well-established [3] and more innovative approaches [4].

VCI is used for all forms of cognitive disorder associated with cerebrovascular disease (CVD) regardless of the pathogenesis (e.g. cardioembolic, atherosclerotic, ischaemic, haemorrhagic, genetically-related CVD, and even potential interactions with Alzheimer's Disease [AD] and other so-called neurodegenerative disorders). The VCI construct has also brought greater attention to to opportunities for prevention, early intervention, and the coexistence of AD pathology [5].

An overview of the neurobiological aspects of VCI that may be relevant to its management is beyond the scope of this paper, and in any case was recently thoroughly analysed in the consensus report by Bordet et al. [6].

Over the last decade, by recognising that only about half the population of patients with cerebrovascular pathology exhibit full blown dementia, the term VCI has become more appropriate to describe the whole spectrum of cognitive-behavioural deficits due to cerebrovascular pathology. Different approaches have been proposed for the classification of VCI, but no particular criteria set has gained universal acceptance. The five most common criteria sets are: the DSM-5 [7]; the International Classification of Diseases, 11th Ed (ICD 11) [8]; the State of California Alzheimer's Disease Diagnostic and Treatment Centres (ADDTC) criteria [9]; the National Institute of Neurological Disorders and Stroke with the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria [10]; and VASCOG [11]. Although NINDS-AIREN and ADDTC are not fundamentally different, the latter do not include haemorrhagic and anoxic lesions. VASCOG criteria correspond to DSM-V [12].

Aim of the study

Understanding of the cognitive and behavioural aspects of VCI and their clinical assessment is still insufficient.

This paper was aimed at reviewing published data on cognitive and behavioural disturbances through the whole spectrum of vascular cognitive impairment in order to propose a set of clinically accepted and valid testing procedures that could be used to identify patients with possible cognitive and/ /or behavioural disturbances in generic as well as in specialised neurological settings.

By doing so, pertinent literature (excluding case studies) published in PubMed and MEDLINE (containing the search items "vascular dementia" OR "vascular cognitive impairment" AND "neuropsychology" OR "cognition" between 1990 and 2020 was identified and reviewed by the workgroup. Our workgroup focused mainly on identifying diagnostic approaches applicable in different settings, as most other consortia or task-forces aim to improve the diagnosis and treatment of VCI [13] through standardising assessment and treatment approaches that seem to be based mainly on resources available from inpatient stroke units.

As discussed above, the terminology related to VCI and VaD has changed over the years. According to O'Brien et al., vascular dementia itself has the following subtypes: multi-infarct dementia, small vessel dementia, strategic infarct dementia, hypoperfusion dementia, haemorrhagic dementia, hereditary vascular dementia and mixed dementia [1]. VaD may be also divided into subcortical (sVaD) and cortical (cVAD) [14]. Unfortunately, only in some of the studies has the clinical cohort been defined in line with this terminology. Also, we did not limit our search on VCI to dementia cohorts. Whenever available, when describing study results, we used more specific terms.

Epidemiology of VCI

Vascular disease is a major cause of cognitive impairment and dementia, but is under-investigated and poorly characterised compared to Alzheimer's Disease (AD). Depending on the age cohorts under study, the prevalence estimates of VaD can vary substantially, generally showing an exponential increase in prevalence and incidence as age increases. These estimates seem to mirror the pattern of stroke, though dementia after stroke may be more frequent in the very elderly. Thus, while the World Federation of Neurology Dementia Research Group [15] has estimated VaD in developing countries to be in the range between 0.6% and 2.1%, a pooled analysis of European population-based studies reported VaD to be prevalent in 1.6% of subjects over the age of 65, with substantial variation in 5-year age-specific prevalence rates. While some studies were able to show a higher incidence of VaD in men than in women [16], a pooled analysis of incidence studies found no sex differences [17]. Similarly to Western countries, AD is the leading cause of dementia in Asian populations. The prevalence of AD doubles every 4.3 years, whereas the prevalence of vascular dementia (VaD) doubles every 5.3 years. Recent reports from China have suggested that previous estimates of the dementia burden, based on smaller datasets, might have underestimated the burden of dementia in China to date [18].

As indicated by a recent study in which dementia diagnosis was established on the basis of a cognitive screening (Montreal Cognitive Assessment, MoCA) three months after middle cerebral artery territory ischaemic stroke, dementia may be present in about 25% of cases [19]. Thus the frequency of VaD diagnosis could be be both underestimated and overestimated if patients with focal language and cognitive deficits are not neuropsychologically assessed.

The heterogeneity of the VCI construct (principally the inclusion of the vascular variant of mild cognitive impairment, VaMCI) creates challenges for descriptive epidemiology, much of which still refers to VaD terminology. In the Canadian Study of Health and Aging, it was estimated that approximately 5% of people over the age of 65 had VCI, with 2.4% having VaMCI, 0.9% having mixed dementia, and 1.5% having VaD [20]. Gorelick et al. [5] and Rincon and Wright [21] report the overall prevalence of VaD to be 5-10% in people older than 65 years, and this increases rapidly thereafter,with a prevalence of as much as 50% of the population aged over 85.

Is there a neuropsychological 'fingerprint' of VCI?

VCI has both cognitive and behavioural manifestations. VaMCI is characterised by executive dysfunction, slowed information processing, episodic memory deficits, with mood and personality disorders. Although there were significant differences in all cognitive domains between VCI without dementia and healthy controls, deficits in processing speed, working memory and visuospatial construction were more prevalent [22]. In contrast to VaMCI, non-vascular MCI had a greater relative deficit in episodic memory [22].

As mentioned above, VCI can present with a variety of neurocognitive symptoms which can be relatively mild or more severe. Although this view has been challenged [23], there are many studies indicating the preponderance of mental slowing in combination with executive dysfunction. The presence of memory impairment (of amnestic type) is highly suggestive of an AD profile, while executive impairment may appear both in non-vascular MCI and VaMCI. When analysing assessment results in a particular patient, the presence and significance of executive impairment based on quantitative scores has to be interpreted in the context of qualitative features and memory functioning [24]. Executive tests, being the most complex neuropsychological measures, are likely to be failed due to factors other than true executive impairments.

The individual neuropsychological profile of VCI is highly dependent on the topography of the underlying vascular pathology, affecting either large or small vessels. If VCI is due to large vessel disease (LVD) and occurs post-stroke (sometimes referred to also as strategic infarct dementia), the neuropsychological profile is characterised mainly by focal deficits corresponding to the localisation of the stroke area (e.g. hemispatial neglect following an infarct in the right middle cerebral artery) (Tab. 1). In accordance with the overall clinical outcome, the severity of the neuropsychological sequelae differs according to different vascular incidents: worse for haemorrhagic than for ischaemic strokes, and less favourable for ruptures of arteriovenous malformations than for cerebral aneurysms [25].

Thalamic strokes are associated with the most heterogeneous clinical manifestations due to reciprocal connections with different cortical areas and several sources of vascular supply [26]. Similarly, strokes affecting the basal ganglia (termed silent lacunar infarcts) lead to various clinical manifestations, affecting mainly language, memory and executive functions [27].

VCI, in the absence of stroke, is characterised by slowed information processing, impaired working memory and executive functions, episodic memory impairment, and visuospatial deficits. Thus, the neuropsychological pattern of VCI is not specific to the underlying vascular deficit, but rather reflects the disconnection of cortico-limbic loops that may be affected either due to vascular or to neurodegenerative pathology [27]. Information processing, working memory and executive function recruit complex brain networks and the severity of their impairment is significantly correlated to white matter pathology [28].

Update on neuroimaging correlates of VCI

Recent literature suggests that the presence of cognitive impairment post-stroke may be more closely related to structural global network competence than to traditional vascular burden scores that were popular in previous years [29]. Deterioration in connectivity following vascular lesions seems to be the key to the development of cognitive impairment [30]. Also, novel MRI approaches show promise in differentiating between amnestic and non-amnestic VCI on the basis of single-shot T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence [31]. As the severity of so-called frontal deficits is associated with a haemodynamic pattern indicative of cerebral hypoperfusion and enhanced vascular resistance on transcranial doppler (TCD) [32], the use of TCD may become more popular, especially in the follow-up of VCI patients, because its cost is lower than MRI. However, the sensitivities of the two methods to change need to be established.

Lesions along association white matter tracts mediating intrahemispheric long-range connectivity are related with psychomotor speed and constructional praxis. Non-amnestic deficits are associated with frontal white matter in particular [33]. Also, callosal fibres seem crucial in the pathophysiology of cognitive impairment in VCI [29]. Of note, there is an ongoing study aimed at using a lesion-mapping approach that will hopefully elucidate the underlying basis of cognitive deficits in VCI [34] (Tab. 1).

Cognitive assessment

The lack of specific cognitive tools that are sensitive enough to detect subtle deficits make the assessment of cognitive impairment difficult. While much work has been done, e.g. in

Table 1. Pattern of most common focal neuropsychological deficits related to localization of infarcts

Localisation of infarct	Most common possible neuropsychological consequences
Left anterior cerebral artery	Executive dysfunction, aphasia
Right anterior cerebral artery	Executive dysfunction
Anterior communicating artery	Executive dysfunction; amnesia, aphasia
Left middle cerebral artery	Aphasia, apraxia, acalculia, verbal memory impairment
Right middle cerebral artery	Unilateral neglect, aprosody, spatial memory impairment
Posterior communicating artery	Memory impairment
Left posterior cerebral artery	Alexia, verbal memory impairment
Right posterior cerebral artery	Unilateral neglect, spatial memory impairment

AD [35], research into comparable protocols relating to VCI to detect subtle changes in cognitive performance is still scarce. Furthermore, culturally and linguistically relevant neuropsychological tests are lacking in populations with a higher incidence of stroke such as Asians, posing additional challenges to establish the prevalence of VCI in these populations.

One of the attempts to standardise the neuropsychological protocol for VaMCI was the introduction of harmonisation standards published by the National Institute of Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN). The authors proposed three neuropsychological test protocols of different lengths (60, 30, and 5 minute protocols) to be used in different settings which could evaluate the following cognitive domains: executive functions (using categorical and letter fluency and Digit Symbol-Coding subtest from Wechsler Adult Intelligence Scale-III (WAIS-III), visuospatial functions (Rey-Osterrieth Complex Figure), language (Boston Naming Test), memory (Hopkins Verbal Learning Test-Revised or California Verbal Learning Test-2) and neuropsychiatric and depressive symptoms (Neuropsychiatric Inventory, NPI) [36]. However, a VCI-subgroup-specific validation of those tests still remains to be carried out.

Following VASCOG criteria [11], there have been efforts to create summary scores that would enable the detection of cognitive impairment post stroke [37]. The drawback of the the proposed battery is the issue that selective but clinically important deficits (e.g. apraxia) might be missed by such summary scores.

Multilevel assessment of cognitive impairment in VCI

Since focal cognitive deficits, as well as overall cognitive decline, may be present in VCI, neuropsychological testing should consider both domain-specific neuropsychological disturbances (e.g. neglect) as well as global deterioration (e.g. dementia). As most patients with suspected VCI are of advanced age and suffer from fatigue, reduced attention capacity, behavioural alterations and other comorbid conditions, the testing needs to be relatively short or divided into two or more sessions. Moreover, significant sensory problems may exist, precluding the use of some cognitive tests with a special emphasis on these sensory abilities. In general, qualitative descriptions of cognitive symptoms are less favourable compared to operational definitions of cognitive impairment (e.g. performance 1 or 1.5 standard deviations below that of an appropriate comparison group) [5].

Hence, we suggest **a 2-level assessment procedure**, consisting of a primary screening (level A) which, at least in part, should also offer the possibility to be used at the bedside, plus a thorough evaluation (level B). This approach also takes into account the setting in which the neuropsychological assessment takes place (Tab. 2). Thus, while in the primary care setting (family physician or allied health professional) there is a need for time-efficient, global and sensitive cognitive measures, specific settings have different requirements: intensive care units (stroke units) follow a more tailored approach using measures that are able to identify specific deficits or core-syndromes (e.g. aphasia, apraxia), while memory clinic services are generally located more downstream in the diagnostic algorithm, thus allowing more in-depth protocols in order to postacutely describe the cognitive and behavioural profile for prognostic and rehabilitative purposes. When there are abnormal results in level A, patients should be referred to level B facilities, in order to i) submit them to a more specialised diagnostic setup once vascular pathology is suspected on the basis of level A findings, or ii) to optimise therapeutic efforts on the basis of an extended cognitive and behavioural assessment.

Neuropsychological tools should also offer the possibility of documenting changes over time in clinical status. As attention and executive deficits are regarded as core symptoms of VCI, particular measures should be used that are supposed to identify these deficits. However, since time-consuming and multiple-domain-involving tasks may obscure the underlying core deficit, neuropsychological testing should include straightforward as well as complex procedures. Moreover, in order to avoid ceiling, floor and practice effects, simple and short tasks with validated parallel versions, if available, should be administered.

Importantly, it must be considered that different tests have different sensitivities in different stages of a cognitive trajectory. Thus, while some tests (e.g. working memory-related tasks) may be useful in documenting incipient decline, they

Table 2. Extended neuropsychological assessment

	Stroke clinic	Memory clinic
Battery approach	Birmingham Cognitive Screen (BCoS); if no deficits evidenced – more extended memory and executive testing (see below)	Repeatable Battery for Assessment of Neuropsychological Status (RBANS); if no deficits evidenced – more extended executive testing (see below)
Tailored testing	Aimed at capturing focal syndromes as well as overall cognitive efficiency, so as to diagnose VCI or VaD	Aimed at specifying pattern of deficits to help with differential diagnosis
Language	Minimal assessment: naming, repetition, comprehension	Naming (e.g. BNT, SydBAT) comprehension (e.g. commands from BDAE)
Visuospatial functions	VOSP, line bisection, cancellation tasks	VOSP (Incomplete letters, Cube analysis)
Praxis	Praxis tasks with one hand (without motor impairment)	Interlocking fingers test
Episodic memory	If no aphasia and/or hearing impairment: CVLT/RAVLT/other verbal learning task	
	For individuals with particularly slowed information processing and/or impaired hearing: verbal learning lists presented visually (rate of presentation is adjusted to patient's slowing)	
	If visuospatial functions are mostly preserved: Location Learning Test BVMT-R	
Working memory	Months backwards; serial sevens, Digit Span, Spatial Span, TMT	
Executive functions	If confrontation naming is preserved: phonemic fluency tasks if visuospatial function is relatively preserved: Weigl block sorting task, picture sequencing task, Tower tests, Brixton Spatial Anticipation Test	

BDAE — Boston Diagnostic Aphasia Examination; BNT — Boston Naming Test; BVMT-R — Brief Visuospatial Memory Test-Revised; CVLT — California Verbal Learning Test; RAVLT — Rey Auditory Verbal Learning Task; SYDBAT — Sydney Language Battery; TMT — Trail Making Test; VCI — Vascular Cognitive Impairment; VaD — Vascular Dementia; VOSP — Visual Object and Space Perception Test

show a plateau (the floor effect) in more advanced stages and do not offer any specific diagnostic information. Hence for monitoring purposes it is mandatory to use tests which have more linear decelerating properties (e.g. semantic fluency and flexibility-related tasks). As information processing speed is usually compromised in VCI, in tasks assessing other aspects of cognition, the scoring should not be entirely time-dependent.

Finally, a neuropsychological diagnosis should consider both quantitative and qualitative data and take into account the apparent validity of the cognitive measures used. In some cases, one prominent deficit (e.g. executive deficit) may lead to low scores in almost all tasks. Conversely, some singular tests may require a set of different abilities and functions, thus qualifying them as global screening procedures and economising time for administration. Consequently, neuropsychological test results need to be interpreted in the context of behavioural observations, as a purely quantitative approach can lead to false conclusions.

Brief cognitive screening tests

The most commonly used instrument, MMSE, has only a low sensitivity in detecting MCI [38]. Using MMSE, only one study has provided information about conversion from MCI to VaD, presenting a sensitivity of 36%, and a specificity of 80% with incidence of VaD of 6.2% [39]. Despite the greater than MMSE sensitivity of MoCA to the milder forms of cognitive impairment with cerebrovascular disease [40], further longitudinal research is needed to verify its validity in detecting the progression of VCI [41]. A cut-off of 24/25 is suggested to detect post-stroke cognitive impairment [42]. However, MoCA is not sensitive enough to information processing deficits and visual memory impairment that are common in stroke survivors [43]. Also, it is much less sensitive to cognitive impairment following right-hemisphere strokes [44].

The short NINDS-CNS is a 5-minute protocol that can be used to identify high-risk groups for post-stroke dementia after acute ichaemic stroke. However, this test has been employed only in Korea [45] and China [46].

The cognitive screening instrument DemTect [47] is a short-screening test that has been extensively validated in different settings and languages. It was first published in 2000 in a German version, then in 2002 in a French, in 2004 in an English [48], and in 2016 in a Polish version [49]. In 2010, a parallel test, the DemTect B, was published [50] and in 2013, norms for people below 40 years and over 80 years were added [51]. In 2010, a modification of DemTect was developed by a Canadian workgroup to identify at-risk drivers [52]. DemTect consists of five subtests measuring short and long-term verbal memory, working memory, executive function, and number processing. The administration time is 8–10 minutes. Sensitivity and specificity of DemTect in studies with patients with dementia or MCI and healthy controls has been summarised in Kalbe et al. [53]. A condensed version which is suited for primary care settings is also available (RDST, rapid dementia screening test) [54].

Another screening instrument has recently been developed specifically for vascular MCI: the Brief Memory and Executive Test (BMET) covering executive functioning, processing speed, orientation, and memory [55]. MoCA and BMET are more sensitive in the detection of VCI than MMSE [56].

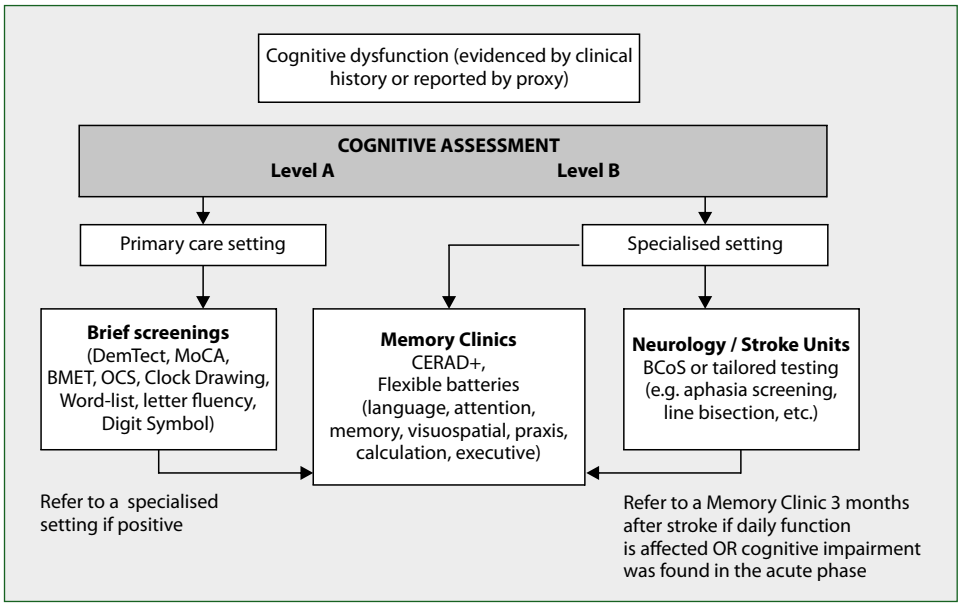


Figure 1. Cognitive assessment if vascular cognitive impairment is suspected.
BCoS — Birmingham Cognitive Screen; BMET — Brief Memory and Executive Test; CERAD+ — Consortium to Establish a Registry for Alzheimer's Disease; DemTect — Demenz Detection; MoCA — Montreal Cognitive Assessment; OCS — Oxford Cognitive Screen

The Oxford Cognitive Screen (OCS) incorporates tests for five cognitive domains: executive function, language, memory, number processing, and praxis [57], while the Cognitive Assessment for Stroke Patients (CASP) addresses language, visuospatial function, memory, praxis, and executive function [58]. CASP, unlike MMSE and MoCA, is applicable also in aphasic patients [59]. Both OCS and CASP address hemispatial neglect and apraxia. These are far more important in VaD than in neurodegenerative dementias. Although the diagnostic value of the Clock Drawing Test (CDT) depends on the scoring method, including quantitative and qualitative aspects [60], it is also regarded as a useful screening tool. Therefore it is recommended in a primary care setting since it probes executive as well as spatial functions. CDT together with a word learning trial, a letter fluency procedure and a naming task, is regarded as suited to a primary care setting to identify global cognitive deficits (Figure 1). Depending on the available assessment time and the patient's condition, these tasks can be either administered as single tasks or combined in a comprehensive short screening (e.g. MoCA, DemTect). Also, the Trail Making Test is sometimes recommended in the short screening context [61]. VASCOG experts suggest also other test combinations for shorter and longer screening, with semantic fluency - animal naming being the most commonly recommended measure [62].

Overall, cognitive screening tests, originally developed to screen for cognitive deficits in memory clinics, are not optimal measures to screen for cognitive impairment during the first month post stroke [63].

An alternative method for cognitive screening is the NeuroPsychological Examination (NPE). NPE is based on observation of the patient's behaviour during an examination. This semi-structured interview gives an opportunity to examine patients and acquire information about their daily functioning. However, its validity is strongly dependent on the clinician's experience [64] (Fig. 1).

Assessment of VCI at a stroke unit

Specialised units (e.g. stroke units/memory clinics) generally offer a far more sophisticated approach due to their extended resources in terms of time and personnel. Nonetheless, considering the patient's overall status when referred to these units, the examination procedure is presumed to be short and adaptable. As aphasia and unilateral neglect are quite common in stroke survivors, and most traditional neuropsychological assessments are not designed for people with language and/or hemispatial deficits, cognitive assessment at stroke units is particularly challenging e.g. when disentangling executive or memory deficits that might exist secondary to language or perceptual problems. Hence, some of the above-mentioned tests can be used or, alternatively, some intermediate batteries may turn out to be useful. As an example, the Birmingham Cognitive Screen (BCoS) offers the possibility to test cognition with minimal involvement of speech (e.g. orientation in time is tested in a multiple choice format). There is only a basic requirement of spatial attention (e.g. vertical alignment of stimuli), also probing for important cognitive aspects that are not included in most neuropsychological test batteries (praxis, calculation, spatial attention) [65]. Since this approach may contain

areas that could not adequately be assessed in some cases, a flexible battery of neuropsychological tests may be adopted.

Such a flexible battery involves the selection and administration of an array of tests that are based on the neuropsychologist's perception of the kind of brain damage that is allegedly present. Regarding the symptom variability, tests should probe the information processing speed, semantic and phonemic fluency, set-shifting, verbal learning (including free and cued short- and long-term recall), visuospatial functions and language abilities, as well as praxis and calculation.

Assessment of VCI at a memory clinic

Patients with suspected VCI are referred for neuropsychological assessment at a memory clinic usually in the context of a differential diagnosis with a primary neurodegenerative disease such as AD, dementia with Lewy bodies (DLB), or frontotemporal-dementia (FTD). Most memory clinics use a comprehensive and fixed battery of tests, all of which were standardised on the same group of people. This approach is called a fixed comprehensive standardised test battery.

The most commonly used test following this approach is the CERAD-NAB (Consortium to Establish a Registry for Alzheimer's Disease – Neuropsychological Assessment Battery). Though this battery was constructed to assess cognitive disturbances in suspected AD, and hence focuses primarily on cortical functions, a more recent extension of this battery was validated [66] by adding measures of speed and flexibility in order to improve diagnostic acuracy in VaD.

In case of a flexible approach, the cognitive assessment protocol should comprise at least one memory task with spontaneous delayed recall followed by either cued delayed recall or recognition to discriminate between storage (typical for AD and other pathologies involving the hippocampus) and retrieval deficit (typical for subcortical dementias). However, as neuropsychological profiles of VCI and DLB may overlap, neuropsychological assessment seems more promising in differentiating between VCI and AD than between VCI and DLB.

Mixed dementia (MD), i.e. the coexistence of Alzheimer's Disease (AD) and cerebrovascular disease (CVD), is a common dementia subtype [67]. It is increasingly recognised that patients with dementia and probable AD dementia commonly have mixed pathologies contributing to cognitive impairment. A study by Lei et al. [68] of 653 autopsied cases from two ongoing longitudinal cohort studies of individuals who were cognitively healthy at baseline (mean age = 79.1 years) analysing cognitive and neuropathological features, showed patients with AD pathology alone doubled the odds of developing dementia, and patients displaying mixed pathologies such as AD with macroinfarcts and/or Lewy body (LB) pathology markedly increased the odds, suggesting that AD pathology as well as vascular pathology are both associated with cognitive impairment.

Several studies have reported macroscopic and microscopic infarcts as well as amyloid angiopathy to be associated with a decline in perceptual speed and episodic memory loss [69]. In light of the striking overlap between AD and VaD contributing to cognitive impairment, it is difficult to establish a profile specific to degenerative or to vascular pathology. One of the few comparative studies, performed by Dong et al. [70], found the neuropsychological profile of patients with MD of mild-moderate severity to be characterised by a poorer global cognitive performance, as well as attention and visuoconstruction, than those with AD of mild-moderate severity. The TRACE–VCI study aimed to define the phenotype of VCI in a memory clinic setting by comparing different forms of vascular brain damage such as white matter hyperintensities, lacunar and non-lacunar infarcts and microbleed. However, the cognitive profiles of these vascular brain injuries were not signicantly different regardless of co-occurring AD [71].

Taken together, the neuropsychological differentiation between AD and MD still remains a diagnostic challenge. More comparative studies adopting comprehensive neuropsychological test batteries are needed to establish the cognitive profiles of mild-moderate MD, and compare it to the profiles of AD.

A more focused approach may also benefit from qualitative data on memory profile. Considering the performance pattern in verbal learning tasks, patients with AD profile reveal marked recency effect and less prominent primacy effect, while in MCI related to white matter hyperintensities either the opposite pattern or low serial position effects may be observed [72].

Behavioural and psychological symptoms in VCI/VaD

Behavioural and psychological symptoms of dementia (BPSD) affect almost all people at some point during the progression of VCI/VaD. In community-based studies, the prevalence of BPS ranges from 60% to 93% [73], whereas in memory units it is higher, ranging from 85% to 100% [74–76]. Besides the type of population (clinical, community or nursing-home settings), the definition of VCI/VaD and the instruments used to study the symptoms, differences in the prevalence and patterns of BPS between various studies may be due to other, often unconsidered, factors such as gender, age, education, use of medication and VCI/VaD severity.

In fact, except for depression, anxiety and euphoria, the frequency and diversity of BPS increases with the severity of cognitive impairment, leading to agitation, hallucinations, irritability, and disinhibition [75, 77]. There is still controversy regarding differences in BPS in different patient groups. While some authors have proposed that overall frequency and severity of BPS are higher in patients with VaD than in those with AD [77], some other groups have reported no significant difference [73, 74, 76, 78].

Although the literature dealing with BPSD in VCI/VaD is modest, some of these symptoms have been included in the criteria proposed for a diagnosis of VaD. The Hachinski Ischaemic Scale, a tool thought to be helpful in the differentiation of AD (cut-off score ≤ 4) from VaD (score ≥ 7), gives one

point for each of the following features: relative preservation of personality, depression and emotional incontinence [79]. Similarly, the NINDS-AIREN criteria include personality and mood changes, abulia, depression and emotional incontinence in the clinical features consistent with the diagnosis of probable VaD [10]. Most studies that have relied on VaD terminology have shown apathy to be the most common symptom (23–94%; [75]), followed by depression (21–85%; [73]), irritability (18–78%; [75, 76]), sleep disturbances (4–78%; [76, 78]) and agitation (21–77%; [75, 78]). Euphoria was the least common symptom (1.6–25%; [76]). A median number of three symptoms per patient has usually been reported [80].

When comparing VaD to AD, the most consistent findings are higher prevalence of delusions, aberrant motor behaviours [73, 74, 78], and hallucinations [74, 75] in AD. Other BPS such as agitation, anxiety, sleep disturbances and changes in appetite have been reported as being more common in AD in some studies, and in VaD in others [74, 76–78]. Compared to patients with DLB, patients with VaD had a lower score in hallucinations, agitation, irritability, anxiety and aberrant motor behaviours [74]. In contrast to FTD, disinhibition, aberrant motor behaviour and changes in appetite were less frequent in VaD [75].

These inconsistent results may be due to the fact that VCI/VaD is a heterogeneous entity with multiple causes (large vessel disease, small vessel disease, haemorrhagic stroke, strategically located lesions) being characterised by various clinical presentations. There appear to be differences in the individual BPS symptoms between sVaD and cVaD. Patients with sVaD had a higher severity of apathy [14, 80], aberrant motor behaviour and hallucinations [80] than patients with cVaD. In VaD, agitation and sleep disturbances are more common than in AD patients, and depression and aberrant motor behaviours appear more commonly in VaD than in mixed AD/VaD patients [81]. In contrast, symptoms of agitation [77, 80], sleep disturbances [77], and euphoria [80] were more severe in cVaD compared to sVaD.

In the most recent study, euphoria, apathy, irritability and agitation were more common in cVaD than in AD, while apathy and irritability were more frequent in sVaD than in AD. Psychotic symptoms and aberrant motor behaviour were more common in AD. A higher risk of euphoria, apathy, irritability and sleep disturbance was found in cVaD than in AD, and more apathy and irritability in sVaD than in AD. In contrast, AD subjects had a higher risk of delusions and hallucinations than patients with cVaD, as well as more aberrant motor behaviour than both cVaD and sVaD [82].

Recently there has been a tendency to conceptualise BPSD into "clusters" of symptoms that appear together: a) "affective" (including depression, anxiety); b) "apathy" (apathy, reduced appetite); c) "hyperactivity" (agitation, euphoria, irritability, disinhibition); and d) "psychosis" (hallucinations, delusions, abnormal motor behaviour (AMB) and sleep disturbances) [83]. Others have described three clusters: a) "mood" (anxiety, apathy, dysphoria); b) "psychosis" (irritability, delusions, hallucinations, agitation); and c) "frontal" (euphoria and disinhibition) in VaD [84].

Finally, it has been debated whether some BPSD in VaD are clinically distinct from those in other types of dementias. For example, compared to depression in AD, psychomotor symptoms such as loss of energy, and vegetative symptoms such as weight loss and loss of appetite, have been reported to be more prevalent in depression co-occurring within VaD [85]. One of the scales most commonly used to assess BPSD symptoms is the Neuropsychiatric Inventory (NPI), covering 12 areas of BPSD [86]. In addition, there are also available scales focused on the assessment of specific BPSD. Commonly used screening tests for depression in patients with suspected VCI include the Geriatric Depression Scale, the nine-item Patient Health Questionnaire, the Beck Depression Inventory, and the Centre for Epidemiologic Studies Depression Scale [87–89]. The Stroke Aphasic Depression Questionnaire or the Depression Intensity Scale Circles can be used to identify mood disturbance in VCI patients with aphasia [90, 91]. The Hamilton Depression Rating Scale and Hospital Anxiety and Depression Scale [HADS] are anxiety- and depression-specific case-finding instruments validated for use in stroke research [87, 92]. Also apathy can be identified by informant-rated specific scales such as the Apathy Evaluation Scale [93]. Of note, the presence of baseline VCI is predictive of apathy but not depression at 12-month follow-up [94].

The BPSD are associated with shorter life expectancy, excess disability, impaired quality of life for subjects and carers, high levels of caregiver distress, early institutionalisation, and increased direct cost of care. However, BPSD can be treated efficiently to improve the situation when correctly diagnosed [95].

The Neuropsychiatric Inventory Caregiver Distress Scale (NPI-D) is an instrument that provides a quantitative measure of the distress experienced by caregivers in relation to the individual symptom domains assessed by the NPI [96]. The Zarit Burden Interview (ZBI) is another validated and comprehensive instrument measuring caregiver burden [97]. Since the interview is a statement which the caregiver is asked to endorse, it is less appropriate to evaluate the burden associated with individual BPSD.

Prognosis and long-term management

Applying DSM–V criteria for major neurocognitive disorders (NCD) helps with defining a psychometric threshold for transition from MCI and small vessel disease (SVD) to major NCD. A longitudinal observation of 138 patients found that one–third of the multi–domain MCI patients with SVD progressed to major NCD after two years [98]. Interestingly, post-stroke cognitive impairment (PSCI) may be more closely related to the overall integrity of brain tissue that the volume of the new ischaemic lesion, as proved in a study in which 20% of patients developed PSCI during a 2-year observation [99].

Post-stroke VCI, unlike MCI in the context of neurodegenerative diseases (e.g. AD or Parkinson's Disease), or VCI with small vessel disease (VCI/SVD), may be quite stable for a couple of years and may thus hinder long-term prognosis about the conversion from VCI (at the mild cognitive impairment stage) to overt VaD. In VCI due to SVD, the conversion of VCI to VaD is usually heralded by the emergence of parkinsonian features. Thus, in a case of SVD or genetically caused vascular pathologies that are known to have a progressive course (e.g. cerebral autosomal dominant/recessive arteriopathy with subcortical infarcts and leukoencephalopathy — CADASIL / CARASIL, and mitochondrial encephalomyopathy lactic acidosis with stroke-like episodes — MELAS), regular neuropsychological follow-ups may be required to track the disease progression and formulate the recommendations for the patient and his/her family.

Such recommendations should include the preparations of powers of attorney for property and personal care, and the patient's ability to manage medication, which is particularly important in individuals with co-morbid insulin-dependent diabetes. Similarly, the impact of VCI on driving capacity needs to be considered.

Summary

Vascular cognitive impairment is an umbrella term comprising different forms and stages of cognitive decline, ranging from mild impairment to overt dementia. It is characterised most commonly by progressive accumulation of microvascular, or subcortical strokes, which results in progressive neurological dysfunction and cognitive as well as behavioural disturbances.

Dementia due to vascular damage is widely considered to be the second most common cause of dementia after AD. The diagnosis of vascular dementia is based on the presence of cerebrovascular disease of different origins, the identification of cognitive dysfunction, and a likely causal relationship between the two. Thus, once other causes of cognitive impairment have been excluded, the diagnosis can be established, if cognitive, as well as behavioural and motor symptoms characteristic of vascular origin and evidence of stroke or white matter lesions on neuroimaging arise. Given the various pathologies leading to VCI, it is no surprise that clinical symptoms can vary substantially in individual patients. Nonetheless, some cognitive features, executive dysfunctions, together with a reduced processing speed and failures of episodic memory are common, and make neuropsychological assessment mandatory.

Given that patients with vascular deficits can appear in different clinical settings, we suggest a two-level assessment procedure consisting of a primary short screening (level A) and an in-depth evaluation (level B). This proposal is in agreement with a recent UK consensus on VCI which advocates the same approach, stating that a single mandated outcome assessment would not be suitable for a complex construct such as VCI [100].

Behavioural disturbances are also common in VCI and may even dominate the clinical picture at some stages, leading to a significant caregiver burden. Compared to AD, there is still a great need for prospective, cross-sectional and longitudinal studies on BPS in VCI. Although there are no consensus criteria about the methodology for screening and investigating BPS in VCI, it is strongly recommended to use standardised protocols to assess BPSD (NPI) as well as caregiver burden (ZBI).

Acknowledgements: *An international workgroup, facilitated by Prof. Pasquale Calabrese, was convened on the occasion of the International Congress on Vascular Dementia (ICVD) which was held in Ljubljana (Slovenia) in October 2015.*

References

1. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. Lancet Neurol. 2003; 2(2): 89–98, doi: 10.1016/s1474-4422(03)00305-3, indexed in Pubmed: 12849265.
2. Graff-Radford J. Vascular Cognitive Impairment. Continuum (Minneap Minn). 2019; 25(1): 147–164, doi: 10.1212/CON.0000000000000684, indexed in Pubmed: 30707191.
3. Frantellizzi V, Pani A, Ricci M, et al. Neuroimaging in Vascular Cognitive Impairment and Dementia: A Systematic Review. J Alzheimers Dis. 2020; 73(4): 1279–1294, doi: 10.3233/JAD-191046, indexed in Pubmed: 31929166.
4. Carnevale L, Lembo G. Innovative MRI Techniques in Neuroimaging Approaches for Cerebrovascular Diseases and Vascular Cognitive Impairment. Int J Mol Sci. 2019; 20(11), doi: 10.3390/ijms20112656, indexed in Pubmed: 31151154.
5. Gorelick PB, Scuteri A, Black SE, et al. American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke. 2011; 42(9): 2672–2713, doi: 10.1161/STR.0b013e3182299496, indexed in Pubmed: 21778438.
6. Bordet R, Ihl R, Korczyn AD, et al. Towards the concept of disease-modifier in post-stroke or vascular cognitive impairment: a consensus report. BMC Med. 2017; 15(1): 107, doi: 10.1186/s12916-017-0869-6, indexed in Pubmed: 28539119.
7. Diagnostic and statistical manual of mental disorders: DSM-5. Arlington, VA: American Psychiatric Association. ; 2017.
8. World Health Organization. (2018). International classification of diseases for mortality and morbidity statistics (11th Revision). https://icd.who.int/browse11/l-m/en.
9. Chui HC, Victoroff JI, Margolin D, et al. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology. 1992; 42(3 Pt 1): 473–480, doi: 10.1212/wnl.42.3.473, indexed in Pubmed: 1549205.
10. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993; 43(2): 250–260, doi: 10.1212/wnl.43.2.250, indexed in Pubmed: 8094895.

11. Sachdev P, Kalaria R, O'Brien J, et al. Internationlal Society for Vascular Behavioral and Cognitive Disorders. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. Alzheimer Dis Assoc Disord. 2014; 28(3): 206–218, doi: 10.1097/WAD.0000000000000034, indexed in Pubmed: 24632990.
12. Sachdev PS, Lipnicki DM, Crawford JD, et al. The Vascular Behavioral and Cognitive Disorders criteria for vascular cognitive disorders: a validation study. Eur J Neurol. 2019; 26(9): 1161–1167, doi: 10.1111/ene.13960, indexed in Pubmed: 30927497.
13. Gladman JT, Corriveau RA, Debette S, et al. Vascular contributions to cognitive impairment and dementia: Research consortia that focus on etiology and treatable targets to lessen the burden of dementia worldwide. Alzheimers Dement (N Y). 2019; 5: 789–796, doi: 10.1016/j.trci.2019.09.017, indexed in Pubmed: 31921967.
14. Gupta M, Dasgupta A, Khwaja GA, et al. Behavioural and psychological symptoms in poststroke vascular cognitive impairment. Behav Neurol. 2014; 2014: 430128, doi: 10.1155/2014/430128, indexed in Pubmed: 24825957.
15. Kalaria RN, Maestre GE, Arizaga R, et al. World Federation of Neurology Dementia Research Group. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. Lancet Neurol. 2008; 7(9): 812–826, doi: 10.1016/S1474-4422(08)70169-8, indexed in Pubmed: 18667359.
16. Ruitenberg A, Ott A, van Swieten JC, et al. Incidence of dementia: does gender make a difference? Neurobiol Aging. 2001; 22(4): 575–580, doi: 10.1016/s0197-4580(01)00231-7, indexed in Pubmed: 11445258.
17. Andersen K, Launer LJ, Dewey ME, et al. Gender differences in the incidence of AD and vascular dementia: The EURODEM Studies. EURODEM Incidence Research Group. Neurology. 1999; 53(9): 1992–1997, doi: 10.1212/wnl.53.9.1992, indexed in Pubmed: 10599770.
18. Chan KY, Wang W, Wu JJ, et al. Global Health Epidemiology Reference Group (GHERG). Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990-2010: a systematic review and analysis. Lancet. 2013; 381(9882): 2016–2023, doi: 10.1016/S0140-6736(13)60221-4, indexed in Pubmed: 23746902.
19. Esmael A, Elsherief M, Eltoukhy K. Prevalence of cognitive impairment in acute ischaemic stroke and use of Alberta Stroke Programme Early CT Score (ASPECTS) for early prediction of post-stroke cognitive impairment. Neurol Neurochir Pol. 2021 [Epub ahead of print], doi: 10.5603/PJNNS.a2021.0006, indexed in Pubmed: 33507530.
20. Rockwood K, Wentzel C, Hachinski V, et al. Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. Neurology. 2000; 54(2): 447–451, doi: 10.1212/wnl.54.2.447, indexed in Pubmed: 10668712.
21. Rincon F, Wright CB. Vascular cognitive impairment. Curr Opin Neurol. 2013; 26(1): 29–36, doi: 10.1097/WCO.0b013e32835c4f04, indexed in Pubmed: 23254555.
22. Vasquez BP, Zakzanis KK. The neuropsychological profile of vascular cognitive impairment not demented: a meta-analysis. J Neuropsychol. 2015; 9(1): 109–136, doi: 10.1111/jnp.12039, indexed in Pubmed: 24612847.
23. Edwards JD, Jacova C, Sepehry AA, et al. A quantitative systematic review of domain-specific cognitive impairment in lacunar stroke. Neurology. 2013; 80(3): 315–322, doi: 10.1212/WNL.0b013e31827deb85, indexed in Pubmed: 23319476.
24. Andriuta D, Roussel M, Barbay M, et al. Godefroy and GRECogVASC study group. Differentiating between Alzheimer's disease and vascular cognitive impairment: Is the "memory versus executive function" contrast still relevant? J Alzheimers Dis. 2018; 63(2): 625–33.
25. Libon D, Price C, Swenson R, et al. Vascular Cognitive Impairment. Neurovascular Neuropsychology. 2009: 75–86, doi: 10.1007/978-0-387-70715-0_6.
26. Schmahmann JD. Vascular syndromes of the thalamus. Stroke. 2003; 34(9): 2264–2278, doi: 10.1161/01.STR.0000087786.38997.9E, indexed in Pubmed: 12933968.
27. Chen Y, Wang A, Tang J, et al. Association of white matter integrity and cognitive functions in patients with subcortical silent lacunar infarcts. Stroke. 2015; 46(4): 1123–1126, doi: 10.1161/STROKEAHA.115.008998, indexed in Pubmed: 25737316.
28. Liu X, Cheng R, Chen Li, et al. Alterations of White Matter Integrity in Subcortical Ischemic Vascular Disease with and Without Cognitive Impairment: a TBSS Study. J Mol Neurosci. 2019; 67(4): 595–603, doi: 10.1007/s12031-019-01266-3, indexed in Pubmed: 30685818.
29. Du J, Wang Y, Zhi N, et al. Structural brain network measures are superior to vascular burden scores in predicting early cognitive impairment in post stroke patients with small vessel disease. Neuroimage Clin. 2019; 22: 101712, doi: 10.1016/j.nicl.2019.101712, indexed in Pubmed: 30772684.
30. Sang L, Liu C, Wang Li, et al. Disrupted Brain Structural Connectivity Network in Subcortical Ischemic Vascular Cognitive Impairment With No Dementia. Front Aging Neurosci. 2020; 12: 6, doi: 10.3389/fnagi.2020.00006, indexed in Pubmed: 32063840.
31. Chen Qi, Wang Y, Qiu Y, et al. A Deep Learning-Based Model for Classification of Different Subtypes of Subcortical Vascular Cognitive Impairment With FLAIR. Front Neurosci. 2020; 14: 557, doi: 10.3389/fnins.2020.00557, indexed in Pubmed: 32625048.
32. Vinciguerra L, Lanza G, Puglisi V, et al. Transcranial Doppler ultrasound in vascular cognitive impairment-no dementia. PLoS One. 2019; 14(4): e0216162, doi: 10.1371/journal.pone.0216162, indexed in Pubmed: 31017968.
33. Giorgio A, Di Donato I, De Leucio A, et al. VMCI-Tuscany Study Group. Relevance of brain lesion location for cognition in vascular mild cognitive impairment. Neuroimage Clin. 2019; 22: 101789, doi: 10.1016/j.nicl.2019.101789, indexed in Pubmed: 30927600.
34. Weaver NA, Zhao L, Biesbroek JM, et al. Meta VCI Map consortium. The Meta VCI Map consortium for meta-analyses on strategic lesion locations for vascular cognitive impairment using lesion-symptom mapping: Design and multicenter pilot study. Alzheimers Dement (Amst). 2019; 11: 310–326, doi: 10.1016/j.dadm.2019.02.007, indexed in Pubmed: 31011619.
35. Tales A, Snowden RJ, Haworth J, et al. Abnormal spatial and non-spatial cueing effects in mild cognitive impairment and Alzheimer's disease. Neurocase. 2005; 11(1): 85–92, doi: 10.1080/13554790490896983, indexed in Pubmed: 15804929.
36. Hachinski V, Iadecola C, Petersen RC, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke. 2006; 37(9): 2220–2241, doi: 10.1161/01.STR.0000237236.88823.47, indexed in Pubmed: 16917086.
37. Barbay M, Taillia H, Nédélec-Ciceri C, et al. GRECOG-VASC Study Group. Prevalence of Poststroke Neurocognitive Disorders Using National Institute of Neurological Disorders and Stroke-Canadian Stroke Network, VASCOG Criteria (Vascular Behavioral and Cognitive Disorders), and Optimized Criteria of Cognitive Deficit. Stroke. 2018; 49(5): 1141–1147, doi: 10.1161/STROKEAHA.117.018889, indexed in Pubmed: 29643258.

38. Pendlebury ST, Mariz J, Bull L, et al. MoCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and stroke. Stroke. 2012; 43(2): 464–469, doi: 10.1161/STROKEAHA.111.633586, indexed in Pubmed: 22156700.
39. Arevalo-Rodriguez I, Smailagic N, Roqué I Figuls M, et al. Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev. 2015(3): CD010783, doi: 10.1002/14651858.CD010783.pub2, indexed in Pubmed: 25740785.
40. Sokołowska N, Sokołowski R, Oleksy E, et al. Usefulness of the Polish versions of the Montreal Cognitive Assessment 7.2 and the Mini-Mental State Examination as screening instruments for the detection of mild neurocognitive disorder. Neurol Neurochir Pol. 2020; 54(5): 440–448, doi: 10.5603/PJNNS.a2020.0064, indexed in Pubmed: 32808669.
41. Koski L. Validity and applications of the Montreal cognitive assessment for the assessment of vascular cognitive impairment. Cerebrovasc Dis. 2013; 36(1): 6–18, doi: 10.1159/000352051, indexed in Pubmed: 23920318.
42. Potocnik J, Ovcar Stante K, Rakusa M. The validity of the Montreal cognitive assessment (MoCA) for the screening of vascular cognitive impairment after ischemic stroke. Acta Neurol Belg. 2020; 120(3): 681–685, doi: 10.1007/s13760-020-01330-5, indexed in Pubmed: 32193731.
43. Chan E, Khan S, Oliver R, et al. Underestimation of cognitive impairments by the Montreal Cognitive Assessment (MoCA) in an acute stroke unit population. J Neurol Sci 2014;343(1–2. : 176–9.
44. Chan E, Altendorff S, Healy C, et al. The test accuracy of the Montreal Cognitive Assessment (MoCA) by stroke lateralisation. J Neurol Sci. 2017; 373: 100–104, doi: 10.1016/j.jns.2016.12.028, indexed in Pubmed: 28131163.
45. Lim JS, Oh MiS, Lee JH, et al. Prediction of post-stroke dementia using NINDS-CSN 5-minute neuropsychology protocol in acute stroke. Int Psychogeriatr. 2017; 29(5): 777–784, doi: 10.1017/S1041610216002520, indexed in Pubmed: 28120733.
46. Chen X, Wong A, Ye R, et al. Validation of NINDS-CSN neuropsychological battery for vascular cognitive impairment in Chinese stroke patients. BMC Neurol. 2015; 15: 20, doi: 10.1186/s12883-015-0270-z, indexed in Pubmed: 25886571.
47. Kessler, J., Calabrese, P., Kalbe, E. and Berger. F. DemTect. Ein neues Screening-Verfahren zur Unterstützung der Demenzdiagnostik. Psycho. 2000; 6: 343–347.
48. Kalbe E, Kessler J, Calabrese P, et al. DemTect: a new, sensitive cognitive screening test to support the diagnosis of mild cognitive impairment and early dementia. Int J Geriatr Psychiatry. 2004; 19(2): 136–143, doi: 10.1002/gps.1042, indexed in Pubmed: 14758579.
49. Wojtyńska R, Szcześniak D. DemTect®--effective to asses MCI and dementia--validation study of the Polish language version. Aging Ment Health. 2016; 20(5): 510–516, doi: 10.1080/13607863.2015.1023763, indexed in Pubmed: 25811731.
50. Kessler J, Calabrese P, Kalbe E. DemTect-B: ein Äquivalenztest zum kognitiven Screening DemTect-A®. Fortschritte der Neurologie · Psychiatrie. 2010; 78(09): 532–535, doi: 10.1055/s-0029-1245452.
51. Kessler J, Fengler S, Kaesberg S, et al. DemTect 40– und DemTect 80+: Neue Auswertungsroutinen für diese Altersgruppen. Fortschritte der Neurologie · Psychiatrie. 2014; 82(11): 640–645, doi: 10.1055/s-0034-1385278.
52. Dobbs BM, Schopflocher D. The Introduction of a New Screening Tool for the Identification of Cognitively Impaired Medically At-Risk Drivers: The SIMARD A Modification of the DemTect. J Prim Care Community Health. 2010; 1(2): 119–127, doi: 10.1177/2150131910369156, indexed in Pubmed: 23804373.
53. Kalbe E, Calabrese P, Fengler S, et al. DemTect, PANDA, EASY, and MUSIC: cognitive screening tools with age correction and weighting of subtests according to their sensitivity and specificity. J Alzheimers Dis. 2013; 34(4): 813–834, doi: 10.3233/JAD-122128, indexed in Pubmed: 23313929.
54. Kalbe E, Calabrese P, Schwalen S, et al. The Rapid Dementia Screening Test (RDST): a new economical tool for detecting possible patients with dementia. Dement Geriatr Cogn Disord. 2003; 16(4): 193–199, doi: 10.1159/000072802, indexed in Pubmed: 14512713.
55. Brookes RL, Hannesdottir K, Lawrence R, et al. Brief Memory and Executive Test: evaluation of a new screening test for cognitive impairment due to small vessel disease. Age Ageing. 2012; 41(2): 212–218, doi: 10.1093/ageing/afr172, indexed in Pubmed: 22267862.
56. Ghafar MZ, Miptah HN, O'Caoimh R. Cognitive screening instruments to identify vascular cognitive impairment: A systematic review. Int J Geriatr Psychiatry. 2019; 34(8): 1114–1127, doi: 10.1002/gps.5136, indexed in Pubmed: 31050033.
57. Demeyere N, Riddoch MJ, Slavkova ED, et al. The Oxford Cognitive Screen (OCS): validation of a stroke-specific short cognitive screening tool. Psychol Assess. 2015; 27(3): 883–894, doi: 10.1037/pas0000082, indexed in Pubmed: 25730165.
58. Benaim C, Barnay JL, Wauquiez G, et al. The Cognitive Assessment scale for Stroke Patients (CASP) vs. MMSE and MoCA in non-aphasic hemispheric stroke patients. Ann Phys Rehabil Med. 2015; 58(2): 78–85, doi: 10.1016/j.rehab.2014.12.001, indexed in Pubmed: 25766087.
59. Barnay JL, Wauquiez G, Bonnin-Koang HY, et al. Feasibility of the cognitive assessment scale for stroke patients (CASP) vs. MMSE and MoCA in aphasic left hemispheric stroke patients. Ann Phys Rehabil Med. 2014; 57(6-7): 422–435, doi: 10.1016/j.rehab.2014.05.010, indexed in Pubmed: 24953703.
60. Tan LP, Herrmann N, Mainland BJ, et al. Can clock drawing differentiate Alzheimer's disease from other dementias? Int Psychogeriatr. 2015; 27(10): 1649–1660, doi: 10.1017/S1041610215000939, indexed in Pubmed: 26138809.
61. Richards E, Bayer A, Hanley C, et al. Reaction Time and Visible White Matter Lesions in Subcortical Ischemic Vascular Cognitive Impairment. J Alzheimers Dis. 2019; 72(3): 859–865, doi: 10.3233/JAD-190823, indexed in Pubmed: 31658059.
62. Skrobot OA, Black SE, Chen C, et al. VICCCS group. Progress toward standardized diagnosis of vascular cognitive impairment: Guidelines from the Vascular Impairment of Cognition Classification Consensus Study. Alzheimers Dement. 2018; 14(3): 280–292, doi: 10.1016/j.jalz.2017.09.007, indexed in Pubmed: 29055812.
63. Van Heugten CM, Walton L, Hentschel U. Can we forget the Mini-Mental State Examination? A systematic review of the validity of cognitive screening instruments within one month after stroke. Clin Rehabil. 2015; 29(7): 694–704, doi: 10.1177/0269215514553012, indexed in Pubmed: 25381346.
64. Abbate C, Trimarchi PD, Inglese S, et al. Signs and symptoms method in neuropsychology: A preliminary investigation of a standardized clinical interview for assessment of cognitive decline in dementia. Appl Neuropsychol Adult. 2021; 28(3): 282–296, doi: 10.1080/23279095.2019.1630626, indexed in Pubmed: 31269816.

65. Bickerton WL, Demeyere N, Francis D, et al. The BCoS cognitive profile screen: Utility and predictive value for stroke. Neuropsychology. 2015; 29(4): 638–648, doi: 10.1037/neu0000160, indexed in Pubmed: 25545235.
66. Schmid NS, Ehrensperger MM, Berres M, et al. The Extension of the German CERAD Neuropsychological Assessment Battery with Tests Assessing Subcortical, Executive and Frontal Functions Improves Accuracy in Dementia Diagnosis. Dement Geriatr Cogn Dis Extra. 2014; 4(2): 322–334, doi: 10.1159/000357774, indexed in Pubmed: 25298776.
67. Korczyn AD. Mixed dementia–the most common cause of dementia. Ann N Y Acad Sci. 2002; 977: 129–134, doi: 10.1111/j.1749-6632.2002.tb04807.x, indexed in Pubmed: 12480742.
68. Yu L, Boyle PA, Leurgans S, et al. Effect of common neuropathologies on progression of late life cognitive impairment. Neurobiol Aging. 2015; 36(7): 2225–2231, doi: 10.1016/j.neurobiolaging.2015.04.006, indexed in Pubmed: 25976345.
69. Schneider JA, Bennett DA. Where vascular meets neurodegenerative disease. Stroke. 2010; 41(10 Suppl): S144–S146, doi: 10.1161/STROKEAHA.110.598326, indexed in Pubmed: 20876491.
70. Dong Y, Gan DZ, Tay SZ, et al. Patterns of neuropsychological impairment in Alzheimer's disease and mixed dementia. J Neurol Sci. 2013; 333(1-2): 5–8, doi: 10.1016/j.jns.2013.05.011, indexed in Pubmed: 23978422.
71. Boomsma JMF, Exalto LG, Barkhof F, et al. behalf of the TRACE-VCI study group. How Do Different Forms of Vascular Brain Injury Relate to Cognition in a Memory Clinic Population: The TRACE-VCI Study. J Alzheimers Dis. 2019; 68(3): 1273–1286, doi: 10.3233/JAD-180696, indexed in Pubmed: 30909212.
72. Chander RJ, Foo H, Yong T, et al. Serial position effects differ between Alzheimer's and vascular features in mild cognitive impairment. Aging (Albany NY). 2018; 10(12): 3866–3880, doi: 10.18632/aging.101678, indexed in Pubmed: 30540261.
73. Ikeda M, Fukuhara R, Shigenobu K, et al. Dementia associated mental and behavioural disturbances in elderly people in the community: findings from the first Nakayama study. J Neurol Neurosurg Psychiatry. 2004; 75(1): 146–148, indexed in Pubmed: 14707327.
74. Caputo M, Monastero R, Mariani E, et al. Neuropsychiatric symptoms in 921 elderly subjects with dementia: a comparison between vascular and neurodegenerative types. Acta Psychiatr Scand. 2008; 117(6): 455–464, doi: 10.1111/j.1600-0447.2008.01175.x, indexed in Pubmed: 18363771.
75. Srikanth S, Nagaraja AV, Ratnavalli E. Neuropsychiatric symptoms in dementia-frequency, relationship to dementia severity and comparison in Alzheimer's disease, vascular dementia and frontotemporal dementia. J Neurol Sci. 2005; 236(1-2): 43–48, doi: 10.1016/j.jns.2005.04.014, indexed in Pubmed: 15964021.
76. Hsieh CJ, Chang CC, Lin CC. Neuropsychiatric profiles of patients with Alzheimer's disease and vascular dementia in Taiwan. Int J Geriatr Psychiatry. 2009; 24(6): 570–577, doi: 10.1002/gps.2156, indexed in Pubmed: 19051223.
77. Fuh JL, Wang SJ, Cummings JL. Neuropsychiatric profiles in patients with Alzheimer's disease and vascular dementia. J Neurol Neurosurg Psychiatry. 2005; 76(10): 1337–1341, doi: 10.1136/jnnp.2004.056408, indexed in Pubmed: 16170072.
78. Fernández-Martínez M, Castro J, Molano A, et al. Prevalence of neuropsychiatric symptoms in Alzheimer's disease and vascular dementia. Curr Alzheimer Res. 2008; 5(1): 61–69, doi: 10.2174/156720508783884585, indexed in Pubmed: 18288933.
79. Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral blood flow in dementia. Arch Neurol. 1975; 32(9): 632–637, doi: 10.1001/archneur.1975.00490510088009, indexed in Pubmed: 1164215.
80. Staekenborg SS, Su T, van Straaten ECW, et al. Behavioural and psychological symptoms in vascular dementia; differences between small- and large-vessel disease. J Neurol Neurosurg Psychiatry. 2010; 81(5): 547–551, doi: 10.1136/jnnp.2009.187500, indexed in Pubmed: 19965852.
81. Anor CJ, O'Connor S, Saund A, et al. Neuropsychiatric Symptoms in Alzheimer Disease, Vascular Dementia, and Mixed Dementia. Neurodegener Dis. 2017; 17(4-5): 127–134, doi: 10.1159/000455127, indexed in Pubmed: 28245482.
82. Manso-Calderón R, Cacabelos-Pérez P, Sevillano-García MD, et al. The impact of vascular burden on behavioural and psychological symptoms in older adults with dementia: the BEVASDE study. Neurol Sci. 2020; 41(1): 165–174, doi: 10.1007/s10072-019-04071-3, indexed in Pubmed: 31494822.
83. Aalten P, Verhey FRJ, Boziki M, et al. Consistency of neuropsychiatric syndromes across dementias: results from the European Alzheimer Disease Consortium. Part II. Dement Geriatr Cogn Disord. 2008; 25(1): 1–8, doi: 10.1159/000111082, indexed in Pubmed: 18025783.
84. Johnson DK, Watts AS, Chapin BA, et al. Neuropsychiatric profiles in dementia. Alzheimer Dis Assoc Disord. 2011; 25(4): 326–332, doi: 10.1097/WAD.0b013e31820d89b6, indexed in Pubmed: 22086220.
85. Park JH, Lee SB, Lee TJ, et al. Depression in vascular dementia is quantitatively and qualitatively different from depression in Alzheimer's disease. Dement Geriatr Cogn Disord. 2007; 23(2): 67–73, doi: 10.1159/000097039, indexed in Pubmed: 17114882.
86. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. Neurology. 1997; 48(5 Suppl 6): S10–S16, doi: 10.1212/wnl.48.5_suppl_6.10s, indexed in Pubmed: 9153155.
87. Aben I, Verhey F, Lousberg R, et al. Validity of the beck depression inventory, hospital anxiety and depression scale, SCL-90, and hamilton depression rating scale as screening instruments for depression in stroke patients. Psychosomatics. 2002; 43(5): 386–393, doi: 10.1176/appi.psy.43.5.386, indexed in Pubmed: 12297607.
88. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001; 16(9): 606–613, doi: 10.1046/j.1525-1497.2001.016009606.x, indexed in Pubmed: 11556941.
89. Radloff L. The CES-D Scale. Applied Psychological Measurement. 2016; 1(3): 385–401, doi: 10.1177/014662167700100306.
90. Benaim C, Cailly B, Perennou D, et al. Validation of the aphasic depression rating scale. Stroke. 2004; 35(7): 1692–1696, doi: 10.1161/01.STR.0000130591.95710.20, indexed in Pubmed: 15143288.
91. Turner-Stokes L, Kalmus M, Hirani D, et al. The Depression Intensity Scale Circles (DISCs): a first evaluation of a simple assessment tool for depression in the context of brain injury. J Neurol Neurosurg Psychiatry. 2005; 76(9): 1273–1278, doi: 10.1136/jnnp.2004.050096, indexed in Pubmed: 16107367.
92. Sagen U, Vik TG, Moum T, et al. Screening for anxiety and depression after stroke: comparison of the hospital anxiety and depression scale and the Montgomery and Asberg depression rating scale. J Psychosom Res. 2009; 67(4): 325–332, doi: 10.1016/j.jpsychores.2009.03.007, indexed in Pubmed: 19773025.
93. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res. 1991; 38(2): 143–162, doi: 10.1016/0165-1781(91)90040-v, indexed in Pubmed: 1754629.
94. Douven E, Köhler S, Schievink SHJ, et al. Baseline Vascular Cognitive Impairment Predicts the Course of Apathetic Symptoms After Stroke:

The CASPER Study. Am J Geriatr Psychiatry. 2018; 26(3): 291–300, doi: 10.1016/j.jagp.2017.09.022, indexed in Pubmed: 29079017.

95. Kim JM, Lyons D, Shin IS, et al. Differences in the behavioral and psychological symptoms between Alzheimer's disease and vascular dementia: are the different pharmacologic treatment strategies justifiable? Hum Psychopharmacol. 2003; 18(3): 215–220, doi: 10.1002/hup.466, indexed in Pubmed: 12672174.
96. Kaufer DI, Cummings JL, Christine D, et al. Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: the Neuropsychiatric Inventory Caregiver Distress Scale. J Am Geriatr Soc. 1998; 46(2): 210–215, doi: 10.1111/j.1532-5415.1998.tb02542.x, indexed in Pubmed: 9475452.
97. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist. 1980; 20(6): 649–655, doi: 10.1093/geront/20.6.649, indexed in Pubmed: 7203086.
98. Salvadori E, Poggesi A, Pracucci G, et al. VMCI-Tuscany Study Group. Application of the DSM-5 Criteria for Major Neurocognitive Disorder to Vascular MCI Patients. Dement Geriatr Cogn Dis Extra. 2018; 8(1): 104–116, doi: 10.1159/000487130, indexed in Pubmed: 29706987.
99. Molad J, Hallevi H, Korczyn AD, et al. Vascular and Neurodegenerative Markers for the Prediction of Post-Stroke Cognitive Impairment: Results from the TABASCO Study. J Alzheimers Dis. 2019; 70(3): 889–898, doi: 10.3233/JAD-190339, indexed in Pubmed: 31282420.
100. McFall A, Hietamies TM, Bernard A, et al. UK consensus on pre-clinical vascular cognitive impairment functional outcomes assessment: Questionnaire and workshop proceedings. J Cereb Blood Flow Metab. 2020; 40(7): 1402–1414, doi: 10.1177/0271678X20910552, indexed in Pubmed: 32151228.

REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4, pages: 346–350
DOI: 10.5603/PJNNS.a2021.0041

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

Battery for deep brain stimulation depletion in Parkinson's Disease and dystonia patients — a systematic review

Filip Przytuła[1], Jarosław Dulski[1,2], Michał Sobstyl[3], Jarosław Sławek[1,2]

[1]Neurology & Stroke Dpt., St. Adalbert Hospital, Gdansk, Poland
[2]Department of Neurological-Psychiatric Nursing, Medical University of Gdansk, Poland
[3]Neurosurgery Dpt., Institute of Neurosurgery and Psychiatry, Warsaw, Poland

ABSTRACT

Introduction. Deep brain stimulation (DBS) therapy for Parkinson's Disease (PD) and dystonia is associated with the possibility of both minor and major complications. One possible side effect is the depletion of implantable pulse generator (IPG) battery and the associated sudden recurrence of PD or dystonia symptoms, which can be potentially life-threatening. Delayed or postponed outpatient visits due to COVID -19 may be a risk factor of battery end-of-life consequences.

Objective. To analyse the clinical outcomes in reported PD and dystonia patients treated with DBS, who, as a result of the sudden depletion of the neurostimulator battery, developed life-threatening symptoms.

Materials and methods. The databases of PubMed, Scopus, EMBASE and Google Scholar were searched using pre-established criteria.

Results. A total of 244 articles was found, of which 12 met the adopted criteria. Selected papers presented a total of 17 case reports of DBS-treated patients — 11 with PD, and six with dystonia — who had depleted IPG batteries and due to rapid worsening of PD/dystonia symptoms required urgent hospital admission. IPG battery replacement was the only effective treatment in the majority of cases.

Conclusions. IPG battery depletion can result in fatal outcomes. Sudden recurrence of PD or dystonia symptoms in patients treated by DBS can be potentially life-threatening, so scheduling the replacement of a discharged IPG battery should not be postponed. The COVID-19 pandemic should alert staff at emergency, neurology and movement disorders wards not to postpone the visits of patients with an implanted DBS system.

Key words: Parkinson's Disease, dystonia, deep brain stimulation, battery depletion, COVID-19

(*Neurol Neurochir Pol 2021; 55 (4): 346–350*)

Introduction

Deep brain stimulation (DBS) has become an established treatment option for patients with movement disorders including Parkinson's Disease (PD) and dystonia. In numerous clinical trials, DBS has shown improvement in quality of life, mobility in patients with advanced PD suffering bothersome motor fluctuations, treatment-resistant dyskinesias, the majority of non-motor symptoms, as well as motor symptoms of drug-resistant focal/segmental or generalised dystonia. DBS has been approved by the US Food and Drug Administration as an effective therapy for PD since 2002, and since 2003 for the treatment of dystonia [1–3]. Nevertheless, DBS implantation is associated with the possibility of both minor and major complications due to the implanted system [4, 5].

One possible side effect is the depletion of the implantable pulse generator (IPG) battery and the associated sudden recurrence of PD or dystonia symptoms. These symptoms can be potentially life-threatening, so scheduling the replacement of a discharged IPG battery should not be postponed. During the COVID-19 pandemic, medical centres have postponed scheduled procedures, admitted only urgent cases in order to limit

Address for correspondence: Jarosław Sławek, Neurology and Stroke Department., St. Adalbert Hospital, Al. Jana Pawła II 50, 80–462 Gdansk, Poland; e-mail: jaroslaw.slawek@gumed.edu.pl

Received: 11.02.2021 Accepted: 8.04.2021 Early publication date: 31.05.2021

the spread of Sars-CoV-2, and allocated hospital resources to control the pandemic [6, 7]. Patients with depleted batteries of DBS systems cannot wait, because the potential consequences of abrupt cessation of stimulation can be fatal, such as parkinsonism-hyperpyrexia syndrome, sudden akinesia with falls and bone fractures, venous thrombosis and pulmonary embolism or aspiration pneumonia in PD, and dystonic state in dystonia patients with rhabdomyolysis and renal failure.

Materials and methods

We searched the available literature using the PubMed, Scopus, EMBASE and Google Scholar databases for the keywords 'deep brain stimulation', 'depletion', 'withdrawal', 'battery exhaustion', 'hardware failure', 'Parkinson disease' and 'dystonia' in various combinations. A total of 244 articles was found. The literature review included studies published from 1996 (i.e. from the introduction of DBS into clinical practice) to 2020 (31 December). The study did not include cases where brain stimulation was interrupted by infection of IPG system or electrodes, or for reasons other than discharge of the IPG battery. Papers were written in English, published as full-length texts. Abstracts as well as review papers were not included.

Results

We found a total of 244 articles, from which 12 met the established criteria. Selected papers presented a total of 17 case reports of DBS-treated patients — 11 with PD, six with dystonia — who had depleted IPG batteries (Tab. 1, 2), who required urgent hospital admission. Ten patients with PD developed acute akinetic syndrome. Six of them were finally diagnosed with parkinsonism-hyperpyrexia syndrome (PHS), three had pulmonary embolism, deep vein thrombosis and aspiration pneumonia, and one had disseminated intravascular coagulation (DIC) and consequently multi-organ failure and death. One patient developed a coma as a result of IPG battery discharge. 2/11 patients with PD were reported during the COVID-19 pandemic. In the reported cases, the sudden recurrence of symptoms did not result from a reduction of oral antiparkinsonian treatment.

Among patients treated with DBS GPi for dystonia, six reports of IPG battery depletion and sudden motor deterioration were found (Tab. 2). Of these six patients, three developed acute dystonic state (two required urgent ICU admission - one patient developed cardio-respiratory failure and died despite intensive treatment, the other developed cardiopulmonary failure, rhabdomyolysis-related acute renal failure, and DIC as a result of dystonic state). 3/6 patients had dystonia symptoms worsening as a result of IPG battery depletion. Urgent battery replacement resulted in motor function improvement in two patients; one patient reported during the pandemic postponed their surgical procedure for financial reasons.

Discussion

The presented reports of PD and dystonia patients treated with DBS have shown that IPG battery depletion can result in fatal outcomes and must be avoided.

This abrupt cessation of DBS function may be due to delayed or postponed outpatient visits. Two PD patients described by Holla et al. had postponed follow-up visits due to the COVID-19 pandemic, resulting in IPG battery depletion and akinetic state [6]. COVID-19 may be a risk factor because many hospitals have limited access for ambulatory patients and also for planned surgeries. Patients, especially those with chronic diseases and co-morbidities, have avoided hospital and outpatient visits to protect themselves against infection. In some regions, a shortage of medical staff has also forced movement disorder neurologists to provide care for patients with COVID-19 [19].

In severe cases, where symptoms cannot be relieved with increased doses of oral or intravenous/subcutaneous/transcutaneous medications and general treatment, an urgent IPG battery replacement should be performed. This was the only effective treatment in the majority of cases (Tab. 1, 2). The range of PD duration was in reported cases 12–22 years with long-lasting DBS therapy (3–14 years) and in such patients, the replacement of only pharmacological therapy instead of combined treatment with DBS is usually ineffective.

Parkinsonism-hyperpyrexia syndrome is one of the potentially fatal complications in PD patients, most often occurring after a sudden reduction or discontinuation of antiparkinsonian medications, but also DBS battery depletion [20, 21]. This was a main complication in 5/11 patients (Tab. 1) and manifested itself as muscle stiffness, fever, impaired consciousness, and dysautonomia. It is characterised by leukocytosis and elevated levels of creatine kinase (CK) in laboratory tests.

The most common direct causes of death in patients with PHS are aspiration pneumonia, acute renal failure, deep vein thrombosis, pulmonary embolism, and DIC [22]. Nevertheless, akinetic-rigid state as the result of IPG battery depletion, reported in 6/11 PD cases, can also result in pneumonia, falls and bone fractures or head injuries, deep vein thrombosis with pulmonary embolism, and dysphagia with the risk of aspiration pneumonia, and should be recognised and treated vigorously.

Dystonic state (DS), the main complication in 3/6 patients reported (Tab. 2), is characterised by muscle rigidity, muscle pain and fever. Muscle contractions involve also respiratory muscles and abdomen and lead to respiratory failure and hypoxaemia. Abnormal muscle contractions in the gastrointestinal tract can lead to dysphagia and aspiration pneumonia. Another potentially fatal complication of DS is rhabdomyolysis and acute renal failure [23]. Rapidly worsening symptoms are life-threatening. In patients with dystonia treated with DBS-GPi, there have been reports of a dystonic state resulting in cardio-respiratory failure requiring hospitalisation in the ICU.

Table 1. Published PD cases with abrupt IPG battery depletion (in all patients bilateral STN was anatomical target)

Article	Age/sex	PD duration /DBS treatment duration	Battery depletion effect	Treatment/outcome
Chou et al. [8]	63/M	17 years/4 years	• Acute akinetic state • Deep vein thrombosis, pulmonary embolism	• Oral levodopa treatment/no effect • Inferior vena cava filter, anticoagulation treatment • IPG battery replacement (5 days after hospital admission)/ improvement of motor function
	76/M	14 years/3 years	• Acute akinetic state	• Oral levodopa treatment/ no effect • IPG battery replacement (a few days after motor function worsening)/improvement of motor function
Neuneier et al. [9]	77/M	18 years/5 years	• PHS • DIC • Multi organ failure	• Oral levodopa treatment/ no effect • Antibiotic therapy, fluid therapy, amantadine infusion, antipyretic treatment/no effect • IPG battery replacement (10 days after hospital admission)/no effect • Death
Artusi et al. [10]	63/M	13 years/5 years	• PHS	• Fluid therapy, antipyretic therapy/general improvement • Oral levodopa treatment/no effect • IPG battery replacement (4 days after symptom onset)/improvement of motor function
R. Rajan et al. [11]	51/M	18 years/7 years	• Acute akinetic state • PHS	• Oral levodopa treatment, amantadine infusion/no effect • Fluid therapy, antipyretic treatment, antibiotic therapy/no effect • IPG battery replacement (11 days after hospital admission)/ general and motor function improvement
	54/F	22 years/11 years	• Acute akinetic state • Aspiration pneumonia	• Oral levodopa treatment, pramipexol, amantadine infusion/no effect • Antibiotic therapy, CPAP • IPG battery replacement (8 days after hospital admission)/ general and motor function improvement
Liu et al. [12]	69/M	12 years/3 years	• PHS	• Antibiotic therapy, fluid therapy, antipyretic therapy/no effect • Oral levodopa treatment, bromocriptine, dantrolen, benzodiazepine admission/no effect • IPG battery replacement (2 days after hospital admission)/ general and motor improvement
Azar et al. [13]	67/F	23 years/7 years	• PHS	• Antibiotic therapy, B1 vitamin admission, fluid therapy/no effect • Oral levodopa treatment/ no effect • IPG battery replacement (17 days after hospital admission)/ general and motor improvement
Kamel et al. [14]	73/M	21 years/14 years	• Coma (GCS 4)	• Oral levodopa treatment/no effect • IPG battery replacement (urgent surgery)/general improvement
Holla et al. [6]	67/M	17 years/4 years	• Acute akinetic state	• IPG battery replacement/motor function improvement
	60/F	17 years/4 years	• Acute akinetic state	• Oral levodopa treatment/minimal motor function improvement • IPG battery replacement/motor function improvement

CPAP — continuous positive airway pressure; DIC — disseminated intravascular coagulation; GCS — Glasgow Coma Scale; IPG — internal pulse generator; PHS — parkinsonism hyperpyrexia syndrome

Table 2. Published dystonia cases with abrupt IPG battery depletion

Article	Age/sex	Dystonia type/dystonia duration/DBS treatment duration	Anatomical target	Battery depletion effect	Treatment/effect
Li et al. [15]	17/F	PKAN/6 years/5 years	STN	• Dystonic state	• IPG battery replacement/motor function improvement
Rohani et al. [16]	41/F	TD/8l years/3 years	GPi	• Dystonic state • Cardio-pulmonary failure=	• ICU admission • Mechanical ventilation • Death
Sobstyl et al. [17]	15/M	DYT1/6 years/5 years	GPi	• Dystonic state • Cardio-pulmonary failure • Rhabdomyolysis, acute disease failure • DIC	• Mechanical ventilation circulatory support • Dialysis therapy • IPG battery replacement (1 day after hospital admission)/motor function improvement
Yanni et al. [18]	25/F	Secondary dystonia/7 years/2 years	GPi	• Worsening symptoms of dystonia	• IPG battery replacement (urgent surgery at admission day)/motor function improvement
	9/F	Idiopathic dystonia/6 years/2 years	GPi	• Worsening symptoms of dystonia	• IPG battery replacement (urgent surgery)/motor function improvement
Holla et al. [6]	33/M	Idiopathic generalised dystonia/9 years/3 years	GPi	• Worsening symptoms of dystonia	• Postponing procedure due to patient's finances, optimising pharmacological treatment

DIC — disseminated intravascular coagulation; DYT1 — early onset torsion dystonia; GPi — Internal Globus Pallidus; ICU — intensive care unit; IPG — internal pulse generator; PKAN — Pantothenate Kinase-Associated Neurodegeneration; STN — subthalamic nucleus; TD — tarditive dystonia

In one case described, the battery was discharged and resulted in the death of the patient. Dystonic state should be treated as a neurological emergency and battery depletion has a worse prognosis in patients with dystonia than with PD: in PD patients with sudden DBS shutdown, symptoms can be partly relieved with increased doses of antiparkinsonian medications, while in dystonia patients there is no such emergency treatment and the only effective treatment is battery replacement.

Mitchel et al. analysed patient satisfaction with rechargeable IPGs. Patient experience, especially those with dystonia, was positive, and they especially valued the fewer surgeries [24]. Considering the above, and the higher total electrical energy delivered and higher battery consumption in dystonia than in PD, the implantation of rechargeable batteries should be considered in every patient with dystonia treated with DBS.

Conclusions

This situation should warn medical staff at emergency, neurology and movement disorders wards against postponing the visits of patients with an implanted DBS system. Despite the progress and development of DBS technology, there are still no programmes or applications available for remote battery checking. Manufacturers of equipment for deep brain stimulation should also ensure smooth delivery of the necessary elements of DBS systems, especially during a pandemic, to ensure constant access to depleted IPGs and shorten possible replacement delays. To avoid a sudden shutdown of DBS pacing due to battery depletion, battery status and electrical integrity may be checked through telemedicine or telephone consultation [7]. If the battery power is low, the elective procedure of IPG replacement should be planned and performed as soon as possible. One possible solution would be replacing IPG batteries as an outpatient procedure. To minimise the risk of sudden cessation of stimulation, reduction of amperage and frequency of the stimulation should be considered to reduce temporarily total electrical energy delivered and battery consumption [25].

Despite many years of practice of using DBS in patients with PD and dystonia, no studies including larger groups of patients with battery depletion were found in our search of databases. It is difficult to assess the percentage of patients with battery depletion, and the number appears to be underreported. Nevertheless, all presented case reports are valuable and show the potentially fatal risks of delaying battery replacement.

References

1. Hu W, Stead M, Klassen BT. Surgery for movement disorders. J Neurosurg Sci. 2011; 55(4): 305–317, indexed in Pubmed: 22198583.
2. Krack P, Volkmann J, Tinkhauser G, et al. Deep brain stimulation in movement disorders: from experimental surgery to evidence-based therapy. Mov Disord. 2019; 34(12): 1795–1810, doi: 10.1002/mds.27860, indexed in Pubmed: 31580535.

3. Dulski J, Schinwelski M, Konkel A, et al. The impact of subthalamic deep brain stimulation on polysomnographic sleep pattern in patients with Parkinson's disease - Preliminary report. Neurol Neurochir Pol. 2018; 52(4): 514–518, doi: 10.1016/j.pjnns.2018.05.006, indexed in Pubmed: 29887129.
4. Sobstyl M, Stapińska-Syniec A, Giziński J, et al. Deep brain stimulation hardware-related complications and their management: A single-center retrospective analysis of 65 patients with various dystonic conditions. J Neurol Sci. 2019; 407: 116513, doi: 10.1016/j.jns.2019.116513, indexed in Pubmed: 31678789.
5. Sobstyl M, Stapińska-Syniec A, Rylski M. Deep brain stimulation procedure complicated by spontaneously resolved pneumothorax in a patient with cervical dystonia. Neurol Neurochir Pol. 2021; 55(1): 110–112, doi: 10.5603/PJNNS.a2020.0091, indexed in Pubmed: 33274433.
6. Holla VV, Neeraja K, Surisetti BK, et al. Deep brain stimulation battery exhaustion during the COVID-19 pandemic: crisis within a crisis. J Mov Disord. 2020; 13(3): 218–222, doi: 10.14802/jmd.20073, indexed in Pubmed: 32854480.
7. Miocinovic S, Ostrem JL, Okun MS, et al. Recommendations for deep brain stimulation device management during a pandemic. J Parkinsons Dis. 2020; 10(3): 903–910, doi: 10.3233/JPD-202072, indexed in Pubmed: 32333552.
8. Chou KL, Siderowf AD, Jaggi JL, et al. Unilateral battery depletion in Parkinson's disease patients treated with bilateral subthalamic nucleus deep brain stimulation may require urgent surgical replacement. Stereotact Funct Neurosurg. 2004; 82(4): 153–155, doi: 10.1159/000081348, indexed in Pubmed: 15475657.
9. Neuneier J, Barbe MT, Dohmen C, et al. Malignant deep brain stimulation-withdrawal syndrome in a patient with Parkinson's disease. Mov Disord. 2013; 28(12): 1640–1641, doi: 10.1002/mds.25494, indexed in Pubmed: 23857820.
10. Artusi CA, Merola A, Espay AJ, et al. Parkinsonism-hyperpyrexia syndrome and deep brain stimulation. J Neurol. 2015; 262(12): 2780–2782, doi: 10.1007/s00415-015-7956-4, indexed in Pubmed: 26530506.
11. Rajan R, Krishnan S, Kesavapisharady KK, et al. Malignant subthalamic nucleus-deep brain stimulation withdrawal syndrome in Parkinson's disease. Mov Disord Clin Pract. 2016; 3(3): 288–291, doi: 10.1002/mdc3.12271, indexed in Pubmed: 30363553.
12. Liu CJJ, Crnkovic A, Dalfino J, et al. Whether to proceed with deep brain stimulator battery change in a patient with signs of potential sepsis and Parkinson hyperpyrexia syndrome: a case report. A A Case Rep. 2017; 8(8): 187–191, doi: 10.1213/XAA.0000000000000462, indexed in Pubmed: 28166109.
13. Azar J, Elinav H, Safadi R, et al. Malignant deep brain stimulator withdrawal syndrome. BMJ Case Rep. 2019; 12(5), doi: 10.1136/bcr-2018-229122, indexed in Pubmed: 31092485.
14. Kamel WA, Al-Hashel JY, Damier P, et al. Decreased level of consciousness due to a depleted deep brain stimulator battery: Paving the way to wake up the brain? Rev Neurol (Paris). 2019; 175(4): 274–275, doi: 10.1016/j.neurol.2018.06.009, indexed in Pubmed: 30879605.
15. Li H, Zhang C, Pan Y, et al. Status dystonicus in pantothenate kinase-associated neurodegeneration due to internal pulse generator depletion: Case study and literature review. J Neurol Sci. 2019; 400: 44–46, doi: 10.1016/j.jns.2019.02.038, indexed in Pubmed: 30903858.
16. Rohani M, Munhoz RP, Shahidi G, et al. Fatal status dystonicus in tardive dystonia due to depletion of deep brain stimulation's pulse generator. Brain Stimul. 2017; 10(1): 160–161, doi: 10.1016/j.brs.2016.10.006, indexed in Pubmed: 28017319.
17. Sobstyl M, Ząbek M, Kmieć T, et al. Status dystonicus due to internal pulse generator depletion in a patient with primary generalized dystonia. Mov Disord. 2014; 29(2): 188–189, doi: 10.1002/mds.25553, indexed in Pubmed: 23868498.
18. Yianni J, Nandi D, Ch M, et al. Failure of chronic pallidal stimulation in dystonic patients is a medical emergency. Neuromodulation. 2004; 7(1): 9–12, doi: 10.1111/j.1525-1403.2004.04008.x, indexed in Pubmed: 22151121.
19. Fasano A, Antonini A, Katzenschlager R, et al. Management of advanced therapies in Parkinson's disease patients in times of humanitarian crisis: the COVID-19 experience. Mov Disord Clin Pract. 2020; 7(4): 361–372, doi: 10.1002/mdc3.12965, indexed in Pubmed: 32373652.
20. Newman EJ, Grosset DG, Kennedy PGE. The parkinsonism-hyperpyrexia syndrome. Neurocrit Care. 2009; 10(1): 136–140, doi: 10.1007/s12028-008-9125-4, indexed in Pubmed: 18712508.
21. Factor SA. Fatal Parkinsonism-hyperpyrexia syndrome in a Parkinson's disease patient while actively treated with deep brain stimulation. Mov Disord. 2007; 22(1): 148–149, doi: 10.1002/mds.21172, indexed in Pubmed: 17080464.
22. Newman EJ, Grosset DG, Kennedy PGE. The parkinsonism-hyperpyrexia syndrome. Neurocrit Care. 2009; 10(1): 136–140, doi: 10.1007/s12028-008-9125-4, indexed in Pubmed: 18712508.
23. Sobstyl MR, Sławek JW, Ząbek M. The neurosurgical treatment of patients in dystonic state - overview of the literature. Neurol Neurochir Pol. 2014; 48(1): 63–70, doi: 10.1016/j.pjnns.2013.04.002, indexed in Pubmed: 24636773.
24. Mitchell KT, Volz M, Lee A, et al. Patient experience with rechargeable implantable pulse generator deep brain stimulation for movement disorders. Stereotact Funct Neurosurg. 2019; 97(2): 113–119, doi: 10.1159/000500993, indexed in Pubmed: 31288242.
25. Bin-Mahfoodh M, Hamani C, Sime E, et al. Longevity of batteries in internal pulse generators used for deep brain stimulation. Stereotact Funct Neurosurg. 2003; 80(1-4): 56–60, doi: 10.1159/000075161, indexed in Pubmed: 14745210.

REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4, pages: 351–356
DOI: 10.5603/PJNNS.a2021.0047

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

Screening and diagnosis for mood and anxiety disorders in epilepsy: Polish population reference values

Agata M. Grzegorzewska, Wiesław J. Cubała, Mariusz S. Wiglusz

Department of Adult Psychiatry, Medical University of Gdansk, Poland

ABSTRACT

Introduction. Epilepsy is one of the world's most prevalent noncommunicable diseases and tends to have a chronic course, often with comorbid psychiatric disorders, of which depressive disorders (DDs) and anxiety disorders (ADs) are the most common.

Background. As anxiety and depressive disorders are underdiagnosed and so undertreated in people with epilepsy (PWE), this could have implications for the course of both of these medical conditions and the response to treatment and health outcomes. Thus it is crucial to perform screening for psychiatric disorders in populations with epilepsy using specific psychometric screening instruments optimised for that group of patients. Polish versions of the Hospital Anxiety and Depression Scale (HADS), the Hamilton Rating Scale for Depression (HRSD), the Hamilton Anxiety Rating Scale (HARS), the Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory (STAI) and the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) were validated against 'gold standards' in a Polish population with epilepsy.

Clinical implications. Using well-validated screening instruments that can be easily implemented in a clinical setting may contribute to better diagnosis, and consequently treatment, of comorbid psychiatric disorders, which would have a great impact on the course and prognosis of epilepsy management.

Conclusions. Based on the outcomes of Polish studies aimed at validating psychometric instruments for screening for mood and anxiety disorders, HADS is recommended as a first-choice screening tool.

Key words: epilepsy, mood disorders, anxiety disorders, screening tools

(*Neurol Neurochir Pol 2021; 55 (4): 351–356*)

Introduction

Epilepsy is a noncommunicable disease of the brain that affects approximately 50 million people globally, leading to poor health-related quality of life and a deterioration in psycho-social everyday functioning. Epilepsy tends to have a chronic course, often with comorbid psychiatric disorders of which depressive disorders (DDs) and anxiety disorders (ADs) are the most common, occuring with a prevalence ranging from 5–25% [1, 2] (ADs) and from 11–62% [3] (DDs). Anxiety and depressive disorders are commonly underdiagnosed and undertreated in people with epilepsy (PWE), which could have adverse effects on the course and prognosis of epilepsy management, with lower overall health-related quality of life and increased risk of suicidal ideation and suicide attempts [4].

The 'gold standard' tools used in the recognition of anxiety and depressive disorders are different types of psychometric instruments based on structured interviews [5–13]. Semi-structured interviews, e.g. the Structured Clinical Interview for DSM (SCID), are designed to be administered by clinically trained professionals with experience in diagnosis [5–8]. The output of the SCID is a record of the presence or absence of each of the disorders being considered for current episode (past month) and for lifetime occurrence. Fully structured interviews, on the other hand, such as the Composite International Diagnostic Interview (CIDI) [6, 9], have been designed specifically to address the high cost of using clinician-administered interviews in epidemiological surveys and can be administered by trained lay interviewers. The Mini-International Neuropsychiatric Interview (M.I.N.I.) is a very

Address for correspondence: Agata Maria Grzegorzewska, Department of Psychiatry, Medical University of Gdansk, Dębinki 7 St. Build. 25, 80–952 Gdansk, Poland, e-mail: a.grzegorzewska@gumed.edu.pl

Received: 15.03.2021 Accepted: 12.05.2021 Early publication date: 17.06.2021

brief, fully structured, diagnostic interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) psychiatric disorders [10, 11]. With an administration time of approximately 15 minutes, it meets the need for a short but accurate structured psychiatric interview for clinical trials and epidemiology studies, and can be used as a screening instrument in clinical settings [10, 11]. Undoubtedly the main advantage of using gold standard tools such as MINI, SCID or CIDI is that they are structured interviews to be performed by a specialist, and thereby a proper psychiatric diagnosis can be determined. The detection of mood and anxiety disorders is of vital clinical importance in patients with epilepsy. Measures of severity must also be assessed against population-specific criteria. Several factors, including antiepileptic drug (AED) side effects as well as atypical symptomatology can affect the accuracy of psychiatric diagnosis in PWE. In particular, screening instruments lacking reference to a standardised structured psychiatric interview may not produce a credible diagnosis, as tools used in the general population may not be valid and reliable in PWE [12, 13].

Therefore, defining PWE specific cut-off scores is of prime importance. A psychometric instrument may exhibit substantial variability for the targeted population. Thus, with limited data and some conflicting results, there is a need for validation studies against the gold standard, such as standardised structured psychiatric interviews, in order to produce a conclusive cut-off with valid diagnosis points for specific psychometric screening instruments that are optimised for PWE [13].

The aim of this study was to present and discuss screening tools for mood and anxiety disorders in a Polish population with epilepsy.

Materials and methods

A PubMed and Scholar Google literature search was performed to identify articles regarding Polish validations of depression and anxiety screening tools in people with epilepsy.

Results and discussion

This review includes seven articles regarding Polish validations of HARS, STAI-T, BDI, HRSD, HADS-A, HADS-D and NDDI-E. Before we discuss the results of our review, we would like to mention factors to be considered when validating screening tools, as well as to briefly describe depression and anxiety screening psychometric instruments.

Population-specific factors and rationale for cultural adaptation

When validating screening tools, it is important to consider the fact that they were developed in different cultures and languages from that in which they have been applied. Differences between the psychometric properties of the original and adapted versions may be encountered. Therefore it is necessary to acquire normative data to make the translated tools useful. Maters et al. drew attention to the fact that cross-culturally valid, but literally translated, versions of HADS may not be obtainable and specific cut-off points may not be valid across cultures and languages. It is crucial to take this into consideration and to remember that optimal cut-offs may differ between the general population and specific populations such as PWE.

Screening tools in mood disorders

Screening psychometric tools for depression in PWE include the Beck Depression Inventory (BDI) [15–18], the Hospital Anxiety and Depression Scale (HADS-D) [15–17, 19], the Hamilton Rating Scale for Depression [20] and the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) [18, 21]. NDDI-E is a screening instrument developed specifically for use in PWE and is designed to minimise the potential for confounding factors related to AEDs or epilepsy itself. In the original version, a score above 15 points has a high predictive value for major depression [21]. The BDI-I contains 21 items on a 4-point scale from 0 (symptom absent) to 3 (severe symptoms) and is a self-report inventory for evaluating the severity of depression in normal and psychiatric populations. It assesses depressive symptoms within the preceding week, with high scores reflecting a more severely depressed mood (range 0–63) [18, 22, 23]. The Hospital Anxiety and Depression Scale (HADS) was developed by Zigmond and Snaith in 1983 [19] to identify possible and probable anxiety disorders and depression among patients in non-psychiatric hospital clinics. It has been broadly used in the general population and in many populations with different somatic illnesses. The tool includes 14 items, seven related to anxiety (HADS-A) and seven related to depression (HADS-D). Zigmond and Snaith recommended that a score > 8 on an individual scale should be considered as a possible case, and this threshold value has been found to be optimal for HADS-A and HADS-D in the general population [4, 17, 19, 24].

Screening tools in anxiety disorders

Screening instruments for anxiety disorders comprise the Hamilton Anxiety Rating Scale (HARS) [13, 25], the State-Trait Anxiety Inventory (STAI) [26, 27] and the Hospital Anxiety and Depression Scale (HADS) [4, 19]. STAI [26, 27] consists of 40 items measuring respectively transient and enduring levels of anxiety and includes two separate self-report scales for assessing the distinct concepts of state and trait anxiety. This is used as an indicator of general anxiety, general psychological distress, and general emotional distress. Wiglusz et al. [27] used the Polish version of the original Spielberger STAI, usually referred to as the STAI-X [26, 28]. STAI-X is a self-administered inventory of two sections containing 20 items each, designed to explore anxiety in its temporary

condition of 'state anxiety' (STAI-S) and the more general and persistent 'trait anxiety' (STAI-T) [26]. STAI-S evaluates how respondents feel 'right now, at this moment', while STAI-T estimates how respondents 'generally feel'. A total score of 40 or more specifies an anxious condition. The higher the score, the more severe the anxiety [26, 27].

HARS was one of the first rating scales developed to assess the severity of anxiety symptoms, and is still widely used today in both clinical and research settings. The scale includes 14 items, each defined by a number of symptoms, measuring both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety) [13, 25]. As there has been a constant need for validation studies against the gold standard, in order to produce conclusive cut-off points for specific psychometric screening instruments that are optimised for PWE, attempts were made to validate the screening tools in Polish populations [4, 13, 17, 18, 27, 29, 30]. Wiglusz et al. [4, 13, 17, 18, 27, 30] in their study on a Polish population with epilepsy validated the Polish versions of HADS, HRSD, HARS, BDI and STAI against 'gold standards'. A Polish version of NDDI-E was validated as well by Gmaj et al. [29], as set out in Table 1.

Among the presented scales, HARS and HRSD are clinician-rated while the others are self-reported. The scales validated by Wiglusz et al. (HARS, STAI-T, HADS-A, HADS-D, BDI and HRSD) are of high NPV so perform better in terms of ruling out depression or anxiety than in confirming the diagnosis. It is noticeable that, except for HARS, the cut-off scores for PWE differ from those established for the general population i.e. are lower in PWE for STAI-T, HADS-D, P-NDDI-E (compared to the original study), for BDI (for any depressive disorder) and for HADS-A (for definite cases). In HADS-A (for possible cases), BDI (for MDD) and HRSD, the cut-off scores are higher in PWE. The highest sensitivity was found in HRSD (100%), BDI and HADS-D (90.5%) as well as in STAI-T and HADS-A (81.3%), while HRSD, HARS and P-NNDI-E (89.3%, 87.5% and 85.8% respectively) presented the highest specificity. Wiglusz et al. [4, 13, 17, 18, 27, 30] in their study used data collected as part of a larger study reported elsewhere [2]. 96 PWE from a tertiary epilepsy centre were

Table 1. Review of Polish research study

Validated tool	Authors	Year of research	Cut-off score for general population	Cut-off score for PWE	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]	Comment
HARS	Wiglusz et al.	2019	≥ 17	≥ 17	68.8	87.5	52.4	93.3	Clinician-rated evaluation, performs better in ruling out anxiety
STAI-T	Wiglusz et al.	2019	≥ 54	≥ 52	81.3	77.5	41.9	95.4	Self-reported symptom scale, performs better in ruling out anxiety
P-NDDI-E	Gmaj et al.	2018	15 (in the original study)	9	76.6	85.8	No data	No data	Self-reported symptom scale, standard for depressive disorders screening in PWE
HADS-A	Wiglusz et al.	2018	≥ 8 possible case ≥ 11 definite case	≥ 10	81.3	70.0	31.5	94.9	Self-reported symptom scale, performs better in ruling out anxiety
BDI	Wiglusz et al.	2017	14	18 (MDD) 11 (any depressive disorder)	90.5	70.7	46.3	96.4	Self-reported symptom scale, performs better in ruling out depression
HRSD	Wiglusz et al.	2016	≤ 6 remission for depression	11 (MDD)	100	89.3	72.4	100	Clinician-rated evaluation, performs better in ruling out depression
HADS-D	Wiglusz et al.	2016	≥ 8	≥ 7	90.5	70.7	46.3	96.4	Self-reported symptom scale, performs better in ruling out depression

BDI — Beck Depression Inventory; HADS-A — Hospital Anxiety and Depression Scale for Anxiety; HADS-D — Hospital Anxiety and Depression Scale for Depression; HARS — Hamilton Anxiety Rating Scale; HRSD — Hamilton Rating Scale for Depression; MDD — major depressive disorder; NDDI-E — Neurological Disorders Depression Inventory for Epilepsy; NPV — negative predictive value; PPV — positive predictive value; PWE — people with epilepsy; STAI — State-Trait Anxiety Inventory

enrolled. Subjects who had received a diagnosis of active epilepsy according to the International League Against Epilepsy criteria [4, 13, 17, 18, 27, 30], who had been receiving stable antiepileptic treatment in the past two months, and who were aged 18–65 were included. It is worth mentioning that in the study to validate HARS in a Polish population of PWE [13], Wiglusz et al. also compared HARS and HADS-A validation data on the same study sample [4, 13]. The authors highlighted several important differences between the two scales. The first is a different approach (self-rated vs. observer-rated) and time of administration (2–5 min *vs.* 10–15 min). In the study, HADS-A showed higher sensitivity than HARS. Another distinction in both scales is the presence of somatic symptoms. HADS was designed in a way to avoid somatic items [15–17, 19] that may help minimise the risk of false positives in PWE. On the other hand, half of the items on HARS assess somatic symptoms of anxiety [13, 25], which makes it sometimes difficult to determine whether the ratings reflect symptoms of anxiety or the side effects of common epilepsy medication [13]. Lastly, each HADS-A question concentrates on the evaluation of one symptom, whereas each item on the HARS scale includes multiple symptoms [13]. In epilepsy, symptoms such as fear are part of the seizure itself, and anxiety often accompanies aura of epilepsy attack. Thus, the physiological and cognitive symptoms of epilepsy could be indistinguishable from symptoms of psychiatric anxiety disorders in individuals with epilepsy.

It has to be emphasised that screening for depression in PWE should cover not only major depressive disorder (MDD) but also all subthreshold forms of depression and atypical mood disorders specific to epilepsy, namely interictal dysphoric disorder (IDD) [17, 32, 33], which may not be precisely identified with DSM-IV criteria [16] or may also overlap with Depressive Disorder Not Otherwise Specified (DD-NOS) criteria [17, 34]. In psychiatric studies, it is very important to perform a whole psychiatric examination in order to exclude other psychiatric disorders which may significantly influence the HADS results.

Limitations

The key limitation of Polish validation studies is the methodology as the study results refer to the small sample size of the population and selection bias due to the tertiary reference centre being associated with a risk of a complicated course of epilepsy. In order to minimise the influence of peri-ictal and ictal psychiatric symptoms, subjects with a seizure within 24 hours of examination and those experiencing more than 10 seizures in the last month before participation were excluded. Thus, the results may underscore in the depressive symptomatology and 'atypical' presentations of depression [18]. Also, the presentation of anxiety disorder may be confounded with seizure phenomena. Also, the relatively low anxiety rates for a tertiary clinic population may reflect this exclusion criterion as patients with frequent seizures would generally be expected to have higher anxiety levels [13]. Because of the small sample size, the analysis was performed in all subjects with anxiety disorders regardless of the type of disorder, including those with comorbid major depression [4]. As far as the BDI is concerned, it has to be pointed out that the BDI cut-off score of 11 for any depressive disorder is of low clinical significance as it represents a broad spectrum of depressive symptoms and should be approached with caution [18].

As the study procedures occurred during a single visit at the interview site and were completed by one rater, no test–retest reliability measure for the test results' consistency was performed. Thus, the observations may be biased and no conclusions may be drawn regarding the stability and reliability of the instrument over time. The independent raters might reduce the inflation bias with regard to the concordance between psychometric results. There was also no control group of patients with non-epileptic mood or anxiety disorders, or a control group with non-epileptic neurological disorders. Another important study limitation pointed out by Wiglusz et al. is psychiatric assessment with SCID-I for DSM-IV-TR, which is now updated to version 5 (SCID-5-CV for DSM-5) [13, 35, 36]. The use of an outdated instrument could affect the diagnosis rates and the resulting predictive values.

However, considering the anxiety disorder diagnoses profile in the study sample, we assumed that this would not have a huge impact on our study results. All these limitations together mean that the results of the studies cannot be generalised to the entire population of PWE.

Conclusions

As there is a frequent comorbidity of anxiety or/and depressive disorders with epilepsy, which may have implications for the course of both medical conditions, responses to treatment and health outcomes, it is of vital importance to perform screening for psychiatric disorders in a population of PWE using proper, well-validated instruments that could be easily implemented in a clinical setting. Based on the outcomes of Polish studies aimed at validating the psychometric instruments for screening for mood and anxiety disorders, HADS is recommended as a first-choice screening tool.

Conflict of interest: *None.*
Funding: *None.*

References

1. Brandt C, Schoendienst M, Trentowska M, et al. Prevalence of anxiety disorders in patients with refractory focal epilepsy — a prospective clinic based survey. Epilepsy Behav. 2010; 17(2): 259–263, doi: 10.1016/j.yebeh.2009.12.009, indexed in Pubmed: 20075009.
2. Wiglusz MS, Landowski J, Cubała WJ. Prevalence of anxiety disorders in epilepsy. Epilepsy Behav. 2018; 79: 1–3, doi: 10.1016/j.yebeh.2017.11.025, indexed in Pubmed: 29223931.

3. Kanner AM, Barry JJ. Is the psychopathology of epilepsy different from that of nonepileptic patients? Epilepsy Behav. 2001; 2(3): 170–186, doi: 10.1006/ebeh.2001.0192, indexed in Pubmed: 12609362.
4. Wiglusz MS, Landowski J, Cubała WJ. Validation of the Polish version of the hospital anxiety and depression scale for anxiety disorders in patients with epilepsy. Epilepsy Behav. 2018; 84: 162–165, doi: 10.1016/j.yebeh.2018.04.010, indexed in Pubmed: 29803946.
5. First MB, Gibbon M. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II). In: Hilsenroth MJ, Segal DL. ed. Comprehensive handbook of psychological assessment. Personality assessment. John Wiley and Sons Inc., Hoboken 2004: 134–143.
6. Wu Y, Levis B, Sun Y, et al. Probability of major depression diagnostic classification based on the SCID, CIDI and MINI diagnostic interviews controlling for hospital anxiety and depression scale—depression subscale scores: an individual participant data meta-analysis of 73 primary studies. J Psychosom Res. 2020; 129: 109892, doi: 10.1016/j.jpsychores.2019.109892, indexed in Pubmed: 31911325.
7. Brugha TS, Bebbington PE, Jenkins R. A difference that matters: comparisons of structured and semi-structured psychiatric diagnostic interviews in the general population. Psychol Med. 1999; 29(5): 1013–1020, doi: 10.1017/s0033291799008880, indexed in Pubmed: 10576294.
8. Brugha TS, Jenkins R, Taub N, et al. A general population comparison of the Composite International Diagnostic Interview (CIDI) and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). Psychol Med. 2001; 31(6): 1001–1013, doi: 10.1017/s0033291701004184, indexed in Pubmed: 11513368.
9. Robins LN, Wing J, Wittchen HU, et al. The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry. 1988; 45(12): 1069–1077, doi: 10.1001/archpsyc.1988.01800360017003, indexed in Pubmed: 2848472.
10. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998; 59(Suppl 20): 22–33; quiz 34–57, indexed in Pubmed: 9881538.
11. Lecrubier Y, Sheehan DV, Weiller E, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. European Psychiatry. 2020; 12(5): 224–231, doi: 10.1016/s0924-9338(97)83296-8.
12. Fiest KM, Patten SB, Jetté N. Screening for depression and anxiety in epilepsy. Neurol Clin. 2016; 34(2): 351–361, vii–viii, doi: 10.1016/j.ncl.2015.11.003, indexed in Pubmed: 27086983.
13. Wiglusz MS, Landowski J, Cubała WJ. Psychometric properties of the Polish version of the Hamilton Anxiety Rating Scale in patients with epilepsy with and without comorbid anxiety disorder. Epilepsy Behav. 2019; 94: 9–13, doi: 10.1016/j.yebeh.2019.02.017, indexed in Pubmed: 30884410.
14. Maters GA, Sanderman R, Kim AY, et al. Problems in cross-cultural use of the hospital anxiety and depression scale: "no butterflies in the desert". PLoS One. 2013; 8(8): e70975, doi: 10.1371/journal.pone.0070975, indexed in Pubmed: 23976969.
15. de Oliveira GN, Lessa JM, Gonçalves AP, et al. Screening for depression in people with epilepsy: comparative study among neurological disorders depression inventory for epilepsy (NDDI-E), hospital anxiety and depression scale depression subscale (HADS-D), and Beck depression inventory (BDI). Epilepsy Behav. 2014; 34: 50–54, doi: 10.1016/j.yebeh.2014.03.003, indexed in Pubmed: 24681386.
16. Fiest KM, Patten SB, Wiebe S, et al. Validating screening tools for depression in epilepsy. Epilepsia. 2014; 55(10): 1642–1650, doi: 10.1111/epi.12754, indexed in Pubmed: 25169800.
17. Wiglusz MS, Landowski J, Michalak L, et al. Validation of the hospital anxiety and depression scale in patients with epilepsy. Epilepsy Behav. 2016; 58: 97–101, doi: 10.1016/j.yebeh.2016.03.003, indexed in Pubmed: 27064829.
18. Wiglusz MS, Landowski J, Michalak L, et al. Validation of the polish version of the Beck depression inventory in patients with epilepsy. Epilepsy Behav. 2017; 77: 58–61, doi: 10.1016/j.yebeh.2017.09.023, indexed in Pubmed: 29111504.
19. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983; 67(6): 361–370, doi: 10.1111/j.1600-0447.1983.tb09716.x, indexed in Pubmed: 6880820.
20. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960; 23(1): 56–62, doi: 10.1136/jnnp.23.1.56, indexed in Pubmed: 14399272.
21. Gilliam FG, Barry JJ, Hermann BP, et al. Rapid detection of major depression in epilepsy: a multicentre study. Lancet Neurol. 2006; 5(5): 399–405, doi: 10.1016/S1474-4422(06)70415-X, indexed in Pubmed: 16632310.
22. Parnowski T, Jernajczyk W. Beck's depression inventory in the rating of mood in normal subjects and in patients with affective disturbances [article in Polish]. Psychiatr Pol. 1977; 11(4): 417–421, indexed in Pubmed: 594229.
23. Grabowska-Grzyb A, Jedrzejczak J, Nagańska E, et al. Risk factors for depression in patients with epilepsy. Epilepsy Behav. 2006; 8(2): 411–417, doi: 10.1016/j.yebeh.2005.12.005, indexed in Pubmed: 16466966.
24. Snaith RP. The hospital anxiety and depression scale. Health Qual Life Outcomes. 2003; 1: 29, doi: 10.1186/1477-7525-1-29, indexed in Pubmed: 12914662.
25. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959; 32(1): 50–55, doi: 10.1111/j.2044-8341.1959.tb00467.x, indexed in Pubmed: 13638508.
26. Spielberger CD, Gorsuch RL, Lushene RE. Manual for the state-trait anxiety inventory. Consulting Psychologist Press, Palo Alto 1970.
27. Wiglusz MS, Landowski J, Cubała WJ. Psychometric properties and diagnostic utility of the State-Trait Anxiety Inventory in epilepsy with and without comorbid anxiety disorder. Epilepsy Behav. 2019; 92: 221–225, doi: 10.1016/j.yebeh.2019.01.005, indexed in Pubmed: 30690323.
28. Wrześniewski K, Sosnowski T, Matusik D. Inwentarz stanu i cechy lęku STAI. Polska adaptacja STAI (State-Trait Anxiety Inventory STAI). Pracownia Testów Psychologicznych Polskiego Towarzystwa Psychologicznego, Warszawa 2002.
29. Gmaj B, Majkowski J, Szczypiński J, et al. Validation of the Polish version of the neurological disorders depression inventory for epilepsy (P-NDDI-E). Journal of Epileptology. 2018; 26(1–2): 59–64, doi: 10.21307/jepil-2018-007.
30. Wiglusz MS, Landowski J, Michalak L, et al. Validation of the Polish version of the hamilton rating scale for depression in patients with epilepsy. Epilepsy Behav. 2016; 62: 81–84, doi: 10.1016/j.yebeh.2016.06.030, indexed in Pubmed: 27450310.
31. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia. 1989; 30(4): 389–399,

doi: 10.1111/j.1528-1157.1989.tb05316.x, indexed in Pubmed: 2502382.
32. Blumer D, Montouris G, Davies K. The interictal dysphoric disorder: recognition, pathogenesis, and treatment of the major psychiatric disorder of epilepsy. Epilepsy Behav. 2004; 5(6): 826–840, doi: 10.1016/j.yebeh.2004.08.003, indexed in Pubmed: 15582829.
33. Amiri M, Hansen CP. The interictal dysphoric disorder in patients with epilepsy: A doubtful disorder lacking diagnostic tools. Seizure. 2015; 24: 70–76, doi: 10.1016/j.seizure.2014.08.009, indexed in Pubmed: 25246233.
34. Wiglusz MS, Landowski J, Michalak L, et al. Reevaluating the prevalence and diagnostic subtypes of depressive disorders in epilepsy. Epilepsy Behav. 2015; 53: 15–19, doi: 10.1016/j.yebeh.2015.09.029, indexed in Pubmed: 26515153.
35. First MB, Williams JBW, Karg RS, Spitzer RL. Structured clinical interview for DSM-5 disorders, clinician version (SCID-5-CV). American Psychiatric Association, Arlington 2016.
36. American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5™. 5th ed. American Psychiatric Publishing, Inc, Arlington 2013.

REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4, pages: 357–368
DOI: 10.5603/PJNNS.a2021.0051

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

Multiple sclerosis immunomodulatory therapies tested for effectiveness in COVID-19

Bożena Adamczyk[1], Natalia Morawiec[1], Monika Arendarczyk[1], Monika Baran[1], Krzysztof Wierzbicki[1], Paweł Sowa[2], Monika Adamczyk-Sowa[1]

[1]Department of Neurology in Zabrze, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[2]Department of Laryngology in Zabrze, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland

ABSTRACT

Introduction. The global pandemic of COVID-19 began in Wuhan, China in December 2019. Research into effective therapies has been conducted worldwide. Currently, there is no antiviral treatment and many patients develop a severe course of the disease, including severe respiratory failure. Due to similar pathomechanisms of inflammation in multiple sclerosis (MS) and COVID-19, immunomodulatory drugs that are registered for the treatment of MS are under study in the SARS-CoV-2 infection in clinical trials.

Materials and methods. Using clinicaltrials.gov, we found information related to ongoing clinical studies on potential drugs for COVID-19 which are also used in MS therapy. The outcomes of several trials were published on pubmed.ncbi.nlm.nih.gov.

Results. There were 18 clinical trials evaluating the effectiveness and safety of interferon-β, fingolimod, or leflunomide in COVID-19. Some trial outcomes available at pubmed.ncbi.nlm.nih.gov suggested an association of these drug treatments with improvements in signs and symptoms, and the disease course.

Conclusion. The administration of immunomodulatory drugs in COVID-19 may result in potential beneficial effects probably associated with their anti-inflammatory and antiviral properties. Further research is warranted to confirm the long-term effects of immunomodulatory therapies in patients with COVID-19.

Key words: multiple sclerosis, COVID-19, SARS-CoV-2, immunomodulatory therapies

(*Neurol Neurochir Pol 2021; 55 (4): 357–368*)

Introduction

Previously, two epidemics were caused by coronaviruses: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 [1]. Coronaviruses (CoVs) are responsible for many diseases in humans and animals. The resulting infections may affect respiratory, enteric, hepatic, and neurological systems with varying severity [2]. The current COVID-19 is caused by an RNA virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The outbreak of COVID-19 was first reported in Wuhan, China in December 2019. The global pandemic was declared in March, 2020 [3]. According to data from the World Health Organisation, 66,243,918 laboratory-confirmed cases, including 1,528,984 deaths, had been reported by 7 December, 2020 [4]. Respiratory droplets and contact transmission are the major routes of SARS-CoV-2 infection [5]. There are different courses of the disease, i.e. asymptomatic infections or mild cases (80–90%), severe cases with dyspnoea and hypoxemia (10%), critical cases with respiratory failure, shock and multiorgan failure (5%), and, in the most serious cases, death associated with progression to acute respiratory distress syndrome (ARDS) and multiorgan failure [6]. The most common symptoms of infection include fever (98%), cough (76%), myalgia or fatigue (44%) [1]. Of note, the severity, course, and rapid progression to ARDS are related to comorbidities and older age of patients. In-hospital mortality is approximately

Address for correspondence: Bożena Adamczk, Department of Neurology in Zabrze, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland, e-mail: badamczyk@sum.edu.pl

Received: 20.01.2021 Accepted: 30.03.2021 Early publication date: 3.08.2021

60% for patients aged > 80 years and about 5% in patients under the age of 40 [7].

Many clinical studies on COVID-19 are underway worldwide. However, currently there has been no effective therapy available. Trials of experimental agents for treatment and chemoprophylaxis are under way. Most patients are monitored and given symptomatic supportive treatment such as oxygen and antipyretics. Umbilical cord blood and convalescent plasma are also used. Research studies have tested antiviral drugs and other molecules [8–10].

Multiple sclerosis (MS) is a chronic immune-mediated central nervous system (CNS) disorder. Immune response plays a key role in the pathogenesis, course, and progression of the disease. Immunomodulatory drugs used in the treatment of MS target the peripheral immune system. These treatments have side effects, but are also specific and selective for molecules of the immune system [11]. Some of these medications are currently under study for their efficacy in COVID-19.

Disorders in the cytokine system have been reported in the course of MS and immunomodulatory therapy is believed to silence the immune system and halt disease progression. Interestingly, the significant role of cytokine dysregulation and immune response in the pathogenesis of COVID-19 has led to a hypothesis about the potential effectiveness of immunomodulatory drugs in the treatment of the disease. This is important in patients with MS infected with SARS-CoV-2. In the future, appropriate modification of the immunomodulatory treatment during infection may result in a milder course of both diseases and a shorter hospital stay. These drugs can be effective in both diseases by regulating the immune response, reducing the activity of cytokines and proinflammatory factors.

The present paper reviews immunomodulatory drugs used in the treatment of MS which are currently under study for COVID-19.

Materials and methods

We searched clinicaltrials.gov and found 18 ongoing clinical studies on potential drugs for COVID-19 which are currently used in MS therapy (Tab. 1). Through the pubmed.ncbi.nlm.nih.gov database, we found several trial outcomes. Three immunomodulatory drugs registered for MS treatment are under study in COVID-19. These are interferon (IFN)-β, fingolimod, and leflunomide (with teriflunomide as its active metabolite). Vidofludimus calcium (IMU-838), an inhibitor of dihydroorotate dehydrogenase, is in Phase II clinical trials for effectiveness in relapsing-remitting MS [12]. This drug is also under study for the treatment of COVID-19. There are four ongoing trials investigating IMU-838 in the SARS-CoV-2 infection but, currently, it is not officially registered as a treatment for MS. Therefore, we did not include it in our research.

Results and discussion

Pathophysiology of multiple sclerosis *vs.* pathophysiology of COVID-19

The precise aetiology of MS is still unclear. Many factors have an impact on the development of MS, including environmental and genetic factors such as vitamin D deficiency, Epstein–Barr Virus (EBV) and smoking. All of these agents initiate immune-mediated mechanisms that contribute to demyelination and neurodegeneration [13]. The disease process starts when autoreactive T-lymphocytes with a pro-inflammatory activity cross the blood-brain barrier.

In turn, the immune response to the SARS-CoV-2 infection consists of two phases, i.e. the immune phase and tissue damage [14]. The virus has an affinity for angiotensin-converting enzyme 2 (ACE2) receptors, which are located on epithelial cells in the apical parts of the lungs. Other organs expressing ACE2 include the oral and nasal mucosa, nasopharynx, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney and brain, which may also be affected by SARS-CoV-2 [15].

The virus consists of four proteins which are important in the immune response. The spike protein (S) binds to ACE2 receptors. Neutralising antibodies and T-cell receptors recognise it during the immune response. Nucleocapsid proteins (N) in complex with viral RNA are the target for antibodies. The matrix protein (M) forms epitopes of T-cell receptors and interacts with the envelope protein (E). The S protein may as well bind to CD26 or CD147 and may enable SARS-CoV-2 to enter cells which do not express ACE2 [16]. The antiviral response is mainly mediated by CD4+ and CD8+.

During the development of MS, primary activation of T-cells occurs in the blood. There are different hypotheses related to this phenomenon. It may occur as a result of infection with EBV [17] or contact with myelin antigens in the lymph nodes [18]. Activated T-lymphocytes show increased adhesion molecule activity, facilitating their interaction with endothelial cells. It appears that the presentation of viral antigens may play a role in the development of MS and the excessive inflammatory response in COVID-19 (Fig. 2).

In MS, dendritic cells, microglia, and B-lymphocytes are the main antigen-presenting cells (APCs). Adhesive molecules, matrix metalloproteinases and chemokines play an important role in cell migration to the CNS [19]. In the CNS, another activation of CD4+ lymphocytes occurs.

In COVID-19, pattern recognition receptors (PRRs), such as toll-like receptors (TLR-7, TLR-8), NOD-like receptors (NRL) and RIG-I-like receptors (RLR), recognise viral antigens, which results in production of IFN I, III and several chemokines by infected cells [20]. Dendritic cells and macrophages are APCs. The virus binds to dendritic cells via the specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) and DC-SIGN-related protein. DC-SIGN is highly expressed

Table 1. Ongoing trials on potential COVID-19 therapies used in MS treatment based on clinicaltrials.gov and studies with published outcomes according to pubmed.ncbi.nlm.nih.gov/

Drug	Mechanism of action	Ongoing trial	Phase of study	Details of study	Area and country
Interferons	— antiviral properties — increase in expression of anti-inflammatory agents — reduction in expression of pro-inflammatory cytokines	Efficacy and safety evaluation of therapeutic regimen of lopinavir/ritonavir and interferon-β-1b (IFNβ-1b) in patients with COVID-19	Phase II-III	N: 70 Age: 18+ Gender: both Date of registration: April 2020 Estimated study completion date: no information	Sari, Iran
		Effect of interferon-β 1 (zifron) on clinical improvement and prognosis of COVID-19	Phase II	N: 60 Age: no age limit Gender: both Date of registration: May 2020 Estimated study completion date: no information	Tabriz, Iran
		Clinical study for treatment with interferon-β-1a (IFNβ-1a) of COVID-19 patients: randomised, controlled, open label	Phase II	N: 126 Age: 18+ Gender: both Date of registration: June 2020 Estimated study completion date: April, 2021	Milan, Italy
		Comparative study of effects of tocilizumab, interferon-gamma and vitamin C on recovery of critically ill COVID-19 patients and cytokine storm	Phase II	N: 60 Age: 18–65 Gender: both Date of registration: July 2020 Estimated study completion date: no information	Tabriz, Iran
		Evaluation of effect of raltegravir and raltegravir/interferon-β combination on COVID-19 patients	Phase III	N: 60 Age: 18+ Gender: both Date of registration: June 2020 Estimated study completion date: no information	Jahrom, Iran
		Using interferon to treat COVID-19	Phase II/III	N: 76 Age: 18+ Gender: both Date of registration: June 2020 Estimated study completion date: no information	Mashhad, Iran
		Effect of interferon on treatment of COVID-19 patients	Phase III	N: 60 Age: 18–70 Gender: both Date of registration: May 2020 Estimated study completion date: no information	Qom, Iran
		Efficacy evaluation of inhalation therapy (nasal spray) of interferon-β-1a in hospitalised COVID-19 patients	Phase III	N: 50 Age: 20–65 Gender: both Date of registration: May 2020 Estimated study completion date: no information	Tehran, Iran
		Evaluation of interferon treatment in high-risk COVID-19 patients	Phase III	N: 60 Age: 18–70 Gender: both Date of registration: May 2020 Estimated study completion date: no information	Qom, Iran

→

Table 1 cont. Ongoing trials on potential COVID-19 therapies used in MS treatment based on clinicaltrials.gov and studies with published outcomes according to pubmed.ncbi.nlm.nih.gov/

Drug	Mechanism of action	Ongoing trial	Phase of study	Details of study	Area and country
Interferons		Heberon Alfa R in COVID-19	Phase IV	N: no information Age: no age limit Gender: both Date of registration: May 2020 Estimated study completion date: no information	Havana, Cuba
		Phase II, randomised, controlled, open-label study to evaluate efficacy and safety of pegylated-IFN alpha-2b in treatment of adult patients diagnosed with SARS-CoV-2 (COVID-19)	Phase II	N: 40 Age: 18–85 Gender: both Date of registration: June 2020 Estimated study completion date: no information	Gujarat, India
		Determination and comparison of effect of two antiviral drugs (interferon-β-1a and interferon alpha-2A) on prognosis of patients with COVID-19	Phase II/III	N: 76 Age: 18+ Gender: both Date of registration: June 2020 Estimated study completion date: no information	Mashhad, Iran
		Interferon-β-1b in COVID-19	Phase II/III	N: 70 Age: 18+ Gender: both Date of registration: April 2020 Estimated study completion date: no information	Sari, Iran
		Investigating efficacy and safety of interferon-β-1a nasal spray in controlling symptoms of patients with COVID-19	Phase III	N: 100 Age: 18+ Gender: both Date of registration: May 2020 Estimated study completion date: no information	Tehran, Iran
		Safety and efficacy of inhaled nebulised interferon-β-1a (SNG001) for treatment of SARS-CoV-2 infection: randomised, double-blind, placebo-controlled, phase II trial (Monk et al., 2020)double-blind, placebo-controlled, phase 2 pilot trial at nine UK sites. Adults aged 18 years or older and admitted to hospital with COVID-19 symptoms, with a positive RT-PCR or point-of-care test, or both, were randomly assigned (1:1)	Phase II Published outcomes	N: 100 Age: 18+ Gender: both Date of registration: May 2020 Estimated study completion date: May, 2021	United Kingdom
		Evaluating efficacy and safety of interferon β-1b (IFN β-1b) in treatment of COVID-19 (Rahmani et al., 2020)	Phase II/III Published outcomes	N: 33 Age: 18–75 Gender: both Date of registration: March 2020 Estimated study completion date: no information	Tehran, Iran
		Evaluating therapeutic and adverse effects of interferon-β-1a subcutaneous administration in patients with novel Coronavirus (COVID-19) (Dastan et al., 2020)	Phase III Published outcomes	N: 20 Age: 18+ Gender: both Date of registration: March 2020 Estimated study completion date: no information	Tehran, Iran

→

Table 1 cont. Ongoing trials on potential COVID-19 therapies used in MS treatment based on clinicaltrials.gov and studies with published outcomes according to pubmed.ncbi.nlm.nih.gov/

Drug	Mechanism of action	Ongoing trial	Phase of study	Details of study	Area and country
		Repurposed Antiviral Drugs for COVID-19 - Interim WHO Solidarity Trial Results (Pan et al., 2021)hydroxychloroquine, lopinavir, and interferon beta-1a - in patients hospitalized with coronavirus disease 2019 (COVID-19)	Phase III Published outcomes	N: 11,330 Age: 18+ Gender: both Date of registration: March 2020 Estimated study completion date: March 2023	Multi-country study (30 countries)
Fingolimod	— angiogenic factor — preventing lymphocyte T and B egress from lymphoid tissues — reduction in IL-17, IL-10, IL-12 levels -reduction in levels of CD4+ and CD8+	Effect of fingolimod for treatment of COVID-19-induced cytokine storm	Phase III	N: 40 Age: 18–80 Gender: both Date of registration: April 2020 Estimated study completion date: no information	Tabriz, Iran
Leflunomide	— antiviral properties — reduction in expression of pro-inflammatory cytokines — killing activated T- and B-lymphocytes	Multicentre, randomised, double-blind, controlled clinical trial for leflunomide in treatment of novel coronavirus pneumonia (COVID-19)	Phase III	N: 100 Age: 18–70 Gender: both Date of registration: February 2020 Estimated study completion date: no information	Wuhan, China
		Efficacy and safety of leflunomide for refractory novel coronavirus pneumonia (COVID-19): non-randomised controlled study	Phase 0	N: 30 Age: 43–70 Gender: both Date of registration: May 2020 Estimated study completion date: no information	Shandong, China
		DEFEAT-COVID Study	Phase III	N: 178 Age: 18+ Gender: both Date of registration: July 2020 Estimated study completion date: no information	Chertsey, Surrey, United Kingdom
		Treatment of Coronavirus Disease 2019 Patients With Prolonged Postsymptomatic Viral Shedding With Leflunomide: A Single-Centre Randomised Controlled Clinical Trial (Wang et al., 2020)	Published outcomes	N: 50 Age: 18–70 Gender: both Date of registration: May 2020 Published: September, 2020	Wuhan, China
		A Small-Scale Medication of Leflunomide as a Treatment of COVID-19 in an Open--Label Blank-Controlled Clinical Trial (Hu et al., 2020)	Published outcomes	N: 10 Age: 18–70 Gender: both Date of registration: February 2020 Published: July, 2020	Wuhan, China

on dendritic cells and macrophages. Then APCs phagocytose cells infected with the virus migrate to the lymph nodes to present the antigen to T-lymphocytes [21]. In the development of COVID-19 and MS, the presentation of antigen in lymph nodes by dendritic cells may play a significant role (Fig. 2).

In MS, CD4+ lymphocytes have the ability to differentiate into Th1, Th2 and Th17 cells [22]. Th1 lymphocytes are involved in inflammatory processes related to the activity of macrophages and the production of pro-inflammatory cytokines such as IFN-γ, tumour necrosis factor-α (TNF-α), interleukin (IL)-2, IL-12, and IL-15. Th2 lymphocytes have an anti-inflammatory activity and produce anti-inflammatory cytokines such as IL-4, IL-5 and IL-13 [23, 24]. They can also stimulate an autoreactive B-cell response. Th17 lymphocytes secrete IL-17 and other pro-inflammatory cytokines (IL-21, IL--22) [24]. An increase in IL-17 expression in the cerebrospinal

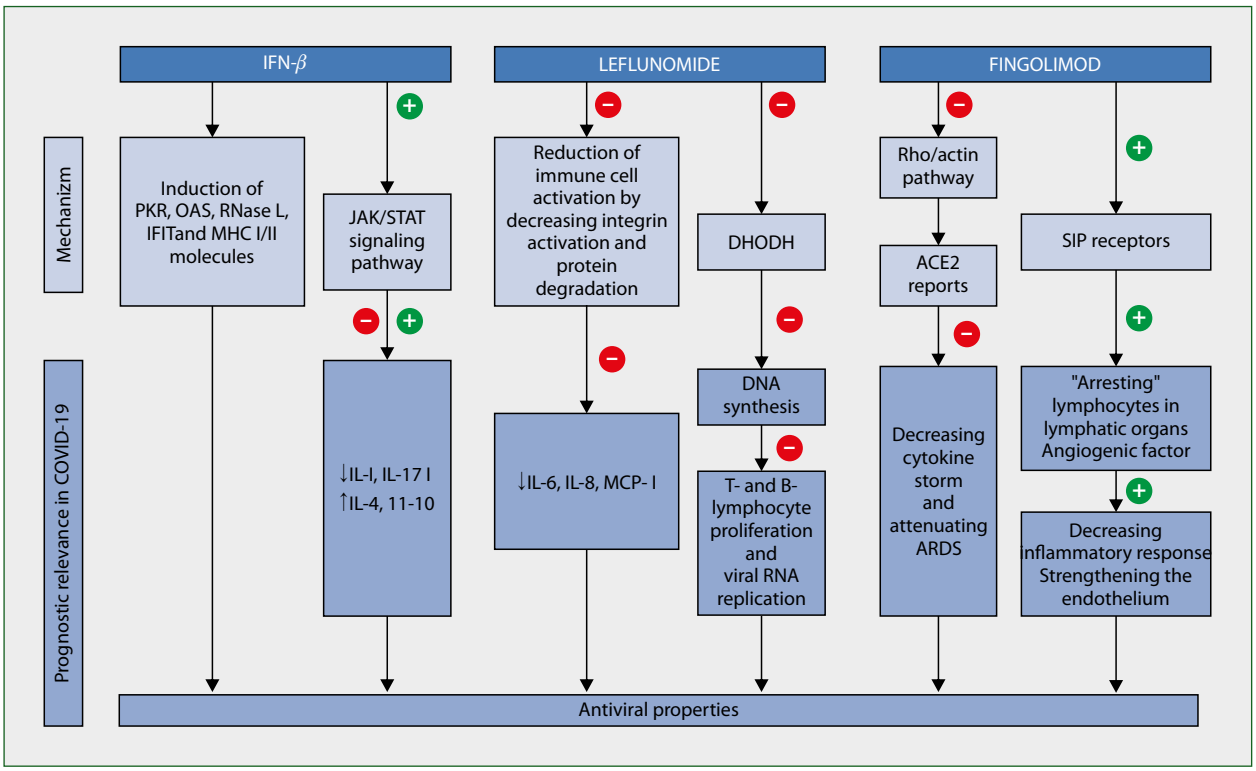


Figure 1. Prognostic relevance of IFN-β, leflunomide and fingolimod in COVID-19 according to their mechanisms. IFN-β induces proteins important in antiviral action (PKR, OAS, RNase, IFIT, MHC I/II molecules). This results in inhibition of viral entry, transcription, replication, translation, assembly, or egress. IFN-β increases expression of anti-inflammatory factors (IL-10, IL-4), whereas it reduces expression of pro-inflammatory cytokines (IL-1, IL-17 and osteopontin) via JAK/STAT pathway. Leflunomide suppresses DHODH, which results in inhibition of *de novo* pyrimidine synthesis and reduction in lymphocyte proliferation (diminishing release of proinflammatory cytokines IL-6, IL-8 and MCP-1). Leflunomide impairs viral RNA replication. Fingolimod decreases inflammation by binding to S1P receptors (S1P1, S1P3, S1P4 and S1P5), arresting lymphocytes in lymphoid organs and reducing macrophage movement via RhoA/actin pathway. Fingolimod acts as angiogenic factor; it enhances lung endothelial cell integrity and possibly reduces cytokine storm and ARDS by inhibiting ACE2 receptor expression and recruiting macrophages to lungs.

ACE2 — angiotensin-converting enzyme 2; ARDS — acute respiratory distress syndrome; DHODH — dihydroorotate dehydrogenase; IFIT — IFN-induced protein with tetratricopeptide repeats; JAK/STAT — Janus kinase-signal transducer and activator of transcription; OAS — 2'-5'-oligoadenylate synthetase; PKR — protein kinase R; S1P — sphingosine-1-phosphate

fluid (CSF) and blood is characteristic of patients with MS, especially during a relapse [25].

In COVID-19, CD8+ lymphocytes kill infected cells [21]. Immune dysregulation leads to cytokine storm and tissue damage. The concentration of pro-inflammatory cytokines correlates with the severity of the disease. In COVID-19 patients, higher levels of the following have been found: IL-1, IL-2, IL-4, IL-6, IL-10, IL-12, IL-13, IL-17, macrophage colony-stimulating factor (M-CSF), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-induced protein-10 (IP-10), monocyte chemotactic protein-1 (MCP-1), TNF-α, IFN-γ and vascular endothelial growth factor (VEGF) [26]. IL-6 level is particularly related to the severity of the disease [27, 28].

In the development of MS, T-regulatory (Treg) lymphocytes have a weakened ability to control immune reactions, which also leads to demyelination and neurodegeneration [29]. CD8+ cells are the main components of demyelinating plaques. They can recognise brain antigens and destroy oligodendrocytes and neurons [30]. B-lymphocytes are responsible for the humoral response. They produce antibodies, specifically recognise the antigen, present the antigen, produce cytokines, and regulate the differentiation and function of dendritic cells and T-lymphocytes.

During COVID-19, many patients develop lymphopenia. A decrease in the levels of CD4+, CD8+, B-lymphocytes and natural killer (NK) cells is also reported [31]. T-cell levels correlate negatively with IL-6, IL-10 and TNF-α concentrations [32]. There is also an increase in the release of IFNs, mainly IFN I and III. Their function is to limit the spread of the virus. However, SARS-CoV-2 inhibits IFN release [42]. In terms of the humoral response, CD4+ cells activate B-lymphocytes to generate natural IgM and IgG antibodies against the virus.

According to the described data, overexpression of both interleukins and chemokines may be characteristic of MS and

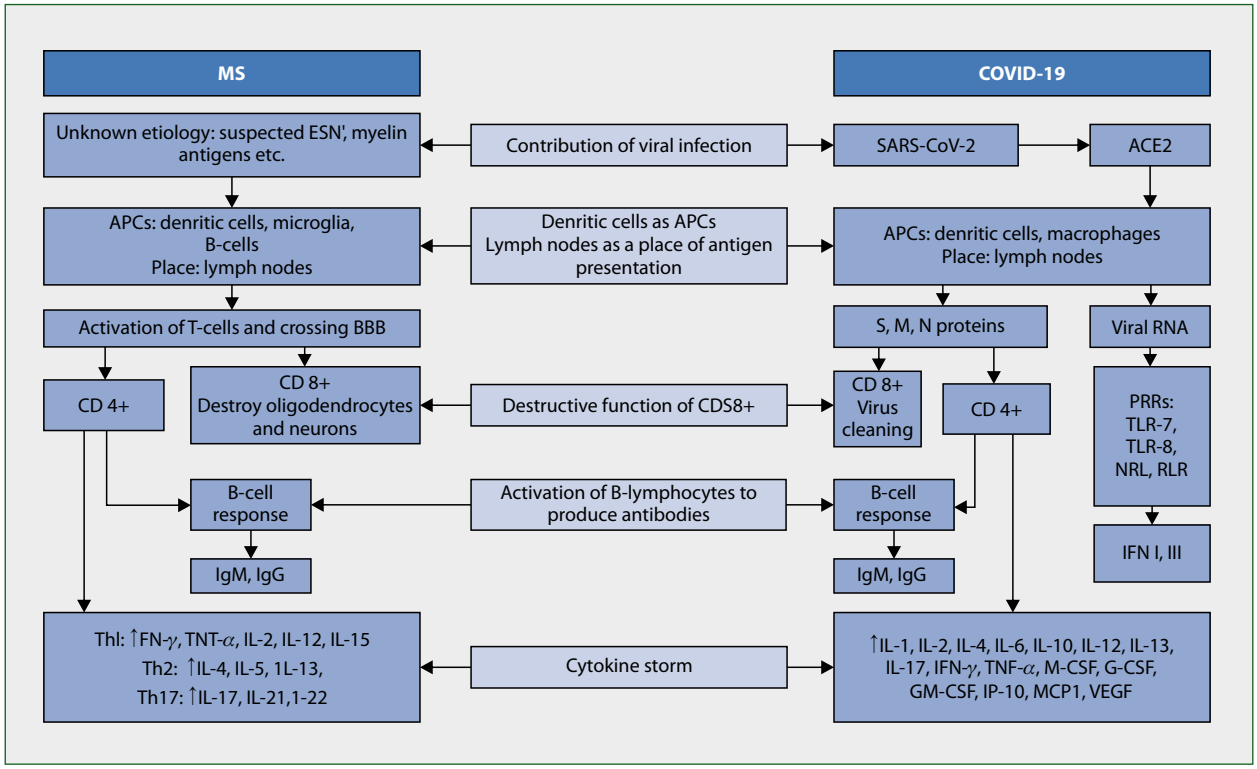


Figure 2. Comparison of pathophysiology of MS and COVID-19 and their common mechanisms. Aetiology of MS is unknown. However, important role of EBV, myelin antigens and other factors is suspected. In COVID-19, SARS-CoV-2 is causative pathogen. In both cases, viral infection may contribute to disease development. In MS and COVID-19, dendritic cells are main APCs, whereas antigen presentation occurs in lymph nodes. CD4+ and CD8+ play an important role in immune response in both diseases. CD 4+ activation leads to B-cell response and cytokine overproduction. Cytokine storm is present in MS or COVID-19. Probable common elements of pathomechanisms shown in bold. APCs — Antigen-Presenting Cells; BBB — Blood-Brain Barrier; EBV — Epstein-Barr Virus; G-CSF — Granulocyte Colony-Stimulating Factor; GM-CSF — Granulocyte-Macrophage Colony-Stimulating Factor; IFN-γ — Interferon Gamma; IgG — immunoglobulin G; IgM — immunoglobulin M; IL — interleukin; IP10 — Interferon-induced protein-10; MCP-1 — Monocyte Chemotactic Protein-1; M-CSF — Macrophage Colony-Stimulating Factor; NRL — NOD-like receptors; PRRs — Pattern Recognition Receptors; RLR — RIG-I-like receptors; IFN I, III — Interferon I, III; TLR — Tolllike receptors; TNF-α — Tumour Necrosis Factor Alpha; VEGF — Vascular Endothelial Growth Factor

COVID-19. In MS, the loss of immune system control due to the impaired function of regulatory T-lymphocytes has been reported (Fig. 2). SARS-CoV-2 may also cause impairment of the immune system. The development of both diseases is closely related to the dysfunction of CD4+ and CD8+ lymphocytes, as well as B-lymphocytes (Fig. 2). As discussed above, certain elements of the pathomechanisms are common to COVID-19 and MS. Therefore, immunomodulatory drugs may be highly effective in disease-modifying treatment.

MS immunomodulatory drugs tested for COVID-19

Interferon-β

Mechanism of action

IFN-β is an immunomodulatory agent. It increases the expression and concentration of some anti-inflammatory factors such as IL-10, II-4, whereas it reduces the expression of pro-inflammatory cytokines such as IL-1, IL-17 and osteopontin. Pro-inflammatory cytokines induce the activation and proliferation of additional T-cells, B-cells and macrophages, stimulate major histocompatibility complex (MHC) class II expression on APCs, decrease the level of anti-inflammatory cytokines, and intensify the cytolytic activity of CD8+ cells, macrophages and certain NK cells [33]. IFN-β leads to a reduction in the number of inflammatory cells which cross the blood-brain barrier, and increased production of nerve growth factor. These cells are important in the production of anti-inflammatory mediators, and have the potential to reduce neuronal inflammation [33, 34].

Prognostic relevance in COVID-19

The IFN response is the first line of defence against viruses. Diagnosis of viral infections is possible due to innate immune vigilance activating, in particular, IFN I and III responses. Type I IFN (IFN-α, IFN-β, IFN-ε, IFN-κ, IFN-ω) binds to the common type I IFN receptor (IFNAR) on the cell surface. IFN induced by virus-infected cells acts in autocrine and paracrine

ways, binding to cell surface receptors, and leads to the expression of antiviral IFN-stimulated genes (ISGs), 2'-5'-oligoadenylate synthetase (OAS), RNase L, dsRNA-dependent protein kinase R (PKR) and IFN-induced protein with tetratricopeptide repeats (IFIT) to perpetuate antiviral signalling [35]. This activates the antiviral defence mechanism made up of hundreds of ISGs, thereby interfering with every step of the virus replication (Fig. 1) [36, 34]. IFN-mediated signalling and transcriptional activation of cellular gene expression are best understood in the context of the JAK-STAT pathway protein. The signal transducer and activator of transcription (STAT) family of proteins are latent cytoplasmic transcription factors that become tyrosine phosphorylated by the Janus family of tyrosine kinase (JAK) enzymes in response to cytokine stimulation. Different members of the JAK and STAT families have distinct functions in cytokine signalling. Receptor-associated JAKs are activated following the binding of IFNs to their cognate multi-subunit transmembrane receptor. This plays central roles in mediating IFN-dependent biological responses and could shift the pathogenic Th1/Th17 responses to Th2/Treg responses, which results in increased production of anti-inflammatory cytokines such as IL-2, IL-4, IL-5 and IL-10 (Fig. 1) [37, 38]. An insufficient IFN response promotes uncontrolled viral replication, increases viral load, and leads to poor outcomes in SARS-CoV infection. A strong IFN response has been observed following SARS-CoV-2 infection. ISG expression was significantly increased in COVID-19 patients [39]. Blanco-Melo et al. showed a similar relationship after analysis of serum from COVID-19 patients [40]. Pro-inflammatory cytokines and chemokines were significantly elevated with no detectable levels of IFN I and III. Moreover, IFN-β may show beneficial antiviral activity against SARS-CoV-2 in combination with conventional antiviral drugs as shown in a recent open-label Phase II clinical trial. This study showed that the triple action of injectable IFN (IFN-β 1b), an oral protease inhibitor (lopinavir-ritonavir) and an oral nucleoside analogue (ribavirin) administered for seven days from the day of symptom onset completely inhibited the excretion of SARS-CoV-2, not only in nasopharyngeal swabs, but in all clinical specimens compared to lopinavir and ritonavir alone. Additionally, the duration of a positive RT-PCR reaction and the duration of viremia were shorter. It was associated with clinical improvement and shortening of hospital stay [41]. Initiating IFN-β treatment in patients with newly diagnosed MS appears safe. The action of IFN-β rarely lowers lymphocyte levels. The associated lymphopenia is mild. Therefore, it is unlikely that it will affect the early or delayed immune response to SARS-CoV-2 or will significantly increase the susceptibility to infections. Despite the optimal safety of IFN-β compared to other drugs, and the fact that it is an appropriate treatment option for patients with mild MS, its potency is low and it may not be suitable for patients with highly active MS during the pandemic [42].

On clinicaltrials.gov, we found 16 ongoing trials on IFNs for COVID-19, 11 of which are focused on IFN-β. Most of them are in Phases II or III (Tab. 1). We found some outcomes evaluating the effectiveness of IFN-β among patients with COVID-19. The efficacy and safety of inhaled nebulised IFN-β-1a were assessed among hospitalised patients with COVID-19 in the UK. This was a randomised, double-blind, placebo-controlled, Phase II pilot trial including 101 patients. The symptoms of infection improved more rapidly in patients who received IFN-β compared to those who received a placebo. Moreover, there were three deaths in the placebo group and none in the active treatment group [43]. Another clinical trial was conducted in Imam Khomeini Hospital Centre in Iran from 20 April to 20 May, 2020 and included 66 patients. IFN-β was administered subcutaneously every other day for two weeks. The control group received lopinavir/ritonavir or atazanavir/ritonavir plus hydroxychloroquine. Rahmani et al. showed a shorter time to clinical improvement and discharge and lower mortality in patients with IFN therapy compared to the control group [39]. IFN-β is often combined with other drugs. Hong et al. described five severe COVID-19 pneumonia patients who recovered 7–15 days after treatment with lopinavir/ritonavir, hydroxychloroquine and IFN-β-1b [44]. On 2 December, 2020, the New England Journal of Medicine published interim WHO SOLIDARITY trial results of four antiviral drugs, i.e. remdesivir, hydroxychloroquine, lopinavir, and IFN-β-1a in patients hospitalised with COVID-19. None of the above drugs had a significant effect on the disease course as indicated by overall mortality, initiation of ventilation, or duration of hospital stay. Only remdesivir slightly reduced time to recovery. Given the size of the trial, these findings seem reliable [45]. Dastan et al. conducted a prospective non-controlled trial [46]. They also used IFN-β-1a in combination with hydroxychloroquine and lopinavir/ritonavir. Their study revealed a reduction of disease symptoms, which were supported by lung CT and chest X-ray images. Davoudi-Monfared et al. carried out a very similar study with IFN-β-1a added to hydroxychloroquine plus lopinavir-ritonavir or atazanavir-ritonavir [47]. They showed that only early IFN-β-1a administration was related to a significant reduction in mortality. Their study did not reveal an influence of IFN on shortening hospital stay or the duration of mechanical ventilation. Many randomised clinical trials aimed at evaluating the efficacy and safety of IFN-β in COVID-19 treatment have shown that treatment with IFN-β could lead to faster recovery from infection. The trials are still underway and their aim is to confirm the benefits of this form of therapy.

Fingolimod

Mechanism of action

Fingolimod, sphingosine-1-phosphate (S1P) analogue, is the first oral disease-modifying drug for relapsing-remitting MS. Fingolimod binds to four of the five known S1P receptors

(S1P1, S1P3, S1P4 and S1P5) on lymphocytes, leading to receptor internalisation and lymphocyte 'arrest' in lymphatic organs (Fig. 1). As a result, the damaging infiltration into the CNS is reduced [48, 49]. It also inhibits the expression of RhoA and RhoA/actin-dependent macrophage receptors (Fig. 1) [50].

Prognostic relevance of fingolimod in COVID-19

The action of fingolimod in COVID-19 is complex. Acting as an immunomodulatory drug, it inhibits naive T-cells and memory T-cells in the lymph nodes, thus preventing autoimmune reactions. However, memory effector T-cells, which are less affected by fingolimod treatment, are of crucial importance in defending against infectious disease antigens [51]. The pathological process of infection in COVID-19 includes pulmonary oedema and diffuse alveolar injury with cellular fibromyxoid exudates [52]. Fingolimod is a potent angiogenic factor and its action enhances the integrity of lung endothelial cells. S1P enhances vascular permeability and alveolar hemorrhage in preclinical animal models of acute lung injury. Moreover, in the case of a cytokine storm, immunomodulation may be beneficial in reducing mortality [53]. Fingolimod inhibits macrophage movement and expression of macrophage receptors via the RhoA/actin pathway. It may also inhibit the expression of ACE2 receptors and macrophage recruitment to the lung tissue, which is the main cause of ARDS (Fig. 1) [50].

We found one ongoing trial on fingolimod in COVID-19, which was conducted at the Tabriz University of Medical Sciences in Iran (Phase III study involving 40 patients) (Tab. 1). Unfortunately, no outcomes of COVID-19 treatment with fingolimod have been published yet. Therefore, further research is warranted.

Leflunomide

Mechanism of action

Leflunomide acts by suppressing dihydroorotate dehydrogenase (DHODH), which results in the inhibition of *de novo* pyrimidine synthesis and reduction in B- and T-lymphocyte proliferation. The effect of leflunomide is related to a decrease in the release of pro-inflammatory cytokines such as IL-6, IL-8 and MCP-1 (Fig. 1) [54, 55]. The inflammatory imbalance seems to be crucial in the onset and propagation of MS [56]. Leflunomide has already been clinically used in autoimmune diseases to inhibit pathogenic cytokines and chemokines [57]. Teriflunomide is the main active metabolite of leflunomide. The effectiveness of therapy with leflunomide is possible, but this drug has not been registered for the treatment of MS yet, as opposed to teriflunomide, which is a licenced drug in MS. However, its efficacy in COVID-19 has not been confirmed [58].

Prognostic relevance in COVID-19

Leflunomide reduces the level of immune activation without cell apoptosis. It kills only rapidly proliferating lymphocytes. On the other hand, it can use the salvage pathway to proliferate and self-renew [59]. Thus, an adequate defence against the virus may be provided, while decreasing host immune response [54]. That mechanism could prevent the cytokine storm that occurs in severe acute infections, including influenza and COVID-19 [57].

Three clinical trials are currently underway to investigate the efficacy of leflunomide in COVID-19 (Tab. 1). We also found two completed randomised controlled clinical trials. The former was performed by scientists from RenMin Hospital of Wuhan University, China. This trial assessed the effects of treatment with leflunomide and IFN-α-2a compared to IFN-α-2a alone. The study group consisted of 50 patients. No differences were found in duration of hospital stay or viral shedding. Two patients in the leflunomide group were unable to complete therapy due to adverse effects [60]. The latter study was performed on a small group of 10 patients. This small-scale investigation is a part of the Open-Label Blank-Controlled Clinical Trial which is currently in Phase III as reported by clinicaltrials.gov. The study revealed a decrease in C-reactive protein levels in the leflunomide treatment group. In this group, a shorter duration of viral shedding was also found. The chest CT imaging from one representative patient showed much smaller areas of ground-glass opacity and obvious absorption of lesions in the bilateral lung after seven days of treatment with leflunomide [61]. Despite the small size of the group, the outcomes from the above investigation may be crucial, although the findings require further analysis.

Drugs in NMOSD tested for COVID-19

Neuromyelitis optica spectrum disorder (NMOSD) is another neurological disease with an important role in the inflammatory process. NMOSD is an autoimmune disorder characterised by inflammatory and demyelinating lesions in the optic nerve, spinal cord brainstem, and cerebrum, which can lead to a decrease or loss of vision and disability [62]. NMOSD is often misdiagnosed as MS. Therefore, it seems necessary to mention the drugs which are tested in COVID-19 and used in the treatment of neuromyelitis optica (NMO) and which are registered and used in clinical trials.

There are studies on the effectiveness of anti-IL-6 receptor monoclonal antibodies (sarilumab, tocilizumab, satralizumab), anti-IL-6 monoclonal antibody (siltuximab) and inhibition of the C5 protein of the complement system (eculizumab) [63,64,65].

Inhibition of IL-6 may attenuate the early immune response against the virus by T-cell suppression. It could also increase the risk of secondary bacterial infection in COVID-19 patients. On the other hand, inhibition of the IL-6 signalling pathway could result in a decrease in the cytokine storm [62]. Suppression of the inflammatory process would certainly be very beneficial for patients with severe COVID-19 pneumonia. There are also studies on a potential benefit of complement inhibition in the SARS-CoV-2 infection. A clinical trial of

eculizumab in COVID-19 patients is underway (clinicaltrials.gov, NCT04288713).

Currently, the guidelines by the National Institutes of Health (NIH) suggest against the routine use of anti-IL-6 receptor monoclonal antibodies (tocilizumab and sarilumab) or anti-IL-6 monoclonal antibody (siltuximab) for hospitalised patients with COVID-19 outside clinical trials [64].

Conclusion

Many drugs are under study for their effectiveness in the treatment of COVID-19. According to most scientists, the pandemic will last for months or even years. Due to the presented pathophysiology of COVID-19 and the crucial role of the immune response, the above immunomodulatory drugs may be effective in some cases of the SARS--CoV-2 infection.

IFN-β largely counteracts the pathogenic processes by increasing the production of anti-inflammatory factors, while inhibiting the pro-inflammatory cytokines. It has been shown to have antiviral activity and inhibit the SARS-CoV-2 replication. Some of the cited clinical studies revealed that administration of IFN-β with other antiviral drugs resulted in a reduction of symptoms as evidenced by chest CT scans and X-rays. It may also contribute to a shorter time to clinical improvement.

Fingolimod acts as an angiogenic factor. It may inhibit ACE2 receptors. As an immunomodulatory drug, fingolimod inhibits lymphocytes in lymphatic nodes, thus reducing the inflammatory response. There are no published outcomes about its efficacy in COVID-19. However, some studies suggest that it may prevent the development of ARDS.

Leflunomide, an inhibitor of DHODH, leads to a reduced proliferation of both T- and B-lymphocytes. Moreover, it lowers pro-inflammatory cytokine levels, thus reducing inflammation. Studies show that it could contribute to a shorter duration of viral shedding and a reduction in disease symptoms.

The findings that we have presented suggest that immunomodulatory drugs may be effective in some cases of COVID-19. Due to the similar pathophysiology of COVID-19 and MS, IFN- β, leflunomide and fingolimod may be equally effective in both conditions due to their antiviral activity and the influence on the immune response.

Of note, many drugs used or tested in MS have also been included in COVID-19 clinical trials, which may suggest that these drugs have a common mechanism of action in both diseases. Currently, data on their potential effects is limited. Most studies have not been completed yet and there have been no published outcomes. Until solid outcomes from patient samples are published, drawing conclusions about drug effectiveness is impossible. The recommendations of professional organisations should be followed. However, they will change over time depending on the further development of the COVID-19 pandemic or viral mutations and changes. The long-term effects of MS immunomodulatory treatment in patients with COVID-19 should be monitored.

Conflict of interest *The authors declare no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.*

References

1. Tu YF, Chien CS, Yarmishyn AA, et al. A Review of SARS-CoV-2 and the Ongoing Clinical Trials. Int J Mol Sci. 2020; 21(7), doi: 10.3390/ijms21072657, indexed in Pubmed: 32290293.
2. Wong ACP, Li X, Lau SKP, et al. Global Epidemiology of bat coronaviruses. Viruses. 2019; 11(2), doi: 10.3390/v11020174, indexed in Pubmed: 30791586.
3. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed. 2020; 91(1): 157–160, doi: 10.23750/abm.v91i1.9397, indexed in Pubmed: 32191675.
4. World Health Organization. Weekly Operational Update on COVID-19 November 6, 2020. World Health Organization (WHO), Health Emergencies Programme 2020:1–12. https://www.who.int/publications/m/item/weekly-update-on-covid-19---16-october-2020.
5. Esakandari H, Nabi-Afjadi M, Fakkari-Afjadi J, et al. A comprehensive review of COVID-19 characteristics. Biol Proced Online. 2020; 22: 19, doi: 10.1186/s12575-020-00128-2, indexed in Pubmed: 32774178.
6. Pascarella G, Strumia A, Piliego C, et al. COVID-19 diagnosis and management: a comprehensive review. J Intern Med. 2020; 288(2): 192–206, doi: 10.1111/joim.13091, indexed in Pubmed: 32348588.
7. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review. JAMA. 2020; 324(8): 782–793, doi: 10.1001/jama.2020.12839, indexed in Pubmed: 32648899.
8. Wu C, Liu Y, Yang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B. 2020; 10(5): 766–788, doi: 10.1016/j.apsb.2020.02.008, indexed in Pubmed: 32292689.
9. Huang J, Song W, Huang H, et al. Pharmacological therapeutics targeting RNA-dependent RNA polymerase, proteinase and spike protein: from mechanistic studies to clinical trials for COVID-19. J Clin Med. 2020; 9(4), doi: 10.3390/jcm9041131, indexed in Pubmed: 32326602.
10. Abd El-Aziz TM, Stockand JD. Recent progress and challenges in drug development against COVID-19 coronavirus (SARS-CoV-2) - an update on the status. Infect Genet Evol. 2020; 83: 104327, doi: 10.1016/j.meegid.2020.104327, indexed in Pubmed: 32320825.
11. Hemmer B, Kerschensteiner M, Korn T. Role of the innate and adaptive immune responses in the course of multiple sclerosis. The Lancet Neurology. 2015; 14(4): 406–419, doi: 10.1016/s1474-4422(14)70305-9.
12. Muehler A, Peelen E, Kohlhof H, et al. Vidofludimus calcium, a next generation DHODH inhibitor for the Treatment of relapsing-remitting multiple sclerosis. Mult Scler Relat Disord. 2020; 43: 102129, doi: 10.1016/j.msard.2020.102129, indexed in Pubmed: 32428844.
13. Yadav SK, Mindur JE, Ito K, et al. Advances in the immunopathogenesis of multiple sclerosis. Curr Opin Neurol. 2015; 28(3): 206–219, doi: 10.1097/WCO.0000000000000205, indexed in Pubmed: 25887768.

14. Baker D, Amor S, Kang AS, et al. The underpinning biology relating to multiple sclerosis disease modifying treatments during the COVID-19 pandemic. Mult Scler Relat Disord. 2020; 43: 102174, doi: 10.1016/j.msard.2020.102174, indexed in Pubmed: 32464584.
15. Hamming I, Timens W, Bulthuis MLC, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004; 203(2): 631–637, doi: 10.1002/path.1570, indexed in Pubmed: 15141377.
16. Sariol A, Perlman S. Lessons for COVID-19 immunity from other coronavirus infections. Immunity. 2020; 53(2): 248–263, doi: 10.1016/j.immuni.2020.07.005, indexed in Pubmed: 32717182.
17. Serafini B, Rosicarelli B, Veroni C, et al. Epstein-Barr virus-specific CD8 T cells selectively infiltrate the brain in multiple sclerosis and interact locally with virus-infected cells: clue for a virus-driven immunopathological mechanism. J Virol. 2019; 93(24), doi: 10.1128/JVI.00980-19, indexed in Pubmed: 31578295.
18. Zhang H, Podojil JR, Luo X, et al. Intrinsic and induced regulation of the age-associated onset of spontaneous experimental autoimmune encephalomyelitis. J Immunol. 2008; 181(7): 4638–4647, doi: 10.4049/jimmunol.181.7.4638, indexed in Pubmed: 18802066.
19. Wu GF, Alvarez E. The immunopathophysiology of multiple sclerosis. Neurol Clin. 2011; 29(2): 257–278, doi: 10.1016/j.ncl.2010.12.009, indexed in Pubmed: 21439440.
20. Pawliczak R. The immune response to SARS-CoV-2. Focus on severe COVID-19 pathogenesis. Alergologia Polska - Polish Journal of Allergology. 2020; 7(3): 146–152, doi: 10.5114/pja.2020.99243.
21. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020; 215: 108427, doi: 10.1016/j.clim.2020.108427, indexed in Pubmed: 32325252.
22. Frohman EM, Racke MK, Raine CS. Multiple sclerosis–the plaque and its pathogenesis. N Engl J Med. 2006; 354(9): 942–955, doi: 10.1056/NEJMra052130, indexed in Pubmed: 16510748.
23. Sredni-Kenigsbuch D. TH1/TH2 cytokines in the central nervous system. Int J Neurosci. 2002; 112(6): 665–703, doi: 10.1080/00207450290025725, indexed in Pubmed: 12325311.
24. Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations (*). Annu Rev Immunol. 2010; 28: 445–489, doi: 10.1146/annurev-immunol-030409-101212, indexed in Pubmed: 20192806.
25. Li YF, Zhang SX, Ma XW, et al. Levels of peripheral Th17 cells and serum Th17-related cytokines in patients with multiple sclerosis: A meta-analysis. Mult Scler Relat Disord. 2017; 18: 20–25, doi: 10.1016/j.msard.2017.09.003, indexed in Pubmed: 29141810.
26. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, et al. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. Cytokine Growth Factor Rev. 2020; 54: 62–75, doi: 10.1016/j.cytogfr.2020.06.001, indexed in Pubmed: 32513566.
27. Wong CK, Lam CWK, Wu AKL, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol. 2004; 136(1): 95–103, doi: 10.1111/j.1365-2249.2004.02415.x, indexed in Pubmed: 15030519.
28. Okabayashi T, Kariwa H, Yokota Si, et al. Cytokine regulation in SARS coronavirus infection compared to other respiratory virus infections. J Med Virol. 2006; 78(4): 417–424, doi: 10.1002/jmv.20556, indexed in Pubmed: 16482545.
29. Compston A, Coles A. Multiple sclerosis. The Lancet. 2008; 372(9648): 1502–1517, doi: 10.1016/s0140-6736(08)61620-7.
30. Lemus HN, Warrington AE, Rodriguez M. Multiple sclerosis: mechanisms of disease and strategies for myelin and axonal repair. Neurol Clin. 2018; 36(1): 1–11, doi: 10.1016/j.ncl.2017.08.002, indexed in Pubmed: 29157392.
31. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020; 395(10223): 497–506, doi: 10.1016/s0140-6736(20)30183-5.
32. Diao Bo, Wang C, Tan Y, et al. Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19). MedRxiv. 2020, doi: 10.1101/2020.02.18.20024364.
33. Kieseier BC. The mechanism of action of interferon-β in relapsing multiple sclerosis. CNS Drugs. 2011; 25(6): 491–502, doi: 10.2165/11591110-000000000-00000, indexed in Pubmed: 21649449.
34. Park A, Iwasaki A. Type I and Type III Interferons - Induction, Signaling, Evasion, and Application to Combat COVID-19. Cell Host Microbe. 2020; 27(6): 870–878, doi: 10.1016/j.chom.2020.05.008, indexed in Pubmed: 32464097.
35. Manivannan P, Siddiqui M, Malathi K. RNase L amplifies Interferon signaling by inducing PKR-mediated antiviral stress granules. BioRxiv. 2020, doi: 10.1101/2020.02.07.939645.
36. Schoggins JW, Rice CM. Interferon-stimulated genes and their antiviral effector functions. Curr Opin Virol. 2011; 1(6): 519–525, doi: 10.1016/j.coviro.2011.10.008, indexed in Pubmed: 22328912.
37. Seif F, Khoshmirsafa M, Aazami H, et al. The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells. Cell Commun Signal. 2017; 15(1): 23, doi: 10.1186/s12964-017-0177-y, indexed in Pubmed: 28637459.
38. Samuel CE. Antiviral actions of interferons. Clin Microbiol Rev. 2001; 14(4): 778–809, table of contents, doi: 10.1128/CMR.14.4.778-809.2001, indexed in Pubmed: 11585785.
39. Rahmani H, Davoudi-Monfared E, Nourian A, et al. Interferon β-1b in treatment of severe COVID-19: A randomized clinical trial. Int Immunopharmacol. 2020; 88: 106903, doi: 10.1016/j.intimp.2020.106903, indexed in Pubmed: 32862111.
40. Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell. 2020; 181(5): 1036–1045.e9, doi: 10.1016/j.cell.2020.04.026, indexed in Pubmed: 32416070.
41. Hung IN, Lung KC, Tso EK, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. The Lancet. 2020; 395(10238): 1695–1704, doi: 10.1016/s0140-6736(20)31042-4.
42. Zheng C, Kar I, Chen CK, et al. Multiple sclerosis disease-modifying therapy and the COVID-19 pandemic: implications on the risk of infection and future vaccination. CNS Drugs. 2020; 34(9): 879–896, doi: 10.1007/s40263-020-00756-y, indexed in Pubmed: 32780300.
43. Monk P, Marsden R, Tear V, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet Respiratory Medicine. 2021; 9(2): 196–206, doi: 10.1016/s2213-2600(20)30511-7.
44. Hong SIn, Ryu BH, Chong YP, et al. Five severe COVID-19 pneumonia patients treated with triple combination therapy with lopinavir/ritonavir, hydroxychloroquine, and interferon β-1b. Int J Antimicrob Agents. 2020; 56(2): 106052, doi: 10.1016/j.ijantimicag.2020.106052, indexed in Pubmed: 32544570.
45. Pan H, Peto R, Karim Q, et al. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. Med Rxiv. 2020, doi: 10.1101/2020.10.15.20209817.
46. Dastan F, Nadji SA, Saffaei A, et al. Subcutaneous administration of interferon beta-1a for COVID-19: A non-controlled prospective trial. Int Immunopharmacol. 2020; 85: 106688, doi: 10.1016/j.intimp.2020.106688, indexed in Pubmed: 32544867.

47. Davoudi-Monfared E, Rahmani H, Khalili H, et al. A Randomized clinical trial of the efficacy and safety of interferon β-1a in treatment of severe COVID-19. Antimicrob Agents Chemother. 2020; 64(9), doi: 10.1128/AAC.01061-20, indexed in Pubmed: 32661006.
48. Groves A, Kihara Y, Chun J. Fingolimod: direct CNS effects of sphingosine 1-phosphate (S1P) receptor modulation and implications in multiple sclerosis therapy. J Neurol Sci. 2013; 328(1-2): 9–18, doi: 10.1016/j.jns.2013.02.011, indexed in Pubmed: 23518370.
49. Cross AH, Naismith RT. Established and novel disease-modifying treatments in multiple sclerosis. J Intern Med. 2014; 275(4): 350–363, doi: 10.1111/joim.12203, indexed in Pubmed: 24444048.
50. Kloc M, Ghobrial RM. The multiple sclerosis (MS) drugs as a potential treatment of ARDS in COVID-19 patients. Mult Scler Relat Disord. 2020; 45: 102437, doi: 10.1016/j.msard.2020.102437, indexed in Pubmed: 32763844.
51. Pinschewer DD, Brinkmann V, Merkler D. Impact of sphingosine 1-phosphate modulation on immune outcomes. Neurology. 2011; 76(8 Suppl 3): S15–S19, doi: 10.1212/WNL.0b013e31820d9596, indexed in Pubmed: 21339486.
52. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respiratory Medicine. 2020; 8(4): 420–422, doi: 10.1016/s2213-2600(20)30076-x.
53. Foerch C, Friedauer L, Bauer B, et al. Severe COVID-19 infection in a patient with multiple sclerosis treated with fingolimod. Mult Scler Relat Disord. 2020; 42: 102180, doi: 10.1016/j.msard.2020.102180, indexed in Pubmed: 32408155.
54. Maghzi AH, Houtchens MK, Preziosa P, et al. COVID-19 in teriflunomide-treated patients with multiple sclerosis. J Neurol. 2020; 267(10): 2790–2796, doi: 10.1007/s00415-020-09944-8, indexed in Pubmed: 32494856.
55. Aly L, Hemmer B, Korn T. From Leflunomide to Teriflunomide: Drug Development and Immunosuppressive Oral Drugs in the Treatment of Multiple Sclerosis. Curr Neuropharmacol. 2017; 15(6): 874–891, doi: 10.2174/1570159X14666161208151525, indexed in Pubmed: 27928949.
56. Ruiz F, Vigne S, Pot C. Resolution of inflammation during multiple sclerosis. Semin Immunopathol. 2019; 41(6): 711–726, doi: 10.1007/s00281-019-00765-0, indexed in Pubmed: 31732775.
57. Xiong R, Zhang L, Li S, et al. Novel and potent inhibitors targeting DHODH are broad-spectrum antivirals against RNA viruses including newly-emerged coronavirus SARS-CoV-2. Protein Cell. 2020; 11(10): 723–739, doi: 10.1007/s13238-020-00768-w, indexed in Pubmed: 32754890.
58. Faissner S, Gold R. Oral therapies for multiple sclerosis. Cold Spring Harb Perspect Med. 2019; 9(1), doi: 10.1101/cshperspect.a032011, indexed in Pubmed: 29500302.
59. Bar-Or A, Pachner A, Menguy-Vacheron F, et al. Teriflunomide and its mechanism of action in multiple sclerosis. Drugs. 2014; 74(6): 659–674, doi: 10.1007/s40265-014-0212-x, indexed in Pubmed: 24740824.
60. Wang M, Zhao Y, Hu W, et al. Treatment of COVID-19 patients with prolonged post-symptomatic viral shedding with leflunomide - a single-center, randomized, controlled clinical trial. Clin Infect Dis. 2020 [Epub ahead of print], doi: 10.1093/cid/ciaa1417, indexed in Pubmed: 32955081.
61. Hu Ke, Wang M, Zhao Y, et al. A small-scale medication of leflunomide as a treatment of COVID-19 in an open-label blank-controlled clinical trial. Virol Sin. 2020; 35(6): 725–733, doi: 10.1007/s12250-020-00258-7, indexed in Pubmed: 32696396.
62. Abboud H, Zheng C, Kar I, et al. Current and emerging therapeutics for neuromyelitis optica spectrum disorder: Relevance to the COVID-19 pandemic. Mult Scler Relat Disord. 2020; 44: 102249, doi: 10.1016/j.msard.2020.102249, indexed in Pubmed: 32526698.
63. Castelnovo L, Tamburello A, Lurati A, et al. Anti-IL6 treatment of serious COVID-19 disease: A monocentric retrospective experience. Medicine (Baltimore). 2021; 100(1): e23582, doi: 10.1097/MD.0000000000023582, indexed in Pubmed: 33429732.
64. NIH. Immunomodulators Under Evaluation for the Treatment of COVID-19 2020. https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/.
65. Heo YA. Satralizumab: first approval. Drugs. 2020; 80(14): 1477–1482, doi: 10.1007/s40265-020-01380-2, indexed in Pubmed: 32797372.
66. ClinicalTrials.gov. National Library of Medicine (U.S.). (2020, February -). Soliris to Stop Immune Mediated Death in Covid 19 Infected Patients. A Trial of Distal Complement Inhibition. https://clinicaltrials.gov/ct2/show/NCT04288713 (February 21, 2021).

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4, pages: 369–379
DOI: 10.5603/PJNNS.a2021.0042

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

Structural brain assessment of temporal lobe epilepsy based on voxel-based and surface-based morphological features

Zhensheng Li[1], Jianjie Kang[1], Quwen Gao[1], Kairun Peng[1], Wei Wang[2], Jian Lin[1], Weimin Wang[1], Xiaofei Guo[2]

[1]Department of Neurology, General Hospital of Southern Theatre Command, PLA, Guangzhou, China
[2]Department of Neurosurgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

ABSTRACT

Aim of the study. This study aimed to assess the cerebral voxel-based and surface-based morphological abnormalities of patients with temporal lobe epilepsy (TLE).

Materials and methods. A total of 100 healthy adults and 73 patients with TLE were enrolled in this study, and their 3D T1-weighted MRI data were collected. Voxel-based morphology (VBM) and surface-based morphology (SBM) tools were used to compare the morphological differences between healthy adults and patients with TLE. Receiver-operating characteristic (ROC) curves were used to acquire the boundary values for detecting morphological abnormalities in regions of interest from the corrected VBM and SBM analysis.

Results. Our results showed that cortical voxels and decreased thickness areas were located in the widespread cortex and subcortical structures in the TLE group. However, after completing the analysis, we found that the left-TLE lesions were limited to the left temporal pole and left hippocampus, while the right-TLE lesions were located in the bilateral medial temporal lobe, including the right hippocampus and bilateral amygdala. ROC-curve results showed that the volume of the left hippocampus at 4,124.45 mm^3 and the thickness of the left temporal pole cortex at 3.50 mm could be used as optimal boundary values based on the curves of the left-TLE group. The right-TLE group curves were poor.

Conclusions. Widespread cerebral morphological TLE abnormalities were represented in this study. However, the lesions may be limited after completing a corrected comparison with clinical information. Boundary values of left-TLE group lesions were also obtained.

Key words: structural assessment, temporal lobe epilepsy, morphological atlas, hippocampal sclerosis, 3D T1-weighted images

(*Neurol Neurochir Pol 2021; 55 (4): 369–379*)

Introduction

Temporal lobe epilepsy (TLE) is a common type of drug-resistant epilepsy [1]. Research studies have shown that patients with TLE suffer from widespread cortical and subcortical morphological abnormalities, such as decreased volume and cortical atrophy. The regions were mostly located in the frontal, temporal, occipital, and central cortex, and the thalamus [2, 3]. These studies have also found damage in white matter fibres [4]. Therefore, it is expected that patients with TLE suffer a certain degree of cognitive impairment, in addition to frequent seizures, that are closely related to the structural abnormalities [5, 6]. A certain amount of neural network damage is also related to cerebral emotional functions [7]. It is considered that factors such as long-term duration, frequent seizures, and medication have an influence on the impairments of the cortical and subcortical structures [8], but it has also been found that progressive cortical atrophy is still present with the disease's prolongation, even in the case of seizure freedom [9]. It is currently believed that epilepsy is a neurodegenerative disease, and the spread of epileptiform discharges are considered to be detrimental to the widespread cortical and subcortical structures [10].

Address for correspondence: Weimin Wang, Department of Neurosurgery, General Hospital of Southern Theatre Command, PLA, No. 111 of Liuhua Road, Yuexiu District, Guangzhou, 510010, China; e-mail: weimin_wang11@163.com

Received: 20.02.2021 Accepted: 27.04.2021 Early publication date: 2.06.2021

Quantitative measurements have been used as a non-invasive tool for brain morphology assessments, and the effects have also been shown to be consistent with actual measurements [11]. However, widespread cortical atrophy has been discovered in patients with TLE, with no benefits in terms of locating the epileptogenic lesions. Fully quantitative cerebral morphological assessments could provide a path for predicting curative effects, cognitive evaluation, and early surgical decisions [12]. They also provide precise boundary evaluations for detecting morphological abnormalities that have been difficult to recognise in conventional imaging. Therefore, this study aimed to assess the cerebral morphology for patients with TLE based on voxel-based morphometry (VBM) [13] and surface-based morphometry (SBM) [14].

Materials and methods

Subjects

In this study, we collected the 3D T1-weighted MRI data of healthy adults and patients with TLE who were recruited from 2015 to 2019.

Standard protocol approvals, registration, and participant consent: all participants provided written consent. The institutional review board at the General Hospital of Southern Theatre Command, PLA, approved this study.

Inclusion and exclusion criteria

In the healthy adults' group, the inclusion criteria were: 1. healthy adult; 2. aged over 18; 3. right-handed; 4. EEG and cerebral MR examinations taken with normal results. The exclusion criteria were : 1. a history of neurological or mental illness; 2. a history of chronic disease such as hypertension, diabetes, or coronary heart disease; 3. a positive family history of hereditary disease.

In the TLE group, the inclusion criteria were: 1. patients with unilateral TLE, with a diagnosis that fulfilled the criteria of the International League Against Epilepsy (ILAE) [15] (this criterion was established based on a comprehensive investigation that included the collection of seizure semiology, the inspection of discharge from unilateral temporal areas on inter-ictal/ictal EEGs, video-telemetry recordings, and the inspection of MR images for evidence of structural abnormalities in the mesial temporal lobe); 2. Aged over 16. The exclusion criteria were: 1. Patients with TLE caused by inflammation; 2. Patients with TLE caused by trauma; 3. Patients with TLE caused by brain tumors; 4. Patients with bilateral TLE.

Materials

General demographic information, such as the gender and age of each participant, was collected. For patients with TLE, it was also necessary to collect clinical information such as disease duration, age at onset, seizure types, seizure frequency, and medication use (Tab. 1).

MR acquisition: The visual interpretation of the findings in this study was conducted by an experienced clinician. Cerebral MR scans were performed on 173 participants using a General Electric (GE) 3.0T MR scanner and a SIEMENS 3.0T MR scanner. The scan sequences included the conventional T1-weighted, T2-weighted, and T2 FLAIR images. Three-dimensional T1-weighted MPRAGE sequences (TE = 3.24 ms, TR = 2300 ms, TI = 900 ms, flip angle = 9 degrees, bandwidth = 210 Hz/pixel, FOV = 256 mm, matrix = 256 × 256, resolution 1.0 × 1.0 × 1.0 mm^3, a total of 176 sagittal images) were also necessary.

Methods

SPM [16] was used for the cortical assessment of TLE patients.

For the 3D T1-weighted magnetisation, prepared rapid gradient echo (MPRAGE) sequences were preprocessed, including the DARTEL normalisation of images to MNI152 spacing, the segmentation of grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF), and the estimation of cortical surface and thickness and smooth areas.

Before entering the GM images into a statistical model, GM-image data was required for the estimation of the cortical surface and thickness and the smooth areas through the 'Estimate Surface Models' function.

The cortical surface images and smoothed GM images were then entered into the statistical models for a comparison between the healthy group and the group with TLE.

The subcortical structures, including the hippocampus, amygdala, caudate nucleus, putamen, globus pallidus, nucleus accumbens, and the brainstem, were segmented and reconstructed within a Freesurfer 5.3 software package [17]. The T1-weighted NIFTI format images were input into Freesurfer and automatically reconstructed through the 'recon-all' function. These processes included removing non-brain tissue, volumetric labelling, intensity normalisation, GM and WM segmentation, subcortical mass creation, and data estimation (Fig. 1).

Statistical analysis

T-test statistical models using the standard VBM and SBM 'Specify 2nd Level' or 'Basic Models' modules were performed for grey-matter volume and thickness comparison at two different significance thresholds: an uncorrected threshold of $p < 0.001$ and a threshold of $p < 0.05$ corrected for FDR. Comparisons were performed again when corrected by covariates, including disease duration, age at onset, seizure type, seizure frequency, number of current medications, and total intracranial volume. The regions of interest (ROIs) were then detected from these comparisons. SPSS 19.0 software program (IBM, Chicago, IL, USA) was used for statistical data. The cortical thickness data of ROIs were derived from SBM analysis,

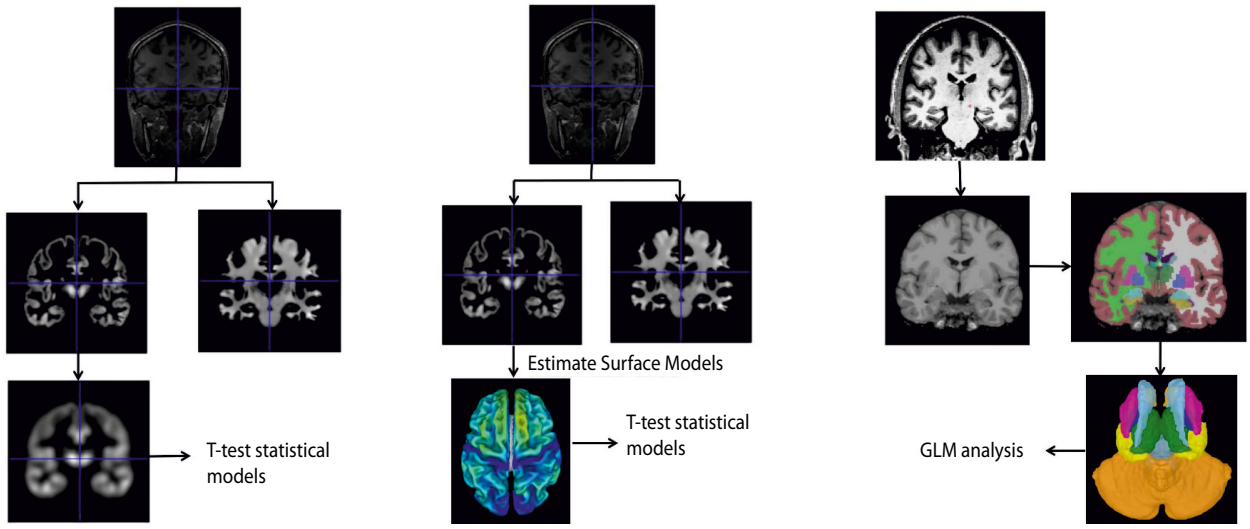


Figure 1. Processing streams for 3D T1-weighted magnetisation: prepared rapid gradient echo (MPRAGE) sequences

and the subcortical structural volumes were derived from the Freesurfer 5.3 results. The data was imported into the SPSS. A general linear model (GLM) was used for the covariance comparison of cortical and subcortical structural data between the groups. We used the covariates above for correction and the ROC curves to acquire the boundary values with the highest sensitivity and specificity for detecting morphological abnormalities. A value of $p < 0.05$ was considered statistically significant.

Results

General characteristics

We recruited 100 healthy adults for the first group. These included 50 males and 50 females, and their ages ranged from 18 to 40. We recruited 73 patients with TLE for the second group, including 38 left-TLE patients and 35 right-TLE patients. Their ages ranged from 16 to 44.

Cortical morphological comparison between healthy group and TLE group

The VBM comparison results between the groups showed that voxel-decreased areas in patients with TLE were found in the widespread cortical and subcortical structures in addition to the temporal lobe, including the bilateral cingulate, temporal cortex, and thalamus ($p < 0.001$, uncorrected). The cortical thickness comparison results based on the SBM analysis between the groups were shown based on the Destrieux 2009 parcellation [18]. In addition, we found that the cortical thickness atrophy areas of the patients with TLE were also present in the widespread cortex, with the most obvious areas in the bilateral frontal, temporal, and central cortex (Fig. 2, 3) ($p < 0.05$, FDR corrected). The cortical atrophy ranges of the left TLE were more extensive than for the right TLE.

Corrected cortical morphological comparison between healthy and TLE groups

The corrected VBM comparisons between the healthy group and the left-TLE patients demonstrated that the morphologically abnormal areas were limited to the left hippocampus ($p < 0.001$, uncorrected), while the morphologically abnormal areas in the patients with right TLE were found in the bilateral medial temporal lobe, based on the corrected VBM comparisons. In the corrected SBM analysis, the cortical atrophy area of the patients with left TLE was confined to the left temporal pole area (original data 3.71 ± 0.27 mm *vs.* 3.48 ± 0.45 mm, adjusted $p = 0.027$). No significant results were found in the corrected SBM analysis between the healthy group and the right-TLE group (Fig. 4, 5).

Corrected subcortical structure volume comparison between healthy and TLE groups

The corrected comparison of the subcortical structure volumes by GLM also confirmed that the left hippocampus volume of the left-TLE patients was reduced (original data 4,325.62 ± 454.70 mm^3 *vs.* 3,849.32 ± 761.36 mm^3, adjusted $p = 0.033$). The volume-decreased areas were located in the right hippocampus (4,542.17 ± 418.28 mm^3 *vs.* 4,049.94 ± 985.20 mm^3, adjusted $p = 0.002$) and the bilateral amygdala (left side: 1,685.50 ± 214.54 mm^3 *vs.* 1,504.43 ± 227.38 mm^3, adjusted $p = 0.003$, right side: 1,717.50 ± 170.92 mm^3 *vs.* 1,563.72 ± 269.38 mm^3, adjusted $p = 0.001$) of the right-TLE patients.

ROC curves for detection of morphological abnormalities in ROIs

For the left-TLE patients, ROC curves of the left hippocampus volume and left temporal pole area thickness were performed. The area under the ROC curve of the left hippocampus volume was 0.699, and the optimal boundary value

Table 1. Demographic characteristics and clinical information of healthy adults and TLE patients

Index		Healthy adults	Left-TLE group	Right-TLE group	F/X^2	P
Age (years)		27.71 ± 4.00	26.84 ± 8.52	26.86 ± 8.34	0.401	0.670
Sex	Male	50 (50)	25 (65.8%)	15 (42.9%)	4.227	0.121
	Female	50 (50)	13 (34.2%)	20 (57.1%)		
Disease duration (years)	0–5	—	16 (42.1%)	14 (40.0%)	1.732	0.630
	6–10	—	9 (23.7%)	10 (28.6%)		
	11–15	—	8 (21.1%)	4 (11.4%)		
	≥ 16	—	5 (13.2%)	7 (20.0%)		
Onset age (years)	0–10	—	6 (15.8%)	7 (20.0%)	0.302	0.960
	11–20	—	19 (50.0%)	16 (45.7%)		
	21–30	—	7 (18.4%)	7 (20.0%)		
	≥ 16	—	6 (15.8%)	5 (14.3%)		
Seizure type	CPS	—	28 (73.7%)	23 (65.7%)	0.55	0.458
	sGTCS	—	34 (89.5%)	31 (88.6%)	0.015	0.902
CPS frequency (times per year)	< 10	—	3 (7.9%)	6 (17.6%)	5.966	0.31
	10–20	—	6 (15.8%)	4 (11.4%)		
	21–30	—	5 (13.2%)	3 (8.6%)		
	31–40	—	4 (10.5%)	0 (0%)		
	> 41	—	9 (23.7%)	9 (25.7%)		
sGTCS frequency (times per year)	< 10	—	17 (44.7%)	22 (62.9%)	7.109	0.213
	10–20	—	13 (34.2%)	6 (17.1%)		
	21–30	—	0 (0%)	2 (5.7%)		
	31–40	—	1 (2.6%)	0 (0%)		
	> 41	—	3 (7.9%)	1 (2.9%)		
Febrile seizures history		—	13 (34.20%)	7 (20.0%)	1.85	0.174
Family history		—	1 (2.6%)	1 (2.9%)	0.003	0.953
Medication	Sodium Valproate	—	16 (42.1%)	19 (54.3%)	1.083	0.298
	Carbamazepine	—	11 (28.9%)	7 (20%)	0.785	0.376
	Oxcarbazepine	—	4 (10.5%)	3 (8.6%)	0.08	0.777
	Topiramate	—	5 (13.2%)	4 (11.4%)	0.05	0.822
	Lamotrigine	—	1 (2.6%)	10 (28.6)	9.579	0.02
	Levetiracetam	—	3 (7.9%)	4 (11.4%)	0.262	0.608
	Phenytoin	—	2 (5.3%)	1 (2.9%)	0.268	0.605
	Benzodiazepine	—	4 (10.5%)	2 (5.7%)	0.559	0.455

CPS — complex partial seizures; sGTCS — secondary generalised tonic-clonic seizures

was 4,124.45 mm^3, with sensitivity 60.5% and specificity 77.0%. The area under the ROC curve of the left temporal pole thickness was 0.711, and the optimal boundary value was 3.50 mm, with sensitivity 60.5% and specificity 78.0%. However, for the right-TLE patients, the ROC curves for the right hippocampus and amygdala volume showed poor efficiency. The area under the ROC curve of the right hippocampus volume was 0.605, and the optimal boundary value was 4,487.95 mm^3, with sensitivity only 57.1% and specificity 58.0%. The area under the ROC curve of the right amygdala volume was 0.679, and the optimal boundary value was 1,658.45 mm^3, with sensitivity 62.9% and specificity 64.0% (Fig. 6).

Discussion

This study showed that grey-matter volume and cortical thickness-decreased areas were located in the widespread cortex and subcortical structures in the TLE group. However, after our corrected analysis, we found that left-TLE lesions were limited to the left temporal pole and left hippocampus.

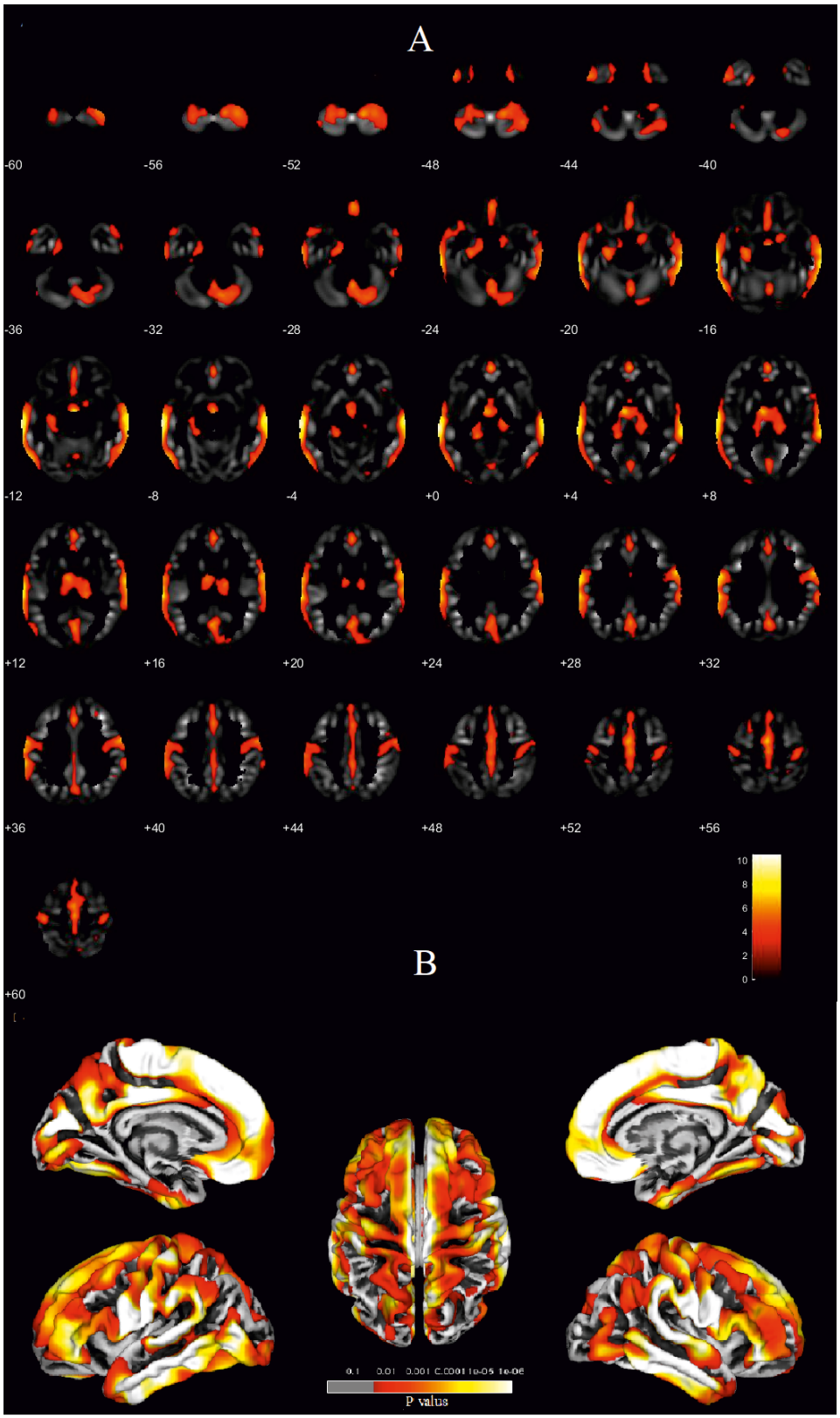


Figure 2. VBM and SBM analysis between healthy group and left-TLE patients

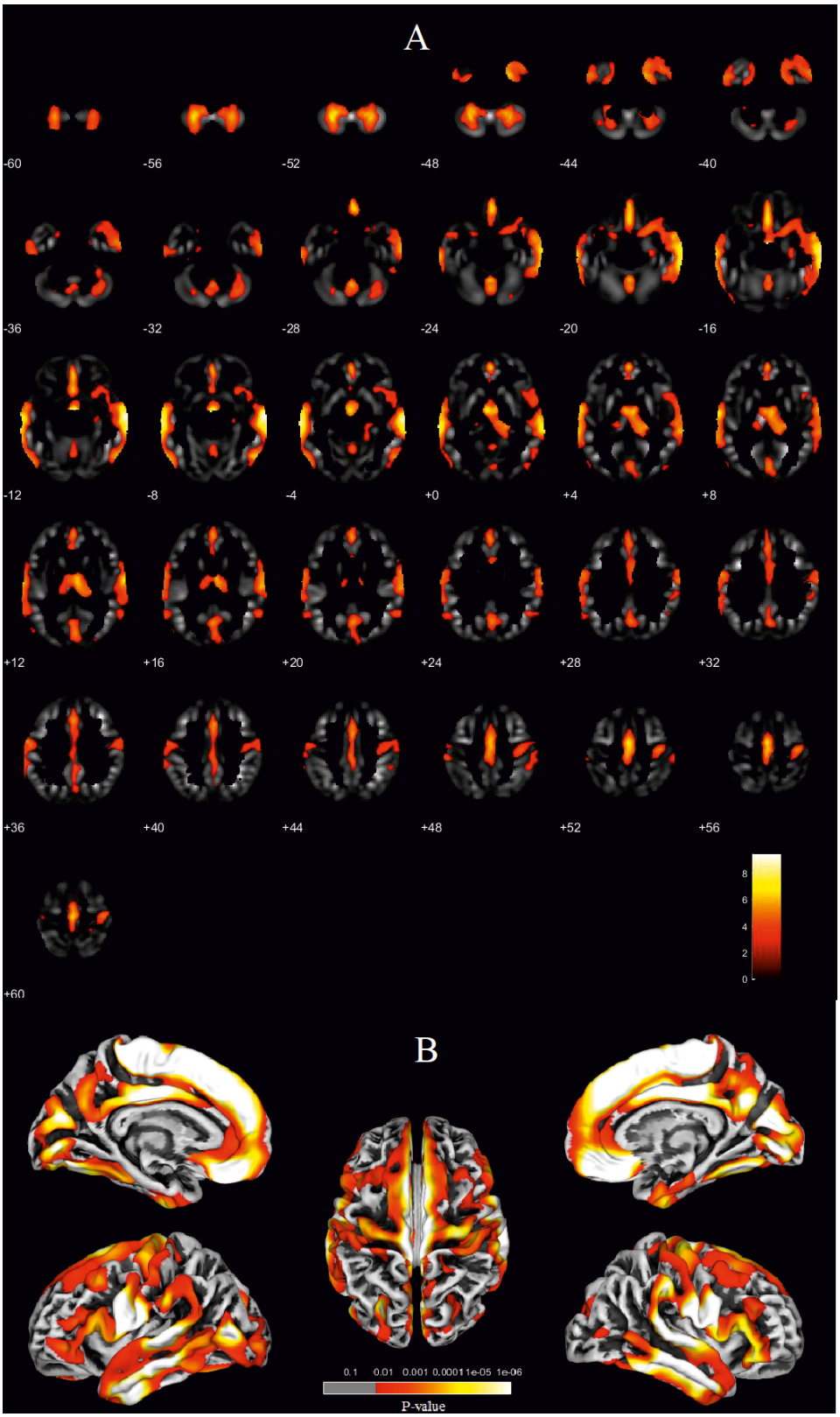


Figure 3. VBM and SBM analysis between healthy group and right-TLE patients

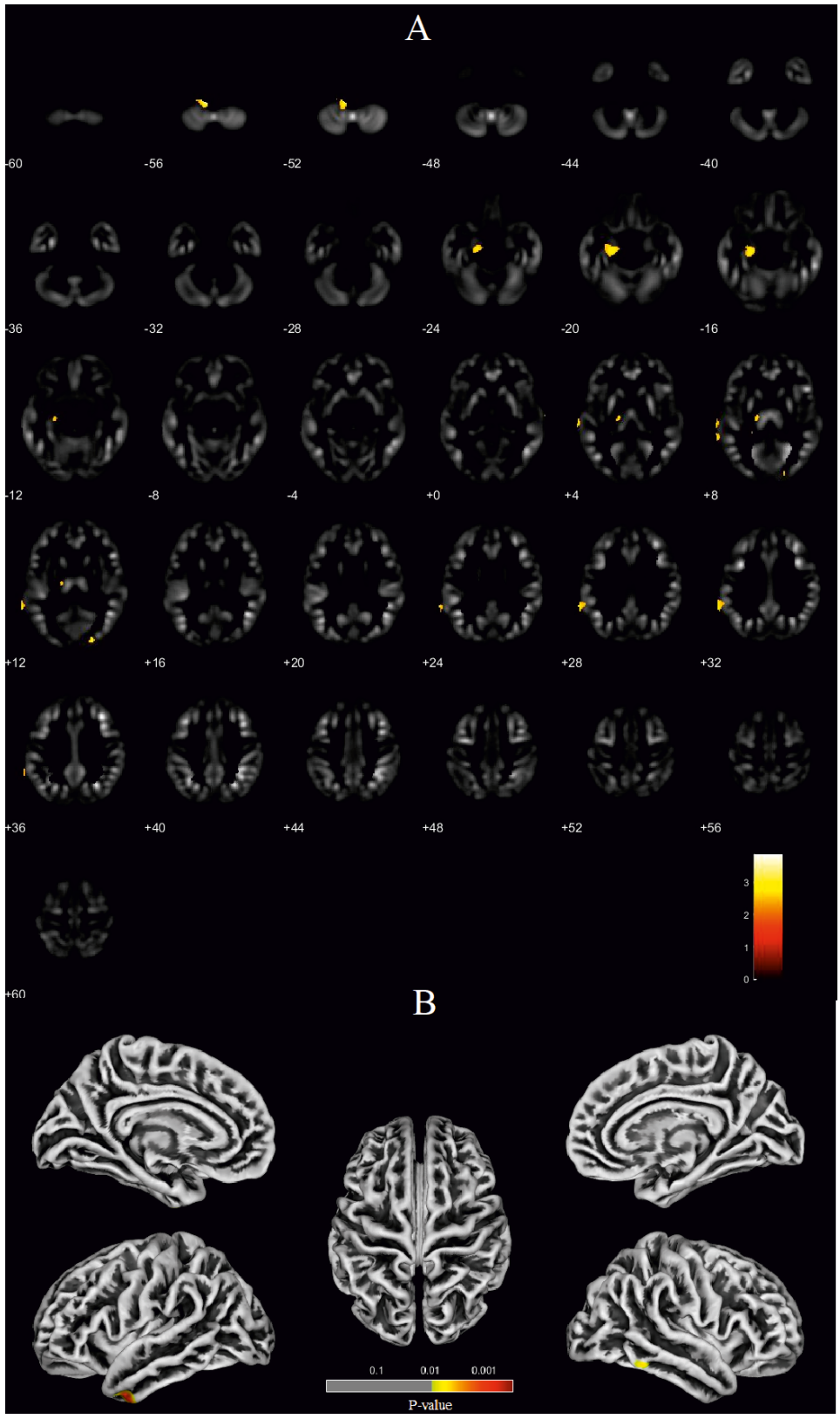


Figure 4. Corrected VBM and SBM analysis between healthy and left-TLE groups

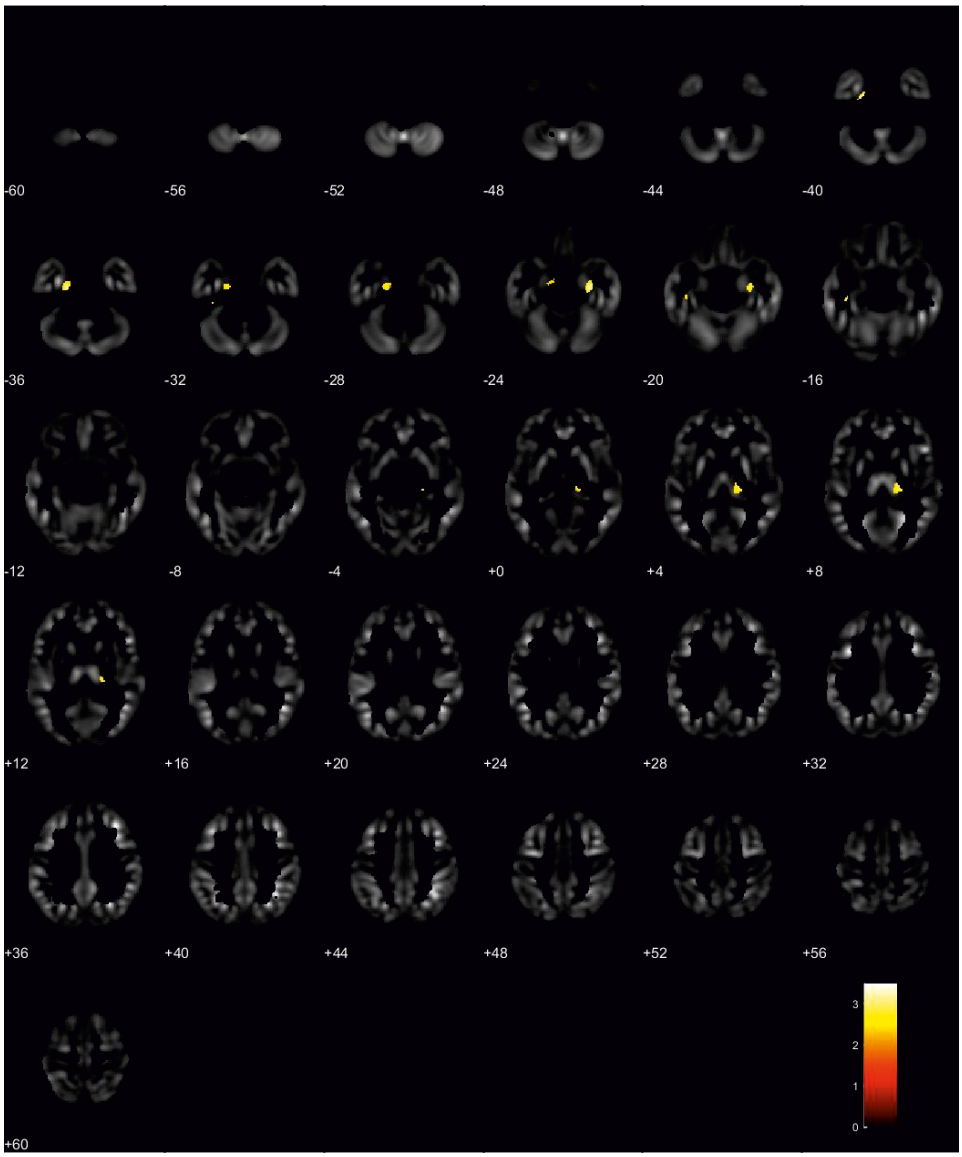


Figure 5. Corrected VBM analysis between healthy and right-TLE groups

The lesions in patients with right TLE were located in the bilateral medial temporal lobe, including the right hippocampus and bilateral amygdala. The results of the ROC curves showed that the volume of the left hippocampus at 4,124.45 mm^3 and the thickness of the left temporal pole cortex at 3.50 mm could be used as the optimal boundary values based on the left-TLE group curves. However, the right-TLE results were relatively insignificant.

Based on innovations in imaging processing methods, especially the widespread application of VBM, it has been reported that temporal lobe epilepsy is a network disorder. Even a multicentric study of advanced morphological neuroimaging in lateral temporal lobe epilepsy has been performed in recent years [19].

We found similar results in the uncorrected VBM and SBM analysis in this study, demonstrating widespread cortical and sub-cortical atrophy areas in TLE. However, these results have no benefits for lesion localisation, something which is also highlighted in previous studies. VBM based on grey-matter volume appeared unfavourable in presurgical focal epilepsy patients, but VBM based on T2-FLAIR and junction maps might achieve higher specificity and sensitivity [20].

Furthermore, as discussed above, these results were mixed, with many confounding clinical factors. Some scholars have been able to detect morphological alterations confined to the medial temporal lobe after excluding the influence of disease duration and onset age [21]. But these studies were only focused on hippocampal sclerosis patients, which is not conducive to determining morphological abnormalities in patients who have normal imaging on visual inspection. Nor was medication involved in the cerebral

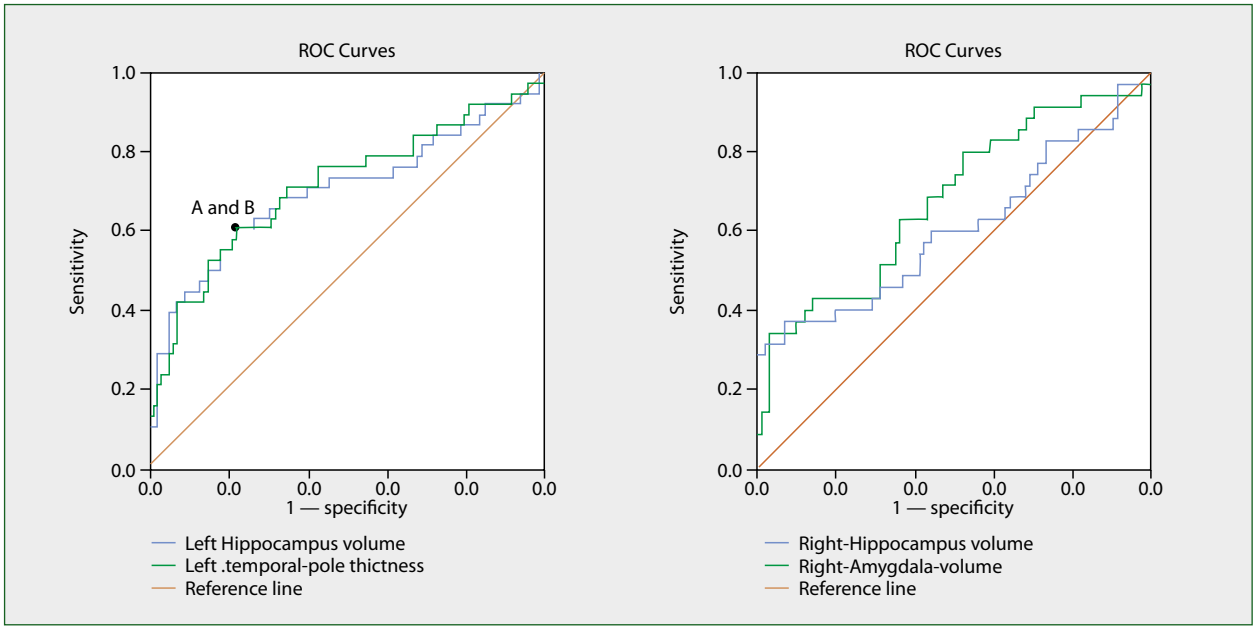


Figure 6. ROC curves of ROIs for detecting morphological abnormalities in patients with TLE

morphological changes of the patients with TLE. For this reason, we recruited TLE patients who even had MRI negative conditions, and we also considered the influence of medication factors.

A decrease in the left hippocampus volume and left temporal pole cortical thickness was the main morphological alteration in the left-TLE patients, who still had to be identified by corrected VBM and SBM analysis, respectively, in this study. The volume decrease of the left hippocampus was also supported by a corrected comparison of subcortical structure volumes. The volume decrease in the TLE hippocampus has long been documented and is related to memory impairment [22]. Moreover, studies concerning the cortical thickness of the left-TLE lesions showed the left temporal polar thickness thinning specifically. This result could provide evidence for the early detection of temporal cortical dysplasia. Likewise, the most significant morphological change in right-TLE patients was right hippocampus volume loss.

Thus, it can be concluded that ipsilateral hippocampus volume decrease was still the most intrinsic morphological abnormality of unilateral TLE. Quantitative morphological analysis for TLE has been refined in hippocampal subfields [23]. The CA1 field is receiving attention from researchers and has proved to be related to the histopathology in TLE [24]; however, total hippocampal volume atrophy was found in the patients of this study, suggesting that hippocampal subfields other than CA1 should be considered equally in the morphological assessment of TLE. We expect to prove this assumption in further studies. In addition, the results also suggest that confounding factors had a considerable influence on extensive extratemporal cortical damage. These factors need to be excluded in lesion localisation, especially in the pre-surgery assessment.

We further attempted to use ROC curves to analyse the ROI data from the corrected VBM and SBM analysis to determine the criteria of morphological abnormalities for left-TLE patients. This showed that the areas under the ROC curves of the left hippocampus and left temporal pole reached 0.7. The volume of the left hippocampus at 4,124.45 mm^3 and the cortical thickness of the left temporal pole at 3.50 mm was the optimal boundary value based on the current curves. However, the results of the ROC curves of the right-TLE group were quite poor.

Under the corrected comparison, the grey-matter volume decrease in the bilateral medial temporal lobe was found in the corrected VBM analysis of the right-TLE patients. The corrected GLM analysis of the subcortical structures also confirmed a volume decrease in the right hippocampus and bilateral amygdala areas. These results are in contrast to studies that have suggested more widespread abnormalities with left TLE than right TLE [2, 3]. In fact, the results of our uncorrected morphological analysis support previous conclusions. The different results between the left and right TLE in the corrected analysis may suggest a variance in the intrinsic epileptic networks in patients with unilateral TLE. Another recent study has also confirmed a contralateral shape inflation of the left hippocampus in the right TLE [25]. The connectivity between bilateral temporal lobes has been clearly shown [26, 27]. Furthermore, another study using interictal connectivity analysis on a high-density EEG found a stronger connection from the ipsilateral to the contralateral medial temporal pole in the right TLE than the left TLE [28].

It could be assumed that the seizures in right-TLE patients are more likely to be caused by a linkage between bilateral medial temporal lobe structures. This also suggests that we should pay more attention to the possibility of contralateral temporal lobe damage in the clinical assessment of patients with right TLE.

There were several limitations to this study. Firstly, this study was a single-centre trial, and the sample size was limited. Secondly, the ROC-curve analysis failed to achieve higher sensitivity and specificity, which may be due to the use of raw data. An accurate correction algorithm is required to obtain corrections for better boundaries. Thirdly, we only used VBM and SBM tools to validate morphological abnormalities. More structural and functional data, such as diffusion tensor imaging (DTI), EEG, and fMRI, should be included in future clinical assessments. Fourthly, in this study, hippocampal volumes and volumetric measurements were not corrected for total intracranial volume, which may have caused a certain bias. Finally, no pathological information was provided in this study. This should be included in future studies.

Conclusions

Widespread cerebral morphological TLE abnormalities were presented in this study. However, the lesions could be limited after a corrected comparison with the clinical information. The boundary values of the left-TLE group lesions were also obtained.

Acknowledgments: *The authors thank the patients and healthy adults who took part in this study.*
Funding: *This work was supported by the National Technology Research and Development Programme (863 programme) of China (2015137). The funding body had no role in the design of the study and collection, analysis and interpretation of data, or in writing the manuscript.*
Conflicts of interest: *None.*
Ethical permission: *This study was approved by the institutional review board at the General Hospital of Southern Theatre Command, PLA.*

References

1. Sanz-Garcia A, Vega-Zelaya L, Pastor J, et al. When does Post-Ictal period start in temporal lobe epilepsy? A quantitative EEG perspective. Rev Neurol. 2017; 64(8): 337–346, indexed in Pubmed: 28368080.
2. Whelan CD, Altmann A, Botía JA, et al. Structural brain abnormalities in the common epilepsies assessed in a worldwide ENIGMA study. Brain. 2018; 141(2): 391–408, doi: 10.1093/brain/awx341, indexed in Pubmed: 29365066.
3. Bernasconi N, Bernhardt B, Concha L, et al. Cortical thickness analysis in temporal lobe epilepsy: reproducibility and relation to outcome. Neurology. 2010; 74(22): 1776–1784, doi: 10.1212/WNL.0b013e3181e0f80a, indexed in Pubmed: 20513813.
4. Xu Y, Qiu S, Wang J, et al. Disrupted topological properties of brain white matter networks in left temporal lobe epilepsy: a diffusion tensor imaging study. Neuroscience. 2014; 279: 155–167, doi: 10.1016/j.neuroscience.2014.08.040, indexed in Pubmed: 25194789.
5. Bell B, Lin JJ, Seidenberg M, et al. The neurobiology of cognitive disorders in temporal lobe epilepsy. Nat Rev Neurol. 2011; 7(3): 154–164, doi: 10.1038/nrneurol.2011.3, indexed in Pubmed: 21304484.
6. Keller SS, Richardson MP, O'Muircheartaigh J, et al. Morphometric MRI alterations and postoperative seizure control in refractory temporal lobe epilepsy. Hum Brain Mapp. 2015; 36(5): 1637–1647, doi: 10.1002/hbm.22722, indexed in Pubmed: 25704244.
7. Toller G, Adhimoolam B, Rankin KP, et al. Right fronto-limbic atrophy is associated with reduced empathy in refractory unilateral mesial temporal lobe epilepsy. Neuropsychologia. 2015; 78: 80–87, doi: 10.1016/j.neuropsychologia.2015.09.010, indexed in Pubmed: 26363299.
8. Caciagli L, Bernasconi A, Wiebe S, et al. A meta-analysis on progressive atrophy in intractable temporal lobe epilepsy: Time is brain? Neurology. 2017; 89(5): 506–516, doi: 10.1212/WNL.0000000000004176, indexed in Pubmed: 28687722.
9. Alvim M, Coan A, Campos B, et al. Progression of gray matter atrophy in seizure-free patients with temporal lobe epilepsy. Epilepsia. 2016; 57(4): 621–629, doi: 10.1111/epi.13334.
10. Bernasconi N. Is epilepsy a curable neurodegenerative disease? Brain. 2016; 139(Pt 9): 2336–2337, doi: 10.1093/brain/aww202, indexed in Pubmed: 27559105.
11. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci U S A. 2000; 97(20): 11050–11055, doi: 10.1073/pnas.200033797, indexed in Pubmed: 10984517.
12. He X, Doucet GE, Pustina D, et al. Presurgical thalamic „hubness" predicts surgical outcome in temporal lobe epilepsy. Neurology. 2017; 88(24): 2285–2293, doi: 10.1212/WNL.0000000000004035, indexed in Pubmed: 28515267.
13. Good CD, Johnsrude IS, Ashburner J, et al. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage. 2001; 14(1 Pt 1): 21–36, doi: 10.1006/nimg.2001.0786, indexed in Pubmed: 11525331.
14. Dahnke R, Yotter RA, Gaser C. Cortical thickness and central surface estimation. Neuroimage. 2013; 65: 336–348, doi: 10.1016/j.neuroimage.2012.09.050, indexed in Pubmed: 23041529.
15. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010; 51(4): 676–85, doi: 10.1111/j.1528-1167.2010.02522.x, indexed in Pubmed: 20196795.
16. Gaser C, Dahnke RC. A Computational Anatomy Toolbox for the Analysis of Structural MRI Data. HBM. : 2016.
17. Fischl B. FreeSurfer. NeuroImage. 2012; 62(2): 774–781, doi: 10.1016/j.neuroimage.2012.01.021.
18. Fischl B, van de, Destrieux C. Automatically Parcellating the Human. Cerebral Cortex. 2004; 14(1): 11–22, doi: https://doi.org/10.1093/cercor/bhg087.
19. Vasta R, Sarica A, Bisulli F, et al. Advanced morphological neuroimaging study in lateral temporal lobe epilepsy: A multicentric study. Epilepsy & Behavior. 2017; 74: 69–72, doi: 10.1016/j.yebeh.2017.06.017.

20. Martin P, Winston GP, Bartlett P, et al. Voxel-based magnetic resonance image postprocessing in epilepsy. Epilepsia. 2017; 58(9): 1653–1664, doi: 10.1111/epi.13851, indexed in Pubmed: 28745400.
21. Alhusaini S, Whelan CD, Doherty CP, et al. Temporal cortex morphology in mesial temporal lobe epilepsy patients and their asymptomatic siblings. Cereb Cortex. 2016; 26(3): 1234–1241, doi: 10.1093/cercor/bhu315, indexed in Pubmed: 25576532.
22. Bernhardt BC, Worsley KJ, Kim H, et al. Longitudinal and cross-sectional analysis of atrophy in pharmacoresistant temporal lobe epilepsy. Neurology. 2009; 72(20): 1747–1754, doi: 10.1212/01.wnl.0000345969.57574.f5, indexed in Pubmed: 19246420.
23. Bernhardt BC, Fadaie F, Vos de Wael R, et al. Preferential susceptibility of limbic cortices to microstructural damage in temporal lobe epilepsy: A quantitative T1 mapping study. Neuroimage. 2018; 182: 294–303, doi: 10.1016/j.neuroimage.2017.06.002, indexed in Pubmed: 28583883.
24. Schoene-Bake JC, Keller SS, Niehusmann P, et al. In vivo mapping of hippocampal subfields in mesial temporal lobe epilepsy: relation to histopathology. Hum Brain Mapp. 2014; 35(9): 4718–4728, doi: 10.1002/hbm.22506, indexed in Pubmed: 24638919.
25. Yoo JG, Jakabek D, Ljung H, et al. MRI morphology of the hippocampus in drug-resistant temporal lobe epilepsy: Shape inflation of left hippocampus and correlation of right-sided hippocampal volume and shape with visuospatial function in patients with right-sided TLE. J Clin Neurosci. 2019; 67: 68–74, doi: 10.1016/j.jocn.2019.06.019, indexed in Pubmed: 31221579.
26. Pail M, Brázdil M, Marecek R, et al. An optimized voxel-based morphometric study of gray matter changes in patients with left-sided and right-sided mesial temporal lobe epilepsy and hippocampal sclerosis (MTLE/HS). Epilepsia. 2010; 51(4): 511–518, doi: 10.1111/j.1528-1167.2009.02324.x, indexed in Pubmed: 19817822.
27. Besson P, Dinkelacker V, Valabregue R, et al. Structural connectivity differences in left and right temporal lobe epilepsy. Neuroimage. 2014; 100: 135–144, doi: 10.1016/j.neuroimage.2014.04.071, indexed in Pubmed: 24814212.
28. Coito A, Plomp G, Genetti M, et al. Dynamic directed interictal connectivity in left and right temporal lobe epilepsy. Epilepsia. 2015; 56(2): 207–217, doi: 10.1111/epi.12904, indexed in Pubmed: 25599821.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4 pages: 380–386
DOI: 10.5603/PJNNS.a2021.0045

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

This Research Paper is accompanied by Invited Editorial, see page 331

Migraine diagnosis and treatment in Poland: survey of primary care practitioners

Izabela Domitrz[1], Aurelia Lipa[2], Jacek Rożniecki[3], Adam Stępień[4], Wojciech Kozubski[5]

[1]Department of Neurology, Faculty of Medical Sciences, Medical University of Warsaw, Poland
[2]Medical Department, Teva Pharmaceuticals Polska Sp. z o.o., Warsaw, Poland
[3]Department of Neurology, Stroke, and Neurorehabilitation, Medical University of Lodz, Poland
[4]Department of Neurology, Military Institute of Medicine in Warsaw, Poland
[5]Department of Neurology, Charles Marcinkowski University of Medical Sciences, Poznan, Poland

ABSTRACT

Aim of the study. This study aimed to analyze the daily clinical practice of primary care practitioners (PCPs) in Poland concerning migraine patients.

Clinical rationale for the study. Migraine is a common chronic primary headache disease, which can be disabling if insufficiently managed. Numerous studies suggest that migraine remains underdiagnosed and undertreated. The first consultation of migraine patients is usually undertaken by a PCP.

Materials and methods. This study was conducted in June and July 2019 in Poland using a computer-assisted web interview with 51 PCPs. The interview questions concerned knowledge of diagnostic criteria and methods of migraine treatment.

Results. On average, each PCP consulted 12 patients with migraine per month. More than half of PCPs (63%) listed partial diagnostic criteria for migraine without aura or mentioned aura in their responses. Only 10% of PCPs listed all diagnostic criteria for migraine without aura. Although 55% of PCPs said that they distinguished between episodic and chronic migraine, 18% provided the wrong definition. The most commonly prescribed drugs were triptans (66%), paracetamol, metamizole, or non-steroidal anti-inflammatory drugs (42%).

Conclusions and clinical implications. PCPs play a critical role in diagnosing, treating, and monitoring migraine; however, many of them have insufficient knowledge about its diagnosis and correct differentiation between chronic and episodic forms.

Key words: chronic migraine, episodic migraine, headache, primary care practitioner

(*Neurol Neurochir Pol 2021; 55 (4): 380–386*)

Introduction

Migraine is a widespread, chronic primary headache disease characterised by recurrent headaches with or without aura. It affects up to 18% of women and 6% of men [1]. Chronic migraine prevalence in the general population ranges from 1.4–2.2% [2]. In Poland, chronic migraine accounts for 49% of chronic daily headaches [3]. Migraine is associated with considerable functional impairment, with both physical and emotional consequences that can impact upon occupational and family life [4, 5].

Despite the burden of disease, and the increasing availability of effective treatment, the management of migraine remains less than satisfactory. People with migraine are underdiagnosed and undertreated. This is observed not only in developing countries, but also in Europe and North America [6–8]. According to an online survey among Polish adults in January 2019, 25% of respondents reported some migraine symptoms in the last 12 months, yet only 37% of them had been diagnosed with migraine by a physician in the past [9].

Headaches account for 4.4% of primary care practitioner (PCP) visits [10]. Most migraine patients consult their PCPs. Although PCPs play a critical role in the diagnosis, treatment initiation, and monitoring of migraine [11, 12], insufficient knowledge of diagnostic criteria often leads to misdiagnosis [13, 14]. Thus, it is important to evaluate PCP knowledge and

Address for correspondence: Izabela Domitrz, Department of Neurology, Faculty of Medical Sciences, Medical University of Warsaw, ul. Cegłowska 80, 01-809 Warsaw, Poland; e-mail: izabela.domitrz@wum.edu.pl
Received: 8.02.2021 Accepted: 9.03.2021 Early publication date: 16.06.2021

educate PCPs as to the proper diagnosis and effective treatment of migraine patients.

Clinical rationale for the study

Migraine is a frequent reason for PCP visits. Usually, a PCP is the first healthcare professional diagnosing migraine or referring to a specialist. As migraine is poorly recognized in many countries, it is important to improve knowledge of migraine diagnosis among PCPs. This study aimed to analyze the daily clinical practice of PCPs in Poland concerning migraine patients.

Materials and methods

In June and July 2019, we conducted a computer-assisted web interview with general practitioners (GPs) in Poland who had agreed to participate in the study during a phone call. The physicians were selected from the Health Data Management database [15]. Physician sampling was based on 24 strata (16 voivodeship regions of Poland and two types of locations based on the physician's place of work — voivodeship capital cities and other locations), taking into account the structure of GPs in the mentioned database. The inclusion criteria confirmed during the phone call were: a PCP (e.g. internal medicine doctor, family doctor, general practitioner) who sees at least six patients with migraine per month.

All PCPs filled out a questionnaire (spontaneous answers, open-ended questions) concerning the number and characteristics of migraine patients under constant care, their knowledge of diagnostic criteria for migraine, and the type of treatment for migraine patients.

Statistical analysis

The results of the study were analyzed based on descriptive statistics. Most data were presented as nominal variables using percentage distributions, while continuous variables were presented as an arithmetic mean and median as measures of central tendency. Calculations were performed using IBM SPSS Statistics Version 24.

Results

The study involved 51 PCPs, with a mean age of 46.1 and an average working experience of 20.1 years. Nearly all PCPs (98%) attended to patients in a public outpatient clinic. On average, each PCP consulted 12 patients with migraine per month (median 10 patients/month). The PCPs included in the study declared experience in treating migraine patients, which was defined in the study design as treatment of at least six patients per month. Almost half of the PCPs (45%) admitted 6–9 patients each month (Fig. 1). On average, PCPs had 39 patients with migraine under continuous care (median 30 patients); however, 37% looked after 11–20 patients (Fig. 1).

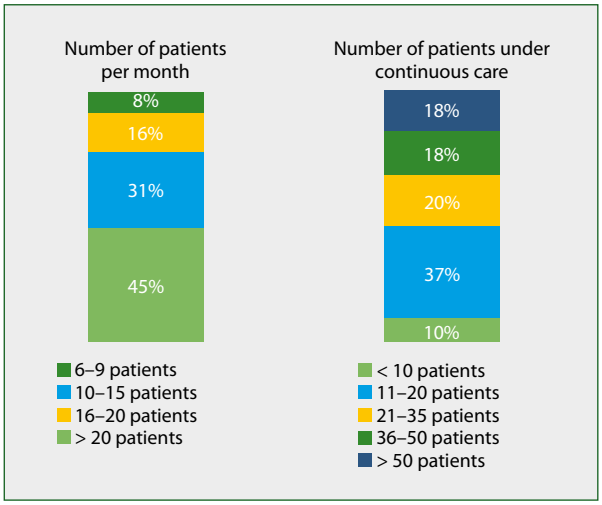


Figure 1. Number of migraine patients seen monthly and under constant care of PCPs

Respondents declared that in 19% of patients, they performed a diagnosis and initiated treatment. PCPs suspected migraine and referred patients to a neurologist for further diagnosis and treatment in 37.9% of cases; in 30.8% they ordered temporary treatment, and in 7.1% no treatment was administered. In 32.7% of patients, PCPs continued treatment prescribed by a neurologist. It is estimated that 56.4% of patients with migraine attending PCPs were previously undiagnosed. The detailed answers are set out in Figure 2. Our study suggests that 32.8% of new patients were diagnosed and treated by PCPs only.

Migraine diagnosis

PCPs were asked to list the criteria or signs and symptoms they used to diagnose migraine (the categories of answers are shown in Figure 3). More than half of PCPs (63%) listed partial diagnostic criteria for migraine without aura or mentioned aura in their responses; only 10% listed all diagnostic criteria for migraine without aura. Very few (2%) diagnosed migraine if the pain was related to menstruation or was accompanied by nausea and vomiting.

Figure 3 presents the understanding of migraine diagnostic criteria among primary care practitioners.

Those PCPs who declared that they distinguished between episodic and chronic migraine (n = 28; 55%) were asked about the definition of those two types of the disease. Most of them (79%) differentiated between chronic and episodic migraine: 18% knew the full, correct definitions, 60% described partial definitions, 18% gave the wrong definition, and 4% gave a general answer without detailed criteria. Figure 4 presents more categories of answers.

When distinguishing the type of migraine, most PCPs asked patients about the number of days per month with headache (94%) and with migraine headache (90%).

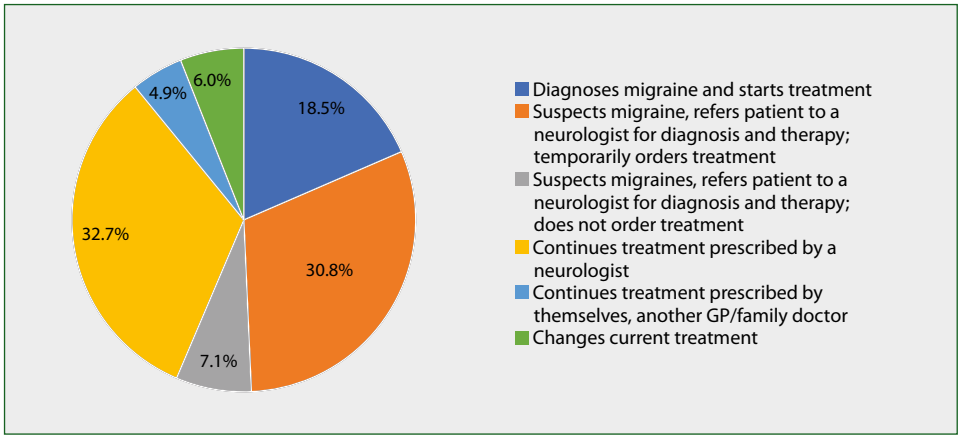


Figure 2. Role of primary care practitioners in migraine diagnosis and treatment. Diagram shows percentage of patients under each intervention

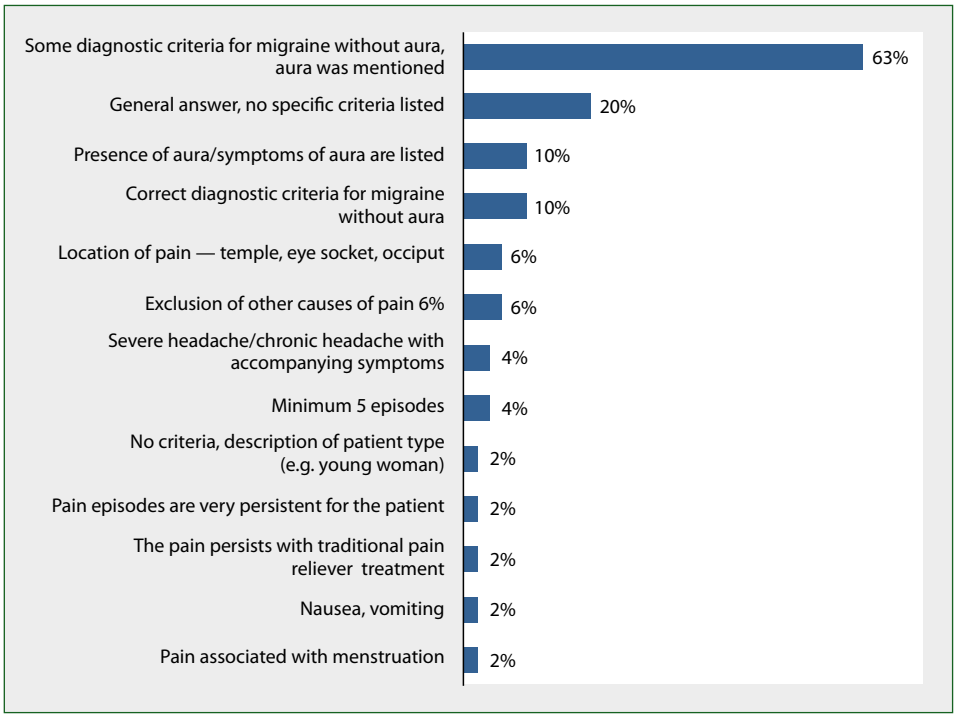


Figure 3. Knowledge of diagnostic criteria among primary care practitioners

Management of migraine patients

Among patients whose PCPs suspected migraine, 61% visited a physician during a headache episode (39% presented without headache). More than half of the patients (59%) had been self-treating for a long time before visiting a PCP, and 39% had recently started self-treatment. The results of patients whose PCPs diagnosed migraine mirrored those of patients with suspected migraine, i.e. 62% visited a physician during a headache episode (37% presented without headache), and 55% had been self-treating for a long time before visiting a PCP (44% started self-treatment recently).

Over half (59%) of the patients were consulted by a neurologist every 11 months (on average), 29% remained only under the care of a PCP, and 12% were consulted by other specialists, e.g. a laryngologist, ophthalmologist, or psychiatrist.

On average, 32% of patients (four patients/month) required sick leave from work or school (mean duration three days). Additionally, 15% of patients (two patients/month) asked for a medical certificate for migraine diagnosis and treatment confirmation.

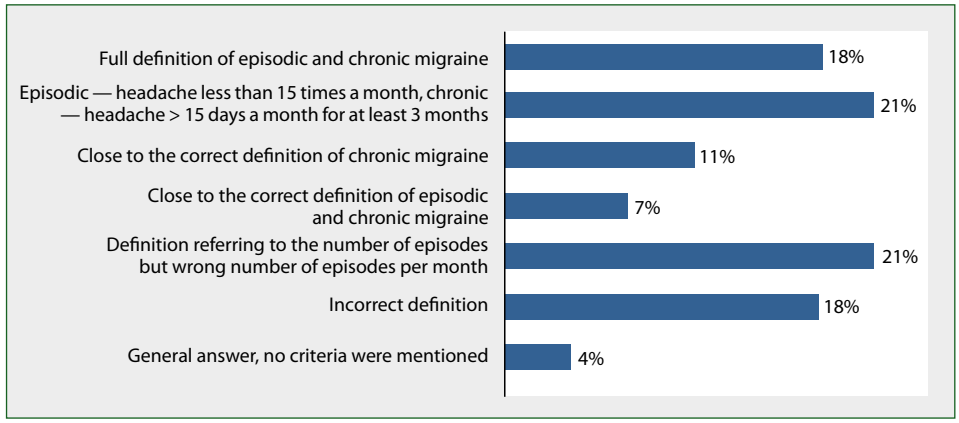


Figure 4. Knowledge of diagnostic criteria for episodic and chronic migraine among primary care practitioners

Migraine treatment

All 28 PCPs who declared ability to distinguish between episodic and chronic migraine reported starting treatment of episodic migraine in their clinical practice. The most commonly prescribed drugs were triptans (66%) and paracetamol, metamizole, or non-steroidal anti-inflammatory drugs (NSAIDs) (42%). Only 46% (n = 13) of PCPs who declared ability to distinguish between episodic and chronic migraine reported starting treatment for the chronic form, most frequently with triptans (81%) and paracetamol, metamizole, or NSAIDS (34%). Detailed results are included in Table 1.

Most PCPs (68%) used only acute medications for episodic migraine patients. In treating patients with chronic migraine, most PCPs (72%) used both acute and preventative treatments. In the PCPs' opinion, treatment was effective in 63% of migraine cases.

When asked about migraine prophylaxis, 35% of PCPs pointed to lifestyle factors such as avoiding triggers, proper hydration, exercise, and relaxation. Fourteen PCPs (27%) reported preventative treatment to reduce the frequency and intensity of migraine attacks. Other answers included long-term medications to prevent headache episodes (25%) or permanent medications (12%).

PCPs most commonly mentioned the possibility of using β-blockers (75%), calcium channel blockers (55%), antiepileptic drugs (53%), and antidepressants (51%) in migraine prevention. However, only 18% of PCPs were aware that antibodies targeting the calcitonin-gene related peptide (CGRP) pathway were available in Poland for migraine prevention.

Discussion

Headaches are one of the most common reasons for consulting PCPs, who are the first line doctors for diagnosing and starting treatment for migraine or providing a referral to a specialist. Indeed, according to a large populational study conducted in the United Kingdom, 6.4/100 patients/year in women and 2.5/100 patients/year in men consulted PCPs due to headache. In this study, each PCP had an average of 12 patients (median 10) with migraine per month and average of 39 patients (median 30) under constant care. Moreover, in the International Burden of Migraine Study conducted in the United States (US) and Canada, 13.9% of US patients and 12.3% of Canadian ones with episodic migraine (and 26.2% of US patients and 48.2% Canadian ones with chronic form) had visited a PCP at least once in the last three months [16].

Table 1. Drugs prescribed by primary care practitioners as initial migraine treatment

Drug type	Chronic migraine	Episodic migraine
Triptans	81%	66%
Non-steroidal anti-inflammatory drugs (including acetylsalicylic acid), paracetamol, and metamizole	34%	42%
β-blockers	11%	4%
Anti-epileptic drugs	2%	6%
Tricyclic antidepressants	6%	5%
Calcium channel blockers	4%	1%
Angiotensin II receptor antagonists	0%	0.4%
Other	0%	1%

These findings confirm that PCPs consult a large number of migraine patients seeking a diagnosis and effective treatment.

About 1% of the adult population in Poland is estimated to be affected by chronic migraine; however, only 48% of migraine patients had had migraine diagnosed within the last five years [9]. Misdiagnosis is a significant reason for migraine underestimation. In a telephone survey conducted among UK and US patients fulfilling the criteria of migraine diagnosis, only 67% of the UK and 56% of the US respondents had received a migraine diagnosis [17]. Those findings may be related to insufficient knowledge of the diagnostic criteria for migraine among physicians. Indeed, in our study, only 10% of PCPs listed all diagnostic criteria for migraine without aura as used in their practice, and more than half (63%) of them listed partial criteria. Moreover, the ability to distinguish between chronic and episodic migraine was declared by 55% of respondents, but only 18% provided the correct definitions. Notably, 18% provided an incorrect definition of chronic and episodic types of the disease. Similarly, in a previous study [8] on migraine treatment in Poland among neurologists, only one (2%) knew the exact definition for migraine with and without aura, and only five (10%) could provide the diagnostic criteria for migraine without aura. Likewise, in Turkey, only 10.5% of PCPs knew the diagnostic criteria for migraine without aura [18]. Furthermore, some general practitioners tend to underuse the specific recommendations for migraine diagnosis and may diagnose patients intuitively without any criteria, as described in an interview narrative study [19]. Thus, improving understanding of diagnostic criteria is essential for accurate diagnosis and treatment of patients with migraine.

Chronic migraine was added as a separate category to the third version of the International Classification of Headache Disorders (ICHD-III) in 2013 [20]. It is estimated that episodic migraine progresses into chronic migraine in 2.5% cases/year [21]. Differentiation of the migraine type is pivotal because chronic migraine is associated with a greater personal and economic burden than episodic migraine. Also, the identification of patients with chronic migraine allows the initiation of preventative treatment [22, 23].

Well-educated staff could explain the disease mechanisms to patients, which may encourage them to implement lifestyle changes. For example, Aguirrezbal et al. reported that 68.9% of patients who received a neuroscience-based educational intervention achieved more than a 50% decrease in disability level (as measured by the Migraine Assessment Disability Test [MIDAS] score) compared to 34.6% of patients in the control group [24]. Similarly, the duration and intensity of headache were significantly lower in the intervention group. Therefore, education by PCPs could improve the quality of life of migraine patients by reducing the number of days with headache and the medication intake.

In our study, in 66% of episodic migraine cases and 81% of chronic migraine ones, PCPs prescribed triptans. The second most common group of drugs used in both episodic and chronic migraine were NSAIDs and paracetamol.

Triptans are considered the most effective drugs for the treatment of acute migraine episodes. If insufficient, they can be combined with NSAIDs [25]. In the US, triptans account for over 80% of prescriptions for migraine patients [26]. However, the amount and frequency of acute medications must be monitored, as at least 50% of chronic migraine patients overuse analgesics. It is recommended that patients should use analgesics for no more than 15 days per month (and for less than 10 days for triptans or ergots, opioids and complex analgesics) to avoid medication overuse headache [27].

Migraine preventative therapy is intended to reduce the duration and frequency of migraine episodes and days with headache. This approach may enhance the response to acute treatment and reduce disability. Recommended pharmacotherapy for the prevention of episodic migraine includes antiepileptic drugs and β-blockers (level of recommendation: 1A) [28, 29]. In our study, most PCPs possessed knowledge about using β-blockers (75%), calcium channel blockers (55%), antiepileptic drugs (53%), and antidepressants (51%) in preventative therapy of either chronic or episodic migraine. However, for the preventative treatment of chronic migraine, only topiramate and valproate (antiepileptics), amitriptyline (antidepressant), and botulinum toxin are recommended (level of recommendation: A or B) [28]. The use of monoclonal antibodies (mAbs) against CGRP or its receptor is a novel treatment strategy for patients with migraine [30]. Yet only 18% of PCPs were aware of the availability of treatment targeting the CGRP-pathway in Poland (i.e. erenumab — mAb against CGRP-R — during the study period). In comparison, in the previous study, 80% of neurologists had such knowledge [8].

Migraine carries a large economic burden due to both the disease itself and absenteeism. In the presented study, 32% of migraine patients required sick leave from work or school for an average three days/month. According to the National Health Fund, in 2017, costs due to absenteeism of migraine patients were 31 million PLN [31]. Moreover, there are also significant costs related to presenteeism, ranging from 6 to 8.5 billion PLN per year [31]. Therefore, precise diagnosis and treatment may improve the quality of life of migraine patients, and that could indirectly reduce the significant costs related to this disease.

Study limitations

The major limitation of this study is the small sample size.

Clinical implications and conclusions

Most patients with migraine initially consult PCPs, and 32.8% of new migraine patients are diagnosed and treated only by PCPs. Therefore, the role of PCPs in migraine diagnosis and treatment initiation is crucial. Unfortunately, many PCPs in Poland have insufficient command of migraine diagnosis and the differentiation between episodic and chronic types of the disease. Therefore, PCPs need more tools and training to correctly diagnose migraine and institute effective, individualised

treatment according to standardised management guidelines. The impact of PCP training on clinical outcomes of patients with migraine needs to be further investigated.

Ethical permission: *Ethical approval was not necessary for this study.*

Funding: *The research was funded by Teva Pharmaceuticals Polska Sp. z o.o., Poland and was conducted in cooperation with PEX PharmaSequence, Poland.*

Acknowledgements: *We would like to thank all the physicians and interviewers involved in the research. Special thanks to Mrs. Katarzyna Proga, Mrs. Joanna Głażewska, and Mrs. Katarzyna Wróbel from PEX PharmaSequence.*

Medical writing, professional editing, and language assistance was provided by Proper Medical Writing, Warsaw, Poland.

Conflict of interest: *AL is a Teva Pharmaceuticals Polska employee. ID, JR, AS, and WK declare no conflict of interest.*

References

1. Goadsby PJ, Lipton RB, Ferrari MD. Migraine--current understanding and treatment. N Engl J Med. 2002; 346(4): 257–270, doi: 10.1056/NEJMra010917, indexed in Pubmed: 11807151.
2. Natoli JL, Manack A, Dean B, et al. Global prevalence of chronic migraine: a systematic review. Cephalalgia. 2010; 30(5): 599–609, doi: 10.1111/j.1468-2982.2009.01941.x, indexed in Pubmed: 19614702.
3. Karbowniczek A, Domitrz I. Frequency and clinical characteristics of chronic daily headache in an outpatient clinic setting. Neurologia i Neurochirurgia Polska. 2011; 45(1): 11–17, doi: 10.1016/s0028-3843(14)60054-2.
4. Leonardi M, Steiner TJ, Scher AT, et al. The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF). J Headache Pain. 2005; 6(6): 429–440, doi: 10.1007/s10194-005-0252-4, indexed in Pubmed: 16388337.
5. Linde M, Dahlöf C. Attitudes and burden of disease among self-considered migraineurs--a nation-wide population-based survey in Sweden. Cephalalgia. 2004; 24(6): 455–465, doi: 10.1111/j.1468-2982.2004.00703.x, indexed in Pubmed: 15154855.
6. Radtke A, Neuhauser H. Low rate of self-awareness and medical recognition of migraine in Germany. Cephalalgia. 2012; 32(14): 1023–1030, doi: 10.1177/0333102412454945, indexed in Pubmed: 22807571.
7. World Health Organization, Lifting The Burden Atlas of headache disorders and resources in the world 2011. Geneva. 2011.
8. Domitrz I, Lipa A, Rożniecki J, et al. Treatment and management of migraine in neurological ambulatory practice in Poland by indicating therapy with monoclonal anti-CGRP antibodies. Neurol Neurochir Pol. 2020; 54(4): 337–343, doi: 10.5603/PJNNS.a2020.0054, indexed in Pubmed: 32687594.
9. Domitrz I, Lipa A, Rozniecki J, et al. Polish omnibus online survey on migraine conducted in a population of 2000 adults. Migrena news. 2019; 3(6): 98–100.
10. Latinovic R, Gulliford M, Ridsdale L. Headache and migraine in primary care: consultation, prescription, and referral rates in a large population. J Neurol Neurosurg Psychiatry. 2006; 77(3): 385–387, doi: 10.1136/jnnp.2005.073221, indexed in Pubmed: 16484650.
11. Lantéri-Minet M. The role of general practitioners in migraine management. Cephalalgia. 2008; 28 Suppl 2: 1–8, doi: 10.1111/j.1468-2982.2008.01684.x, indexed in Pubmed: 18715326.
12. Becker WJ. The diagnosis and management of chronic migraine in primary care. Headache. 2017; 57(9): 1471–1481, doi: 10.1111/head.13089, indexed in Pubmed: 28548676.
13. Silberstein SD. Considerations for management of migraine symptoms in the primary care setting. Postgrad Med. 2016; 128(5): 523–537, doi: 10.1080/00325481.2016.1175912, indexed in Pubmed: 27078039.
14. Katsarava Z, Mania M, Lampl C, et al. Poor medical care for people with migraine in Europe - evidence from the Eurolight study. J Headache Pain. 2018; 19(1): 10, doi: 10.1186/s10194-018-0839-1, indexed in Pubmed: 29392600.
15. Health Data Management database, FarmaProm Polska. . https://www.farmaprom.pl/en/database (01.06.2019).
16. Stokes M, Becker WJ, Lipton RB, et al. Cost of health care among patients with chronic and episodic migraine in Canada and the USA: results from the International Burden of Migraine Study (IBMS). Headache. 2011; 51(7): 1058–1077, doi: 10.1111/j.1526-4610.2011.01945.x, indexed in Pubmed: 21762134.
17. Lipton RB, Scher AI, Steiner TJ, et al. Patterns of health care utilization for migraine in England and in the United States. Neurology. 2003; 60(3): 441–448, doi: 10.1212/wnl.60.3.441, indexed in Pubmed: 12578925.
18. Gültekin M, Balci E, İsmailoğullari S, et al. Awareness of migraine among primary care physicians in Turkey: A regional study. Noro Psikiyatr Ars. 2018; 55(4): 354–357, doi: 10.5152/npa.2016.19228, indexed in Pubmed: 30622393.
19. Bösner S, Hartel S, Diederich J, et al. Diagnosing headache in primary care: a qualitative study of GPs' approaches. Br J Gen Pract. 2014; 64(626): e532–e537, doi: 10.3399/bjgp14X681325, indexed in Pubmed: 25179066.
20. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013; 33(9): 629–808, doi: 10.1177/0333102413485658, indexed in Pubmed: 23771276.
21. Bigal ME, Serrano D, Buse D, et al. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache. 2008; 48(8): 1157–1168, doi: 10.1111/j.1526-4610.2008.01217.x, indexed in Pubmed: 18808500.
22. May A, Schulte LH. Chronic migraine: risk factors, mechanisms and treatment. Nat Rev Neurol. 2016; 12(8): 455–464, doi: 10.1038/nrneurol.2016.93, indexed in Pubmed: 27389092.
23. Bigal ME, Serrano D, Reed M, et al. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. Neurology. 2008; 71(8): 559–566, doi: 10.1212/01.wnl.0000323925.29520.e7, indexed in Pubmed: 18711108.
24. Aguirrezabal I, Pérez de San Román MS, Cobos-Campos R, et al. Effectiveness of a primary care-based group educational intervention in the management of patients with migraine: a randomized controlled trial. Prim Health Care Res Dev. 2019; 20: e155, doi: 10.1017/S1463423619000720, indexed in Pubmed: 31833464.
25. Becker WJ. Acute migraine treatment in adults. Headache. 2015; 55(6): 778–793, doi: 10.1111/head.12550, indexed in Pubmed: 25877672.

26. Smitherman TA, Burch R, Sheikh H, et al. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. Headache. 2013; 53(3): 427–436, doi: 10.1111/head.12074, indexed in Pubmed: 23470015.
27. Dodick D. Migraine. The Lancet. 2018; 391(10127): 1315–1330, doi: 10.1016/s0140-6736(18)30478-1.
28. Silberstein SD. Considerations for management of migraine symptoms in the primary care setting. Postgrad Med. 2016; 128(5): 523–537, doi: 10.1080/00325481.2016.1175912, indexed in Pubmed: 27078039.
29. Silberstein SD, Holland S, Freitag F, et al. Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012; 78(17): 1337–1345, doi: 10.1212/WNL.0b013e3182535d20, indexed in Pubmed: 22529202.
30. Sacco S, Bendtsen L, Ashina M, et al. European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention. J Headache Pain. 2019; 20(1): 6, doi: 10.1186/s10194-018-0955-y, indexed in Pubmed: 30651064.
31. Społeczne znaczenie migreny z perspektywy zdrowia publicznego i systemu ochrony zdrowia. Zakład Analiz Ekonomicznych i Systemowych Narodowy Instytut Zdrowia Publicznego – Państwowy Zakład Higieny. 2019. https://www.pzh.gov.pl/wp-content/uploads/2019/06/RAPORT-MIGRENA-ca%C5%82y.pdf.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4, pages: 387–393
DOI: 10.5603/PJNNS.a2021.0055

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

Clinical and laboratory parameters by age for patients diagnosed with multiple sclerosis between 2000 and 2015

Inga Małecka[1], Joanna Przybek-Skrzypecka[2], Katarzyna Kurowska[1], Dagmara Mirowska-Guzel[3], Anna Członkowska[1]

[1]2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland
[2]Department of Ophthalmology, Medical University of Warsaw, Poland
[3]Centre for Preclinical Research and Technology (CePT), Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Poland

ABSTRACT

Aim of the study. To compare the demographic, clinical and laboratory characteristics of patients with multiple sclerosis (MS) analysed based on the age at which they were diagnosed.

Clinical rationale for the study. Most cases of MS are diagnosed between the ages of 20 and 40 years, but the clinical characteristics of patients with MS over this age range have rarely been studied.

Material and methods. 182 patients diagnosed with MS between 2000 and 2015 were divided into four groups by age at diagnosis: < 30 years (n = 62), 30–39 years (n = 54), 40–49 years (n = 27), and ≥ 50 years (n = 39). The demographic, clinical and laboratory features of each age group were investigated and between-groups comparisons analysed.

Results. There were no significant differences in the female-to-male ratio between groups, which was close to 3:1 in every group ($p = 0.98$). Motor symptoms were more common as the first manifestation of MS with increasing age (< 30: 19.3%; 30–39: 37.0%; 40–49: 44.4%; ≥ 50: 61.5%). Visual and sensory symptoms were responsible for nearly half of first manifestations in patients < 30 to 49, but affected a significantly lower proportion of patients in the oldest group ($p = 0.01$). Median (interquartile range [IQR]) Expanded Disability Status Scale at diagnosis was higher with advancing age (2 [1.5–3], 2.25 [1.5–3.5], 3 [2–3.5], and 3.5 [3–5]; $p < 0.01$). There was also a higher proportion of patients with progressive forms of the disease with age, especially primary progressive MS (0.0%, 3.7%, 14.8%, and 51.3%; $p < 0.01$). The median (IQR) time needed to confirm the diagnosis of MS became significantly longer as age increased (7 [2–25], 9 [2–32], 12 [6–58], and 26 [12–60] months; $p < 0.01$). In laboratory tests, significant differences were found only in the rate of post-contrast enhancement by magnetic resonance imaging, which was lower in the older age groups (63.2%, 50.0%, 31.6%, and 30.0%; $p < 0.01$).

Conclusions and clinical implications. Our study indicates significant differences in the demographic and clinical picture of MS depending on the age of the patient at diagnosis. Diagnostic delay in older patients is a common problem, and this study shows the features of later forms of MS to help inform neurologists and improve time to diagnosis.

Key words: Multiple sclerosis, age at diagnosis, time from first symptoms to diagnosis, clinical differences

(*Neurol Neurochir Pol 2021; 55 (4): 387–393*)

Introduction

Multiple sclerosis (MS) is the most common cause of neurological disability in young adults in the developed world [1]. MS can follow very different patterns of evolution and variable rates of disability accumulation. Three classifications of MS have been defined based on age at onset: childhood-onset MS (< 18 years), adult-onset MS (AOMS) (18–49 years) and late-onset MS (LOMS) (≥ 50 years). The clinical picture of MS appears different depending on the age at diagnosis, with

Address for correspondence: Anna Członkowska, Institute of Psychiatry and Neurology, ul. Sobieskiego 9, 02–957 Warsaw, Poland; email: czlonkow@ipin.edu.pl

Received: 30.09.2020 Accepted: 11.01.2021 Early publication date: 6.08.2021

the course of the disease tending to be more progressive and disabling in LOMS [2]. Most cases of MS (~70%) are typically diagnosed between 20 and 40 years of age [3, 4] and yet the clinical characteristics of patients with MS over this age have rarely been studied.

Clinical rationale for study

In this retrospective study, we compared the clinical characteristics and laboratory tests results of patients with MS diagnosed at different ages at our centre from 2000 to 2015. The purpose was to investigate differences between age groups, since better understanding of the disease course and predictors of progression would be valuable. We also sought to determine whether older age at diagnosis affects the time to reach a diagnosis of MS, since knowledge of the factors affecting diagnosis delay are important to ensure timely recognition and treatment.

Materials and methods

Study group

The study population included patients diagnosed with MS at the 2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland between 2000 and 2015. Every adult patient who met the contemporary MS diagnostic criteria (McDonald 2000, McDonald 2005, or McDonald 2010) and did not fulfill the exclusion criteria was included, as described previously [5]. The exclusion criteria were: incomplete medical documentation, incomplete information about the differential diagnosis in inconclusive cases, and patient documentation indicating that the MS diagnosis had already been made before attending our department. The database used for further analysis was created from the available records stored at the Institute.

Data analysis

Patients were divided into subgroups according to their age at diagnosis: 18–29 years, 30–39, 40–49, and ≥ 50. Then, we analysed the difference between these groups for chosen demographic and clinical features: sex distribution, first documented symptoms and signs of MS, patient report of undocumented symptoms in the time preceding a documented onset of MS, dominating neurological syndrome at time of diagnosis, disability level measured by the Expanded Disability Status Scale (EDSS), differences in time and number of in-patient stays needed to confirm the diagnosis of MS, and clinical course of the disease preceding the diagnosis. Differences were also analysed in magnetic resonance imaging (MRI) features (including the fulfillment of Barkhof and Tintore criteria and presence of post-contrast enhancement), cerebrospinal fluid (CSF) parameters (including immunoglobulin G [IgG] index and oligoclonal bands [OCB]), and the pattern of visual evoked potentials (VEP) (abnormal P100 latency).

Statistical assessment

Quantitative data are presented as median and interquartile range (IQR) values due to non-normal distribution (mean and standard deviation were shown only for reference), while qualitative data are presented as percentage frequency. Differences in the quantitative variables, EDSS score and time from the first clinical symptom to the diagnosis of MS were evaluated using the Wilcoxon test for two-group comparison and the Kruskal-Wallis test for multi-group comparison. Differences in qualitative parameters, which comprised the rest of our data, were assessed using the Chi-square test or Fisher's exact test. Values of $p < 0.05$ were considered significant. Statistical analysis was performed using SAS 15.1 software.

Results

General features of studied group

Out of 193 patients diagnosed with MS in our department between 2000 and 2015, 182 were analysed; seven patients were excluded due to incomplete documentation and four due to an earlier diagnosis of MS. Of the 182 patients studied, 62 (34%) were diagnosed before the age of 30, 54 (29.7%) were diagnosed aged 30–39, 27 (14.8%) were diagnosed aged 40–49, and 39 (21.4%) were diagnosed aged ≥ 50.

Demographic and clinical characteristics

Differences in demographic and clinical characteristics between the age groups are shown in Table 1. There was a predominance of women in all age groups with a female-to-male ratio of close to 3:1, and no significant differences between groups ($p = 0.98$).

There was no difference in the percentage of patients who reported undocumented neurological symptoms before the documented onset of MS, which was 38.5-40.7% of patients in all age groups ($p = 0.41$). The type of first documented symptom of MS differed between groups: motor dysfunction was far less common in patients aged < 30 years or 30–39 compared to those aged ≥ 50, while there was a prevalence of sensory symptoms and visual symptoms in the younger groups ($p = 0.01$). A detailed neurological examination at the time of diagnosis also differed between age groups. The most significant feature of patients aged < 30 was a predominance of sensory dysfunction and a relatively common lack of any neurological dysfunction at the time of diagnosis. In patients aged 30–39, there was still a high percentage of minimal neurological signs, but a higher proportion of motor signs at first examination than in the youngest group. In patients aged 40–49 or ≥ 50, motor dysfunction became a dominating feature, followed by multifocal syndrome in those ≥ 50 ($p < 0.01$). Median (IQR) EDSS at the time of diagnosis was significantly higher with increasing age (< 30: 2 [1.5–3]; 30–39: 2.25 [1.5–3.5]; 40–49: 3 [2–3.5]; ≥ 50: 3.5 [3–5]). Median (IQR) time to reach a diagnosis of MS was longer with increasing age: 7 [2–25] months in patients < 30 ($p < 0.05$ *vs.* 40–49 and ≥ 50), 9 [2–32] months

Table 1. Demographic and clinical characteristics of patients by age group

	Group I (18–29 y) n = 62	Group II (30–39 y) n = 54	Group III (40–49 y) n = 27	Group IV (≥ 50 y) n = 39	P-value
Female:male ratio	3.4:1	3.1:1	2.8:1	2.9:1	*p = 0.98
First documented symptom of MS, %					
Motor	19.3	37.0	44.4	61.5	*p = 0.01 **p < 0.05 for I/IV; II/IV
Sensory	22.6	18.5	22.2	10.2	
Visual	22.6	25.9	18.5	5.1	
Brainstem	14.5	9.3	11.1	7.7	
Cerebellar	19.3	9.3	3.7	12.8	
Dominating neurological syndrome at diagnosis, %					
No/minimal signs	14.5	14.8	7.4	0.0	*p < 0.01 **p < 0.05 for I/II; I/III; I/IV; II/III; II/IV
Pyramidal	8.0	29.6	44.4	46.1	
Sensory	35.5	20.4	14.8	7.7	
Visual acuity loss	6.5	7.4	3.7	5.1	
Cerebellar	11.3	9.3	7.4	5.1	
Brainstem	9.7	7.4	3.7	5.1	
Multifocal	14.5	11.1	18.5	30.8	
EDSS at diagnosis					
Median (IQR)	2 (1.5–3)	2.5 (1.5–3.5)	3 (2–3.5)	3.5 (3–5)	*p < 0.01 **p < 0.05 for I/III; I/IV; II/IV; III/IV
Time to diagnosis from first documented symptom					
Median time to diagnosis (IQR), months	7 (2–25)	9 (2–32)	12 (6–58)	26 (12–60)	*p < 0.01 **p < 0.05 for I/III; I/IV; II/IV
% of patients diagnosed within 0–11 months	66.1	59.3	40.7	23.1	*p < 0.01 **p < 0.05 for I/III; I/IV; II/IV
Number of in-patient stays needed for diagnosis, %					
1	38.7	38.9	44.4	38.5	*p = 0.38
2	46.8	46.3	44.4	41.0	
3	11.3	9.3	3.7	7.7	
≥ 4	3.2	5.6	7.4	12.8	
Disease course, %					
Relapsing remitting	96.8	90.7	74.1	30.8	*p < 0.01 **p < 0.05 for I/III; I/IV; II/IV; III/IV
Secondary progressive	3.2	5.6	11.1	17.9	
Primary progressive	0.0	3.7	14.8	51.3	

*p-value for comparison between all groups; **two-groups comparisons (group number/group number)
EDSS — Expanded Disability Status Scale; IQR — interquartile range; MS — multiple sclerosis; SD — standard deviation

in patients aged 30–39 ($p < 0.05$ *vs.* ≥ 50), 12 [6–58] months in patients aged 40–49 ($p < 0.05$ *vs.* ≥ 50) and 26 [12–60] months) in patients aged ≥ 50(trend $p < 0.01$). As a result, the percentage of patients diagnosed 1-11 months from the first symptom of MS became lower as age increased ($p < 0.01$). At the same time, there was no significant correlation between age and the number of in-patient stays needed to make a diagnosis of MS, with 38.7-44.4% of patients needing one in-patient stay and another 41-46.8% of patients needing two in-patient stays ($p = 0.38$).

Disease course before diagnosis was relapsing remitting in more than 90% of patients in the < 30 and 30–39 categories, was 74.1% in patients aged 40–49, but was only 30.8% in patients ≥ 50, where the primarily progressive course dominated ($p < 0.01$).

Laboratory findings

A similarly high percentage of patients in all age groups fulfilled the MRI Barkhof and Tintore criteria ($p = 0.51$). Most patients in the younger groups were given contrast medium (79–90%), but only around half (51%) of patients aged

Table 2. Comparison of laboratory test results by age group

	Group I (18–29 y) n = 62	Group II (30–39 y) n = 54	Group III (40–49 y) n = 27	Group IV (≥ 50 y) n = 39	P-value
MRI results					
Barkhof and Tintore criteria fulfilled, %	84.7	83.0	92.6	74.3	*p = 0.51
Contrast given, %	79	79	90	51	
Post-contrast enhancement, %	63.2	50.0	31.6	30.0	*p < 0.01 **p < 0.05 for I/III; I/IV; II/IV
CSF analysis					
Elevated IgG index, %	66.7	66.7	84.0	75.7	*p = 0.34
Oligoclonal bands positive, %	92.6	89.4	95.4	86.7	*p = 0.74
EEG results					
Abnormal visual evoked potentials, %	86.7	76.2	76.2	81.3	*p = 0.57

*p-value for comparison between all groups; **two-groups comparisons (group number/group number)
CSF — cerebrospinal fluid; EEG — electroencephalogram; IgG — immunoglobulin G; MRI — magnetic resonance imaging

≥ 50 received it. When contrast was used, the proportion of patients with post-contrast enhancement decreased with advancing age, from 63.2% in patients < 30 to 30% in patients aged ≥ 50 (p < 0.01). In an analysis of CSF, the percentage of patients with elevated IgG index was not significantly higher with age (p = 0.34), although the two oldest groups had numerically higher proportions than the younger age groups. Age had no influence on the proportion of patients with positive OCB, which was high in all groups (p = 0.74). The percentage of patients with abnormal VEPs was also not significantly different across the age groups (p = 0.57) (Tab. 2).

Discussion

MS is commonly perceived as a disease of young adults, but in fact it can start at any age. It is of the utmost importance to know the differences in the clinical picture of MS depending on age at onset or diagnosis. A number of studies have compared young MS patients to those whose disease started at 50 or later [6, 8–12, 13–15], but, to the best of our knowledge, none of them have compared patients in different age groups in relation to their age at diagnosis, or concerned a central-eastern Europe population.

Our study shows that the percentage of patients diagnosed after 50 is higher (21.4%) than the percentage of LOMS patients in other studies (1.1–12.7%) [6–14], but is similar to the percentage of patients (21.3%) in an Italian study where MS started at 40 years or older [15]. In our study, the time from the first documented symptom to the diagnosis of MS increased significantly with the age of the patient, suggesting that the diagnostic process is more challenging in older patients. Similar results were obtained by Kis et al. who observed a longer mean time to diagnosis in LOMS patients (three years) compared to younger patients (one year) [9]. A Portuguese study also demonstrated diagnostic delay in older patients [16].

In our study, we found that the proportion of progressive forms of MS was higher in older patients, which may be a factor that contributes to delay in diagnosis. In other studies, delay in diagnosis was related to the primary progressive form of MS [16, 17], prolonged time to first medical consultation [18, 19], patients born in earlier decades [20, 21], and coexisting diseases [22, 23]. Our age groups were not distributed evenly in relation to the different McDonald criteria used, and this raises the question of the influence this might have on median time to diagnosis. However, as we have proven in another study [Przybek-Skrzypecka 2020], differences in time to diagnosis depending on the type of criteria used were not significant in our Department (mean time in months: McDonald 2000 — 39.1 ± 68.4; McDonald 2005 — 36.2 ± 58.5; McDonald 2010 — 33.6 ± 68.2). Also, we did not have enough pre-hospitalisation data to examine other factors that may have contributed to the prolongation of diagnostic process, although we found that number of hospitalisations was not a factor that differed significantly between the age groups.

We noted differences in the clinical picture of MS across the age groups. We observed that motor symptoms were the first documented symptom and sign of MS in all age groups except for patients aged < 30. The presence of motor symptoms was found to be higher as age increased. Our findings are similar to those in studies comparing patients with AOMS and LOMS, where motor deficit was found to be the most common neurological manifestation among late-onset patients, encompassing more than half of the studied group (54.8-80%) [6, 9, 10, 12, 13, 24, 25]. Overrepresentation of motor deficit in older patients may be connected to the overrepresentation of the primary progressive form of the disease. However, Cossburn et al. found that in a population of patients with only relapsing remitting MS, there was also a higher percentage of patients with motor signs at the beginning of the disease [11]. We observed that the frequency of

sensory symptoms and optic neuritis as a first manifestation of MS was similar up to 50 years, but then deceased, which is consistent with studies comparing AOMS and LOMS [9, 12, 14].

As mentioned, progressive forms of MS, mainly primary progressive MS, were more common in older patients. Typically, primary progressive MS starts 10 years later than relapsing remitting MS (around the age of 38–41) [26–29]. Similarly, significant differences in the percentage of primary progressive MS patients in the AOMS versus LOMS group have been described in other studies (AOMS: 5–11%; LOMS: 20–83%) [6, 8–10, 12, 13, 25, 30]. There appears to be a turning point, somewhere between 40 and 50, where a rising advantage of degeneration over demyelination processes changes the clinical picture of the disease to a progressive one with dominating motor deficits.

However, in our youngest age groups there were some cases of secondary progression. Three of those patients, a female aged 22, a female aged 34, and a male aged 39 at diagnosis, had already entered the progressive phase because of the long gap between first symptom and diagnosis (36–58 months). Two other cases were a young woman aged 19, and a 31-year-old male who had a short but aggressive history of disease with a progressive-relapsing course.

EDSS at the time of diagnosis was also influenced by age in our study. We found mean EDSS significantly higher with each passing decade. Our results are comparable to those of Kis et al. where mean EDSS in a late-onset MS group was significantly higher than an adult-onset MS group (3.5 *vs.* 2.7) [9] and similar to a Canadian study, where the percentage of patients with EDSS of 3.0 or more at first neurological examination was higher in LOMS (66.0%) than in AOMS (44.7%) [8]. Most authors agree that the older the patient is at MS onset, the more rapid the accumulation of disability [12, 14, 15, 29–39]. However, it was observed by Tremlett et al. that this was only true for patients up to EDSS 3.0 and beyond this value, which was a turning point for relapsing remitting MS becoming secondary progressive MS, time of onset of MS had no influence on speed of disability accumulation [8]. This observation has been seconded by other authors who observed that age at disease onset only affected the severity of the relapsing remitting phase, not the secondary progressive phase [40, 41].

Brain MRI can become less specific in older MS patients, due to concomitant diseases and different localisation of lesions, necessitating an additional spine MRI to make a diagnosis [7, 9]. However, in our study, we found that brain MRI that fulfilled Barkhof and Tintore criteria was similarly specific in all age groups. The only parameter that became significantly less frequent in older groups was the presence of contrast enhancement. Our results are similar to those of other studies, where Barkhof and Tintore criteria fulfillment stayed high in the late-onset group (65–88%) [7, 10, 25], while contrast enhancement decreased (AOMS: 61–63%; LOMS: 15–35%) [7, 9]. Interestingly, Jasek et al. showed that conventional measures such as T2-lesion load or brain atrophy measures were similar in AOMS and LOMS groups, and that only more sophisticated methods indicated more axonal damage in LOMS [42].

In our study, a high percentage of patients had OCBs in CSF, and this was observed across all age groups, consistent with other studies [9, 10, 24, 30], which indicates that OCB is an effective diagnostic tool in patients of all ages. Patients with abnormal VEP also predominated in our study, in line with the work of Kis et al. (AOMS: 70%; LOMS: 86%) [9] and Noseworthy et al. (AOMS: 67%; LOMS: 62%) [43]. Of note, other diseases of the visual system are common in older patients, so the specificity of an abnormal VEP test may decrease with age, despite its high sensitivity.

We are aware that the present study has certain limitations. Small groups, a single-centre study and retrospective design may have affected our results. However, our centre was a reference hospital and our diagnostic procedure was carefully tailored to meet current diagnostic criteria.

Conclusions and clinical implications

We found significant differences in the demographic and clinical picture of MS depending on the age of the patient at diagnosis. Patients aged ≥ 50 had a more severe clinical picture of MS at diagnosis, with greater neurological impairment, commonly affecting the pyramidal system, and they often had a progressive course. Differences in the clinical picture began to occur between 40 and 50 or even before. A delay in diagnosis was common in older patients, despite diagnostic tools remaining reliable across all age groups.

These findings related to the different features of MS with age at onset may help to inform neurologists and improve time to diagnosis.

Ethical permission: *This study was approved by the Institute of Psychiatry and Neurology Bioethics Committee.*
Funding: *The work was supported financially as part of the internal funding of the Institute of Psychiatry and Neurology.*
Conflict of interest: *None.*

References

1. Thompson A, Baranzini S, Geurts J, et al. Multiple sclerosis. The Lancet. 2018; 391(10130): 1622–1636, doi: 10.1016/s0140-6736(18)30481-1.
2. Martinelli V, Rodegher M, Moiola L, et al. Late onset multiple sclerosis: clinical characteristics, prognostic factors and differential diagnosis. Neurol Sci. 2004; 25 Suppl 4: S350–S355, doi: 10.1007/s10072-004-0339-8, indexed in Pubmed: 15727232.
3. Ascherio A, Munger KL. Epidemiology of multiple sclerosis: from risk factors to prevention-an update. Semin Neurol. 2016; 36(2): 103–114, doi: 10.1055/s-0036-1579693, indexed in Pubmed: 27116717.
4. Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. Brain. 2006; 129(Pt 3): 606–616, doi: 10.1093/brain/awl007, indexed in Pubmed: 16415308.

5. Przybek-Skrzypecka J, Małecka I, Członkowska A, et al. Demographic and clinical profile of patients with multiple sclerosis diagnosed over the last 30 years according to different diagnostic criteria. Neurol Neurochir Pol. 2020; 54(2): 169–175, doi: 10.5603/PJNNS.a2020.0027, indexed in Pubmed: 32242912.
6. Polliack ML, Barak Y, Achiron A. Late-onset multiple sclerosis. J Am Geriatr Soc. 2001; 49(2): 168–171, doi: 10.1046/j.1532-5415.2001.49038.x, indexed in Pubmed: 11207871.
7. de Seze J, Delalande S, Michelin E, et al. Late onset multiple sclerosis. Rev Neurol (Paris). 2002; 158(11): 1082–1087, indexed in Pubmed: 12451340.
8. Tremlett H, Devonshire V. Is late-onset multiple sclerosis associated with a worse outcome? Neurology. 2006; 67(6): 954–959, doi: 10.1212/01.wnl.0000237475.01655.9d, indexed in Pubmed: 17000960.
9. Kis B, Rumberg B, Berlit P. Clinical characteristics of patients with late-onset multiple sclerosis. J Neurol. 2008; 255(5): 697–702, doi: 10.1007/s00415-008-0778-x, indexed in Pubmed: 18283394.
10. Arias M, Dapena D, Arias-Rivas S, et al. Late onset multiple sclerosis. Neurologia. 2011; 26(5): 291–296, doi: 10.1016/j.nrl.2010.09.008, indexed in Pubmed: 21163234.
11. Cossburn M, Ingram G, Hirst C, et al. Age at onset as a determinant of presenting phenotype and initial relapse recovery in multiple sclerosis. Mult Scler. 2012; 18(1): 45–54, doi: 10.1177/1352458511417479, indexed in Pubmed: 21865412.
12. Bove RM, Healy B, Augustine A, et al. Effect of gender on late-onset multiple sclerosis. Mult Scler. 2012; 18(10): 1472–1479, doi: 10.1177/1352458512438236, indexed in Pubmed: 22383227.
13. Roohani P, Emiru T, Carpenter A, et al. Late onset multiple sclerosis: Is it really late onset? Mult Scler Relat Disord. 2014; 3(4): 444–449, doi: 10.1016/j.msard.2014.02.004, indexed in Pubmed: 25877055.
14. Shirani A, Zhao Y, Petkau J, et al. Multiple sclerosis in older adults: the clinical profile and impact of interferon Beta treatment. Biomed Res Int. 2015; 2015: 451912, doi: 10.1155/2015/451912, indexed in Pubmed: 25922836.
15. D'Amico E, Patti F, Zanghì A, et al. Late-onset and young-onset relapsing-remitting multiple sclerosis: evidence from a retrospective long-term follow-up study. Eur J Neurol. 2018; 25(12): 1425–1431, doi: 10.1111/ene.13745, indexed in Pubmed: 29956427.
16. Aires A, Barros A, Machado C, et al. Diagnostic delay of multiple sclerosis in a Portuguese population. Acta Med Port. 2019; 32(4): 289–294, doi: 10.20344/amp.11187, indexed in Pubmed: 31067423.
17. Brola W, Sobolewski P, Żak M, et al. Profile of Polish patients with primary progressive multiple sclerosis. Mult Scler Relat Disord. 2019; 33: 33–38, doi: 10.1016/j.msard.2019.05.009, indexed in Pubmed: 31146082.
18. Fernández O, Fernández V, Arbizu T, et al. Novo Group. Characteristics of multiple sclerosis at onset and delay of diagnosis and treatment in Spain (the Novo Study). J Neurol. 2010; 257(9): 1500–1507, doi: 10.1007/s00415-010-5560-1, indexed in Pubmed: 20383518.
19. Adamec I, Barun B, Gabelić T, et al. Delay in the diagnosis of multiple sclerosis in Croatia. Clin Neurol Neurosurg. 2013; 115 Suppl 1: S70–S72, doi: 10.1016/j.clineuro.2013.09.025, indexed in Pubmed: 24321160.
20. Celius EG, Smestad C. Change in sex ratio, disease course and age at diagnosis in Oslo MS patients through seven decades. Acta Neurol Scand Suppl. 2009(189): 27–29, doi: 10.1111/j.1600-0404.2009.01208.x, indexed in Pubmed: 19566494.
21. Lavorgna L, Borriello G, Esposito S, et al. Impact of early diagnosis on clinical characteristics of an Italian sample of people with multiple sclerosis recruited online. Mult Scler Relat Disord. 2019; 27: 239–246, doi: 10.1016/j.msard.2018.10.113, indexed in Pubmed: 30419509.
22. Marrie RA, Horwitz R, Cutter G, et al. Comorbidity delays diagnosis and increases disability at diagnosis in MS. Neurology. 2009; 72(2): 117–124, doi: 10.1212/01.wnl.0000333252.78173.5f, indexed in Pubmed: 18971448.
23. Thormann A, Sørensen PS, Koch-Henriksen N, et al. Comorbidity in multiple sclerosis is associated with diagnostic delays and increased mortality. Neurology. 2017; 89(16): 1668–1675, doi: 10.1212/WNL.0000000000004508, indexed in Pubmed: 28931645.
24. Lotti CB, Oliveira AS, Bichuetti DB, et al. Late onset multiple sclerosis: concerns in aging patients. Arq Neuropsiquiatr. 2017; 75(7): 451–456, doi: 10.1590/0004-282X20170070, indexed in Pubmed: 28746432.
25. Bermel RA, Rae-Grant AD, Fox RJ. Diagnosing multiple sclerosis at a later age: more than just progressive myelopathy. Mult Scler. 2010; 16(11): 1335–1340, doi: 10.1177/1352458510377334, indexed in Pubmed: 20670982.
26. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain. 1989; 112 (Pt 1): 133–146, doi: 10.1093/brain/112.1.133, indexed in Pubmed: 2917275.
27. Vukusic S, Confavreux C. Primary and secondary progressive multiple sclerosis. J Neurol Sci. 2003; 206(2): 153–155, doi: 10.1016/s0022-510x(02)00427-6, indexed in Pubmed: 12559503.
28. Riise T, Grønning M, Fernández O, et al. Early prognostic factors for disability in multiple sclerosis, a European multicenter study. Acta Neurol Scand. 1992; 85(3): 212–218, doi: 10.1111/j.1600-0404.1992.tb04031.x, indexed in Pubmed: 1575007.
29. Trojano M, Avolio C, Manzari C, et al. Multivariate analysis of predictive factors of multiple sclerosis course with a validated method to assess clinical events. J Neurol Neurosurg Psychiatry. 1995; 58(3): 300–306, doi: 10.1136/jnnp.58.3.300, indexed in Pubmed: 7897410.
30. Hooge JP, Redekop WK. Multiple sclerosis with very late onset. Neurology. 1992; 42(10): 1907–1910, doi: 10.1212/wnl.42.10.1907, indexed in Pubmed: 1407571.
31. Phadke JG. Clinical aspects of multiple sclerosis in north-east Scotland with particular reference to its course and prognosis. Brain. 1990; 113 (Pt 6): 1597–1628, doi: 10.1093/brain/113.6.1597, indexed in Pubmed: 2276037.
32. White AD, Swingler RJ, Compston DA. Features of multiple sclerosis in older patients in South Wales. Gerontology. 1990; 36(3): 159–164, doi: 10.1159/000213192, indexed in Pubmed: 2227469.
33. Bergamaschi R, Berzuini C, Romani A, et al. Predicting secondary progression in relapsing-remitting multiple sclerosis: a Bayesian analysis. J Neurol Sci. 2001; 189(1-2): 13–21, doi: 10.1016/s0022-510x(01)00572-x, indexed in Pubmed: 11535229.
34. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain. 2003; 126(Pt 4): 770–782, doi: 10.1093/brain/awg081, indexed in Pubmed: 12615637.
35. Amato MP, Ponziani G, Bartolozzi ML, et al. A prospective study on the natural history of multiple sclerosis: clues to the conduct and interpretation of clinical trials. J Neurol Sci. 1999; 168(2): 96–106, doi: 10.1016/s0022-510x(99)00143-4, indexed in Pubmed: 10526190.

36. Vukusic S, Confavreux C, Confavreux C, et al. Natural history of multiple sclerosis: a unifying concept. Brain. 2006; 129(Pt 3): 606–616, doi: 10.1093/brain/awl007, indexed in Pubmed: 16415308.
37. Ramachandran S, Strange RC, Jones PW, et al. Associations between onset age and disability in multiple sclerosis patients studied using MSSS and a progression model. Mult Scler Relat Disord. 2014; 3(5): 593–599, doi: 10.1016/j.msard.2014.06.002, indexed in Pubmed: 26265271.
38. Alroughani R, Akhtar S, Ahmed S, et al. Is Time to Reach EDSS 6.0 Faster in Patients with Late-Onset versus Young-Onset Multiple Sclerosis? PLoS One. 2016; 11(11): e0165846, doi: 10.1371/journal.pone.0165846, indexed in Pubmed: 27802328.
39. Cierny D, Lehotsky J, Hanysova S, et al. The age at onset in Multiple Sclerosis is associated with patient's prognosis. Bratisl Lek Listy. 2017; 118(6): 374–377, doi: 10.4149/BLL_2017_071, indexed in Pubmed: 28664749.
40. Scalfari A, Neuhaus A, Daumer M, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. Brain. 2010; 133(Pt 7): 1914–1929, doi: 10.1093/brain/awq118, indexed in Pubmed: 20534650.
41. Guillemin F, Baumann C, Epstein J, et al. LORSEP Group. Older age at multiple sclerosis onset is an independent factor of poor prognosis: A population-based cohort study. Neuroepidemiology. 2017; 48(3-4): 179–187, doi: 10.1159/000479516, indexed in Pubmed: 28793296.
42. Jasek Ł, Śmigielski J, Siger M. Late onset multiple sclerosis - multiparametric MRI characteristics. Neurol Neurochir Pol. 2020; 54(3): 265–271, doi: 10.5603/PJNNS.a2020.0036, indexed in Pubmed: 32368786.
43. Noseworthy J, Paty D, Wonnacott T, et al. Multiple sclerosis after age 50. Neurology. 1983; 33(12): 1537–1544, doi: 10.1212/wnl.33.12.1537, indexed in Pubmed: 6606140.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4, pages: 394–402
DOI: 10.5603/PJNNS.a2021.0057

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

Predictors of cognitive impairment in pseudotumor cerebri

Olga P. Fermo[1], Aruna Rao[2], Amy Schwartzbaum[3], Samhita Sengupta[3], Yifan Zhang[4], Jiangxia Wang[4], Abhay R. Moghekar[2]

[1]Mayo Clinic, Jacksonville, Florida, USA
[2]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[3]University of Maryland, Baltimore, Maryland, USA
[4]Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

ABSTRACT

Aims of the study: We aimed to define the cognitive burden of the largest pseudotumor cerebri syndrome (PTCS) population to date, compare objective to subjective cognitive dysfunction, and determine clinical predictors of cognitive dysfunction amongst an array of previously unstudied factors.

Clinical rationale: Patients with PTCS commonly report cognitive dysfunction, a factor associated with poor quality of life. It is not definitively known whether cognitive impairment is present in these patients, and what features of the syndrome predict impairment.

Materials and methods: We administered a cognitive battery consisting of the National Adult Reading Test, Mini-Mental Status Exam, Digit Span, Boston Naming Test, Rey Auditory Verbal Learning Test, Clock Drawing, Trail Making Test, Controlled Oral Word Association, and Category Fluency. Cognitive impairment was defined as mild-single domain with one test score, and mild-multiple domain with two scores, more than two standard deviations below the mean for age-, gender-, and education-adjusted norms.

Results: One-hundred and one prospectively recruited PTCS patients were enrolled. The objective testing showed 30 patients had mild-single domain impairment, and 25 had mild-multi domain impairment. More patients without objective cognitive impairment had transverse venous sinus stenosis, but otherwise the groups did not differ. Two measures of headache severity, the Headache Impact Test and pain on the Numeric Rating Scale, were negatively associated with the composite cognitive score, as was ocular pain, vision-related disability, and mental health. Opening pressure and visual function were not associated with objective cognitive impairment. We found no association between subjective and objective cognitive impairment.

Conclusions and clinical implications: Patients with PTCS may be cognitively impaired, and this correlates with measures of headache burden. Studies evaluating cognitive impairment before and after remission of the headache disorder would have to be performed to investigate this relationship further. Patients with self-perception of cognitive burden are no more likely to be cognitively impaired.

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

(*Neurol Neurochir Pol 2021; 55 (4): 394–402*)

Introduction

Definite pseudotumor cerebri syndrome (PTCS) is characterised by papilloedema in a patient with a normal neurological exam allowing for cranial nerve abnormalities, normal brain parenchyma on neuroimaging, and elevated lumbar opening pressure (≥ 250 mm H_2O in adults) with a normal cerebrospinal fluid composition [1]. Classic symptoms including headache, transient visual obscurations, diplopia and tinnitus have been extensively reported in the literature [2–5]. While these symptoms contribute to the burden and disability associated with the syndrome, the cognitive dysfunction reported

Address for correspondence: Abhay R. Moghekar, Johns Hopkins University School of Medicine Department of Neurology, Phipps 126 600 N. Wolfe St., Baltimore, MD 21287, USA; e-mail: am@jhmi.edu

Received: 2.04.2021 Accepted: 8.06.2021 Early publication date: 11.08.2021

by these patients can often be an unrecognised source of disability, receiving little attention in the medical literature [6, 7]. In the largest trial on PTCS, 21% of 165 patients reported subjective cognitive dysfunction, which also correlated with poor health-related and vision-related quality of life [8]. This was a young (mean age 29.2) and educated (mean 14 years of schooling) population that is otherwise expected to be cognitively normal at baseline.

To date, only six studies with patient populations of one, five, 10, 30, 31 and 85 have addressed cognitive function in PTCS, with the largest study only utilising a single memory scale [6, 7, 9–12]. Most found deficits in at least one cognitive domain, typically language and memory, though there was no universal agreement [6, 7, 9–12]. None of the previous studies quantified subjective cognitive burden, though they reported it was present. The existing studies did not look extensively at confounding factors such as medication use or the relationships with the magnitude of intracranial hypertension.

The aims of our study were to: 1) determine the cognitive burden of the largest PTCS population to date; 2) compare objective results to patients' subjective cognitive dysfunction; and 3) determine how patients with objective cognitive impairment differed from patients with normal cognition in terms of a wide array of previously unstudied baseline characteristics.

Clinical rationale for study

It is necessary to further study the cognitive concerns in PTCS for several reasons. Firstly, the syndrome affects (mainly) women at an age when many are finishing training, beginning their careers, or starting families, all devastating times in life in which to be held back. Secondly, diagnosing cognitive dysfunction provides physicians with a treatment measure in addition to preservation of vision and headache control. Finally, determining predictors of cognitive dysfunction is necessary for the symptoms to be addressed adequately.

Materials and methods

Patient selection

We prospectively recruited 101 out of 146 new patients referred to the Centre for Cerebrospinal Fluid Disorders at Johns Hopkins Hospital for treatment of PTCS from August 2009 to May 2015. All patients with a diagnosis of PTCS according to published diagnostic criteria who met the inclusion criteria and who consented to cognitive testing were included, regardless of subjective cognitive deficit [1]. Patients with PTCS secondary to venous sinus stenosis were included. Patients with mental health conditions were included. Patients were otherwise healthy, and had no neurological disorder aside from PTCS.

Subjects with the following conditions were excluded: non-native English speaking, language impairment, hearing impairment, and severe visual impairment defined as visual acuity equal to or worse than 20/100 on the Early Treatment Diabetic Retinopathy Study chart, as these could have impaired reliable completion of the cognitive battery. Patients with secondary causes of PTCS including cerebrovascular abnormalities other than venous sinus stenosis (dural arterio-venous fistula), medications (lithium, tetracyclines, oral vitamin A derivatives) and medical conditions (endocrine and autoimmune disorders) were excluded, as these factors could have also influenced cognitive function [1].

History

Details regarding: age, gender, education, headache characteristics, duration of disorder, history of sleep apnoea, medication history, history of lumbar punctures and maximum opening pressure, risk factors for intracranial hypertension including use of: lithium, vitamin A or derivatives, tetracyclines, oral contraceptives, tamoxifen, and corticosteroids, and history of shunt placement were collected from participants. Educational data was missing from one patient.

Examination

Patients underwent a full neurological exam including fundoscopy to assess papilledema grade by Frisén criteria. Two neurologists (AM and OF) tested visual acuity using a retro illuminated Early Treatment Diabetic Retinopathy Study chart and corresponding LogMAR values were recorded. In the same manner, colour vision was tested using Hardy-Rand-Rittler plates.

Investigative methods

Venography with either magnetic resonance imaging or computed tomography was reviewed or ordered during the clinical encounter to assess for transverse venous sinus stenosis. Imaging data was available for 93 of 101 patients. Patients without prior lumbar puncture to document opening pressure, or with inconclusive results, underwent lumbar puncture at a separate visit, with measurement of opening pressure in the lateral decubitus position with legs extended.

Participant-completed questionnaires

Participants completed questionnaires including: the Headache Impact Test (HIT-6), a six item scale to assess headache-related disability which yields a range from 36 (no disability) to 78, where a score of 60 or more is considered severe headache-related disability [13]; the Numerical Rating Pain Scale (NRS) where 0 indicates the absence of pain, while 10 represents the most intense pain possible; the STOP-Bang screening tool for sleep apnoea, in which the presence of three or more characteristics indicates high risk for the condition [14]; the Prospective and Retrospective Memory Questionnaire (PRMQ) to assess for subjective memory failures in everyday situations, where scores range from 16 to a maximum impairment of 80, with the mean in normal adults being c.39 [15]; and the National Eye Institute Visual Function Questionnaire (VFQ 39) to assess vision-related disability [16].

Patients who scored more than 2 on the STOP-BANG questionnaire underwent formal polysomnography to determine if they had obstructive sleep apnoea, defined as an apnoea-hypopnoea index greater than five. Data from the HIT-6 was missing for six patients, from the NRS for four patients, from the VFQ39 for 11 patients, and from the PRMQ for eight patients. The PRMQ was completed by all subjects prior to initiation of the objective cognitive battery.

Cognitive testing

All participants were administered a battery of cognitive tests in a private room in the clinic. This included the following: 1) National adult reading test in English (NART) to estimate premorbid intelligence [17]; 2) Mini Mental Status examination (MMSE); 3) Digit span repetition, forward to test attention and backward to test working memory and executive function [18]; 4) Boston naming test (BNT) for confrontational naming [19]; 5) Rey auditory verbal learning test (RAVLT), a test of verbal memory [20]; 6) Clock drawing for visuospatial function [21]; 7) Trail making test (TMT), part A for psychomotor speed and B for executive function [22]; 8) Controlled oral word association task for letters CFL (COWA) to assess phonemic fluency and executive function [23]; and 9) Category fluency (animals) to test semantic fluency and memory [24]. The battery was administered to patients by a trained psychometrician. The same test instructions were used during all sessions.

Raw test scores were converted to standardised Z scores based on published norms for healthy adults and were adjusted for age, gender, and education. Impairment was defined as a Z score below 2 standard deviations (SD). Performances falling 1 SD, 1.5 SD, and 2 SD have all been suggested as cutoffs demarcating mild cognitive impairment (MCI) in various studies [25]. We chose a conservative cutoff of 2 SD in order to strike a balance between reliability, sensitivity, and specificity. A more radical cutoff of 1 SD in our patient population would have classified the vast majority of our subjects as impaired. We defined MCI-single domain when participants scored in the impaired range in one cognitive test, and MCI multi-domain when performance was impaired in two or more tests [25]. To provide more stable measures of the underlying abilities that can be compared across individuals, composites were formed with unit-weighted Z scores of constituent tests as recommended by Ackerman and Cianciolo and Riordan [26, 27]. A composite cognitive Z score was determined from the mean of tests 2 to 9 inclusive [28].

Statistical analysis

Statistical analysis was performed using Stata 15.1 software (StataCorp LLC). To compare the characteristics between the cognitively normal and the impaired, two sample t-tests or Mann-Whitney U tests (for variables not normally distributed as indicated by the Shapiro-Wilk test) were used for continuous variables and chi-square tests or Fisher's exact tests were used for categorical variables. Simple linear regression models with robust standard error estimates were carried out respectively to evaluate the associations between the composite cognitive Z scores and the baseline factors that could predict cognitive dysfunction. A multiple linear regression model was generated using backward-stepwise selection with likelihood-ratio tests. The predictors for the backward-stepwise selection included disease duration, education, NRS score, Max OP, VA, HIT-6 score, narcotic use, acetazolamide use, and VFQ Mental Health. The considerations for choosing the variables were clinical significance, relatively high association from simple linear regression, low correlation with other variables, and fewer missing values. A p value of 0.05 or less was considered statistically significant. Correlation between Trail Making Test scores with headache and visual function, and between subjective total, retrospective, and prospective memory scores and RAVLT results were explored using Spearman's rank correlation.

Institutional review board approval

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

Results

Demographics

One hundred and one subjects were enrolled. Baseline characteristics of the sample, divided into groups with and without objective cognitive impairment, are set out in Table 1. There were no demographic differences between the groups.

Objective cognitive impairment in PTCS

Eight-six patients completed the entire cognitive battery. Results from one test were missing for 14 patients and results from two tests were missing for one patient. All 101 patients were included in the analysis. More than half of the subjects (n = 55) had MCI when compared to published age-, gender-, and education-adjusted norms. Thirty patients (29.7%) demonstrated MCI in a single domain, and 25 (24.8%) showed multi-domain MCI. Significantly fewer patients with MCI had venous sinus stenosis on head imaging. But other than this, the groups did not differ (Tab. 1).

When analysed with simple regression models, we found negative associations between composite cognitive score and headache intensity and HIT-6 (beta coefficients = –0.088, –0.016, p = 0.013, p = 0.021, respectively). We found positive associations between composite cognitive score and VFQ39 total, mental health and ocular pain subscores (beta coefficients = 0.014, 0.009 and 0.01, p = 0.02, 0.016, and 0.002, respectively) (Tab. 2). With this model, there were no statistically significant associations between composite cognitive score and duration of disease, body mass index,

Table 1. Baseline characteristics of PTCS patients with and without cognitive impairment

Characteristic	Without objective cognitive impairment	With objective cognitive impairment	P value
	n = 46	n = 55	
Age (mean ± SD)	35.6 ± 9.4	32.6 ± 8.4	0.094
Female (%)	40 (87%)	52 (94.5%)	0.29
Education, yrs, median (IQR)	14 (13, 16)	14 (12, 16)	0.51
Duration of disease, yrs, median (IQR)	1.0 (0.33, 2.0)	1.0 (0.25, 2.0)	0.96
BMI kg/m^2 (mean ± SD)	35.6 ± 7.3	36.8 ± 9.3	0.51
Sleep apnoea (%)	9 (19.6%)	9 (16.4%)	0.68
MRI-VSS (%)	35 (83.3%)	30 (61.2%)	0.020
Headache intensity, NRS, median (IQR)	7 (5, 8)	8 (6, 9)	0.15
HIT-6 Score, median (IQR)	62.0 (54.0, 66.0)	66.0 (58.5, 71.0)	0.053
Max OP in cm H_2O (mean ± SD)	35.2 ± 10.8	37.3 ± 9.6	0.31
VA, median (IQR)	–0.05 (–0.09, 0.00)	–0.02 (–0.09, 0.04)	0.26
CV, median (IQR)	10.0 (9.75, 10.0)	10.0 (9.75, 10.0)	0.81
PA (mean ± SD)	1.75 ± 1.09	1.38 ± 1.19	0.11
Total VFQ39, median (IQR)	82.2 (73.3, 90.9)	79.2 (68.2, 90.2)	0.35
VFQ Mental Health, median (IQR)	82.5 (50.0, 90.0)	75.0 (50.0, 90.0)	0.18
VFQ Ocular Pain (mean ± SD)	63.4 ± 22.0	53.9 ± 27.6	0.077
PRMQ (mean ± SD)	39.9 ± 12.9	39.0 ± 14.2	0.76
Narcotic use (%)	4 (8.7%)	6 (10.9%)	0.75
Acetazolamide use (%)	19 (41.3%)	31 (56.4%)	0.13
Topiramate use (%)	5 (10.9%)	4 (7.3%)	0.73

IQR — interquartile range; BMI — body mass index; MRI-VSS — presence of venous sinus stenosis on head imaging; NRS — numerical rating pain scale; HIT-6 — Headache Impact Test 6 score; OP, CSF — opening pressure; VA — visual acuity; CV — colour vision; PA — Frisén papilloedema grade; VFQ-39 — Visual Function Questionnaire 39 score; PRMQ — Prospective and Retrospective Memory Functioning Questionnaire score

sleep apnoea, presence of venous sinus stenosis, maximum opening pressure, mean visual acuity, mean colour contrast, narcotic use, acetazolamide use, topiramate use, or PRMQ score (Tab. 2). A multiple linear regression model adjusting for maximum opening pressure and mental health score showed that as headache intensity increased by one point, composite Z score decreased by 0.077 points (95% CI: –0.149, –0.005, p = 0.037). (Tab. 2, Fig. 1).

Supplementary Table 1 demonstrates raw and Z score ranges for each cognitive test, as well as the percentage of patients scoring 2 SD below the normative cut-off on each test. More patients scored below the cutoff on BNT and TMT part B than any other tests. Supplementary Table 2 shows correlations between TMT and headache intensity and visual function measures. We found negative correlations between TMT and headache intensity and visual acuity, but not colour vision or papilloedema grade.

Subjective cognitive impairment in PTCS

On average, subjective assessment of cognitive impairment in the whole cohort was similar to published norms as evidenced by a total PRMQ T score of 49.9 (Tab. 3). The mean total PRMQ score in the general, healthy adult population is 38.8, and higher scores represent greater subjective impairment [15]. In our study, 11.8% of subjects scored more than 2 SD above this published mean, reflecting more than average subjective concerns over memory (Tab. 4). There was no difference in PRMQ results comparing patients with or without MCI (Tab. 1). When analysed with regression methods, there was a trend but no statistically significant correlation with PRMQ scores and composite cognitive Z score (Tab. 2), although we found negative correlations between the total, retrospective, and prospective PRMQ scores and the RAVLT results (Suppl. Tab. 3).

Discussion

To the best of our knowledge, this was the first study to examine multiple domains of cognition in a population of more than 31 PTCS patients. Over half of our patients showed at least single-domain MCI compared to published norms. Our results agree with previous studies finding objective cognitive impairment in PTCS [6,7, 10–12]. Objective cognitive impairment correlated only with headache

Table 2. Simple and multiple regression model results for associations between composite cognitive Z score and NRS pain score, HIT-6 score, and other potential factors

Characteristic	Simple linear regression model			Multiple linear regression model		
	Coefficient	95% Confidence interval	P value	Coefficient	95% Confidence interval	P value
Age	0.004	–0.017, 0.024	0.707			
Female vs. male	0.138	–0.607, 0.883	0.714			
Education, yrs	0.070	0.009, 0.130	0.024			
Duration of disease, yrs	–0.043	–0.102, 0.015	0.147			
BMI kg/m^2	–0.001	–0.021, 0.019	0.915			
Sleep apnoea: yes vs. no	0.062	–0.378, 0.503	0.780			
MRI-VSS: yes vs. no	0.275	–0.145, 0.696	0.197			
Headache intensity, NRS	–0.088	–0.157, –0.019	0.013	–0.077	–0.149, –0.005	0.037
HIT-6 Score	–0.016	–0.030, –0.003	0.021			
Max OP in cmH_20	–0.011	–0.028, 0.006	0.215	–0.013	–0.029, 0.003	0.111
VA	–0.659	–1.615, 0.296	0.174			
CV	0.058	0.060,0.176	0.332			
Total VFQ39	0.014	0.002, 0.026	0.020			
VFQ Mental Health	0.009	0.002, 0.016	0.016	0.007	–0.001, 0.015	0.083
VFQ Ocular Pain	0.010	0.004, 0.016	0.002			
PRMQ	–0.009	–0.021, 0.003	0.130			
Narcotic use: yes vs. no	–0.405	–1.001, 0.191	0.181			
Acetazolamide use: yes vs. no	–0.232	–0.546, 0.082	0.146			
Topiramate use: yes vs. no	–0.148	–0.929, 0.634	0.709			

BMI — body mass index; CV — mean colour vision; HIT-6 — Headache Impact Test 6 score; MRI-VSS — presence of venous sinus stenosis on head imaging; NRS — numerical rating pain scale; OP, CSF — opening pressure; PA — mean Frisén papilloedema grade; PRMQ — Prospective and Retrospective Memory Functioning Questionnaire score; VA — mean visual acuity; VFQ-39 — total Visual Function Questionnaire 39 score

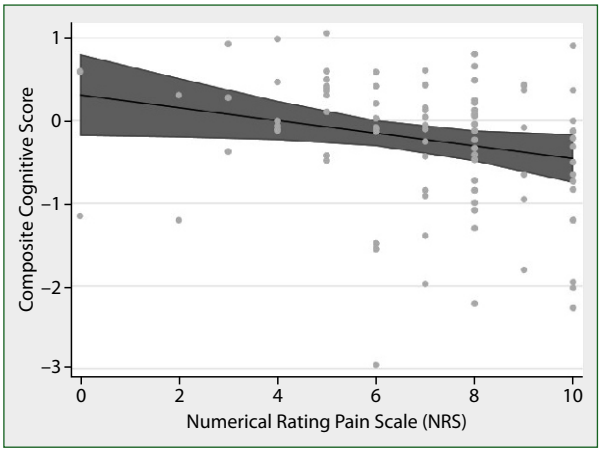


Figure 1. Relationship between composite cognitive score and headache severity. Predictive margins and 95% confidence intervals are from multiple regression model adjusting for maximum opening pressure and VFQ Mental Health

burden, ocular pain, mental health, and visual quality of life, and surprisingly did not correlate with self-perception of cognitive impairment.

Table 3. Prospective and retrospective memory scores in our PTCS patients compared to published norms

	T score
Total PRMQ score ± SD	49.9 ± 14.8
Retrospective PRMQ score ± SD	51.8 ± 13.8
Prospective PRMQ score ± SD	46.5 ± 14.9

This was the first study to quantify patients' impressions of cognitive deficit and compare that to objective cognitive burden. Of the six previous studies on the subject, five reported that patients did note cognitive difficulties [6, 7, 9, 10, 12]. In Kaplan's case report, the single patient self-reported difficulty with concentration and memory, prompting the case study, and this was corroborated by the report of "very high level of difficulty with cognitive tasks" on the administered Chronic Pain Inventory [9]. All five of the patients studied by Sorensen et al. self-reported problems with concentration, learning, and memory, as did half of the patients studied by Kharkar, over half of the patients studied by Yri, and all 30 patients studied by Zur [6, 7, 10, 12]. These were all self-reported concerns of cognitive difficulty, presumably by interview, as self-report

Table 4. Percentage of our patients scoring > 2SD above published norms in PRMQ

	A mean	B SD	C Range	D SEM_{xt}	E Patients scoring > 2SD above mean
Total PRMQ score	38.88	9.15	17–67	2.95	11.8%
Prospective score	20.18	4.91	8–35	3.36	12.9%
Retrospective score	18.69	4.98	8–33	3.58	6.5%

PRMQ — prospective and retrospective memory questionnaire; PTCS — pseudotumor cerebri syndrome
Subjective total, prospective, and retrospective memory burden reported by patients on PRMQ. For ease of interpretation, Table 3a reports scales as T scores, determined from conversion of raw scores based on published norms. Table 3b (columns A to D) represents published norms for PRMQ, and column E reflects percentage of our subjects scoring in a symptomatic range on this measure of subjective cognitive impairment
PTCS — pseudotumor cerebri syndrome; PRMQ — prospective and retrospective memory questionnaire

scales were not mentioned in any study other than Kaplan's [9]. In the large cohort of the Idiopathic Intracranial Hypertension Treatment Trial, the primary aim of which was not to study cognitive impairment, this self-report (no scale) of cognitive difficulty was much lower, at 21% of 165 patients [8]. In contrast to these groups, which unanimously support self-perception of cognitive difficulties in PTCS, we showed that when a formal questionnaire regarding prospective and retrospective memory is administered (rather than directly asking subjects whether they experienced cognitive difficulties), only a minority of subjects showed subjective cognitive impairment. Specifically, less than 12% of our patients scored 2 SD above the mean level of subjective cognitive impairment (referring to total PRMQ score), despite over half the sample showing objective MCI, indicating a possible lack of awareness of the deficit. Other groups had clinically noted a lack of self-awareness in patients with PTCS, raising their suspicion of prefrontal dysfunction [10].

The secondary aim of our study was to explore the predictors of cognitive impairment. In this study, objective cognitive impairment correlated with headache severity at the time of testing, headache-related disability, and ocular pain, all congruent findings. Severity of headache was reported in only one previous study. It is interesting in light of our results that Yri et al. found no association between headache and cognitive performance [10]. It is reported that 71% of Yri's patients had headache at the time of initial testing, with the mean NRS pain score being 2.3 [10]. This discrepancy may be accounted for by the fact that all our patients suffered more severe headache at the time of testing, with mean NRS pain score of 8 in patients with MCI. Taking our results into account, it is also interesting that Zur et al. found cognitive impairment in a PTCS population that was free from severe or chronic headache [12]. This discrepancy could potentially be explained by our larger sample size, and our more stringent definition of cognitive impairment.

It is not surprising that our two measures of headache severity correlated with overall cognitive burden. The evidence for long-term cognitive impairment in migraine has been contradictory, but it is clear that migraineurs experience ictal cognitive impairment, and possible that the ones most affected by headache experience interictal cognitive difficulties as well [29]. Studies comparing migraineurs to subjects with non-migraine headache and non-headache chronic pain found similar mild deficits in cognition, suggesting that poor performance was a factor of general pain rather than intrinsic to the headache disorder [30, 31]. It is often implied that cognitive dysfunction in chronic pain is related to depression [30]. Indeed, depression is common in migraine [32] and more common in PTCS then normal weight controls, and more severe compared to weight-matched controls [33]. However, depression was not associated with poor cognitive performance in Yri's sample [10], and while our simple linear regression model found a correlation between cognitive impairment and worse mental health, this finding was no longer significant in the multiple regression model adjusting for headache severity. Larger cohorts or more detailed measures of mental health would be needed to explore this relationship in the future.

We wanted to understand whether factors intrinsic to the intracranial hypertension itself could predict cognitive dysfunction. This encompasses the risk factors for the disorder — namely BMI, obstructive sleep apnoea, and venous sinus stenosis (when primary), the consequences — including opening pressure, visual function, papilloedema grade, and visual quality of life, and the treatments — specifically medications which could impact cognition, including acetazolamide, topiramate, and narcotics.

In agreement with the earlier work, we found no correlation of cognitive impairment with patient BMI, which is surprising given previous, albeit inconsistent, associations of obesity with cognitive dysfunction in the general population [10, 12, 24]. It is possible that if we had used markers of central obesity, such as waist circumference or weight-to-hip ratio, our results would have differed.

Likewise, we found no relationship between the comorbidity of sleep apnoea and cognitive dysfunction, a surprising new finding given the degree of daytime fatigue, and known reversible cognitive dysfunction that is classically experienced in the sleep disorder [35]. Future studies could explore this relationship in more detail and in larger cohorts, stratifying the patients according to apnoea-hypopnoea-index, and treatment status (with positive airway pressure).

We considered the final risk factor for PTC to be venous sinus stenosis. Most of our patients did have venous sinus stenosis on initial imaging. We expected that the possible venous congestion occurring as a consequence of venous sinus stenosis would have led to cognitive impairment, akin to other conditions described causing venous congestive encephalopathy [36, 37]. We were surprised to find that significantly more of our patients without MCI had stenosis. It is possible that no relationship existed after all, as this difference did not hold up in our simple regression model, or that simply too many of our patients had venous sinus stenosis, making it difficult to discern differences. A future direction could include stratifying patients by primary versus secondary venous sinus stenosis, if known.

The next set of characteristics pertained directly to intracranial hypertension. We did not find any correlation between the composite cognitive score and maximum opening pressure. Yri et al. performed both cognitive testing and lumbar puncture at baseline and 3-month follow up in 31 subjects with PTCS, and found no correlation between change in cognitive performance and change in intracranial pressure, which supports our finding [10]. We demonstrated that objective cognitive impairment, as measured by the composite cognitive score, correlated with worse visual quality of life, especially in the domain of ocular pain, despite no correlation to visual acuity or colour vision. Earlier studies showed that higher headache-related disability correlated with visual quality of life in pseudotumor cerebri [8] and that visual quality of life was substantially reduced in migraineurs without PTCS, especially in the domain of ocular pain [38], so our finding was not surprising in the context of our other results highlighting the effect of headache.

Finally, we studied the relationship between cognitive impairment and potentially confounding medications namely acetazolamide, topiramate, and narcotics, and found none. This is in agreement with previous work looking at acetazolamide [12].

Our results could support additional diagnostics and treatments in the management of PTCS. Consideration should be given to including at least screening cognitive tests in the standard management of PTCS, considering the majority of our patients did not recognise cognitive burden, despite it being present. Secondly, our results cautiously support the treatment of the headache disorder associated with PTCS independent of the treatments aimed at reducing intracranial pressure. While acetazolamide has been proven to improve visual outcomes in PTCS, it does not address the coexistent headache disorder, which often needs separate treatment [39, 40].

Our study has several limitations. This was a non-blinded study, potentially affecting subjects' performance. Secondly, while our study was controlled using published normative data for cognitive testing in healthy adults, we did not control for the presence of chronic headache. This is being addressed in an ongoing study that is quantifying the cognitive burden in a population with chronic daily headaches and will be reported separately. Thirdly, we did not specifically evaluate depression or anxiety, although we administered the VFQ39 which quantifies level of worry, frustration, irritability, isolation, and lack of control, and these are reported as the Mental Health subscore [16]. Finally, we did not perform follow up cognitive testing after resolution of headache to determine reversibility of deficits.

Nevertheless, given the rarity of this disorder and the large number of subjects enrolled, we were able to identify prevalence and predictors of cognitive impairment in subjects with PTCS.

Conclusions, clinical implications, future directions

Single-domain and multi-domain mild cognitive impairment is present in pseudotumor cerebri syndrome, and correlates with headache and ocular pain burden, but not with self-perception of deficit.

Measures representing intracranial hypertension such as cerebrospinal fluid opening pressure, papilloedema grade, and visual function did not correlate with cognitive impairment. Future controlled studies are needed with cognitive testing before and after headache remission in order to understand the full extent of the demonstrated relationships.

Funding: *This research was supported by the Lantry Family Foundation and by the Myers Family Foundation.*
Conflicts of interest: *None.*

References

1. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology. 2013; 81(13): 1159–1165, doi: 10.1212/WNL.0b013e3182a55f17, indexed in Pubmed: 23966248.
2. Ambika S, Arjundas D, Noronha V, et al. Clinical profile, evaluation, management and visual outcome of idiopathic intracranial hypertension in a neuro-ophthalmology clinic of a tertiary referral ophthalmic center in India. Ann Indian Acad Neurol. 2010; 13(1): 37–41, doi: 10.4103/0972-2327.61275, indexed in Pubmed: 20436745.
3. D'Amico D, Curone M, Erbetta A, et al. Intracranial idiopathic hypertension: 1-year follow-up study. Neurol Sci. 2014; 35 Suppl 1: 177–179, doi: 10.1007/s10072-014-1765-x, indexed in Pubmed: 24867861.
4. Liu IH, Wang AG, Yen MY. Idiopathic intracranial hypertension: clinical features in Chinese patients. Jpn J Ophthalmol. 2011; 55(2): 138–142, doi: 10.1007/s10384-010-0907-9, indexed in Pubmed: 21400059.
5. Pollak L, Zohar E, Glovinsky Y, et al. Reevaluation of presentation and course of idiopathic intracranial hypertension–a large cohort comprehensive study. Acta Neurol Scand. 2013; 127(6): 406–412, doi: 10.1111/ane.12060, indexed in Pubmed: 23278763.
6. Sørensen PS, Thomsen AM, Gjerris F. Persistent disturbances of cognitive functions in patients with pseudotumor cerebri. Acta Neurol

Scand. 1986; 73(3): 264–268, doi: 10.1111/j.1600-0404.1986.tb03273.x, indexed in Pubmed: 3716764.
7. Kharkar S, Hernandez R, Batra S, et al. Cognitive impairment in patients with Pseudotumor Cerebri Syndrome. Behav Neurol. 2011; 24(2): 143–148, doi: 10.3233/BEN-2011-0325, indexed in Pubmed: 21606575.
8. Digre KB, Bruce BB, McDermott MP, et al. NORDIC Idiopathic Intracranial Hypertension Study Group. Quality of life in idiopathic intracranial hypertension at diagnosis: IIH Treatment Trial results. Neurology. 2015; 84(24): 2449–2456, doi: 10.1212/WNL.0000000000001687, indexed in Pubmed: 25995055.
9. Kaplan CP, Miner ME, McGregor JM. Pseudotumour cerebri: risk for cognitive impairment? Brain Inj. 1997; 11(4): 293–303, doi: 10.1080/026990597123601, indexed in Pubmed: 9134204.
10. Yri HM, Fagerlund B, Forchhammer HB, et al. Cognitive function in idiopathic intracranial hypertension: a prospective case-control study. BMJ Open. 2014; 4(4): e004376, doi: 10.1136/bmjopen-2013-004376, indexed in Pubmed: 24713214.
11. Arseni C, Simoca I, Jipescu I, et al. Pseudotumor cerebri: risk factors, clinical course, prognostic criteria. . Rom J Neurol Psychiatry. 2016; 30(2): 115–132, indexed in Pubmed: 1520600.
12. Zur D, Naftaliev E, Kesler A. Evidence of multidomain mild cognitive impairment in idiopathic intracranial hypertension. J Neuroophthalmol. 2015; 35(1): 26–30, doi: 10.1097/WNO.0000000000000199, indexed in Pubmed: 25383589.
13. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res. 2003; 12(8): 963–974, doi: 10.1023/a:1026119331193, indexed in Pubmed: 14651415.
14. Chung F, Yegneswaran B, Liao Pu, et al. STOP Questionnaire. Anesthesiology. 2008; 108(5): 812–821, doi: 10.1097/aln.0b013e31816d83e4.
15. Crawford JR, Smith G, Maylor EA, et al. The Prospective and Retrospective Memory Questionnaire (PRMQ): Normative data and latent structure in a large non-clinical sample. Memory. 2003; 11(3): 261–275, doi: 10.1080/09658210244000027, indexed in Pubmed: 12908675.
16. Mangione CM, Lee PP, Pitts J, et al. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). NEI-VFQ Field Test Investigators. Arch Ophthalmol. 1998; 116(11): 1496–1504, doi: 10.1001/archopht.116.11.1496, indexed in Pubmed: 9823352.
17. Crawford JR, Moore JW, Cameron IM. Verbal fluency: a NART-based equation for the estimation of premorbid performance. Br J Clin Psychol. 1992; 31(3): 327–329, doi: 10.1111/j.2044-8260.1992.tb00999.x, indexed in Pubmed: 1393161.
18. Weschler D. WMS-III Administration and Scoring Manual. The Psychological Corportation/Harcourt Brace & Co. ; 1997.
19. Tombaugh TN, Hubley AM. The 60-item Boston Naming Test: norms for cognitively intact adults aged 25 to 88 years. J Clin Exp Neuropsychol. 1997; 19(6): 922–932, doi: 10.1080/01688639708403773, indexed in Pubmed: 9524887.
20. Savage R. Rey auditory-verbal learning test: The effects of age and gender, and norms for delayed recall and story recognition trials. Archives of Clinical Neuropsychology. 1992; 7(5): 407–414, doi: 10.1016/0887-6177(92)90153-e.
21. Rouleau I, Salmon DP, Butters N. Longitudinal analysis of clock drawing in Alzheimer's disease patients. Brain Cogn. 1996; 31(1): 17–34, doi: 10.1006/brcg.1996.0022, indexed in Pubmed: 8790932.
22. Tombaugh T. Trail Making test A and B: normative data stratified by age and education. Archives of Clinical Neuropsychology. 2004; 19(2): 203–214, doi: 10.1016/s0887-6177(03)00039-8.
23. Ross TP, Furr AE, Carter SE, et al. The psychometric equivalence of two alternate forms of the Controlled Oral Word Association Test. Clin Neuropsychol. 2006; 20(3): 414–431, doi: 10.1080/13854040590967153, indexed in Pubmed: 16895856.
24. Acevedo A, Loewenstein DA, Barker WW, et al. Category fluency test: normative data for English- and Spanish-speaking elderly. J Int Neuropsychol Soc. 2000; 6(7): 760–769, doi: 10.1017/s1355617700677032, indexed in Pubmed: 11105466.
25. Jak AJ, Bondi MW, Delano-Wood L, et al. Quantification of five neuropsychological approaches to defining mild cognitive impairment. Am J Geriatr Psychiatry. 2009; 17(5): 368–375, doi: 10.1097/JGP.0b013e31819431d5, indexed in Pubmed: 19390294.
26. Ackerman PL, Cianciolo AT. Cognitive, perceptual-speed, and psychomotor determinants of individual differences during skill acquisition. J Exp Psychol Appl. 2000; 6(4): 259–290, doi: 10.1037//1076-898x.6.4.259, indexed in Pubmed: 11218338.
27. Riordan H. Constructing Composites to Optimize Cognitive Outcomes. J Clin Stud. 2017; 9(2): 40–45.
28. Donohue MC, Sperling RA, Salmon DP, et al. Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing, Alzheimer's Disease Neuroimaging Initiative, Alzheimer's Disease Cooperative Study. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. JAMA Neurol. 2014; 71(8): 961–970, doi: 10.1001/jamaneurol.2014.803, indexed in Pubmed: 24886908.
29. Gil-Gouveia R, Martins IP, Gil-Gouveia R, et al. A subjective cognitive impairment scale for migraine attacks. The MIG-SCOG: development and validation. Cephalalgia. 2011; 31(9): 984–991, doi: 10.1177/0333102411408359, indexed in Pubmed: 21628438.
30. Gil-Gouveia R, Martins IP, Martins IP, et al. Migraine, headaches, and cognition. Headache. 2012; 52(10): 1471–1482, doi: 10.1111/j.1526-4610.2012.02218.x, indexed in Pubmed: 22830358.
31. Bell BD, Primeau M, Sweet JJ, et al. Neuropsychological functioning in migraine headache, nonheadache chronic pain, and mild traumatic brain injury patients. Archives of Clinical Neuropsychology. 1999; 14(4): 389–399, doi: 10.1093/arclin/14.4.389.
32. Domitrz I, Lipa A, Rożniecki J, et al. Treatment and management of migraine in neurological ambulatory practice in Poland by indicating therapy with monoclonal anti-CGRP antibodies. Neurol Neurochir Pol. 2020; 54(4): 337–343, doi: 10.5603/PJNNS.a2020.0054, indexed in Pubmed: 32687594.
33. Kleinschmidt JJ, Digre KB, Hanover R. Idiopathic intracranial hypertension: relationship to depression, anxiety, and quality of life. Neurology. 2000; 54(2): 319–324, doi: 10.1212/wnl.54.2.319, indexed in Pubmed: 10668690.
34. Buie JJ, Watson LS, Smith CJ, et al. Obesity-related cognitive impairment: The role of endothelial dysfunction. Neurobiol Dis. 2019; 132: 104580, doi: 10.1016/j.nbd.2019.104580, indexed in Pubmed: 31454547.
35. Kerner NA, Roose SP. Obstructive sleep apnea is linked to depression and cognitive impairment: evidence and potential mechanisms. Am J Geriatr Psychiatry. 2016; 24(6): 496–508, doi: 10.1016/j.jagp.2016.01.134, indexed in Pubmed: 27139243.
36. Dijk Jv, Willinsky R. Venous congestive encephalopathy related to cranial dural arteriovenous fistulas. Neuroimaging Clinics of North America. 2003; 13(1): 55–72, doi: 10.1016/s1052-5149(02)00063-1.

37. Wang HC, Lin WC, Kuo YL, et al. Factors associated with brainstem congestive encephalopathy in dural arterio-venous fistulas. Clin Neurol Neurosurg. 2009; 111(4): 335–340, doi: 10.1016/j.clineuro.2008.11.004, indexed in Pubmed: 19101079.
38. Hanson LL, Ahmed Z, Katz BJ, et al. Patients with migraine have substantial reductions in measures of visual quality of life. Headache. 2018; 58(7): 1007–1013, doi: 10.1111/head.13330, indexed in Pubmed: 29877580.
39. Bruce BB, Digre KB, McDermott MP, et al. NORDIC Idiopathic Intracranial Hypertension Study Group, NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. JAMA. 2014; 311(16): 1641–1651, doi: 10.1001/jama.2014.3312, indexed in Pubmed: 24756514.
40. Raggi A, Marzoli SB, Chiapparini L, et al. Headache frequency and symptoms of depression as predictors of disability in patients with idiopathic intracranial hypertension. Neurol Sci. 2018; 39(Suppl 1): 139–140, doi: 10.1007/s10072-018-3361-y, indexed in Pubmed: 29904836.

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4, pages: 403–406
DOI: 10.5603/PJNNS.a2021.0030

ISSN 0028–3843

Cross-circulation thrombectomy through posterior communicating artery for acute middle cerebral artery occlusion using Solitaire FR stent with intermediate catheter assisting technique

Di Li[1], Zhongjun Chen[1], Tieping Fan[1], Xusheng Zhao[1], Hengxu Qi[1], Xuesong Liang[2], Aline M. Thomas[3], Shen Li[2]

[1]Department of Neurointervention, Dalian Municipal Central Hospital affiliated with Dalian Medical University, Dalian, China
[2]Department of Neurology, Dalian Municipal Central Hospital affiliated with Dalian Medical University, Dalian, China
[3]Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, USA

Key words: cross-circulation, acute ischaemic stroke, thrombectomy, swim technique

(*Neurol Neurochir Pol 2021; 55 (4): 403–406*)

To the Editors

Cross-circulation thrombectomy gains access to emergent large-vessel occlusions without a favourable direct route through the anterior or posterior communicating artery. Although there have been a few successful cases reported, this approach involves long distance navigation of the endovascular devices in the tortuous Circle of Willis collaterals, accompanied by a high risk of clots escaping and arterial injury.

We here present the first case of cross-circulation thrombectomy with a good outcome for acute middle cerebral artery occlusion and chronic ipsilateral internal carotid artery occlusion via the patent posterior communicating artery using the Solitaire FR/Stent With Intermediate Catheter Assisting (SWIM) technique. We demonstrate that cross-circulation thrombectomy provides an opportunity for recanalisation of occluded arteries with unfavourable direct access or anatomical constraints. The SWIM technique, which employs an intermediate catheter, is beneficial in minimising mechanical injuries and reducing exposure of the retrieved clot to the bloodflow, thus lessening complications.

Acute occlusion of the middle cerebral artery (MCA) with tandem occlusion of ipsilateral internal carotid artery (ICA) has a low recanalisation rate after intravenous thrombolysis, and a poor prognosis [1]. There are currently no treatment guidelines for these patients, and only a few case studies have reported successful cross-circulation thrombectomy through the Willis circle, via trans-anterior or posterior communicating artery (AComA or PComA) routes [2–5].

However, the endovascular devices have to travel long distances in the tortuous intracranial arteries using this approach, thereby increasing the risk of mechanical injury, the escape of clots, and thromboembolisms [6].

The newly developed Solitaire FR/Stent With Intermediate Catheter Assisting (SWIM) technique employing an intermediate catheter could potentially reduce trans-circulation thrombectomy-associated complications.

A 63-year-old male with a 40-year history of smoking, alcohol consumption (30 years), hypertension and coronary artery disease was transferred to the emergency department 90 minutes after the acute onset of somnolence, right hemiplegia, dysarthria, right facial droop, visual field defect, marked left-sided gaze preference, hemidysesthesia, hemi-neglect, and aphasia. A head computed tomography (CT) scan excluded intracranial haemorrhage (Supp. Fig. S1). His baseline National Institute of Health Stroke Scale (NIHSS) score was 20, his Rapid Arterial Occlusion Evaluation (RACE) score was 8, and his Albert Stroke Programme Early CT score (ASPECTS) was 9.

Address for correspondence: Di Li, Department of Neurointervention, Dalian Municipal Central Hospital affiliated with Dalian Medical University, Dalian, China e-mail: jzlidi@126.com; Shen Li, Department of Neurology, Dalian Municipal Central Hospital affiliated with Dalian Medical University, Dalian, China, e-mail: listenlishen@hotmail.com

Received: 2.09.2020 Accepted: 8.03.2021 Early publication date: 14.04.2021

Intravenous recombinant tissue plasminogen activator (rtPA) was administered followed by endovascular therapy with conscious sedation 150 minutes after the onset of symptoms.

A left common carotid artery (CCA) angiogram revealed a small stump at the origin of the left ICA, indicative of chronic occlusion (Fig. 1A). Perfusion into the MCA territory was not observed. Right CCA angiogram demonstrated insufficient leptomeningeal collaterals (ASTIN/SIR:2) reconstituted by a patent AComA (Fig. 1B). Left vertebral artery (VA) angiogram showed flow to the supraclinoid segment of the left ICA and MCA from the left PComA, and revealed an occlusion at the mid M1 segment of the left MCA (Fig. 1C). As the left PComA was 1.3 mm in diameter, a stent-retriever thrombectomy through the collateral PComA was selected. An 8F guide catheter was placed in the left VA followed by a 5F Navien catheter (intermediate catheter, 0.058-inch diameter, Medtronic, Irvine, CA, USA) and a Rebar 18 microcatheter (0.021-inch diameter, Medtronic) that were coaxially advanced over a 0.014-inch microwire (Stryker, Kalamazoo, MI, USA) to the distal basilar artery (BA). Next, the microcatheter was advanced through the left P1 segment, then through the PComA into the M1 segment, and finally placed distal to the clot. A 4×20 mm Solitaire FR stent (Medtronic) was then introduced through the microcatheter and fully deployed across the occluded left MCA (Fig. 1D). After the stent had been maintained in place for five minutes, the 5F Navien catheter was advanced to the left posterior cerebral artery along the guidewire. The stent and microcatheter were slowly pulled back in the Navien catheter (Fig. 1E), and then withdrawn outside the body through the 8F guide catheter. A large red thrombus was retrieved with a single pass (Fig. 1F). During clot retrieval, continuous manual aspiration with both the 5F Navien catheter and the 8F guide catheter was performed, using two 30-mL syringes. A subsequent angiogram revealed significant flow restoration [Thrombolysis in Cerebral Infarction (TICI) score 2b in the left MCA (Fig. 1G)]. Time to revascularisation, defined as the time from the femoral access to the achievement of revascularisation, was 38 minutes.

The patient started to improve immediately after thrombectomy. Head CT following the procedure showed no haemorrhage. A follow-up head CT the next day revealed scattered acute infarction restricted to the MCA territory in the left basal ganglia, as well as the left frontal and temporal lobes, and did not show intracranial haemorrhage (Supp. Fig. S2). There were no new infarcts in the posterior circulation, which confirmed a lack of embolisation in the stent-retriever passing territory. Symptoms that persisted at that time included partial gaze preference, right face droop, right hemiparalysis, sensory aphasia, and dysarthria. The NIHSS score had fallen to 10. A cervical and cerebral CT angiogram performed seven days later confirmed the recanalisation of the previously occluded left MCA (Fig. 1H) and a chronic occlusion at the origin of the right ICA with a small stump (Fig. 1I). At discharge, 10 days post stroke, the patient's symptoms were sensory aphasia and right facial droop. His NIHSS score was 3. At the four-week follow-up visit, patient recovery was nearly complete, with only the right facial droop persisting. His NIHSS score was 2 and modified Rankin Scale (mRS) score was 0. Written informed consent was obtained from the patient.

Nearly 20% of ischaemic strokes are related to severe extracranial carotid lesions, 10% of which are caused by carotid occlusion [7]. Regardless of the mechanism of ICA occlusion, symptoms are usually caused by a coexisting intracranial occlusive embolus, commonly in the middle cerebral artery (MCA) or carotid terminus [7]. Therefore, in most patients the final outcome depends on timely restoration of distal intracranial flow, rather than recanalisation of the proximal occlusion [8, 9]. Using a collateral vascular approach may provide an alternative quick, safe, and effective endovascular treatment for acute stroke patients presenting a large intracranial vessel occlusion without a direct route to the occlusion site. The first successful cross-circulation aspiration thrombectomy via the patent PComA was for an acute MCA occlusion [3]. Then, an anterior-posterior revascularisation of a BA occlusion upon intra-arterial thrombolysis and aspiration thrombectomy through a patent PComA was reported [4]. Kim et al. described a cross-circulation stent-retriever thrombectomy via the patent PComA for acute MCA ischaemic stroke with chronic cervical ICA occlusion [2]. More recently, two cases of trans-AComA stent-retriever thrombectomy were successfully carried out for acute MCA occlusion tandem with ICA occlusion [5]. These cases demonstrate the feasibility of cross-circulation thrombectomy.

To date, there has been no imaging approach that can accurately distinguish acute from chronic ICA occlusions, both of which can establish collateral circulation at the distal end of the occlusion. Recently, Hasan et al. analysed and classified the radiographic findings of 100 chronic ICA occlusion patients into four types with the aim of predicting the feasibility and safety of ICA revascularisation via endovascular therapy [10]. The occlusive morphology and relatively sound primary collateral circulation of our patient supported the diagnosis of chronic ICA occlusion. Moreover, our patient had type C occlusion in Hasan's classification, which has a low recanalisation rate and a high perioperative complication rate [10].

Recanalisation of a chronically occluded cervical carotid before treatment of the intracranial lesion might delay the time to distal recanalisation and potentially lead to a less favourable outcome [11]. In addition, this procedure carries significant risks, including distal embolisation into previously healthy intracranial vessels [e.g. anterior cerebral artery (ACA), carotid terminus], dissection or perforation of the extracranial carotid, and cerebral reperfusion haemorrhage (particularly after thrombolysis or when antiplatelet agents are administered after stent placement).

In our case, symptoms were mainly caused by thrombus or atherosclerotic plaque detachment from the occluded ICA stump and blockage of the left MCA, rather than cerebral

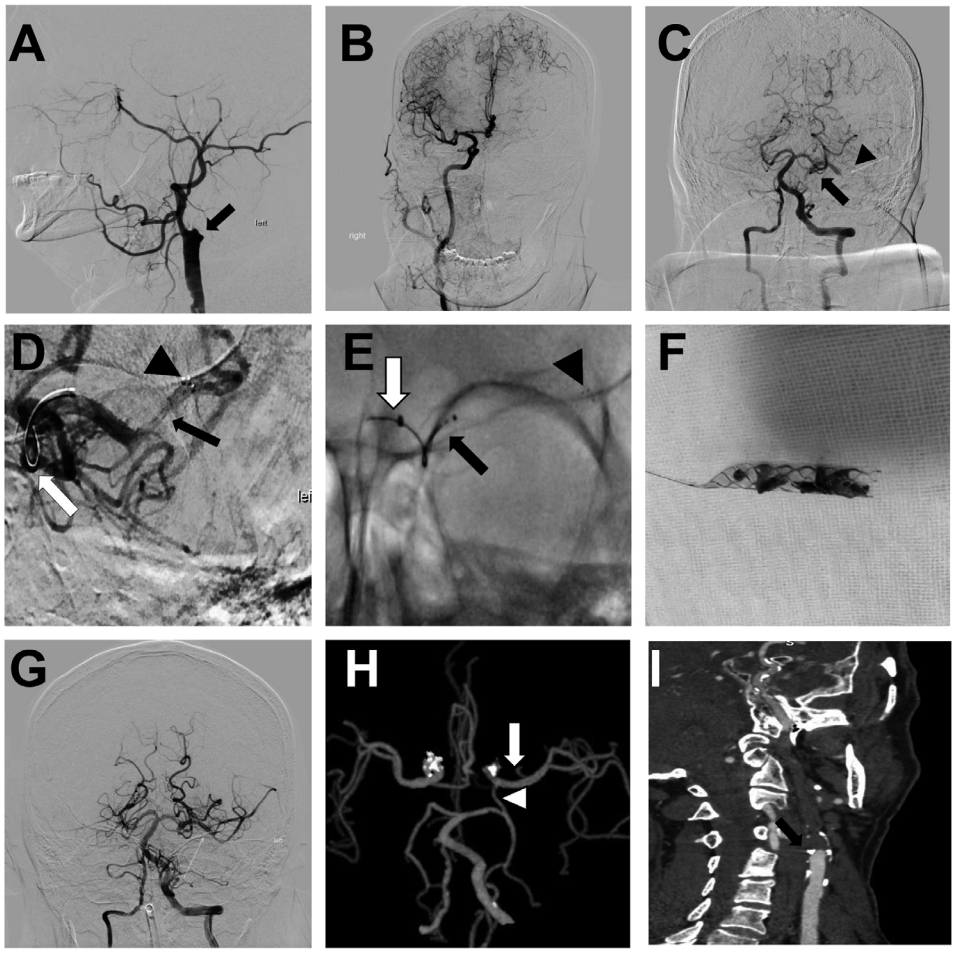


Figure 1. Brain images of patient suffering from acute left MCA occlusion. **A.** Lateral left CCA angiogram shows chronic occlusion at origin of left ICA, with small stump (arrow). **B.** Angiogram of right CCA (anterior-posterior) shows insufficient flow through leptomeningeal collaterals into left hemisphere reconstituted by patent AComA. **C.** Angiogram of left VA (anterior-posterior) reveals occlusion in mid M1 segment of left MCA (arrowhead) reconstituted by patent left PComA with diameter of 1.3 mm (arrow). **D.** A 4 × 20 mm Solitaire FR stent retriever (black arrow) was deployed over whole length of thrombus in left MCA through left PComA (white arrow). Immediate antegrade flow to left MCA was restored. Note filling defect in M1 segment representing trapped thrombus within stent struts (black arrows). Stent has three radiopaque distal markers (black arrowhead). **E.** Stent retriever shown in mid portion of MCA (black arrowhead), microcatheter in proximal segment of MCA (black arrow), and 5F Navien catheter in left PCA (white arrow). **F.** Red clot retrieved using Solitaire FR stent. **G.** Angiogram of left VA (anterior-posterior) after thrombectomy shows significant restoration of flow (TICI score: 2b) in left MCA. **H.** Cervical and cerebral CT angiogram performed seven days after thrombectomy confirmed our previous observations: patent left PComA (white arrowhead), recanalisation of previously occluded left MCA (white arrow). **I.** Chronic occlusion at origin of right ICA with small stump (white arrow)

haemodynamic insufficiency caused by chronic ICA occlusion with poor collateral supply. Prompt reperfusion of viable tissue, and the prevention of subsequent expansion of cerebral infarction, are the keys to successful endovascular revascularisation in acute stroke [12]. Facing a chronic ICA occlusion, we believed that it was best to open the distal occlusion through the collateral pathway to save time. Nevertheless, we recognised that we had to try to open the ICA occlusion itself if the collateral pathway conditions did not allow a cross-circulation thrombectomy. We sought and evaluated alternative routes such as a wide patent AComA or PComA, and we found that the diameter of the PComA was 1.3mm, and thus suitable for the passage of the Rebar 18 microcatheter. Therefore, the opening of the left MCA through the patent PComA would save time, enhance the opening efficiency, and improve the clinical prognosis of the patient.

The cross-circulation technique is currently reserved for selected cases because of a high risk of complications, including dissection, perforation, escaping clots, and thromboembolic occlusions, associated with the advancement of endovascular devices through tortuous Circle of Willis collaterals with small diameters. This risk may be higher in patients with advanced atherosclerotic stenosis in the proximal vertebral and carotid arteries [6]. Newly developed microwires, microcatheters and clot-retrieval devices have been shown to improve the recanalisation rate and decrease complications [6].

The SWIM technique shortens the distance of the stent-retriever in the vascular cavity, which can further minimise the risk of proximal and distal embolisms, and mechanical damage to the vessel wall. In this case report, we placed a Navien, an intermediate catheter, through the BA to the ostium of the left posterior cerebral artery, and achieved recanalisation without complications. Large scale studies are necessary to verify the efficacy and safety of this approach.

Funding: *This work was supported by the Natural Science Foundation of Liaoning Province (2019-MS-075), Liaoning Revitalisation Talents Programme (XLYC1807124), and Dalian Technology Innovation Programme (2019J13SN109). The sponsor had no role in the design or conduct of this research.*

Conflict of interest: *The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be considered as a potential conflict of interest.*

Ethical approval: *All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethical Committee of Dalian Municipal Central Hospital and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.*

Informed consent: *Informed consent was obtained from all individual participants included in the study.*

References

1. Rubiera M, Ribo M, Delgado-Mederos R, et al. Tandem internal carotid artery/middle cerebral artery occlusion: an independent predictor of poor outcome after systemic thrombolysis. Stroke. 2006; 37(9): 2301–2305, doi: 10.1161/01.STR.0000237070.80133.1d, indexed in Pubmed: 16888266.
2. Kim SK, Baek BH, Heo TW, et al. Successful Cross-circulation Stent-Retriever Embolectomy Through Posterior Communicating Artery for Acute MCA Occlusion by Using Trevo XP ProVue. Neurointervention. 2016; 11(1): 55–58, doi: 10.5469/neuroint.2016.11.1.55, indexed in Pubmed: 26958415.
3. Hui FK, Narayanan S, Cawley CM. Posterior-to-anterior circulation access using the Penumbra Stroke System for mechanical thrombectomy of a right middle cerebral artery thrombus. World Neurosurg. 2010; 73(1): 17–21, doi: 10.1016/j.surneu.2009.05.020, indexed in Pubmed: 20452865.
4. Liu W, Kung DK, Mahaney KB, et al. Anterior-to-posterior circulation approach for mechanical thrombectomy of an acutely occluded basilar artery using the penumbra aspiration system. World Neurosurg. 2012; 77(2): 398.E17–398.E20, doi: 10.1016/j.wneu.2011.04.025, indexed in Pubmed: 22120391.
5. Amuluru K, Romero CE, Pyle L, et al. Mechanical Thrombectomy of Acute Middle Cerebral Artery Occlusion Using Trans-Anterior Communicating Artery Approach. World Neurosurg. 2018; 112: 46–52, doi: 10.1016/j.wneu.2018.01.038, indexed in Pubmed: 29339323.

6–12. See supplementary references.

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4, pages: 407–409
DOI: 10.5603/PJNNS.a2021.0043

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

Bed regime as a lifesaving factor in spontaneous intracranial hypotension

Grzegorz Turek[1], Adrian Rogala[1], Mateusz Ząbek[2], Mirosław Ząbek[1,3,4]

[1]Department of Neurosurgery, Brodno Masovian Hospital, Warsaw, Poland
[2]Faculty of Medicine, Collegium Medicum, Cardinal Stefan Wyszynski University, Warsaw, Poland
[3]Gamma Knife Centre, Warsaw, Poland
[4]Department of Neurosurgery, Postgraduate Medical Centre, Warsaw, Poland

Key words: SIH, headache, dural tear, bed rest

(*Neurol Neurochir Pol 2021; 55 (4): 407–409*)

To the Editors

Spontaneous intracranial hypotension (SIH) was first described by Schalltenbrand in 1938. It is a clinical disorder in which cerebrospinal fluid (CSF) volume or pressure drop down due to a dural CSF leakage [1]. Although historically considered a rare condition, SIH has been increasingly recognised, with an incidence estimated at 5 per 100,000 [2]. However, it is frequently initially misdiagnosed [3]. A large number of symptoms can lead to difficulties in diagnosis. It is extremely important to pay particular attention to the fact that symptoms may mimic acute cerebrovascular events (ACE). The condition is characterised by similar symptoms. Research shows an incorrect diagnosis in 66.3%. Incorrect diagnoses are mainly made in the pre-hospital setting, but can also happen in the ED, especially if the treating physician is not a neurologist or stroke physician [4]. The clinical hallmark is debilitating postural headache, exacerbated by standing, and relieved in the recumbent position. Patients may also present with diplopia, tinnitus, vertigo, dizziness, neck stiffness, nausea, vomiting, hyperacusis, deafness, and vision loss [5]. Conservative treatment is limited to bed rest, hydration, caffeine and analgesic drugs [6]. In this letter, we present life-threatening complications of SIH in two patients.

Case 1

A 42-year-old female was admitted to hospital with a two-week history of headache that was persistent, changed depending on the patient's position, and was posture related. The patient also reported nausea and vomiting. No abnormalities were found in blood test or neurological examination, nor did the patient have a history of head or neck trauma. Computed tomography of the brain (CT) revealed bilateral hypodense subdural collections of blood (4 mm and 5 mm), along with the obliteration of the prepontine cistern. Initially, the patient was prescribed bed rest, hydration and steroid therapy. Unfortunately, she did not comply with these. Brain MRI demonstrated an advanced descent of the brainstem with flattening of the pontine surface, dilation of the sagittal sinus, enlargement of the pituitary gland, and expansion of the subdural haematomas (Fig. 1A). Additionally, C6/C7 disc herniation was found on spinal MRI, without accompanying symptoms. Isotopic cisternography and CT myelography results were normal. However, the patient again failed to comply with a strict bed regime. As a result, her score on the Glasgow Coma Scale (GCS) decreased from 15 to 14. CT confirmed the IH and enlargement of the subdural haematomas (7 mm and 11 mm). The patient still did not follow medical orders and a decrease to GCS 7 was recorded. As the aetiology of SIH remained unknown, the

Address for correspondence: Adrian Rogala, Department of Neurosurgery, Brodno Masovian Hospital, Ludwika Kondratowicza 8, 03–242 Warsaw, Poland; e-mail: adrian.kamil.rogala@gmail.com

Received: 27.03.2021 Accepted: 17.05.2021 Early publication date: 10.06.2021

patient was implanted with a both-sided subdural-peritoneal shunt, which caused a transient increase in GCS score up to 15. But the patient's neurological condition again deteriorated to GCS 5 four days after the implantation. This was primarily a consequence of further non-compliance with the bed regime. When emergency decompressive craniectomy was performed, the patient improved to 15 GCS. Another MRI with T2-weighted sequences showed the cause of SIH, a collection of cerebrospinal fluid referred as a 'double dural sac sign' in the extradural space, just above the degenerated C6/C7 segment (Fig. 1B). However, no epidural blood patch (EBP) was carried out at the affected segment of the spine, given the risk of neurological complications. The decision not to perform EBP was driven by the review paper published by Kapoor et al. [7]. Instead, anterior cervical discectomy and fusion at C6/C7, along with the inspection of dura mater at that level, were performed.

A large collection of cerebrospinal fluid was found extradurally, but no evident tear of the dura was identified despite a thorough inspection of the dural sac at the level of the disc herniation. The dura watertight protection was obtained by sealant matrix TachoSil. Despite further non-compliance with the bed regime, no deterioration of the patient's neurological condition was observed post-surgery. The patient was discharged with a GCS score of 15. No signs of SIH were found on a follow-up MRI six months later.

Case 2

A 54-year-old male presented with a four-week history of postural headache, concomitant nausea and vomiting, without neurological signs and symptoms, head or neck trauma. The results of blood tests, levels of paraneoplastic markers, thoracic radiogram, and abdominal ultrasound findings were normal. An initial CT of the brain revealed bilateral hypodense subdural collections of blood (8 mm each side) and the prepontine cistern's obliteration. Initially, the patient was treated with hydration, steroid therapy and ordered a strict bed regime. Failure to comply with medical recommendations contributed to the suspicion of IH. MRI revealed a critical descent of the brainstem with flattening of the pontine surface and enlargement of the pituitary gland. After the administration of a gadolinium-based contrast agent, diffuse pachymeningeal enhancement in the supratentorial and infratentorial regions was observed, ultimately confirming the diagnosis of IH. Spinal MRI showed advanced degenerative disease of the cervical spine. Subsequent CT myelography revealed a significant CSF leakage at the level of C1/C2 (Fig. 1C). To reduce the risk of a spinal cord injury, the patient was qualified to laminectomy with inspection of the dura at the leakage level, rather than to EBP. At the time of the qualification, the patient's GCS score was 15. However, the patient did not comply with the bed regime and his condition suddenly deteriorated, GCS score dropping from

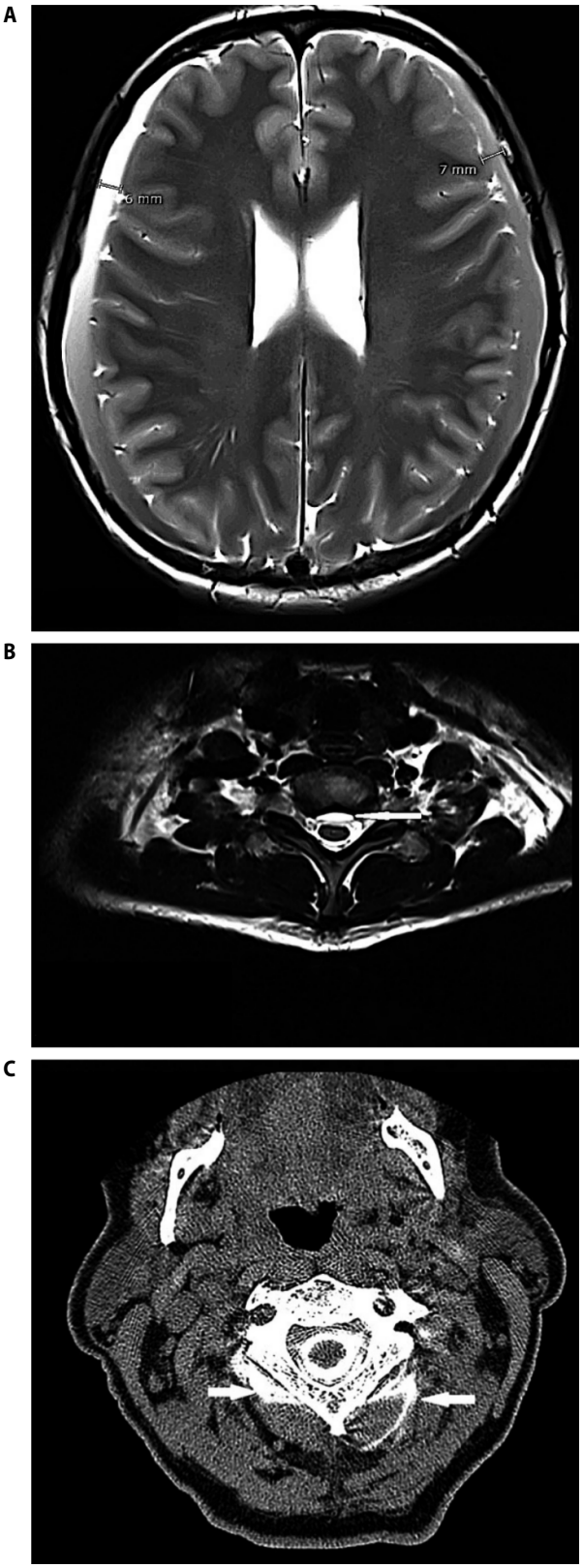


Figure 1. **A.** MRI showing expansion of subdural haematoma — case 1; **B.** MRI with T2-weighted sequences showed collection of CSF within extradural space, just above degenerated C6/C7 segment ('double dural sac sign') — case 1; **C.** CT myelography revealed significant CSF leakage at level of C1/C2 — case 2

15 to 7 within an hour. Control CT revealed a critical descent of cerebellar tonsils to the foramen magnum; the patient was already unconscious at that time, with a GCS score of 7. Large emergency decompressive craniectomy of the posterior fossa with the removal of the posterior edge of the foramen magnum was performed. During subsequent C1–C4 laminectomy, CSF leakage from a large dural laceration at the C2 nerve root level was identified. The laceration was thoroughly sealed by collagen matrix coated with human fibrinogen and thrombin — TachoSil. The subdural collections of blood were evacuated through both-sided decompressive craniectomy. The patient was transferred to the intensive care unit and put into a propofol-induced coma for five days. After recovery from the coma, he was fully conscious, with a GCS score of 15.

A rare condition, such as IH, can constitute a diagnostic and therapeutic challenge. IH is highly likely to be misdiagnosed or overlooked because patients with this condition usually lack objective symptoms. No clear guidelines have been published with regard to the conservative management of IH. While according to some authors an approximately two-week bed rest is sufficient to control this condition [8, 9], some published evidence suggests that conservative treatment might not be enough [10]. The most likely reason behind these discrepancies is patient non-compliance with the bed regime. This is well illustrated by the two cases presented herein; lack of compliance with the bed regime resulted in further CSF leakage, brain sagging and deterioration of the clinical condition, as shown by a rapid decrease in GCS scores. To the best of our knowledge, non-compliance with physician's orders has not been reported as a cause of IH exacerbation to date, and this case series is the first published evidence of potentially fatal complications related to non-compliance with a strict bed regime. While CSF leakage is a major cause of SIH, the underlying mechanisms are yet to be elucidated. Supine position of the body creates favourable conditions for dura mater regeneration, improving the CSF fluctuation and shifting the centre of mass of the brain upward [11, 12].

A bed regime seems to be an effective and vital component of IH treatment [13]. As we have presented in this paper, non-compliance with the bed regime can lead to life-threatening complications.

References

1. Schalltenbrand G. Neuere anschauungen zur pathophysiologie der liquozirkulation. Zentralbl Neurochir. 1938; 3: 290–300.
2. Kranz PG, Gray L, Amrhein TJ. Spontaneous intracranial hypotension: 10 myths and misperceptions. Headache. 2018; 58(7): 948–959, doi: 10.1111/head.13328, indexed in Pubmed: 29797515.
3. Schievink WI. Misdiagnosis of spontaneous intracranial hypotension. Arch Neurol. 2003; 60(12): 1713–1718, doi: 10.1001/archneur.60.12.1713, indexed in Pubmed: 14676045.
4. Kozera-Strzelińska D, Karliński M, Rak G, et al. Stroke and TIA mimics in patients referred to a neurological emergency department by non-ambulance physicians, ambulance physicians and paramedics. Neurol Neurochir Pol. 2019; 53(1): 83–89, doi: 10.5603/PJNNS.a2019.0002, indexed in Pubmed: 30614515.
5. Haritanti A, Karacostas D, Drevelengas A, et al. Spontaneous intracranial hypotension: clinical and neuroimaging findings in six cases with literature review. Eur J Radiol. 2009; 69(2): 253–259, doi: 10.1016/j.ejrad.2007.10.013, indexed in Pubmed: 18182266.
6. Williams EC, Buchbinder BR, Ahmed S, et al. Spontaneous intracranial hypotension: presentation, diagnosis, and treatment. Anesthesiology. 2014; 121(6): 1327–1333, doi: 10.1097/ALN.0000000000000410, indexed in Pubmed: 25118954.
7. Kapoor SG, Ahmed S. Cervical epidural blood patch — a literature review. Pain Med. 2015; 16(10): 1897–1904, doi: 10.1111/pme.12793, indexed in Pubmed: 26122010.
8. Liang H, Xu C, Liu T, et al. Spontaneous intracranial hypotension in Hashimoto's thyroiditis: a case report. Medicine (Baltimore). 2019; 98(18): e15476, doi: 10.1097/MD.0000000000015476, indexed in Pubmed: 31045829.
9. Sugino T, Matsusaka Y, Mitsuhashi Y, et al. Intracranial hypotension due to cerebrospinal fluid leakage detected by radioisotope cisternography. Neurol Med Chir (Tokyo). 2000; 40(8): 404–407, doi: 10.2176/nmc.40.404, indexed in Pubmed: 10979262.
10. Zheng Y, Lian Y, Wu C, et al. Diagnosis and treatment of spontaneous intracranial hypotension due to cerebrospinal fluid leakage. Springerplus. 2016; 5(1): 2108, doi: 10.1186/s40064-016-3775-z, indexed in Pubmed: 28066697.
11. Whedon JM, Glassey D. Cerebrospinal fluid stasis and its clinical significance. Altern Ther Health Med. 2009; 15(3): 54–60, indexed in Pubmed: 19472865.
12. Roberts DR, Zhu X, Tabesh A, et al. Structural brain changes following long-term 6° head-down tilt bed rest as an analog for spaceflight. AJNR Am J Neuroradiol. 2015; 36(11): 2048–2054, doi: 10.3174/ajnr.A4406, indexed in Pubmed: 26185326.
13. Hoffmann J, Goadsby PJ. Update on intracranial hypertension and hypotension. Curr Opin Neurol. 2013; 26(3): 240–247, doi: 10.1097/WCO.0b013e328360eccc, indexed in Pubmed: 23594732.

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4, pages: 410–412
DOI: 10.5603/PJNNS.a2021.0044

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

Asystole during onyx embolisation of dural arteriovenous fistula: a case of trigeminal cardiac reflex

Zihao Song[1], Yongjie Ma[1], Jiewen Geng[1], Peng Hu[1], Na Xu[2], Hongqi Zhang[1]

[1]Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Xicheng District, Beijing, China
[2]Department of Anaesthesiology, Xuanwu Hospital, Capital Medical University, Xicheng District, Beijing, China

Key words: dural arteriovenous fistula, onyx, trigeminal cardiac reflex

(*Neurol Neurochir Pol 2021; 55 (4): 410–412*)

To the Editors

Trigeminal cardiac reflex (TCR), hemifacial hypesthesia, hemifacial palsy, jaw pain, internal jugular vein injury and microcatheter gluing are potential complications in endovascular onyx embolisation of dural arteriovenous fistulas (DAVFs) [1]. TCR is a physiological reflex that occurs in response to stimulation of sensory branches of the trigeminal nerve, which can lead to haemodynamic instability such as bradycardia and asystole. TCR is often reported in craniofacial, ophthalmological, and skull base surgery, and less often reported in endovascular onyx embolisation. We report a case of TCR during endovascular onyx embolisation of a DAVF.

A 37-year-old male presented with a sudden severe headache without apparent cause, most pronounced in the occipital region, accompanied by nausea and vomiting. CT scan showed haemorrhage on right cerebellum, third ventricle and fourth ventricle. Further DSA examination showed a Cognard Class DAVF in right petroclival region. The DAVF was fed by the marginal tentorial branch of right meningohypophyseal trunk, right anterior inferior cerebellar artery, and the petrous branch of right middle meningeal artery (Fig. 1). The patient had no significant cardiac or respiratory disease. After discussion of treatment options, we decided to use transarterial onyx to embolise DAVF.

The procedure was performed under standard anaesthesia and systematic heparinisation. Anaesthesia was induced with

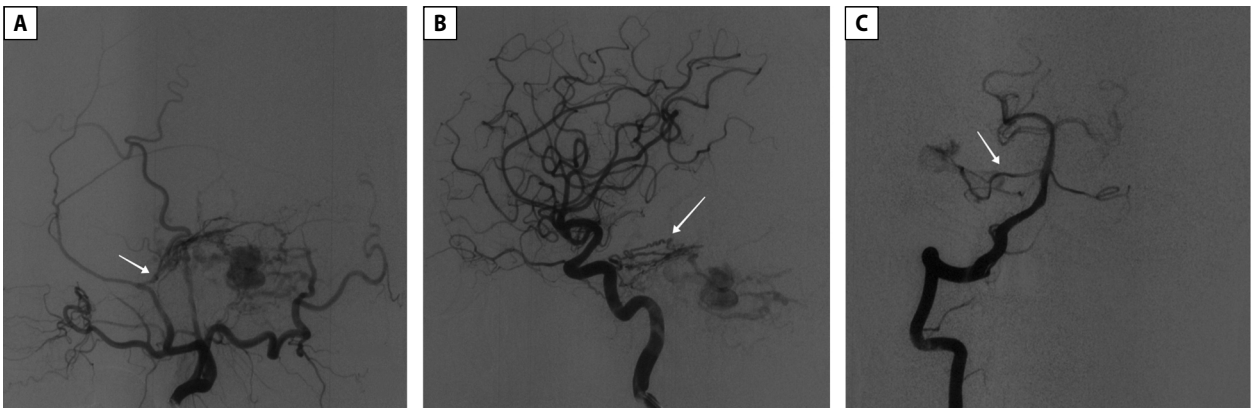


Figure 1. A. Lateral view of left external carotid artery angiogram demonstrates DAVF being fed by petrous branch of right middle meningeal artery (arrow); **B.** Lateral view of left internal carotid artery angiogram demonstrates DAVF being fed by marginal tentorial branch of right meningohypophyseal trunk (arrow); **C.** Anteroposterior view of left vertebral artery angiogram demonstrates DAVF being fed by right anterior inferior cerebellar artery (arrow)

Address for correspondence: Hongqi Zhang, Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, No. 45, Changchun Street, Xicheng District, Beijing 100053, China; e-mail: xwzhanghq@163.com

Received: 23.01.2021 Accepted: 6.05.2021 Early publication date: 11.06.2021

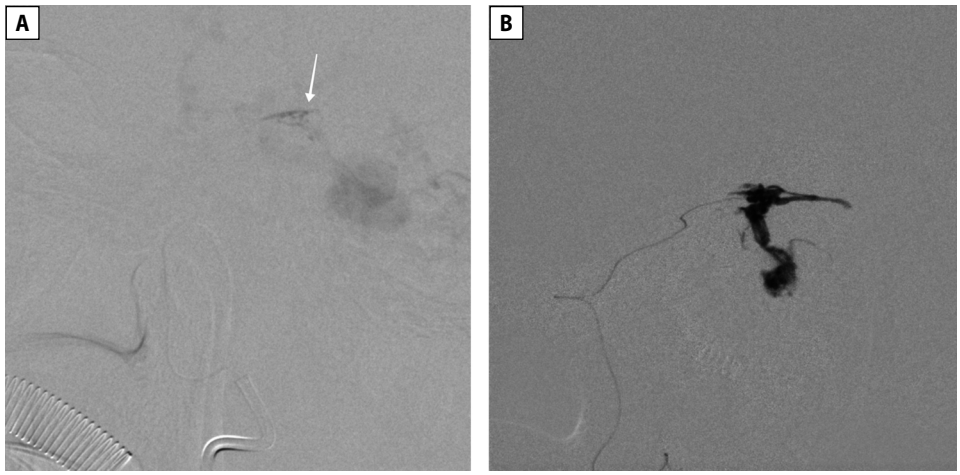


Figure 2. A. Lateral view of petrous branch of right middle meningeal artery superselective microcatheter angiogram demonstrates fistulous point (arrow); **B.** Lateral view of endovascular onyx injection to fistula

sufentanil 15ug, followed by rocuronium (0.8 mg/kg) and etomidate (0.2 mg/kg). After tracheal intubation, we performed mechanical ventilation with pure oxygen. Anaesthesia was maintained with renifentanyl (0.2 g/kg/min), and additional boluses of propofol (2 mg/kg/h), norepinephrine (0.06 ug/kg/min), dexmedetomidine (0.5 ug/kg/h) and sevoflurane (0.4%) were administered.

After transfemoral arterial access was gained, an Envoy 6F guide catheter (Cordis, Miami Lakes, FL, USA) was placed in the right external carotid artery. By using a road-mapping technique and selective control angiogram, a Marathon microcatheter (ev3 Neurovascular, Irvine, CA, USA) with a Synchro 2 0.010-inch microwire (Stryker Neurovascular, Fremont, CA, USA) was advanced into the petrous branch of right middle meningeal artery (Fig. 2A). Dimethyl sulfoxide (DMSO) was injected into the microcatheter without consequence. Then onyx was used to embolise the fistula (Fig. 2B). Near the completion of embolisation, the patient developed bradycardia: heart rate (HR) dropped from 52 to 32 bpm and blood pressure (BP) from 126/68 mmHg to 100/52 mmHg. The injection was immediately paused, and the patient's HR and BP normalised spontaneously. After discussion with the anaesthetist, onyx injection was performed again. But the patient developed asystole and BP dropped to 64/30 mmHg. Immediately, the injection was stopped. After intravenous injection of ephedrine and atropine and chest compressions, the patient returned to spontaneous circulation. The subsequent angiography found that the embolisation was satisfied (Fig. 3), and so the embolisation was terminated. Upon waking up from anaesthesia, the patient developed mania and was sedated with dexmedetomidine (0.5 ug/kg/h) and sent to the intensive care unit (ICU) for 48 hours of close monitoring. The patient did not present bradycardia or asystole during his ICU stay, and no cardiac or respiratory symptoms were reported, except for intermittent headache. Postoperative CT showed that the bleeding was well absorbed and the patient's symptoms had improved, so he was allowed home from hospital.

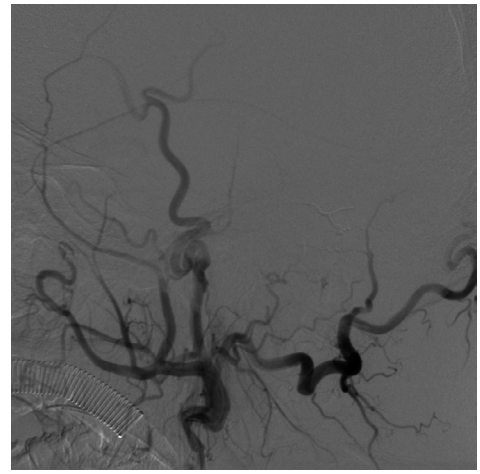


Figure 3. Lateral view of left external carotid artery angiogram demonstrates complete embolisation of fistula

This case presented herein reports bradycardia and asystole during endovascular onyx embolisation of a dural arteriovenous fistula. We consider that this response was caused by TCR, which was first described in endovascular onyx embolisation by Lv et al. [2].

Interestingly, TCR during endovascular embolisation has only been reported when using onyx. The reflex mainly occurred when transarterially injected into the middle meningeal arteries or transvenously injected into the cavernous sinus and inferior petrosal sinus. The injection of DMSO comes before the injection of onyx in order to flush the dead space of microcatheter. The incidence of TCR in endovascular onyx embolisation may be caused by neurotoxicity of DMSO or direct compression of the trigeminal nervous innervation

of the dural mater by the formation of an onyx plug produce [3]. Wang et al. [4] thought that during transarterial onyx embolisation, the injection pressure to middle meningeal artery induced neuronal signals via the Gassarian ganglion to the sensory nucleus of the trigeminal nerve, and thus caused TCR. They also believed that neurotoxicity of DMSO on the ophthalmic nerve within the cavernous sinus, or on the trigeminal nerve innervation of the dura mater, caused TCR during transvenous onyx embolising carotid cavernous fistula. Puri et al. [5] reported a case in which TCR occurred during a pre-onyx DMSO injection. This finding suggests that it is the biochemical action of DMSO, rather than onyx or any mechanical effect of the solidified cast, which elicits the TCR [6].

In our case, TCR occurred near the end of embolisation. We think that this reflex might be due to backflow of onyx to the petrous branch, which increased the pressure of the middle meningeal artery and induced neuronal signals and elicited TCR.

Neurointerventionalists should be very cautious when conducting intravascular manipulation in the middle meningeal artery. Anaesthetists should pay close attention to heart rate changes of patients and be prepared for TCR at any time. The operation should be immediately halted once TCR occurs. Intravenous administration of anticholinergic drugs and chest compressions are efficacious.

References

1. Kawamura Y, Takigawa T, Hyodo A, et al. Transvenous embolisation via an occluded inferior petrosal sinus for cavernous sinus dural arteriovenous fistulas. Neurol Neurochir Pol. 2020; 54(6): 585–588, doi: 10.5603/PJNNS.a2020.0071, indexed in Pubmed: 33026643.
2. Lv X, Li Y, Lv M, et al. Trigeminocardiac reflex in embolization of intracranial dural arteriovenous fistula. AJNR Am J Neuroradiol. 2007; 28(9): 1769–1770, doi: 10.3174/ajnr.A0675, indexed in Pubmed: 17885228.
3. Lv X, Li Y, Jiang C, et al. The incidence of trigeminocardiac reflex in endovascular treatment of dural arteriovenous fistula with onyx. Interv Neuroradiol. 2010; 16(1): 59–63, doi: 10.1177/159101991001600107, indexed in Pubmed: 20377980.
4. Wang J, Wu HC, Wang WW, et al. Trigeminal cardiac reflex caused by onyx embolization of intracranial dural arteriovenous fistula. Turk Neurosurg. 2016; 26(3): 325–330, doi: 10.5137/1019-5149.JTN.8008-13.1, indexed in Pubmed: 27161455.
5. Puri AS, Thiex R, Zarzour H, et al. Trigeminocardiac reflex in a child during pre-Onyx DMSO injection for juvenile nasopharyngeal angiofibroma embolization. A case report. Interv Neuroradiol. 2011; 17(1): 13–16, doi: 10.1177/159101991101700103, indexed in Pubmed: 21561553.
6. Chowdhury T, Schaller B. Trigeminocardiac reflex. Academic Press 2015.

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 4, pages: 413–414
DOI: 10.5603/PJNNS.a2021.0052

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

Post-COVID 19 Neurological Syndrome: a fresh challenge in neurological management

Mauro Antonio González-Herazo[1], Diana Carolina Silva-Muñoz[2], Paula Andrea Guevara-Martínez[3], Ivan David Lozada-Martinez[1]

[1]University of Cartagena, Cartagena, Colombia
[2]University of Santander, Colombia
[3]University Foundation of Health Sciences, Colombia

Key words: Post-COVID 19 Neurological Syndrome, COVID-19, nervous system diseases, prognosis

(*Neurol Neurochir Pol 2021; 55 (4): 413–414*)

To the Editors

We read with great interest the article published recently by Zielińska-Turek et al. [1] entitled 'Clinical features of neurological patients with coronavirus 2019: an observational study of one centre', where the authors investigated a cohort of patients with COVID-19 and previous neurological diseases, finding that most of these patients were elderly, with dementia or a history of stroke, and that these conditions associated with COVID-19 worsened the prognosis and increased the mortality of these patients.

We thank Zielińska-Turek et al. [1] for providing such valuable evidence. However, we would like to make some comments on a recently described entity which poses a challenge in the management of patients with a neurological history or who present with neurological complications during the course of COVID-19.

Disease burden studies of neurological disorders estimate that since 2005 there has been a notable increase in Years Lived with Disability (YLDs) and Disability Adjusted Life Years (DALYs) globally, mainly due to cerebrovascular diseases (50,785 to 53,815 DALYs) and Alzheimer's and other types of dementia (11,078 to 13,540 DALYs) [2], and these figures are projected to increase to 60,864 and 18,394 by 2030, respectively [2].

Based on the above, controlling the burden of neurological diseases is a global health priority.

Considering that the moderate and severe phenotypes of COVID-19 generally present neurological complications, or manifest themselves only through neurological syndromes [3], it is necessary to establish the prognosis of these patients and the impact on their quality of life.

Post-COVID 19 neurological syndrome is a new condition only recently described [4, 5], which consists of medium and long-term involvement of the nervous system due to molecular mechanisms that trigger neuroinflammation, compromising the functional capacity and quality of life of neurological patients in general [4, 5].

Noting that the average age of the patients of Zielińska-Turek et al. [1] was 72 years, and that they also had comorbidities that have a negative impact on the nervous system such as arterial hypertension, type II diabetes mellitus, or dementia [1], it is necessary to pay attention and perform strict follow-up of these patients, because of the increased probability and severity of developing post-COVID-19 neurological syndrome, manifested through the persistence of certain symptoms, or the presentation of neurological disorders in a short period after the resolution of COVID-19 [4, 5].

There is no clear evidence or understanding of the pathophysiology of this syndrome, although meta-analyses have reported results establishing short-term associations between COVID-19 and neurological involvement in patients presenting with neurological symptoms, in the absence of lesions visible on neuroimaging, regardless of age or expression of the COVID-19 phenotype [3].

In this scenario, a strategic plan should be designed by neurology and neurosurgery departments with the aim of creating prospective multicentre studies to evaluate the

Address for correspondence: Ivan David Lozada-Martinez, University of Cartagena, Cartagena, Colombia, e-mail: ivandavidloma@gmail.com

Received: 21.05.2021 Accepted: 24.05.2021 Early publication date: 3.08.2021

evolution of neurological involvement and rehabilitation of these patients, in order to establish effective and safe measures to ensure functional capacity and survival.

Likewise, this event sheds further light on the need to create specialised centres in neurointervention and neurorehabilitation, since the burden of neurological diseases remains one of the highest globally, and can be expected to increase even more rapidly due to this syndrome.

References

1. Zielińska-Turek J, Jasińska A, Kołakowska J, et al. Clinical features of neurological patients with coronavirus 2019: an observational study of one centre. Neurol Neurochir Pol. 2021; 55(2): 195–201, doi: 10.5603/PJNNS.a2021.0011, indexed in Pubmed: 33528832.
2. World Health Organization. Global burden of neurological disorders: estimates and projections. https://www.who.int/mental_health/neurology/chapter_2_neuro_disorders_public_h_challenges.pdf (21 May 2021).
3. Rogers JP, Chesney E, Oliver D, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry. 2020; 7(7): 611–627, doi: 10.1016/S2215-0366(20)30203-0, indexed in Pubmed: 32437679.
4. Camargo-Martínez W, Lozada-Martínez I, Escobar-Collazos A, et al. Post-COVID 19 neurological syndrome: Implications for sequelae's treatment. J Clin Neurosci. 2021; 88: 219–225, doi: 10.1016/j.jocn.2021.04.001, indexed in Pubmed: 33992187.
5. Wijeratne T, Crewther S. Post-COVID 19 Neurological Syndrome (PCNS); a novel syndrome with challenges for the global neurology community. J Neurol Sci. 2020; 419: 117179, doi: 10.1016/j.jns.2020.117179, indexed in Pubmed: 33070003.