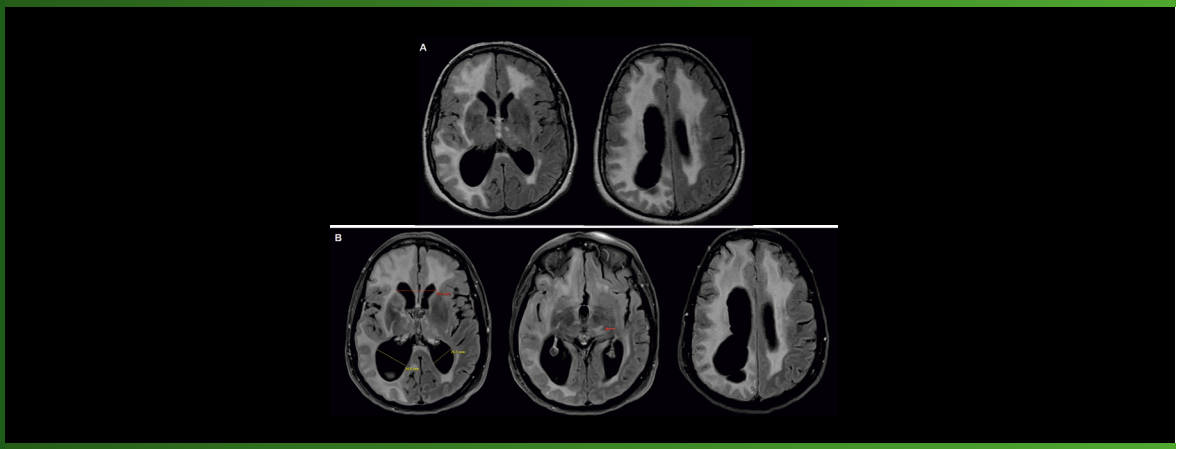
NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF NEUROLOGY AND NEUROSURGERY

The Official Journal of Polish Neurological Society

2020, vol. 54, no. 4



Established: 1938

VIA MEDICA

ISSN 0028-3843

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) 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 (2019) is 1.025

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

Cover photo: Tasneem F. Hasan et al., T2 FLAIR MRI of the brain, see figure on page 314.

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

VIA MEDICA

19-0211.004.001

NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF
NEUROLOGY
AND NEUROSURGERY

The Official Journal of Polish Neurological Society

2020, vol. 54, no. 4

Table of Contents

RESEARCH PAPERS

SHORT COMMUNICATION

LETTER TO THE EDITORS

RESPONSE TO THE LETTER TO THE EDITORS

EDITORIAL NOTE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54, no. 4, pages: 289–290
DOI: 10.5603/PJNNS.2020.0061

ISSN 0028–3843

Further Increase of Impact Factor and CiteScore™ of the Polish Journal of Neurology and Neurosurgery (Neurologia i Neurochirurgia Polska)

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]Co-Editor-in-Chief, Department of Neurology and Psychiatry, Medical University of Gdansk, Gdansk, Poland

(*Neurol Neurochir Pol 2020; 54 (4): 289–290*)

The *Polish Journal of Neurology and Neurosurgery* (PJNNS), also known as *Neurologia i Neurochirurgia Polska* has further increased its bibliometric measures; both its Impact Factor (IF) and CiteScore™ (CS) have improved this year.

The journal IF is analyzed by the Clarivate Analytics (Philadelphia, Pennsylvania, USA). It is usually announced in June or July of the following year to allow for the completeness of its calculations. The journal IF is calculated in the following manner:

The 2019 journal IF = number of citations in 2019 to items published in 2017 and 2018 / number of citable items (research papers, reviews and short communications) in 2017 and 2018.

The 2019 journal IF for PJNNS is 1.025. Figure 1 depicts PJNNS's current IF and its trend from 2009 to 2019.

The CS is calculated by Elsevier (Amsterdam, Netherlands). It is usually announced during late spring of the following year, in order to capture all eligible citations and

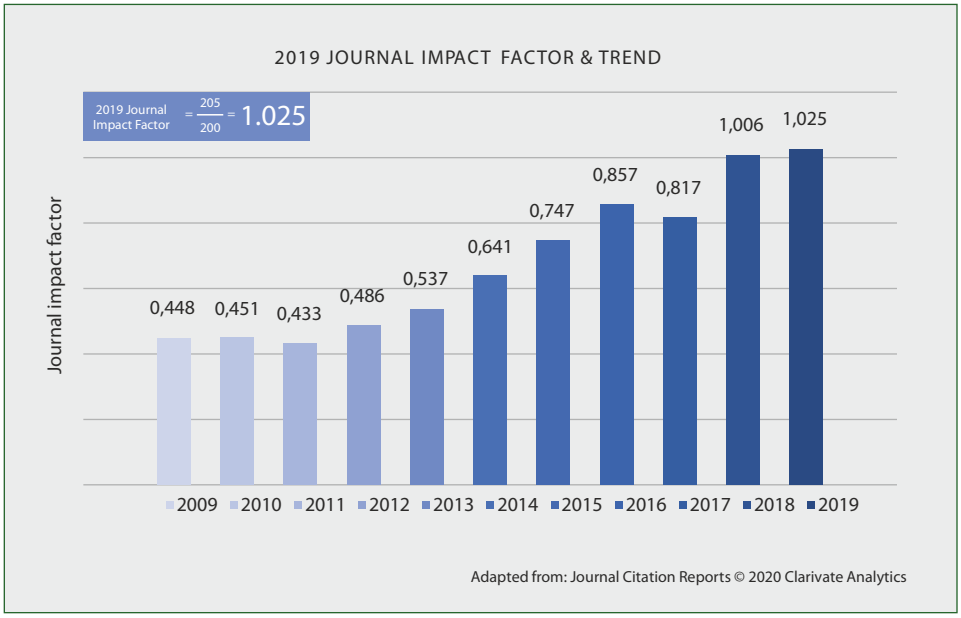


Figure 1. This figure demonstrates the growth of the journal Impact Factor (IF) for the *Polish Journal of Neurology and Neurosurgery* (PJNNS, *Neurologia i Neurochirurgia Polska*) according to Journal Citation Reports. The journal IF is calculated by dividing a number of citations to published items (editorials, review papers, research papers, brief communications, and letters to the editor) obtained by the journal during the year for which IF is calculated to a number of citable items (mostly review manuscripts and original research papers) published by the journal during the previous two years. The calculations for the PJNNS are depicted in the insert box in the right upper corner of this figure

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

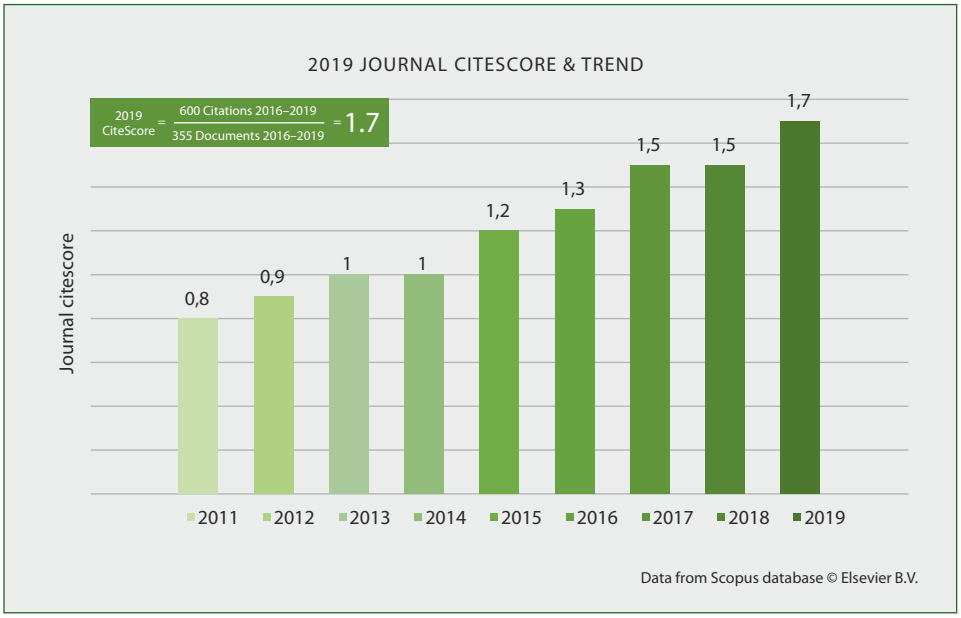


Figure 2. This figure shows the growth of the CiteScore™ (CS) for the *Polish Journal of Neurology and Neurosurgery* (PJNNS, *Neurologia i Neurochirurgia Polska*) according to the Scopus database. CS measures average citations received per document published in the journal over the last three years. The calculations for the PJNNS are depicted in the insert box in the right upper corner of this figure

articles for a more complete calculation. The CS is calculated in the following manner:

2019 CS — number of citations in 2016 to 2019 / number of (all) documents from 2016 to 2019.

The 2019 CS for PJNNS is 1.7. Figure 2 depicts PJNNS's current CS and its trend from 2011 to 2019.

The five most cited articles from PJNNS that significantly contributed to our current journal IF (2019) include three review articles [1–3] and two research papers [4, 5]. Two of the review articles were written by authors from Warsaw, Poland [1] and Lublin, Poland [2], and the third one by authors from Parkville, Victoria, Australia [3]. The first Polish review manuscript described severe disease exacerbation in patients with multiple sclerosis after discontinuation of fingolimod [1]. The second Polish review article discussed the utility of ultra-high field time-of-flight magnetic resonance angiography for a visualization of small cerebral vessels [2]. The Australian review outlined the progress in the treatment of Friedreich's ataxia [3].

The two original research articles were written by authors from Katowice, Poland [4] and from Iasi, Romania [5]. The Polish original research paper outlined the correlations between cognitive impairments in patients with Alzheimer's disease, mild cognitive impairments, and cognitively normal controls, and the serum levels of brain-derived neurotropic factor [4]. The second original research manuscript from Romania discussed the linear and nonlinear parameters of heart rate variability in ischemic stroke patients [5].

We very much thank our authors for submitting their articles to the PJNNS. We hope that our future bibliometric measures further improve with implementation of multiple editorial administrative changes that we introduced to the journal management for over the last two years including technical simplification of the review process (eg. abandoning of double-blinding reviews), faster manuscript processing, and new Journal features such as invited reviews and invited editorials. We also plan to implement in near future a new Journal feature, a "leading topic". We thank our readers and our Scientific Board members for providing us with helpful comments and guidance.

References

1. Członkowska A, Smoliński Ł, Litwin T. Severe disease exacerbations in patients with multiple sclerosis after discontinuing fingolimod. Neurol Neurochir Pol. 2017; 51(2): 156–162, doi: 10.1016/j.pjnns.2017.01.006, indexed in Pubmed: 28209440.
2. Grochowski C, Staśkiewicz G. Ultra high field TOF-MRA: A method to visualize small cerebral vessels. 7T TOF-MRA sequence parameters on different MRI scanners - Literature review. Neurol Neurochir Pol. 2017; 51(5): 411–418, doi: 10.1016/j.pjnns.2017.06.011, indexed in Pubmed: 28774679.
3. Tai G, Corben LA, Yiu EM, et al. Progress in the treatment of Friedreich ataxia. Neurol Neurochir Pol. 2018; 52(2): 129–139, doi: 10.1016/j.pjnns.2018.02.003, indexed in Pubmed: 29499876.
4. Siuda J, Patalong-Ogiewa M, Żmuda W, et al. Cognitive impairment and BDNF serum levels. Neurologia i Neurochirurgia Polska. 2017; 51(1): 24–32, doi: 10.1016/j.pjnns.2016.10.001.
5. Constantinescu V, Matei D, Costache V, et al. Linear and nonlinear parameters of heart rate variability in ischemic stroke patients. Neurol Neurochir Pol. 2018; 52(2): 194–206, doi: 10.1016/j.pjnns.2017.10.002, indexed in Pubmed: 29110883.

INVITED EDITORIAL

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54, no. 4, pages: 291–293
DOI: 10.5603/PJNNS.2020.0034

ISSN 0028–3843

Sexual dysfunction in Huntington's Disease: what do we really know?

Philip W. Tipton

Department of Neurology, Mayo Clinic, Jacksonville, Florida, United States

ABSTRACT

Introduction. In this edition, Szymuś et al. conducted a systematic review revealing sexual dysfunction to be more prevalent in patients with Huntington's Disease compared to controls.

Clinical reflections. Sexual dysfunction in HD (SDHD) is common and significantly affects patient quality of life. Commonly used HD rating scales and treatment guidelines do not explicitly address SDHD, and research studies are limited by size and methodology.

Clinical implications. It is important that validated sexual dysfunction screening tools be utilised in clinical and research settings.

Key words: Huntington's Disease, sexual dysfunction

(*Neurol Neurochir Pol 2020; 54 (4): 291–293*)

Huntington's Disease (HD) is a dominantly inherited neurodegenerative disease caused by an expanded CAG trinucleotide repeat in the *HTT* gene, which encodes the huntingtin protein [1]. Symptoms of HD include a classic triad of movement abnormalities, cognitive impairment, and behavioural disturbances. Due to genetic anticipation, these symptoms occur earlier, and more severely, with successive generations [2]. HD affects people during the prime years of life with an average age at onset of between 30 and 50 [3]. While HD is rare, affecting only 2.71 per 100,000 people worldwide [4], associated symptoms cause significant functional impairment [5]. HD is the most common cause of inherited chorea, and clinicians may focus on the movement disorder at the expense of other symptoms that cause as much, if not more, detriment to quality of life (QoL).

Szymuś et al. conducted a systematic review of HD-associated sexual dysfunction [6]. They found that the majority of patients with HD had sexual disorders, particularly hypo/hyperactive sexual disorder, erectile and ejaculatory dysfunction, lubrication problems, and orgasmic dysfunction. Their findings suggest that SD is more common in HD and correlates with QoL measures [6]. However, their review also illuminates several limitations of the current literature regarding SDHD.

Firstly, the HD literature has consistently underinvestigated sexual function. The DSM-5 has an entire chapter on SD, which includes delayed ejaculation, erectile disorder, female orgasmic disorder, female sexual interest/arousal disorder, genito-pelvic pain/penetration disorder, male hypoactive sexual desire disorder, premature ejaculation, substance/medication-induced SD, and others [7]. This categorisation alone illustrates the variety of elements to consider when evaluating patients for SD. However, widely used HD rating scales e.g. UHDRS and UHDRS-FAP, and current treatment guidelines, do not address SD at all [8–11].

Therefore, it is not surprising that SDHD has been overshadowed by other disease symptoms such as chorea. Moreover, conducting a thorough assessment of sexual function can be time-consuming for clinicians and awkward or uncomfortable for patients and their partners. This method of verbal assessment can lead to underreporting of sexual dysfunction for a variety of reasons relating to one's culture, belief set, or social factors. Validated sexual function scales can help with this problem. The international index of erectile function (IIEF) assesses erectile function, orgasmic function, sexual desire and intercourse satisfaction in males [12]. For females, the female sexual function index (FSFI) yields a valid assessment of sexual domains including desire, arousal, lubrication, orgasm,

Address for correspondence: Philip W. Tipton, Department of Neurology, Mayo Clinic, 4500 San Pablo Rd., Jacksonville, FL 32224, USA, e-mail: tipton.philip@mayo.edu

satisfaction and pain [13]. Validated scales such as the IIEF and FSFI should be the standard for future studies.

Another limitation of the literature is a simple lack of well-designed, fully-powered studies focusing on SDHD as a primary endpoint. Szymuś et al. found only nine studies conducted over a 25-year timespan. These included information on sexual function of at least 20 genetically confirmed HD patients [6]. These studies were conducted an average of 11 years ago, and one third were conducted more than 18 years ago. There also seems to be an inverse relationship between study size and data quality. The largest study, of more than 2,500 patients, used unvalidated online survey questions with no control group [14]. Only two small trials used validated sexual function scales i.e. the IIEF [15] and the FSFI [16]. Non-standardised study methodology, and an apparent trade-off between study size and quality, inhibit us from developing reliable conclusions.

A recent study found that SDHD resulted in the highest life impact among 216 HD-related symptoms [5]. Despite this substantial effect on QoL, we know little about the mechanisms underlying SDHD. It is unclear whether the SD is directly caused by the HD pathomechanism, or whether it is merely a byproduct of other symptoms and/or their treatments. Depression is prevalent in HD [17] and is directly related to erectile/ejaculatory problems [18]. Dopamine depleting agents such as tetrabenazine are effective and widely used to treat HD-related chorea [19]; however, this mechanism can also cause depressive symptoms or exacerbate preexisting depression [20]. There is also a well-established association between antidepressants and SD [21]. These are just some of the factors that are likely to be contributory to SDHD.

This is an exciting time for HD research, with the development of enhanced rehabilitative strategies and promising disease-modifying treatments such as antisense oligonucleotides (ASO) [22–24]. It remains to be seen how these interventions will affect patients at different disease stages. Further research is required to study large patient groups using validated assessment tools. Lastly, clinicians should remember that SDHD substantially affects QoL, and that patients frequently withhold such information due to a variety of cultural and societal factors.

Funding sources for this study: *None*

Financial disclosure/conflict of interest:
Dr. Tipton reports no disclosures or conflicts of interest

References

1. Gusella JF, Wexler NS, Conneally PM, et al. A polymorphic DNA marker genetically linked to Huntington's disease. Nature. 1983; 306(5940): 234–238, doi: 10.1038/306234a0, indexed in Pubmed: 6316146.
2. Kieburtz K, MacDonald M, Shih C, et al. Trinucleotide repeat length and progression of illness in Huntington's disease. J Med Genet. 1994; 31(11): 872–874, doi: 10.1136/jmg.31.11.872, indexed in Pubmed: 7853373.
3. Roos RAC. Huntington's disease: a clinical review. Orphanet J Rare Dis. 2010; 5: 40, doi: 10.1186/1750-1172-5-40, indexed in Pubmed: 21171977.
4. Pringsheim T, Wiltshire K, Day L, et al. The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. Mov Disord. 2012; 27(9): 1083–1091, doi: 10.1002/mds.25075, indexed in Pubmed: 22692795.
5. Glidden AM, Luebbe EA, Elson MJ, et al. Patient-reported impact of symptoms in Huntington disease: PRISM-HD. Neurology. 2020 [Epub ahead of print], doi: 10.1212/WNL.0000000000008906, indexed in Pubmed: 32193209.
6. Szymuś K, Bystrzyński A, Kwaśniak-Butowska M, et al. Sexual dysfunction in Huntington's Disease - a systematic review. Neurol Neurochir Pol. 2020 [Epub ahead of print], doi: 10.5603/JNNS.a2020.0025, indexed in Pubmed: 32242915.
7. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). SpringerReference. , doi: 10.1007/springerreference_179660.
8. Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group. Mov Disord. 1996; 11(2): 136–142, doi: 10.1002/mds.870110204, indexed in Pubmed: 8684382.
9. Winder JY, Achterberg WP, Marinus J, et al. Assessment Scales for Patients with Advanced Huntington's Disease: Comparison of the UHDRS and UHDRS-FAP. Mov Disord Clin Pract. 2018; 5(5): 527–533, doi: 10.1002/mdc3.12646, indexed in Pubmed: 30515443.
10. Youssov K, Dolbeau G, Maison P, et al. The unified Huntington's Disease Rating Scale for advanced patients: validation and follow-up study. Mov Disord. 2013; 28(14): 1995–2001, doi: 10.1002/mds.25678, indexed in Pubmed: 24123464.
11. Armstrong MJ, Miyasaki JM. Evidence-Based Guideline: Pharmacologic Treatment of Chorea in Huntington Disease. 2012. www.neurology.org (27.03.2020).
12. Rosen RC, Riley A, Wagner G, et al. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997; 49(6): 822–830, doi: 10.1016/s0090-4295(97)00238-0, indexed in Pubmed: 9187685.
13. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000; 26(2): 191–208, doi: 10.1080/009262300278597, indexed in Pubmed: 10782451.
14. Simpson JA, Lovecky D, Kogan J, et al. Survey of the Huntington's Disease Patient and Caregiver Community Reveals Most Impactful Symptoms and Treatment Needs. J Huntingtons Dis. 2016; 5(4): 395–403, doi: 10.3233/JHD-160228, indexed in Pubmed: 27983566.
15. Kolenc M, Kobal J, Podnar S. Male sexual function in presymptomatic gene carriers and patients with Huntington's disease. J Neurol Sci. 2015; 359(1-2): 312–317, doi: 10.1016/j.jns.2015.11.015.
16. Kolenc M, Kobal J, Podnar S. Female Sexual Dysfunction in Presymptomatic Mutation Carriers and Patients with Huntington's Disease. J Huntingtons Dis. 2017; 6(2): 105–113, doi: 10.3233/jhd-160224.
17. Aldaz T, Nigro P, Sánchez-Gómez A, et al. Non-motor symptoms in Huntington's disease: a comparative study with Parkinson's disease. J Neurol. 2019; 266(6): 1340–1350, doi: 10.1007/s00415-019-09263-7, indexed in Pubmed: 30834978.
18. Aziz NA, Anguelova GV, Marinus J, et al. Autonomic symptoms in patients and pre-manifest mutation carriers of Huntington's disease.

Eur J Neurol. 2010; 17(8): 1068–1074, doi: 10.1111/j.1468--1331.2010.02973.x, indexed in Pubmed: 20192977.

19. Jankovic J. Dopamine depleters in the treatment of hyperkinetic movement disorders. Expert Opin Pharmacother. 2016; 17(18): 2461–2470, doi: 10.1080/14656566.2016.1258063, indexed in Pubmed: 27819145.
20. Kenney C, Hunter C, Jankovic J. Long-term tolerability of tetrabenazine in the treatment of hyperkinetic movement disorders. Mov Disord. 2007; 22(2): 193–197, doi: 10.1002/mds.21222, indexed in Pubmed: 17133512.
21. Gregorian RS, Golden KA, Bahce A, et al. Antidepressant-induced sexual dysfunction. Ann Pharmacother. 2002; 36(10): 1577–1589, doi: 10.1345/aph.1A195, indexed in Pubmed: 12243609.
22. Mirek E, Filip M, Chwała W, et al. The influence of motor ability rehabilitation on temporal-spatial parameters of gait in Huntington's disease patients on the basis of a three-dimensional motion analysis system: An experimental trial. Neurol Neurochir Pol. 2018; 52(5): 575–580, doi: 10.1016/j.pjnns.2018.02.001, indexed in Pubmed: 29475565.
23. Leavitt B, Kordasiewicz H, Schobel S. Huntingtin-Lowering Therapies for Huntington Disease. JAMA. 2020, doi: 10.1001/jamaneurol.2020.0299.
24. Tabrizi SJ, Leavitt BR, Landwehrmeyer GB, et al. Phase 1–2a IONIS--HTTRx Study Site Teams. Targeting Huntingtin Expression in Patients with Huntington's Disease. N Engl J Med. 2019; 380(24): 2307–2316, doi: 10.1056/NEJMoa1900907, indexed in Pubmed: 31059641.

INVITED REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54, no. 4, pages: 294–304
DOI: 10.5603/PJNNS.a2020.0058

ISSN 0028–3843

Stereotypies in adults: a systematic review

Tanvi Shukla, Sanjay Pandey

Department of Neurology, Govind Ballabh Pant Postgraduate Institute of Medical Education and Research, New Delhi, India

ABSTRACT

Stereotypies are abnormal involuntary non-goal-directed movement patterns or vocalisations which repeat continuously in the same fashion over a period of time and on multiple occasions and are typically distractible. Stereotypies are common in both children and adults, but they are extensively reviewed only in children. There are very few studies, mainly in the form of case reports and case series, focusing on stereotypies occurring in adults as part of different neurological disorders.

In adults, stereotypies can be both physiological and pathological. Common physiological stereotypies in adults are leg shaking, face touching, playing with pens or hair, nail biting, hand tapping, foot tapping, and body rocking. Pathological stereotypies in adults are associated with a variety of neuropsychiatric conditions like neurodegenerative disorders, viral encephalitis, autoimmune encephalitis, stroke, psychiatric illness, and drug use.

In this review, we focus on the various causes of stereotypic movements in adults, and their pathophysiology, clinical manifestations, and treatment.

Key words: stereotypy, physiological, autoimmune encephalitis, drugs, psychiatry, stroke

(*Neurol Neurochir Pol 2020; 54 (4): 294–304*)

Introduction

Stereotypy was defined by Edwards et al. as "*a non–goal-directed movement pattern or vocalisation that is repeated continuously for a period of time in the same form and on multiple occasions, and which is typically distractible*" [1].

The word 'stereotyped' means something which is typical or repeats in the same fashion. So, stereotypies are an abnormal involuntary movement which repeats rhythmically in the same fashion 'in a loop' for a long duration and at the expense of other movements. Stereotypies are more common at times of anxiety, excitement, stress, focused concentration, or boredom, and in blind and deaf children they are a version of coping mechanism in both overstimulating and understimulating environments [2]. They can be differentiated from tics in that stereotypy patients do not have an urge to do the movements, but they however feel gratified and pleased while performing them [2, 3]. Stereotypies are distractible and can be easily suppressed by an external stimulus. However, these patients rarely make a conscious effort to quell movements [1, 4].

Stereotypies can be classified as simple stereotypies such as leg shaking, hair twirling, nail biting, teeth grinding, body rocking, thumb sucking or foot tapping, or as more complex stereotypies like hand waving, playing with hands or repeatedly opening and closing hands, hand posturing, head nodding, headbanging, repeatedly sitting down and getting up from a chair, finger wagging, pacing, lip smacking, chewing, mouth opening, self-biting and other self-injurious behaviours. Apart from motor stereotypies, there are also vocal or phonic stereotypies like humming, grunting, moaning, or repeating words and phrases [1, 3, 4].

Stereotypies can also be classified as primary or secondary depending on the presence or absence of an underlying neurological or psychiatric disorder [5]. They are associated with various genetically determined neurodegenerative disorders or can be acquired secondarily to infectious or non-infectious encephalitis, stroke, or drug exposure. The main pathophysiological mechanism for the occurrence of stereotypies in an individual is a dysfunction of the cortico-striatal-thalamo-cortical pathways leading to dopaminergic overactivity and cholinergic/GABAergic underactivity causing abnormal involuntary movements [2].

Stereotypies are extensively reviewed in children, especially those with an autistic spectrum disorder or a pervasive developmental disorder, but the literature on stereotypies in

Address for correspondence: Sanjay Pandey, Department of Neurology, Academic Block, Room No 503, Govind Ballabh Pant Postgraduate Institute of Medical Education and Research; New Delhi, India 110002, e-mail: sanjaysgpgi2002@yahoo.co.in

adults is sparse. In this review, our focus will be on various conditions associated with stereotypies in adults.

Methodology

We searched the PubMed database on 31 March 2020 using the search terms "Adult-onset stereotypies", "Drug induced stereotypies", "Stereotypies in psychiatry", "Stereotypies in dementia", "Stereotypies in stroke", "Stereotypies in autoimmune disorders" and "Stereotypies in viral encephalitis". After excluding animal studies, we identified 2,552 articles for screening. After removing duplicates and articles in languages other than English, 110 articles were eligible for full text reading. Thirty-one articles were further excluded as they did not describe a motor or phonic stereotypy in detail. Finally, 79 articles were included for our detailed review [Fig. 1, Tab. 1].

Stereotypies in adults

Physiological stereotypies in adults

Physiological stereotypies are common in children, but rarely seen in adults. However, various studies have demonstrated that paediatric stereotypies may persist into adulthood [6-8]. In a study by Harris et al. on 100 non-autistic children presenting with motor stereotypies, it was observed that only six children had a complete resolution of their stereotypies. The remaining 94 children had persistent stereotypies even in adulthood. Children with arm/ hand stereotypies and whose stereotypies initially persisted for more than a year had a greater chance of developing persistent stereotypies throughout adulthood than children with head-nodding stereotypies [6]. In children with persistent stereotypies, as the age advanced the stereotypies remained the same, improved, or became worse. In another study on 49 children (aged 9–20 years) with primary complex motor stereotypies, Oakley et al. reported that stereotypies were persistent in 98% of individuals in a long term follow up; 18% reported the appearance of new stereotypic movements, and 45% reported a change in their original stereotypic movements [7].

'Leg stereotypy disorder' is another movement disorder reported in adults and was first described by Jankovic in 2016 [9]. Stereotypic movements in this disorder are characterised by repetitive 1–4 Hz flexion-extension, abduction-adduction movements of the hip while people are seated with their feet resting on the floor. Stereotypic movements can also occur at knee or ankle joints while sitting cross-legged or sometimes

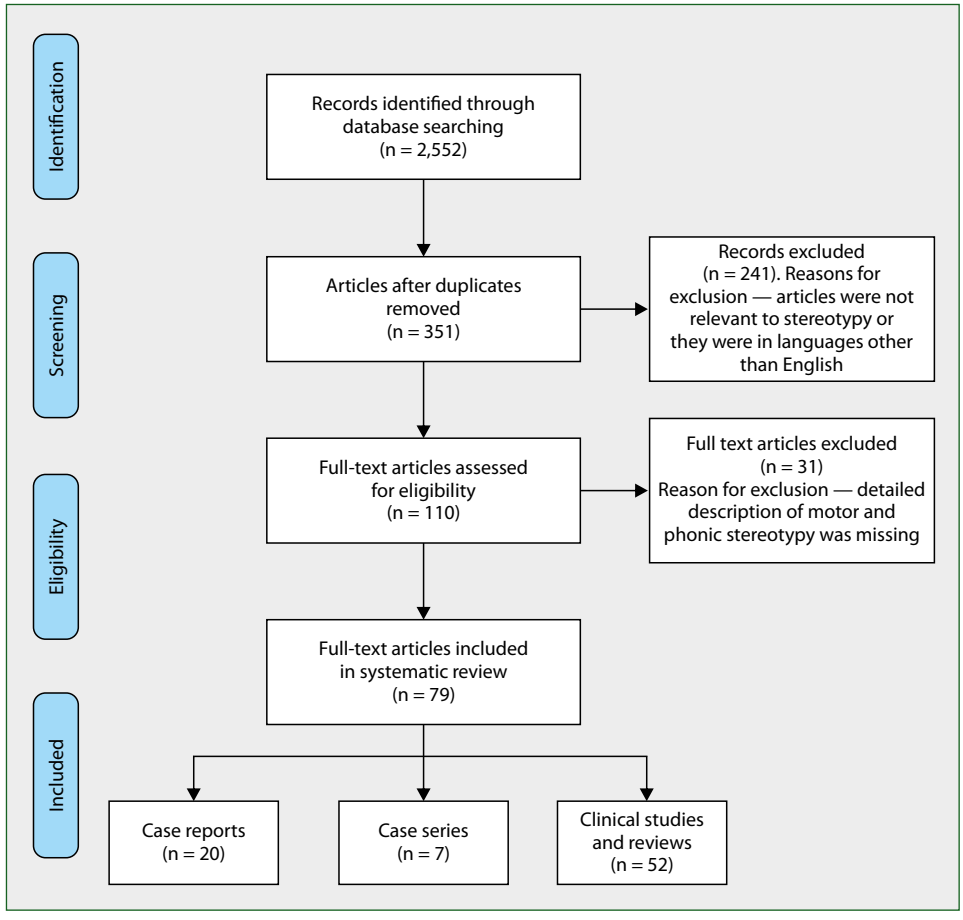


Figure 1. Search strategy for the systematic review

Table 1. PubMed search (on 31 March 2020) results, using different search terms for 'Stereotypies in adults'

Search term	Number of hits	Relevant articles after removing duplication	Articles finally selected
Adult-onset stereotypies	132	33	13
Drug induced stereotypies	1,408	197	21
Stereotypies in psychiatry	773	48	11
Stereotypies in dementia	167	36	13
Stereotypies in stroke	48	20	12
Stereotypies in autoimmune disorders	21	14	6
Stereotypies in viral encephalitis	3	3	3
Total	2,552	351	79

people may just tap their feet on the ground while sitting. Also, there can be associated 'fidgeting' movements of hands and/or other body parts. These movements usually stop while standing or walking, but some patients may have a swaying movement on standing. Patients also report anxiety with the effort to stop the movements. Leg stereotypies are frequently familial, suggestive of a genetic origin. They may or may not be associated with anxiety or Attention Deficit Disorder [9]. A screening questionnaire and rating scale have been proposed for leg stereotypy disorder [9]. Although no definite treatment has been suggested, dopaminergic and GABAergic drugs have been used in some patients, with good improvement [9].

Physiological stereotypies have also been studied in college students [10]. In this study, the most common stereotypies were touching the face (75%), playing with pens (68.2%), and playing with hair (67%). The least common stereotypy was sticking out the tongue (9.9%) [10]. Another stereotypic movement disorder common in adults is a cheek-biting disorder characterised by compulsive biting of the cheeks, tongue, and lips leading to mucosal ulcerations [11]. It is more prevalent in those aged 35 to 44, and is usually associated with increased anxiety and nervousness [11].

Stereotypic headbanging before sleep is a rhythmic movement disorder usually seen in children and rarely reported in adults. However, Chisholm and Morehouse reported two cases of headbanging in adults causing disturbed sleep and daytime somnolence. Both these patients had no other psychiatric comorbidity and they had an excellent response with clonazepam [12]. Another case with stereotypic headbanging in a 19-year-old boy was reported by Alves et al. This patient did not respond to benzodiazepines, but improved with imipramine (a tricyclic antidepressant) [13].

Drug induced stereotypies

Drugs are known to cause tics and stereotypies by altering dopaminergic activity in basal ganglia. Common groups of drugs associated with stereotypies are neuroleptics, amphetamine, cocaine, methylphenidate, levodopa, dopa agonists, apomorphine, morphine, bupropion, disulfiram, and anticholinergics like benztropine. Abnormal movements associated with the use of neuroleptics can be grouped under acute reactions, for example acute dystonia, and chronic reactions such as tardive syndromes [14]. Although tardive dyskinesia (TD) or tardive stereotypies are more commonly associated with first-generation antipsychotics, one series has demonstrated that around 3.4% of patients developed TD with aripiprazole, which is a third-generation antipsychotic [15].

Stereotypic movements in 'classic tardive dyskinesia' typically affect the orolingual region causing repetitive, rhythmic, stereotyped movements like lip smacking, puckering, chewing, tongue protrusion, and tongue movements inside the mouth. Rarely, stereotypic movements may also involve limbs, trunk, and respiratory muscles. 'Tardive stereotypy' is a term exclusively used for these patients with the involvement of limb and body parts other than the orolingual region. They usually manifest as repetitive leg movements, flexion-extension of toes, feet tapping, and head, pelvis, or body rocking. Sometimes they can also produce respiratory disturbances because of the involvement of respiratory muscles. An unusual tardive stereotypy in the form of stereotypic hand clasping has also been described [16]. Many pathophysiological mechanisms have been proposed regarding the genesis of TD, but the most plausible theory suggests that chronic use of a dopamine D2 receptor blocker causes hypersensitisation of D2 receptors, resulting in the disinhibition of globus pallidus and substantia nigra, leading to the production of hyperkinetic movement disorders including tardive stereotypies [15, 17].

Multiple treatment strategies are used for the treatment of tardive stereotypy [14]. The first step is to taper off the offending agent and discontinue drugs that can exacerbate tardive stereotypy like anticholinergics. If antipsychotics are required, then the patient should be switched to atypical antipsychotics with lower D2 receptor blocking action, like clozapine and quetiapine. The first-line agents for the treatment of tardive dyskinesia or tardive stereotypy are vesicular monoamine transporter 2 (VMAT 2) inhibitors including tetrabenazine, deutetrabanazine and valbenazine. They deplete presynaptic dopamine by decreasing the storage and release of dopamine and other monoamines from presynaptic neurons by inhibiting VMAT 2 on presynaptic vesicles. Tetrabenazine has been used

Table 2. Clinical characteristics of stereotypies in adults reported in literature

Aetiology of stereotypies		Onset and course of stereotypies	Treatment given	Outcome
Physiological stereotypies in adults	Paediatric stereotypies persisting in adults [6–8]	Delayed onset stereotypies started by age 3 and persisting in around 95.3% in adulthood. The type and severity of stereotypies changed in adulthood as compared to childhood	Behavioural therapy, pharmacotherapy in the form of clonidine, risperidone, oxcarbazepine, fluoxetine, topiramate, pimozide, levetiracetam, sodium valproate, carbamazapine, clonazepam, phenytoin, and acetazolamide	No improvement in stereotypies
	Leg stereotypy disorder [9]	Delayed onset persistent non progressive stereotypies mostly of genetic origin	Dopaminergic and GABAergic drugs	Improvement in stereotypic movements
	Stereotypic behaviours in college students [10]	Delayed onset, persistent non progressive, non- disabling stereotypies	Clomipramine	Improvement
	Cheek biting [11]	Delayed onset, non-progressive stereotypies, causing mouth ulcerations, associated with anxiety	Fluvoxamine	Significant improvement
	Headbanging during sleep [12, 13]	Delayed onset stereotypies since birth, persisting into adulthood leading to sleep disruption	Benzodiazepines, tricyclic antidepressants (imipramine)	Responded excellently
Drug induced stereotypies	Tardive stereotypies [14–20]	Delayed onset stereotypies started after a few months of taking DRBAs and lasts for at least few weeks after stopping DRBAs	Tetrabenazine, deutetrabenazine valbenazine	Good response to tetrabenazine
	Neuroleptic malignant syndrome [21]	Acute onset stereotypies started with other manifestations of NMS after one month of starting risperidone and resolved within 15 days as patient improved with treatment of NMS	Conservative treatment for NMS and bromocriptine	Stereotypies disappeared as patient improved with treatment
	Punding induced by cocaine and amphetamine abuse [22–25]	Delayed onset stereotypies started after variable time interval from starting drug abuse and were persistent	SSRIs	No improvement
	Levodopa induced punding and dyskinesias [26–29]	Delayed onset stereotypies started 6–22 years after using levodopa for PD	Decrease in dose of levodopa and dopa agonist and addition of amantadine and atypical antipsychotics e.g. clozapine	Improvement
Stereotypies in psychiatric illness	Functional stereotypies [35]	Sudden onset stereotypies with variable clinical course and phenomenology associated with distractibility		
	Repetitive behaviour in schizophrenia [36]	Delayed onset and persistent, started after 16.7 ± 6.7 years of disease	Management of complications as a result of repetitive behaviour such as polydipsia or bulimia	
	Psychosis [38]	Delayed onset and persistent. Started 1–2 years after onset of psychosis		
	Bipolar disorder (in the form of punding) [43]	Delayed onset and persistent. Started 36 years after disease onset	Quitiapine, clotiapine, alprazolam, sodium valproate	No improvement
	Trichotillomania, pathological skin picking, compulsive hoarding [39–42]	Subacute to delayed onset associated with other symptoms of OCD. Improved with SSRIs	Clomipramine	Improvement
	PNES [44, 45]	Acute onset and present only during episodes of PNES		
Stereotypies in dementia	FTD (most common) [46, 47, 49, 51–58]	Delayed onset, progressive and started 6–24 months after disease onset	SSRIs like sertraline and fluvoxamine, tetrabenazine	Improvement in stereotypies and repetitive behaviour in patients with dementia

→

Table 2 cont. Clinical characteristics of stereotypies in adults reported in literature

Aetiology of stereotypies		Onset and course of stereotypies	Treatment given	Outcome
Stereotypies in stroke [63–70]		Acute onset started a variable period (a few days up to one year) after stroke. Usually resolved spontaneously within a few months	Benzodiazepine, sertraline, clonidine, baclofen	Good response to clonazepam. One case of punding responded to sertraline
Stereotypies in autoimmune disorders	Anti-NMDA receptor encephalitis [71–73, 74]	Acute onset associated with other clinical manifestations. Responded to immunosuppressive therapy	Immunomodulatory therapy	Good response
Stereotypies in viral encephalitis	Herpes simplex encephalitis [77]	Acute onset started on second day of illness and persisted for one month	Carbamezapine, haloperidol	No improvement
	Encephalitis lethargica [78, 79]	Subacute onset and improved with dopaminergic therapy within 1–2 months	Levodopa, dopa agonist	Improvement

NMS — neuroleptic malignant syndrome; PNES — psychogenic non epileptic seizures; FTD — frontotemporal dementia; PD — Parkinson's Disease; OCD — Obsessive Compulsive Disorder; SSRI — selective serotonin reuptake inhibitor; NMDA — N-methyl-D-aspartate; GABA — gamma aminobutyric acid

for years, but deutetrabenazine and valbenazine have been recently approved by the US FDA. Compared to tetrabenazine, deutetrabenazine and valbenazine have longer plasma half-life, require less frequent dosing, and produce fewer side effects, making them first line agents [18–20]. Other drugs that have been used in the treatment of TD with inconsistent benefits are clonazepam, baclofen, amantadine, and gingko biloba extract. However, none of these drugs have been approved by the FDA for the treatment of tardive dyskinesia or tardive stereotypy [18, 19].

Apart from tardive dyskinesia or tardive stereotypy, neuroleptics can also cause neuroleptic malignant syndrome (NMS) which is an idiosyncratic reaction characterised by a tetrad of fever, rigidity, altered mental status, and autonomic dysfunction. NMS can feature various hypokinetic and hyperkinetic movements such as rigidity, tremors, dystonia, and chorea, although stereotypy has been reported in only one case [21].

Another example of drug induced stereotypic movements is 'punding', a Swedish word meaning 'blockhead'. This was first described by Rylander in amphetamine and cocaine addicts [22]. Punding is a stereotyped behaviour characterised by an intense fascination with a complex, excessive, non-goal oriented, repetitive activity such as manipulation of technical equipment, handling, examining or sorting common objects, grooming, hoarding or engaging in extended monologues devoid of content. Men tend to repetitively tinker with equipment such as radios, clocks, watches, and engines, the parts of which may be analysed, arranged, sorted, and catalogued but are rarely put back together. Women, in contrast, incessantly sort through their handbags, tidy continuously, brush their hair, or polish their nails [23, 24]. This is the most severe form of repetitive reward-seeking behaviour syndrome [25].

Punders are aware of their abnormal repetitive behaviour, but they find it soothing and calming and become agitated if distracted. Although punding was first described in people using central nervous system stimulants like amphetamine and cocaine, now it is frequently seen in patients with Parkinson's Disease (PD) treated with dopamine replacement therapy (levodopa, apomorphine, and dopa agonists) [24–28]. Levodopa-induced punding and stereotypies in PD patients can be treated by reducing the dose of levodopa and dopa agonists, and adding amantadine or clozapine which are anti-dyskinetic agents [29]. For patients with severe disabling dyskinesias, DBS surgery of the subthalamic nucleus or GPi can be carried out [29].

Other drugs causing punding and stereotypic movements are morphine, disulfiram, bupropion, methylphenidate, and anticholinergics like benztropine [30–34].

Stereotypies in psychiatric disorders

Stereotypies have been reported in many patients with psychiatric illnesses. Also, patients of functional movement disorder (FMD) can have stereotypic movements referred to as functional stereotypy (FS). In the study by Jankovic and Baizabal-Carvallo on 184 patients with FMD, it was observed that 19 (10.3%) patients had FS [35]. The clinical characteristics of movements in these patients were compared to those of 65 patients of tardive dyskinesia. Functional stereotypies were more common in young females and involved the orolingual regions, the limbs, trunk, and respiratory muscles. Compared to TD, patients with FS had a lower frequency of exposure to neuroleptics, had a sudden onset of symptoms, distractibility on examination, and periods of unexplained improvement. Also, patients with functional orolingual stereotypies had pure lingual movements without mouth involvement, abnormal speech, chewing movements or tongue biting [35].

Repetitive behaviours have been described in schizophrenics apart from other symptoms of the disease [36, 37]. A study was done in 32 chronically institutionalised schizophrenia patients [36]. Fifteen (47%) displayed at least one severe, or two moderate, repetitive behaviours. The total score of repetitive behaviours was significantly correlated with positive symptoms

rather than negative symptoms of schizophrenia. Also, it was observed that repetitive behaviours were more common the longer the hospital stay, suggesting the influence of environmental factors (chronic hospitalisation) on the occurrence of repetitive behaviours in schizophrenics.

Compton et al. published a study on abnormal movements in patients presenting with a first episode of psychosis with minimal antipsychotic exposure. They measured stereotypies, dyskinesias, and catatonia-like signs. The stereotypies scores were significantly correlated with age at onset of psychosis and with positive symptom severity score [38].

Other psychiatric disorders with repetitive behaviours are compulsive hoarding, trichotillomania or hair disorder, and pathological skin picking [39–43]. These patients respond to selective serotonin reuptake inhibitors (SSRIs) like sertraline, fluvoxamine and tricyclic antidepressants like clomipramine [42].

Stereotypies have also been reported in patients of psychogenic non-epileptic seizures (PNES). Seneviratne et al. studied different semiologies of ictal events in patients of PNES [44]. The rhythmic motor PNES had rhythmic stereotypic trembling movements of extremities and trunk in a symmetrical and synchronised manner, with more common involvement of upper limbs than of lower limbs. Also, 10% of patients had vocalisations and hyperventilation in addition to rhythmic movements. In another study by Herskovitz on 29 patients with PNES, it was observed that stereotypic behaviour and motor manifestations of PNES in an individual patient were consistent in all seizures, although the duration of episodes of PNES was inconsistent [45].

Stereotypies in dementia

Stereotypic behaviours and stereotypies (motor and phonic) have been described in all types of degenerative dementias with variable frequency [46–49]. In patients with behavioural variant of frontotemporal dementia (bvFTD), the presence of stereotypies indeed forms a supporting criterion for the diagnosis [50]. In a large multicentre observational study, Prioni et al. reported the type, frequency, and severity of stereotypies in different types of degenerative dementias, i.e. bvFTD, Alzheimer's Disease (AD), Parkinson's Disease Dementia (PDD) and progressive supranuclear palsy (PSP). It was observed that stereotypies were present with variable frequency in all types of degenerative dementias, but they were most frequent in bvFTD (86%) and PDD (88.6%), and least frequent in AD (57.8%) [51]. They also assessed stereotypies in these patients using a five domain 'stereotypy rating inventory'. It was observed that multidomain stereotypies were more frequent in bvFTD (80%) patients than in others. Also, the stereotypies were more severe in bvFTD patients. All patients had a high frequency of movement stereotypies, while eating, cooking and speaking stereotypies were most frequent in bvFTD patients. The presence of stereotypies in these patients was directly related to neuropsychiatric dysfunction and cognitive impairment, and inversely related to motor impairment [51].

In another study, Prioni et al. compared stereotypies in 53 patients with bvFTD and 40 patients with the Richardson variant of PSP (PSP-RS) [52]. In total, stereotypies were present in at least one domain in 81% of bvFTD and in 57.5% of PSP-RS patients, and multi-domain in 79% of bvFTD and 40% of PSP-RS patients, indicating a higher frequency of stereotypies in bvFTD compared to PSP-RS. Also, complex stereotypies and stereotypies in the cooking/eating domain were more common in patients with bvFTD. But a much greater proportion of PSP-RS patients (69.5%) than of bvFTD patients (20%) had awareness of their stereotypies. It was initially thought that stereotypies in PSP patients were levodopa-induced. However, these were present in both 'off' and 'on' states, suggesting that they were not in fact drug-induced but rather occurred as a part of the disease spectrum.

Another study demonstrated that simple motor stereotypies were common in all types of degenerative dementias, although complex motor stereotypies and repetitive behaviours were more commonly associated with bvFTD [53]. Mateen and Joseph studied the clinical spectrum of stereotypies in 32 patients of frontotemporal lobar degeneration (FTLD). 19 (60%) patients had stereotypies, with the majority (68%) being female [54]. Only motor stereotypies were present in 13 patients, only vocal stereotypies were present in three patients, and both vocal and motor stereotypies were present in three patients. In patients with only motor stereotypies, nine had appendicular and seven had craniocervical stereotypies. In another study, Nyatsanza et al. reported a higher prevalence of complex stereotypies and stereotypic behaviours in patients with bvFTD than in patients with AD [55].

There have been various radiological studies designed to understand the anatomical correlate of stereotypies in degenerative dementia. In one study, voxel-based morphometric magnetic resonance imaging (MRI) was performed to understand the anatomical correlate of stereotypies in FTD. It was observed that patients with stereotypy had greater striatal to cortical loss compared to patients with no stereotypies, suggesting that striatal degeneration is a pathophysiological correlate of stereotypies [56]. A similar functional imaging study using single-photon emission computed tomography (SPECT) determined that patients with simple stereotypies have greater involvement of the right frontal lobe and patients with complex stereotypies have greater involvement of the left temporal lobe [57]. Also, it has been suggested that complex stereotypies arise from dysfunction of the orbitofrontal and temporal cortex and its subcortical connections, while simple stereotypies arise from dysfunction of the dorsolateral frontal cortex and its subcortical connections [53].

Stereotypies and stereotypic behaviours in patients with FTD usually do not respond well to antidepressants and other medications, although tetrabenazine showed some benefit in a case series of seven patients with probable FTD [58].

Stereotypies in stroke

Stroke (both ischaemic and haemorrhagic) is known to cause a variety of abnormal involuntary movement disorders, but stereotypies have rarely been reported [59–60]. In the Lausanne Stroke Registry, out of 2,500 stroke patients, only 29 (1%) developed post-stroke hyperkinetic abnormal movements, and only two (2/29; 7%) patients developed stereotypies [61]. In another study of 1,500 stroke patients by Alarcon et al., 56 patients developed post stroke movement disorders, but none of them had stereotypies [62].

Stereotypies result from an infarct in the region of parietal, lenticulo-striatal, thalamic, midbrain or left middle cerebral artery territory causing dysfunction of basal ganglia, thalamus, brainstem and cerebellum [60]. These are usually unilateral and contralateral to the side of the lesion [63]. However, bilateral stereotypic movements have also been described [64]. In cases of cerebellar infarcts, stereotypies are unilateral and ipsilateral to the side of the lesion [65]. It is observed that right-sided lesions are more prone to produce stereotypies than left-sided lesions. Post-stroke stereotypies can be simple, for example continuous tapping of the contralateral hand secondary to unilateral thalamic infarct, or complex, like repeated pirouetting while walking or repeated ritualistic movements like hand clapping, flailing arms, whispering, protruding the tongue, sniffing before performing any voluntary movement secondary to right putaminal infarct [64]. Ipsilateral instinctive grasp and stereotyped involuntary movements like groping or picking is described with right frontal lobe infarction [66]. Complex stereotypies like punding and palilalia (repetition of one's own syllables, words, or phrases two or more times in a row) are also described secondary to pontine, thalamic and midbrain infarcts [67, 68].

A patient with locked-in syndrome with infarct in ventral pons has been described who developed synchronous involuntary movements of the soft palate with movements of tongue one-year post-stroke and involuntary chewing, pouting movements and bruxism several months later [69]. Stereotypies usually develop a few days to a few weeks after an acute infarct, and decrease over a few months up to a year. The exact pathophysiology for developing stereotypic movements in stroke patients is still unclear. They are probably caused by the disruption of cortico-striatal-thalamo-cortical and cerebello-thalamic pathways which are required to inhibit involuntary movements while performing voluntary actions. Disruption of these pathways can give rise to abnormal involuntary movements including stereotypies. Some stroke patients may have cognitive dysfunction and abnormal behaviour, and stereotypies are usually an accompanying feature of it [64, 65]. Various drugs like benzodiazepines, anticholinergics, amantadine, and dopamine antagonists have been tried in post-stroke stereotypies, but none have provided any significant benefit [64]. Only a few cases of simple stereotypy benefited from clonazepam, and some cases responded to sertraline [67, 70]. However, post-stroke stereotypic movements usually decrease and sometimes resolve spontaneously over time [68].

Stereotypies in autoimmune encephalitis

Autoimmune encephalitis can present with a wide spectrum of movement disorders including stereotypy [71–73, 74]. But most of the studies reporting stereotypy in autoimmune encephalitis patients are from paediatric populations. Overall, stereotypy is more commonly seen in anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis patients. Mohammad et al. studied abnormal movements in children with a diagnosis of anti-NMDAR encephalitis, autoimmune basal ganglia encephalitis, and Sydenham's Chorea [71]. Stereotypies and perseverations were present exclusively in patients of anti-NMDAR encephalitis, while tremor and akinesia were more common in basal ganglia encephalitis. Granata et al. studied 18 patients of anti-NMDAR encephalitis of paediatric age [72]. All had stereotypic movements along with other movements. In eight patients, abnormal stereotypic movements persisted during sleep. Three patients presented with movement disorder as the initial manifestation. Stereotypies were the most characteristic movements and were present in all patients. Both simple and complex stereotypies were noted. Simple stereotypies included cycling leg movements, thrashing of limbs, repetitive flexion-extension of the trunk, 'yes-yes', and 'no-no' head movements, while complex stereotypies included raising and lowering of the arms, movements which aimlessly produced learned movements such as playing the piano or dance steps. Another type of stereotypic movement observed was perseverations. These are repetitive and persistent motor tasks or vocalisations triggered by a voluntary activity or stimulus. Simple stereotypies were more common in < 12 years of age group, while complex stereotypies were more common in teenagers [72]. Dash et al. studied the spectrum of movement disorder in adolescents and adults with non-neoplastic autoimmune encephalitis [73]. Out of a total of 362 patients screened, 41 were positive for autoantibodies and 21 (51.2%) of the 41 had movement disorders. Stereotypies were present in only three patients (14.2%) and all were positive for anti-NMDAR antibodies. Dash et al. also noted that only 12.5% of anti-NMDAR positive patients had stereotypies and all of them were < 18 years of age, suggesting that stereotypies are more common in children with anti-NMDAR encephalitis than in adults. Baizabal-Carvallo et al. have described abnormal involuntary movements in nine children with anti-NMDA receptor encephalitis aged 3 to 14 [74]. Although stereotypies are described more commonly in anti-NMDAR encephalitis, there is one case report with adult-onset motor stereotypies with anti-basal ganglia antibody positive encephalitis [75].

The exact pathophysiology of stereotypical movements in anti-NMDAR encephalitis is not known, but as suggested there is possible antibody mediated internalisation of NMDA receptors in striatum and brainstem and antibody mediated dysfunction of basal ganglia-cortical connections leading to loss of fronto-striatal inhibition causing abnormal stereotypic movements and perseverations [71, 72]. These movements are more common in paediatric patients than in adults because

of age-related changes in dopamine receptor sensitivity and regional distribution, making children more sensitive to develop stereotypies than adults [72]. Similar to the other clinical features of autoimmune encephalitis, stereotypies are also responsive to immunomodulatory therapy in the form of methylprednisolone, intravenous immunoglobulin, rituximab and cyclophosphamide [76].

Stereotypies in viral encephalitis

Viral encephalitis is known to cause various hypokinetic and hyperkinetic abnormal movements as a result of frequent involvement of the thalamus, basal ganglia, substantia nigra, and brainstem. However stereotypic movements have been reported in only one case of post viral encephalitis [77]. A 34-year-old woman diagnosed with herpes simplex encephalitis with bilateral temporal lobe involvement developed motor stereotypy and hypersexual behaviour after regaining consciousness. She had repetitive, involuntary movements of the right arm, with scratching causing abrasions on the right side of her face. At one-month follow up she was still having these stereotypic movements which were interfering with daily routine activities such as applying makeup, washing and dressing, and these movements did not respond to carbamazepine and haloperidol. This case was proposed to be a partial form of Kluver-Bucy syndrome with involvement of bilateral temporal lobes and stereotypic movements occurring as a result of disruption of dopaminergic transmission in basal ganglia, medial temporal lobe, amygdala and hippocampus.

Another infectious encephalitis associated with stereotypical movements is 'encephalitis lethargica', but its causative agent has not been determined to date. Encephalitis lethargica is associated with complex stereotypical movements along with other clinical features like dystonia, parkinsonism, irritability, psychiatric behaviour, agitation, oculogyric crisis, and autonomic instability. Stereotypies occur more often in the upper limbs in the form of gripping both hands, placing hands on the waist, combing hands through hair, and fiddling with a nasogastric tube [78, 79]. All abnormal movements i.e. parkinsonism, dystonia, and stereotypy respond to dopaminergic drugs (levodopa and D2 agonists) while they do not show any improvement with other classes of drugs. This suggests that these abnormal movements result from limited disruption of dopaminergic neurons in the substantia nigra pars compacta acting via D2 receptors causing a dopaminergic deficiency in the striatum [79].

Differential diagnosis of stereotypies in adults

In adults, stereotypies need to be differentiated from other repetitive movement disorders such as tics, mannerisms, compulsions and habits. Among these, stereotypies are most frequently confused with tics [3]. Tics are sudden, brief, rapid, recurrent, nonrhythmic motor movements or vocalisations, while stereotypies are rhythmic, repetitive movements occurring in a loop [3]. Often, multiple types of tics when occurring in a burst can be confused with stereotypies. But in a tic disorder, there is a non-random occurrence of the same type of tic movement after some time, which is not repetitive as in stereotypies. Also, tics are associated with premonitory urge and are highly variable, with changing patterns and severity as they evolve [3].

Although tics and Tourette's Syndrome are childhood onset disorders, and are more common in children, they are not uncommon in adults. Jankovic has studied the characteristics of Tourette's Syndrome in adults [80]. He compared 43 adult Tourette's patients to 100 paediatric patients. Among the 43 adults, 35 (81.4%) had their tic onset before the age of 18, with either re-emergence or exacerbation of childhood onset TS in adulthood. Only eight (18.6%) patients had onset after the age of 18, with two (4.4%) patients reporting their first tic after the age of 50. Adult patients with TS had more facial and truncal tics, fewer phonic tics, and more frequently suffered from substance abuse and mood disorders compared to children [80]. Different types of tics can be seen in TS patients, including clonic tics, tonic tics and dystonic tics. Dystonic tics are slower and last longer compared to clonic tics, causing a sustained, but not fixed, posture [81]. When dystonic tics occur in succession, they can be confused with stereotypies because of apparent rhythmicity. Self-harming behaviour is also common in TS patients because of either malignant tics or psychiatric comorbidities [82]. Such behaviours should be differentiated from the self-harming behaviours of stereotypic movement disorders. Patients with TS can be treated by behavioural therapy or pharmacotherapy. Antidopaminergic drugs like dopamine receptor blockers and dopamine depletors are used. Recently, aripiprazole has been approved by the FDA for the treatment of TS. It has a similar efficacy and a favourable side effect profile compared to other neuroleptics [83].

Conclusion

Although stereotypic movements are more commonly described in children, they are frequently seen in adults, but often go unidentified. Both physiological and pathological stereotypies are common in adults. Many neuropsychiatric conditions can result in adult-onset stereotypic movements secondary to dysfunction of cortico-striatal-thalamo-cortical pathways and loss of frontal-striatal inhibition. In fact, stereotypic movements form one of the supporting criteria for the diagnosis of bvFTD. Also, stereotypic movements in adults are frequently accompanied by cognitive decline, behavioural disturbance, and other hypokinetic and hyperkinetic movement disorders. Children with stereotypies can be treated by behavioural therapy alone, but adults usually require pharmacotherapy and treatment of the underlying neuropsychiatric conditions.

So, stereotypies in adults are not as uncommon as has been thought. It is important to recognise these abnormal movements because they give a clue to the underlying diagnosis.

Roles of authors: *Dr. Shukla contributed to data collection and manuscript preparation. Dr. Pandey contributed to manuscript preparation, review and critique.*
Funding / Conflict of interest: *None.*

References:

1. Edwards MJ, Lang AE, Bhatia KP. Stereotypies: a critical appraisal and suggestion of a clinically useful definition. Mov Disord. 2012; 27(2): 179–185, doi: 10.1002/mds.23994, indexed in Pubmed: 22161914.
2. Katherine M. Stereotypic Movement Disorders. Semin Pediatr Neurol. 2018; 25: 19–24, doi: 10.1016/j.spen.2017.12.004, indexed in Pubmed: 29735112.
3. Singer HS. Motor stereotypies. Semin Pediatr Neurol. 2009; 16(2): 77–81, doi: 10.1016/j.spen.2009.03.008, indexed in Pubmed: 19501335.
4. Maltête D. Adult-onset stereotypical motor behaviors. Rev Neurol (Paris). 2016; 172(8-9): 477–482, doi: 10.1016/j.neurol.2016.07.002, indexed in Pubmed: 27498241.
5. Muthugovindan D, Singer H. Motor stereotypy disorders. Curr Opin Neurol. 2009; 22(2): 131–136, doi: 10.1097/WCO.0b013e328326f6c8, indexed in Pubmed: 19532036.
6. Harris KM, Mahone EM, Singer HS. Nonautistic motor stereotypies: clinical features and longitudinal follow-up. Pediatr Neurol. 2008; 38(4): 267–272, doi: 10.1016/j.pediatrneurol.2007.12.008, indexed in Pubmed: 18358406.
7. Oakley C, Mahone EM, Morris-Berry C, et al. Primary complex motor stereotypies in older children and adolescents: clinical features and longitudinal follow-up. Pediatr Neurol. 2015; 52(4): 398–403. e1, doi: 10.1016/j.pediatrneurol.2014.11.002, indexed in Pubmed: 25661287.
8. Freeman RD, Soltanifar A, Baer S. Stereotypic movement disorder: easily missed. Dev Med Child Neurol. 2010; 52(8): 733–738, doi: 10.1111/j.1469-8749.2010.03627.x, indexed in Pubmed: 20187883.
9. Jankovic J. Leg stereotypy disorder. J Neurol Neurosurg Psychiatry. 2016 Feb 1. ; 87(2): 220–1.
10. Niehaus DJ, Emsley RA, Brink P, et al. Stereotypies: prevalence and association with compulsive and impulsive symptoms in college students. Psychopathology. 2000; 33(1): 31–35, doi: 10.1159/000029116, indexed in Pubmed: 10601825.
11. Sarkhel S, Praharaj SK, Akhtar S. Cheek-biting disorder: another stereotypic movement disorder? J Anxiety Disord. 2011; 25(8): 1085–1086, doi: 10.1016/j.janxdis.2011.07.006, indexed in Pubmed: 21889295.
12. Chisholm T, Morehouse RL. Adult headbanging: sleep studies and treatment. Sleep. 1996; 19(4): 343–346, doi: 10.1093/sleep/19.4.343, indexed in Pubmed: 8776793.
13. Alves RS, Aióe F, Silva AB, et al. Jactatio capitis nocturna with persistence in adulthood. Case report. Arq Neuropsiquiatr. 1998; 56(3B): 655–657, doi: 10.1590/s0004-282x1998000400022, indexed in Pubmed: 9850765.
14. Vijayakumar D, Jankovic J. Drug-Induced Dyskinesia, Part 2: Treatment of Tardive Dyskinesia. Drugs. 2016; 76(7): 779–787, doi: 10.1007/s40265-016-0568-1, indexed in Pubmed: 27091214.
15. Peña MS, Yaltho TC, Jankovic J. Tardive dyskinesia and other movement disorders secondary to aripiprazole. Mov Disord. 2011; 26(1): 147–152, doi: 10.1002/mds.23402, indexed in Pubmed: 20818603.
16. Kaneko K, Yuasa T, Miyatake T, et al. Stereotyped hand clasping: an unusual tardive movement disorder. Mov Disord. 1993; 8(2): 230–231, doi: 10.1002/mds.870080224, indexed in Pubmed: 8474498.
17. Madruga-Garrido M, Mir P. Tics and other stereotyped movements as side effects of pharmacological treatment. Int Rev Neurobiol. 2013; 112: 481–494, doi: 10.1016/B978-0-12-411546-0.00016-0, indexed in Pubmed: 24295631.
18. Margolius A, Fernandez HH. Current treatment of tardive dyskinesia. Parkinsonism Relat Disord. 2019; 59: 155–160, doi: 10.1016/j.parkreldis.2018.12.022, indexed in Pubmed: 30591350.
19. Niemann N, Jankovic J. Treatment of Tardive Dyskinesia: A General Overview with Focus on the Vesicular Monoamine Transporter 2 Inhibitors. Drugs. 2018; 78(5): 525–541, doi: 10.1007/s40265-018-0874-x, indexed in Pubmed: 29484607.
20. Scorr LM, Factor SA. VMAT2 inhibitors for the treatment of tardive dyskinesia. J Neurol Sci. 2018; 389: 43–47, doi: 10.1016/j.jns.2018.02.006, indexed in Pubmed: 29433808.
21. Pandey S, Shukla T. Stereotypy in Neuroleptic Malignant Syndrome. Movement Disorders Clinical Practice. 2019; 6(5): 411–412, doi: 10.1002/mdc3.12770.
22. Rylander G. Psychoses and the punding and choreiform syndromes in addiction to central stimulant drugs. Psychiatr Neurol Neurochir. 1972; 75(3): 203–212, indexed in Pubmed: 4625014.
23. Rusyniak DE. Neurologic manifestations of chronic methamphetamine abuse. Psychiatr Clin North Am. 2013; 36(2): 261–275, doi: 10.1016/j.psc.2013.02.005, indexed in Pubmed: 23688691.
24. Fasano A, Petrovic I. Insights into pathophysiology of punding reveal possible treatment strategies. Mol Psychiatry. 2010; 15(6): 560–573, doi: 10.1038/mp.2009.95, indexed in Pubmed: 20489735.
25. Fasano A, Barra A, Nicosia P, et al. Cocaine addiction: from habits to stereotypical-repetitive behaviors and punding. Drug Alcohol Depend. 2008; 96(1-2): 178–182, doi: 10.1016/j.drugalcdep.2008.02.005, indexed in Pubmed: 18378407.
26. Spencer AH, Rickards H, Fasano A, et al. The prevalence and clinical characteristics of punding in Parkinson's disease. Mov Disord. 2011; 26(4): 578–586, doi: 10.1002/mds.23508, indexed in Pubmed: 21648123.
27. Silveira-Moriyama L, Evans A, Katzenschlager R, et al. Punding and dyskinesias. Movement Disorders. 2006; 21(12): 2214–2217, doi: 10.1002/mds.21118.
28. Lawrence AJ, Blackwell AD, Barker RA, et al. Predictors of punding in Parkinson's disease: results from a questionnaire survey. Mov Disord. 2007; 22(16): 2339–2345, doi: 10.1002/mds.21702, indexed in Pubmed: 17914729.
29. Vijayakumar D, Jankovic J. Drug-Induced Dyskinesia, Part 1: Treatment of Levodopa-Induced Dyskinesia. Drugs. 2016; 76(7): 759–777, doi: 10.1007/s40265-016-0566-3, indexed in Pubmed: 27091215.
30. Fan CC, Lin SKu, Huang MC. Disulfiram-induced punding. J Clin Psychopharmacol. 2008; 28(4): 473–474, doi: 10.1097/JCP.0b013e31817d8702, indexed in Pubmed: 18626287.
31. Kornetsky C. Brain-stimulation reward, morphine-induced oral stereotypy, and sensitization: implications for abuse. Neurosci Biobehav Rev. 2004; 27(8): 777–786, doi: 10.1016/j.neubiorev.2003.11.014, indexed in Pubmed: 15019427.
32. Jacobsen LK, Chappell P, Woolston JL. Bupropion and compulsive behavior. J Am Acad Child Adolesc Psychiatry. 1994; 33(1): 143–144,

doi: 10.1097/00004583-199401000-00023, indexed in Pubmed: 8138514.
33. Costall B, Naylor RJ. The involvement of dopaminergic systems with the stereotyped behaviour patterns induced by methylphenidate. J Pharm Pharmacol. 1974; 26(1): 30–33, doi: 10.1111/j.2042-7158.1974.tb12815.x, indexed in Pubmed: 4150931.
34. Kulik AV, Wilbur R. Delirium and stereotypy from anticholinergic antiparkinson drugs. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 1982; 6(1): 75–82, doi: 10.1016/s0364-7722(82)80110-0.
35. Baizabal-Carvallo JF, Jankovic J. Functional (psychogenic) stereotypies. J Neurol. 2017; 264(7): 1482–1487, doi: 10.1007/s00415-017-8551-7, indexed in Pubmed: 28653211.
36. Luchins DJ, Goldman MB, Lieb M, et al. Repetitive behaviors in chronically institutionalized schizophrenic patients. Schizophr Res. 1992; 8(2): 119–123, doi: 10.1016/0920-9964(92)90027-3, indexed in Pubmed: 1457389.
37. Daniels JE, Wirth JB, Herrera DG, et al. Head banging on an inpatient psychiatric unit: a vicious circle. Harv Rev Psychiatry. 2007; 15(2): 70–79, doi: 10.1080/10673220701307588, indexed in Pubmed: 17454176.
38. Compton MT, Fantes F, Wan CR, et al. Abnormal movements in first-episode, nonaffective psychosis: dyskinesias, stereotypies, and catatonic-like signs. Psychiatry Res. 2015; 226(1): 192–197, doi: 10.1016/j.psychres.2014.12.048, indexed in Pubmed: 25619434.
39. Stein DJ, Grant JE, Franklin ME, et al. Trichotillomania (hair pulling disorder), skin picking disorder, and stereotypic movement disorder: toward DSM-V. Depress Anxiety. 2010; 27(6): 611–626, doi: 10.1002/da.20700, indexed in Pubmed: 20533371.
40. Odlaug BL, Grant JE. Clinical characteristics and medical complications of pathologic skin picking. Gen Hosp Psychiatry. 2008; 30(1): 61–66, doi: 10.1016/j.genhosppsych.2007.07.009, indexed in Pubmed: 18164942.
41. Pertusa A, Fullana MA, Singh S, et al. Compulsive hoarding: OCD symptom, distinct clinical syndrome, or both? Am J Psychiatry. 2008; 165(10): 1289–1298, doi: 10.1176/appi.ajp.2008.07111730, indexed in Pubmed: 18483134.
42. Sani G, Gualtieri I, Paolini M, et al. Drug Treatment of Trichotillomania (Hair-Pulling Disorder), Excoriation (Skin-picking) Disorder, and Nail-biting (Onychophagia). Curr Neuropharmacol. 2019; 17(8): 775–786, doi: 10.2174/1570159X17666190320164223, indexed in Pubmed: 30892151.
43. Pettorruso M, Di Nicola M, De Risio L, et al. Punding behavior in bipolar disorder type 1: case report. J Neuropsychiatry Clin Neurosci. 2014; 26(4): E8–E9, doi: 10.1176/appi.neuropsych.13090217, indexed in Pubmed: 26037886.
44. Seneviratne U, Reutens D, D'Souza W. Stereotypy of psychogenic nonepileptic seizures: insights from video-EEG monitoring. Epilepsia. 2010; 51(7): 1159–1168, doi: 10.1111/j.1528-1167.2010.02560.x, indexed in Pubmed: 20384722.
45. Herskovitz M. Stereotypy of psychogenic nonepileptic seizures. Epilepsy Behav. 2017; 70(Pt A): 140–144, doi: 10.1016/j.yebeh.2017.02.015, indexed in Pubmed: 28427022.
46. Cipriani G, Vedovello M, Ulivi M, et al. Repetitive and stereotypic phenomena and dementia. Am J Alzheimers Dis Other Demen. 2013; 28(3): 223–227, doi: 10.1177/1533317513481094, indexed in Pubmed: 23512997.
47. Ames D, Cummings JL, Wirshing WC, et al. Repetitive and compulsive behavior in frontal lobe degenerations. J Neuropsychiatry Clin Neurosci. 1994; 6(2): 100–113, doi: 10.1176/jnp.6.2.100, indexed in Pubmed: 8044031.
48. Kobayashi R, Hayashi H, Tokairin T, et al. Suicide as a result of stereotypic behaviour in a case with semantic dementia. Psychogeriatrics. 2019; 19(1): 80–82, doi: 10.1111/psyg.12357, indexed in Pubmed: 30058742.
49. Hwang JP, Tsai SJ, Yang CH, et al. Repetitive phenomena in dementia. Int J Psychiatry Med. 2000; 30(2): 165–171, doi: 10.2190/2QDA-YAL3-2E69-PYJW, indexed in Pubmed: 11001279.
50. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011; 134(Pt 9): 2456–2477, doi: 10.1093/brain/awr179, indexed in Pubmed: 21810890.
51. Prioni S, Fetoni V, Barocco F, et al. Stereotypic behaviors in degenerative dementias. J Neurol. 2012; 259(11): 2452–2459, doi: 10.1007/s00415-012-6528-0, indexed in Pubmed: 22648476.
52. Prioni S, Redaelli V, Soliveri P, et al. Stereotypic behaviours in frontotemporal dementia and progressive supranuclear palsy. Cortex. 2018; 109: 272–278, doi: 10.1016/j.cortex.2018.09.023, indexed in Pubmed: 30399478.
53. Cagnin A, Formentin C, Pompanin S, et al. Simple motor stereotypies are not specific features of behavioural frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2014; 85(8): 945–946, doi: 10.1136/jnnp-2013-307471, indexed in Pubmed: 24534731.
54. Mateen FJ, Josephs KA. The clinical spectrum of stereotypies in frontotemporal lobar degeneration. Mov Disord. 2009; 24(8): 1237–1240, doi: 10.1002/mds.22555, indexed in Pubmed: 19412926.
55. Nyatsanza S, Shetty T, Gregory C, et al. A study of stereotypic behaviours in Alzheimer's disease and frontal and temporal variant frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2003; 74(10): 1398–1402, doi: 10.1136/jnnp.74.10.1398, indexed in Pubmed: 14570833.
56. Josephs KA, Whitwell JL, Jack CR. Anatomic correlates of stereotypies in frontotemporal lobar degeneration. Neurobiol Aging. 2008; 29(12): 1859–1863, doi: 10.1016/j.neurobiolaging.2007.04.027, indexed in Pubmed: 17574708.
57. McMurtray AM, Chen AK, Shapira JS, et al. Variations in regional SPECT hypoperfusion and clinical features in frontotemporal dementia. Neurology. 2006; 66(4): 517–522, doi: 10.1212/01.wnl.0000197983.39436.e7, indexed in Pubmed: 16505304.
58. Ondo WG. Tetrabenazine treatment for stereotypies and tics associated with dementia. J Neuropsychiatry Clin Neurosci. 2012; 24(2): 208–214, doi: 10.1176/appi.neuropsych.11030077, indexed in Pubmed: 22772669.
59. Defebvre L, Krystkowiak P. Movement disorders and stroke. Rev Neurol (Paris). 2016; 172(8-9): 483–487, doi: 10.1016/j.neurol.2016.07.006, indexed in Pubmed: 27476417.
60. Mehanna R, Jankovic J, Mehanna R, et al. Movement disorders in cerebrovascular disease. Lancet Neurol. 2013; 12(6): 597–608, doi: 10.1016/S1474-4422(13)70057-7, indexed in Pubmed: 23602779.
61. Ghika-Schmid F, Ghika J, Regli F, et al. Hyperkinetic movement disorders during and after acute stroke: the Lausanne Stroke Registry. J Neurol Sci. 1997; 146(2): 109–116, doi: 10.1016/s0022-510x(96)00290-0, indexed in Pubmed: 9077506.
62. Alarcón F, Zijlmans JCM, Dueñas G, et al. Post-stroke movement disorders: report of 56 patients. J Neurol Neurosurg Psychiatry. 2004; 75(11): 1568–1574, doi: 10.1136/jnnp.2003.011874, indexed in Pubmed: 15489389.
63. Pandey S, Sarma N. Stereotypy After Acute Thalamic Infarct. JAMA Neurol. 2015; 72(9): 1068, doi: 10.1001/jamaneurol.2015.0916, indexed in Pubmed: 26167677.

64. Maraganore DM, Lees AJ, Marsden CD. Complex stereotypies after right putaminal infarction: a case report. Mov Disord. 1991; 6(4): 358–361, doi: 10.1002/mds.870060418, indexed in Pubmed: 1758457.
65. Lee D, Lee D, Ahn TB. Stereotypy after cerebellar infarction. J Neurol Sci. 2014; 344(1-2): 227–228, doi: 10.1016/j.jns.2014.06.019, indexed in Pubmed: 24974238.
66. Inatomi Y, Nakajima M, Yonehara T, et al. Ipsilateral Tremor-Like Grasp Reaction in a Patient With Ischemic Stroke. Cogn Behav Neurol. 2017; 30(1): 37–41, doi: 10.1097/WNN.0000000000000113, indexed in Pubmed: 28323685.
67. Nguyen FN, Pauly RR, Okun MS, et al. Punding as a complication of brain stem stroke?: report of a case. Stroke. 2007; 38(4): 1390–1392, doi: 10.1161/01.STR.0000260088.07611.6e, indexed in Pubmed: 17332454.
68. Yasuda Y, Akiguchi I, Ino M, et al. Paramedian thalamic and midbrain infarcts associated with palilalia. J Neurol Neurosurg Psychiatry. 1990; 53(9): 797–799, doi: 10.1136/jnnp.53.9.797, indexed in Pubmed: 2246662.
69. Duffey P, Jenkins N, King D. Palatal tremor and orofacial stereotypies within the locked-in syndrome. Mov Disord. 2007; 22(4): 593–595, doi: 10.1002/mds.21327, indexed in Pubmed: 17230478.
70. McGrath CM, Kennedy RE, Hoye W, et al. Stereotypic movement disorder after acquired brain injury. Brain Inj. 2002; 16(5): 447–451, doi: 10.1080/02699050110113660, indexed in Pubmed: 12097226.
71. Mohammad SS, Fung VSC, Grattan-Smith P, et al. Movement disorders in children with anti-NMDAR encephalitis and other autoimmune encephalopathies. Mov Disord. 2014; 29(12): 1539–1542, doi: 10.1002/mds.25999, indexed in Pubmed: 25154478.
72. Granata T, Matricardi S, Ragona F, et al. Pediatric NMDAR encephalitis: A single center observation study with a closer look at movement disorders. Eur J Paediatr Neurol. 2018; 22(2): 301–307, doi: 10.1016/j.ejpn.2018.01.012, indexed in Pubmed: 29396169.
73. Dash D, Ihtisham K, Tripathi M, et al. Proportion and spectrum of movement disorders in adolescent and adult patients of autoimmune encephalitis of non-neoplastic aetiology. J Clin Neurosci. 2019; 59: 185–189, doi: 10.1016/j.jocn.2018.10.076, indexed in Pubmed: 30455136.
74. Baizabal-Carvallo JF, Stocco A, Muscal E, et al. The spectrum of movement disorders in children with anti-NMDA receptor encephalitis. Mov Disord. 2013; 28(4): 543–547, doi: 10.1002/mds.25354, indexed in Pubmed: 23400857.
75. Edwards MJ, Dale RC, Church AJ, et al. Adult-onset tic disorder, motor stereotypies, and behavioural disturbance associated with antibasal ganglia antibodies. Mov Disord. 2004; 19(10): 1190–1196, doi: 10.1002/mds.20126, indexed in Pubmed: 15390017.
76. Baizabal-Carvallo JF, Jankovic J. Autoimmune and paraneoplastic movement disorders: An update. J Neurol Sci. 2018; 385: 175–184, doi: 10.1016/j.jns.2017.12.035, indexed in Pubmed: 29406902.
77. Twardowschy CA, De Paola L, Teive HAG, et al. Stereotypies after herpetic encephalitis with bitemporal lesions. Mov Disord. 2010; 25(16): 2888–2889, doi: 10.1002/mds.22803, indexed in Pubmed: 20882521.
78. Dale RC, Webster R, Gill D. Contemporary encephalitis lethargica presenting with agitated catatonia, stereotypy, and dystonia-parkinsonism. Mov Disord. 2007; 22(15): 2281–2284, doi: 10.1002/mds.21664, indexed in Pubmed: 17914719.
79. Picard F, de Sa, Salmon E, et al. Postencephalitic stereotyped involuntary movements responsive to L-Dopa. Movement disorders: official journal of the Movement Disorder Society. 1996 Sep. ; 11(5): 567–70.
80. Jankovic J, Gelineau-Kattner R, Davidson A. Tourette's syndrome in adults. Mov Disord. 2010; 25(13): 2171–2175, doi: 10.1002/mds.23199, indexed in Pubmed: 20690167.
81. Szejko N, Jakubczyk A, Dunalska A, et al. Dystonic tics in patients with Gilles de la Tourette syndrome. Neurol Neurochir Pol. 2019; 53(5): 335–340, doi: 10.5603/PJNNS.a2019.0046, indexed in Pubmed: 31621889.
82. Szejko N, Jakubczyk A, Janik P. Prevalence and Clinical Correlates of Self-Harm Behaviors in Gilles de la Tourette Syndrome. Front Psychiatry. 2019; 10: 638, doi: 10.3389/fpsyt.2019.00638, indexed in Pubmed: 31543843.
83. Janik P, Szejko N. Aripiprazole in treatment of Gilles de la Tourette syndrome - New therapeutic option. Neurol Neurochir Pol. 2018; 52(1): 84–87, doi: 10.1016/j.pjnns.2017.10.015, indexed in Pubmed: 29154107.

REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54, no. 4, pages: 305–311
DOI: 10.5603/PJNNS.a2020.0025

ISSN 0028–3843

Sexual dysfunction in Huntington's Disease — a systematic review

Klaudia Szymuś[1], Artur Bystrzyński[1], Magdalena Kwaśniak–Butowska[2], Agnieszka Konkel[2], Agata Leśnicka[3], Magdalena Nowacka[4], Jarosław Sławek[2]

[1]Faculty of Medicine, Medical University of Gdansk, Gdansk, Poland
[2]Department of Neurological–Psychiatric Nursing, Medical University of Gdansk, Gdansk, Poland; Neurology Department, St. Adalbert Hospital, Copernicus, Gdansk, Poland; European Huntington's Disease Network
[3]Department of Developmental Psychiatry, Psychotic and Geriatric Disorders, Medical University of Gdansk, Gdansk, Poland
[4]Doctoral School in the Social Sciences, University of Gdansk, Gdansk, Poland

ABSTRACT

Introduction. Huntington's Disease (HD) is a neurodegenerative disorder of which the main symptoms are motor, cognitive and behavioural problems sometimes including sexual dysfunction.

Aim. To review the current knowledge on sexual dysfunction in HD.

Methods. Databases of Pubmed and Scopus were searched. Only original studies performed after 1994 were included (from 1994 a genetic test = proven diagnosis).

Results. 162 publications were found, but only nine met our established criteria. The majority of patients with HD suffer from sexual disorders. The most common are: hypoactive sexual disorder (53–83% of patients), hyperactive sexual disorder (6–30%), erectile (48–74%) and ejaculatory dysfunctions (30–65%), lubrication problems (53–83%), and orgasmic dysfunction (35–78%).

Discussion. Results may be biased for several reasons e.g.: social taboos regarding sex lives, medications that affect sexual function, impaired self–awareness of patients, small study samples, a lack of standardised questionnaires, and a focus only on the presence of sexual problems without describing them.

Conclusions. Sexual disorders in HD are common. This is a problem that is probably underestimated, both by patients/caregivers and physicians, who should focus more on these symptoms in order to improve patient quality of life.

Key words: Huntington's Disease, sexual disorder, sexual dysfunction, sexuality, depression

(*Neurol Neurochir Pol 2020; 54 (4): 305–311*)

Introduction

Huntington's Disease (HD) is an autosomal dominant inherited disorder. The main symptoms consist of cognitive, behavioural and motor dysfunctions. The cause is a mutation in the *HTT* gene located on chromosome 4, which results in CAG codon expansion [1, 2]. The product of the *HTT* gene is a huntingtin protein toxic for cells [3].

According to Wexler et al., when George Huntington described the disease for the first time he mentioned "two married men, whose wives are living, and who are constantly making love to some young lady, not seeming to be aware that there is any impropriety in it" and who "never let an opportunity to flirt with a girl go past unimproved" [4].

Current classifications define sexual dysfunction as a heterogeneous group of disorders that are typically characterised by a clinically significant disturbance in a person's ability to respond sexually or to experience sexual pleasure. An individual may have several sexual dysfunctions at the same time. They affect 41% of women and 34% of men in the general population and include: delayed ejaculation, erectile disorder, female orgasmic disorder, female sexual interest/arousal disorder, genito-pelvic pain/penetration disorder, male hypoactive sexual desire, premature (early) ejaculation,

Corresponding author: Klaudia Szymuś, Medical University of Gdansk, Gdansk, Poland, e-mail: szymus.klaudia@gmail.com

substance/medication–induced sexual dysfunction, as well as other unspecified sexual dysfunctions [5, 6].

HD can affect patient behaviour very early, even at the premotor stage, and at the same time may significantly influence the sex lives of HD patients and their partners [7].

Many factors can interfere with sexual health: the sexual partner (i.e. her/his general health), medications taken (Selective Serotonin Reuptake Inhibitors: SSRIs, H2 and D2 blockers, dopamine depleting agents, beta-adrenolytics), chronicity of the disease, other chronic comorbidities, religiousness, cultural factors, and individual predispositions to face stressful situations [8, 9].

As the problem of sexual dysfunction in HD seems to be important in terms of quality of life (QoL), we searched databases to see how HD affects the sex lives of patients and partners.

Methods

We performed a literature search. We searched through the databases of Scopus and PubMed. The search terms we used were: 'Huntington's disease' and 'sexual disorder', 'sexual dysfunction', and 'sexuality' in different combinations. Titles and abstracts were checked if they matched our criteria; the studies we included in the research were read in full versions.

Eligibility criteria

We included only studies published from 1994 (i.e. after the discovery of the HD gene) up to 2019, in order to include patients with genetically proven diagnosis. Studies needed to examine at least 20 patients with HD (only human subjects) and refer to their sexual life. Case studies, systematic reviews, opinions, and animal studies were excluded.

Results

We found 404 research papers, but 242 were duplicated in the two databases. Of the remaining 162, only nine fulfilled our eligibility criteria.

Almost all of the included studies identified several sexual dysfunctions related to HD, with the most prevalent being sexual desire disorder [7, 10, 11, 12, 13] and hyposexuality rather than hypersexuality.

All sexual dysfunctions were more common in HD patients than in the general population, with the exception of premature ejaculation [7]. The majority of HD patients (85% of males, 75% of females) were affected by at least one sexual disorder [7]. All included studies are presented in concise form in Table 1.

Erectile dysfunction

According to the DSM–V definition, erectile dysfunction is an inability to obtain an erection and/or maintain it sufficiently for sexual performance, or a marked decrease of erectile rigidity. This is the dysfunction with the highest difference between HD patients and control groups in several studies: 48% vs 30% [7], 69% vs 22% [11], and 67% vs 22% [14].

Ejaculatory dysfunction

Premature or delayed ejaculation has been found significantly more frequently in HD patients in several studies: inhibited orgasm – 56% vs 0% [7], premature ejaculation – 30% vs 50% [7], any ejaculation problem – 59% vs 19% [14]. Another study found the difference to be insignificant: 65% vs 63% [11]. The incidence of inhibited male orgasm remained high even after the elimination of the influence of medications. There is also a correlation between age at onset of the disease and age at onset of inhibited male orgasm – the sexual dysfunction occurred a few years after the onset of the disease. Premature ejaculation is the only dysfunction which has been observed less frequently in HD patients than in control groups [7]. Both ejaculatory and erectile dysfunctions were more frequent in patients with HD than in pre–manifest mutation carriers.

Orgasmic dysfunctions

The term 'female orgasmic disorder' refers to a marked delay, infrequency or absence of orgasm or orgasmic sensations that are markedly reduced in intensity [6]. Women with HD have reported more or the same level of problems regarding orgasm than control groups: 42% vs 9% [7], 53% vs 51% [14], and 78% vs 49% [12]. Unlike the male HD population, this problem does not correlate with age at disease onset [7].

Sexual aversion and satisfaction

Sexual aversion is defined as occurring when "the prospect of sexual interaction produces sufficient fear or anxiety that sexual activity is avoided, or, if it occurs, is associated with strong negative feelings and an inability to experience any pleasure" [15]. In females, no difference was found between HD patients and a non–HD group. In males, it was not observed in controls but 15% of HD patients reported sexual aversion [7].

Diminished or lack of sexual enjoyment (intercourse satisfaction) was studied in only one research regarding males, where it was reported by 74% of HD patients vs 37% controls [11].

Arousal problems

Problems with arousal in women (failure of genital response to sexual activity where the principal problem is vaginal dryness or failure of lubrication) [15] have been observed to be more prevalent in HD: 33% vs 14% [7] and 91% vs 62% [12]. Two research papers distinguished a vaginal lubrication problem separately, but the results are inconsistent between the two, with virtually no difference and a significant difference: 53% vs 49% [14] and 83% vs 44% [12].

Vaginismus and dyspareunia

Vaginismus is a spasm of the pelvic floor muscles that surround the vagina, causing occlusion of the vaginal opening [15]. It has not been observed in any study.

Dyspareunia describes a pain during intercourse and was investigated in two studies, showing it to be more common in HD: 33% vs 9% [7] and 61% vs 43% [12]. Dyspareunia in men was measured only in one study, where it was observed neither in control nor patient groups [7].

These two nosological units are distinguished by ICD–10. However, they were merged into 'genito–pelvic pain/penetration disorder' in DSM–5 and classified under 'sexual pain disorders' in ICD–11.

Paraphilia

Paraphilia is defined as "recurrent intense sexual urges and fantasies involving unusual objects or activities" (e.g. paedophilia, exhibitionism, transvestic fetishism) [15]. Only one study has reported paraphilias in HD. The findings show they are more prevalent in the presence of the disease: 19% vs 10% males, 8% vs 0% female [7]. Both non–HD subjects and HD patients who suffered inhibited orgasm and increased sexual interest reported significantly more paraphilias [7].

Correlations and comparative studies

In females, a positive correlation between Total Functioning Capacity (TFC) score and arousal, lubrication and orgasms, as well as total FSFI (Female Sexual Function Index; a standardised questionnaire used to assess sexual dysfunction in women) score was observed. There was a borderline correlation between TFC and pain and sexual satisfaction, but no correlation between TFC and desire. In one study, patients' FSFI score increased with the loss of functional capacity: FSFI = 9.4 with TFC = 3–6; FSFI = 24.6 at TFC = 10–7 [11, 12].

A concomitant decrease of average FSFI and TFC scores was noticed after 2–4 years follow–up [12]. In men, there was a correlation between almost all International Index of Erectile Function domains (IIEF, a standardised questionnaire used to assess sexual dysfunction in men), TFC and motor indices of Unified Huntington's Disease Rating Scale (UHDRS) [11]. Another study associated sexual dysfunctions with all UHDRS indices, depressive disorders and the use of antidepressants [14].

Only two studies have focused on the association between CAG triplets and sexual dysfunction. In men, no significant correlation between the IIEF score and the number of repeats was found [11, 12]. A positive correlation between the number of triplets and sexual desire has been shown in women [11, 12].

The research observed that sexual function worsens as the disease progresses, although it has no correlation with disease duration, but only with decreased functional capacity measured using TFC and TMS [11, 12, 16].

Medications used for the treatment of depression or chorea may have also a negative impact on sexual function. A positive correlation was found for antidepressants, neuroleptics and benzodiazepines [13, 14]. Sexual dysfunctions have been found to be increased with higher Body Mass Index (BMI) and depressive symptoms (in both cases only in men) [11, 14].

One study compared the sex lives of patients with HD to those of patients with multiple sclerosis (MS). HD patients experienced a higher level of arousal at intercourse, more frequently experienced orgasms and satisfaction, and generally had fewer sexual problems than MS patients [17].

Discussion

Sexual dysfunctions are largely ignored symptoms in many diseases, by physicians, patients, caregivers and partners alike. Patients focus on cardinal problems such as depressive, behavioural or motor problems in HD, and are unaware that sexual problems may be disease–related. Nevertheless, they can influence the daily lives of patients and families, and may well have a negative impact on their QoL.

One of the major problems affecting all the studies was the social taboo regarding sex. Many studies reported that patients left blank questionnaires concerning sexual functions or marked them as "not applicable" [12, 14, 16, 17]. This may explain why so few studies performed over the last 25 years have fulfilled the criteria of eligibility, and why it is so difficult to study sexual dysfunction in patients with chronic and multifactorial diseases.

Sexual desire disorders are the most common dysfunctions found in the majority of studies. That might be why the focus has been on hypo– and hypersexuality rather than the wider spectrum of sexual dysfunctions. Erectile and ejaculatory problems, as well as orgasmic disorders and lubrication, are the second most studied group of dysfunctions. The most comprehensive study, by Fedoroff et al., included also dyspareunia, sexual aversion, vaginismus and paraphilia, whereas other studies have treated sexual dysfunction as a generally reported problem or focused on pre–specified problems [16, 18].

The variability of methods used for the assessment and the lack of controls (only 3/9 studies included a control group) make comparisons between studies difficult.

HD patients are also a multi-faceted population in terms of age at disease onset, the wide spectrum of symptoms and co–morbidities, number of CAG triplets, number of medications used for symptomatic treatment, and social and educational level. Therefore, to obtain statistically significant data, larger study groups are required. The number of patients included in the nine studies which we analysed varied from 56 up to 2,591 (Tab. 1). But in the two largest (1,238 and 2,591) there were no control groups and the data was obtained from very simple questionnaires [16, 18]. Some studies have indicated

Table 1. Concise review of studies included into analysis, showing both patient and control groups results

Study	Diagnostic tool	Sexual dysfunction in HD patients	Sexual dysfunction in a control group
Fedoroff et al., 1994 [7] N = 71 M = 37 F = 34 Mean age: 45.8 ± 11.9 years	For sexual dysfunctions diagnosis: DSM–III–R	N = 39, M = 27, F = 12 Hyposexual: 63% M, 75% F Hypersexual: 30% M, 25% F Inhibited orgasm: 56% M, 42% F Erectile dysfunction: 48% Dyspareunia: 0% M, 33% F Female sexual arousal disorder: 33% Premature ejaculation: 30% Sexual aversion disorder: 15% M, 25% F Paraphilias: 19% M, 8% F Vaginismus: 0% Any sexual disorder: 85% M, 75% F	HD–patients' partners, N = 32, M = 10, F = 22 Hyposexual: 50% M, 50% F Hypersexual: 20% M, 0% F Inhibited orgasm: 0% M, 9% F Erectile dysfunction: 30% Dyspareunia: 0% M, 9% F Female sexual arousal disorder: 14% Premature ejaculation: 50% Sexual aversion disorder: 0% M, 18% F Paraphilia: 10% M, 0% F Vaginismus: 0% Any sexual disorder: 60% M, 68% F
Craufurd et al., 2001 [10] N = 134 M = 63 F = 71 Mean age = 50 ± 12 years	For assessing behavioural changes: PBA–HD	Hyposexual: 62% (65% M, 58% F) Hypersexual: sexual disinhibition (6%; 6% M, 6% F), sexually demanding behaviour (5%; 7% M, 3% F)	No control group
Kirkwood et al., 2001 [16] N = 1,238 M = 607 F = 631	For first–degree relatives: AQ	HD–patients with minimum 6–years history of symptomatic disease Any sexual dysfunction: 9.4% after one year, 12.7% after 2–5 years, 9.8% after 6–10 years, 5.1% after more than 10 years	No control group
Aziz et al., 2010 [14] N = 169 M = 75 F = 94	For autonomic symptoms: SCOPA–AUT For motor, cognitive, behavioural functions: UHDRS For depression: BDI	Patients with symptomatic HD, N = 63, M = 29, F = 34, mean age = 48.5 ± 10.7 years Erectile dysfunction: 67% Ejaculatory problems: 59% Vaginal lubrication: 53% Problems with orgasm: 53% F Pre–manifest patients, N = 21, M = 9, F = 12, mean age = 44.4 ± 8.7 years Erectile dysfunction: 22% Ejaculatory problems: 0% Vaginal lubrication: 42% Problem with orgasm: 67% F	Randomly selected non–mutation-carrying family members, partners or acquaintances of participating patients, employees at our department or their acquaintances, N = 64, M = 27, F = 37, mean age = 47.4 ± 10.4 years Erectile dysfunction: 22% Ejaculatory problems: 19% Vaginal lubrication: 49% Problems with orgasm: 51% F
Reininghaus et al., 2012 [17] N = 56 M = 28 F = 28	For progression of HD: UHDRS For progression of MS: EDSS For body image: FBeK For quality of relationship: PFB For partnership satisfaction: ZIP For sexual behaviour: TSST	Patients with genetically proven HD, N = 29, M = 19, F = 10, mean age = 43 years *Percentage assessment was not provided. Instead, mean TSST score was presented.* N = 14 Sexual dysfunction = 1.56 ± 0.69	Patients who met criteria for clinically definite MS, N = 27, M = 9, F = 18, mean age = 42.8 years *Percentage assessment was not provided. Instead, mean TSST score was presented* N = 21 Sexual dysfunction = 2.29 ± 1.03
Kolenc et al., 2015 [11] N = M = 64	For sexual dysfunction: IIEF For neurological assessment: UHDRS and TFC For depression: BDI	Patients with genetically proven HD (pre–symptomatic carriers not included in final analysis), N = M = 23, mean age = 46 years Hyposexual: 74% M Erectile dysfunction: 69% Diminished intercourse satisfaction: 74% M Ejaculatory problems: 65% Orgasmic dysfunction: 35% M	Staff members, general practitioners' patients, HD–negative family members, N = M = 41, mean age = 42 years Hyposexual: 56% M Erectile dysfunction: 24% Diminished intercourse satisfaction: 37% M Ejaculatory problems: 63% Orgasmic dysfunction: 29% M

→

Table 1. cont. Concise review of studies included into analysis, showing both patient and control groups results

Study	Diagnostic tool	Sexual dysfunction in HD patients	Sexual dysfunction in a control group
Simpson et al., 2016 [18] N = 2,591	For symptoms assessment: FDA–approved, self–created surveys	Patients with HD = 536, patients with JDH = 20, mean age = 47.1 years Loss of ability to perform sexual activity: 14.6% Sexual problems: 35.7%	*No control group, but caregivers participated in study assessing which patient symptoms most impactful for them* Past or current caregivers of HD patients = 1,904, past or current caregivers of JHD patients = 109, mean age = 52.5 years Loss of ability to perform sexual activity: 62.3% Sexual problems: 34.4%
Kolenc et al., 2017 [12] N = F = 70	For sexual dysfunction: FSFI For neurological assessment: UHDRS and TFC For depression: BDI	Women with genetically proven HD (also pre–symptomatic carriers), N = F = 23, mean age = 53 years Hyposexual: 83% F Sexual arousal disorder: 91% F Problem with lubrication: 83% Problem with orgasm: 78% F Dyspareunia: 61% F Pre–symptomatic carriers separately, N = F = 8, mean age = 35 years Hyposexual: 25% F Sexual arousal disorder: 0% F Problem with lubrication: 13% Problem with orgasm: 13% F Dyspareunia: 25% F	General practitioners' patients, hospital staff members, HD–negative family members, N = F = 47, mean age = 47 years Hyposexual: 66% F Sexual arousal disorder: 62% F Problem with lubrication: 44% Problem with orgasm: 49% F Dyspareunia: 43% F
Aldaz et al., 2019 [13] N = 123	For motor symptoms: UHDRS–TMS For classification of stage of disease: TFC For non–motor symptoms: PD NMS–Quest	HD patients were participants of ENROLL–HD study, N = 53, M = 24, F = 29, mean age = 52.3 years Sexual desire disorder: 32% Sex difficulty: 30%	HD–negative family members, partners, caregivers, acquaintances, N = 25, M = 11, F = 14, mean age = 55.4 years Sexual desire disorder: 8% Sex difficulty: 12%

AQ – Affected Individual Questionnaire; BDI – Beck Depression Inventory; DSM-III-R – Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised; EDSS – Expanded Disability Status Scale; F – female; FBeK – Fragebogen zur Beurteilung des eigenen Körpers; FDA – Food and Drug Administration; HD – Huntington's Disease; IIEF – International Index of Erectile Function; JHD – Juvenile Huntington's Disease; M – male; MS – multiple sclerosis; PBA-HD – Problem Behaviours Assessment for Huntington Disease; PD NMS-Quest – Parkinson's Disease PD non–motor symptoms questionnaire; PFB – Partnership Questionnaire; SCOPA-AUT – Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction; TFC – Total Functional Capacity; TSST – Tübingen Scales for Sexual Therapy; UHDRS – Unified Huntington's Disease Rating Scale; UHDRS-TMS – Unified Huntington's Disease Rating Scale Total Motor Score; ZIP – a German version of the Relationship Assessment Scale

dysexecutive symptoms to be the most troublesome, which include daily life activities and possibly also sexual performance [18]. Since HD is a rare condition, the problem of sample size was common across the studies. Studies including more than 1,000 participants asked about sexual dysfunction very briefly, and their capacity to provide valuable data is limited. Those studies which were much more detailed featured fewer than 100 participants with the exception of Aziz et al. [14], who collected 169 responses, although the number of HD patients remained below 100 (Tab. 1). Such small samples make all conclusions less credible. Studies with a larger representation concerning detailed records of sexual functioning should be performed.

Neuropsychiatric symptoms like depression and cognitive decline may influence sexual dysfunction, although few correlations have been found so far. In only a few studies, patients' behavioural changes such as apathy or irritability as well as psychiatric problems like depression, anxiety or hallucinations were investigated and correlated with sexual dysfunction [10, 16, 18]. The only neuropsychiatric symptom to be associated with sexual problems in HD was depression [11, 13, 14, 17]. In one study correlation was not possible due to the low response rate to the Beck's questionnaire [12]. Depressive symptoms require further research because their treatment can positively or negatively influence sexual dysfunction.

Other culprits for sexual dysfunctions have been found to be antidepressants, neuroleptics and benzodiazepines, which have generally been associated with hyposexuality [11, 13, 14], maintaining patients' well–being and safety (e.g. antidepressants) and should not be withdrawn in order to improve sex lives. They should be used with caution and not over–prescribed if symptoms such as mild choreatic movements do not imply everyday dysfunction. Not addressing sexual dysfunction in a treatment process might result in the withdrawal of drugs if the patient associates a deterioration of their sex life with them. Although one study suggested that these symptoms are not the result of antidepressant use, but rather the depression itself, the influence remains unclear [14].

We found one of the strongest determinants of sexual dysfunction to be TFC score, which reflects global patient

functioning [11]. This indicates that sexual dysfunction could be caused by dysfunctions in the hypothalamus [19, 20] or in the brainstem and spinal cord [14]. Considering sexual dysfunction as an autonomic symptom makes it unlikely to be secondary to functional impairment. This is proven by the finding that autonomic symptoms' severity in HD with depression was independent of any other accompanying variable, e.g. functional disability. On the other hand, depression might be partially a result of autonomic symptoms [11, 13, 14]. One study stated that males with HD have lower testosterone levels and the percentage mirrors the frequency of hyposexual desire disorder; however, the correlation was not given, hence this remains unconfirmed [21]. Nevertheless, it shows that sexual dysfunction, especially hyposexuality, might be also caused by hormonal imbalance.

In one study that investigated paraphilia it was noted that the usual age of onset for paraphilic symptoms is adolescence, and that for the patients in the study the average age of onset was 32 years. It was therefore suggested that paraphilic behaviour could be an early symptom of HD. However, the study also indicated that it might be a result of increased sexual needs combined with a difficulty in reaching orgasm through conventional means, since significantly more participants with paraphilia had also hypersexual desire disorder and inhibited orgasm [7].

Only two studies analysed sexual dysfunction in pre–symptomatic carriers [11, 12], but, as mentioned before, the number of patients was not representative. The quantity of CAG repeats was taken into consideration in two studies [11, 12], but conclusions were inconsistent.

Another obstacle was that patients with HD may have impaired self–awareness of their symptoms, so they tend to overestimate their performance [22, 23, 24, 25], which might also affect the credibility of their sex problem reporting. That was proven in one study included in the review, where agreement between patient and partner answers was measured. This showed that they were more likely to agree on the absence of dysfunction rather than its presence [7]. That makes all sexual problems more likely to be underreported rather than overreported.

Like patients with HD, partners have reported a higher frequency of sexual dysfunction than the general population [7]. The mental burden of the disease might be one explanation of this phenomenon. Sexual dysfunction in a partner causes a higher risk of its occurrence in an individual, which may explain also the healthy partner's problems [26]. In all papers, the general population comparison was impeded because either control groups were composed of patients' partners and/or only heterosexual and monogamic couples were examined, which might have potentially biased the results.

The major limitation of all studies was the lack of use of standardised questionnaires and different definitions and durations for sexual dysfunctions, not consistent with DSM criteria (Tab. 1.). No studies used the same questionnaires. Only Fedoroff et al. in 1994 used the DSM criteria, and those changed in subsequent years.

Although we did not consider reviews in our paper (as stated in the methodology), one, the most recent performed by Schmidt and Bonelli (2008), should be mentioned. This paper included only five original studies and only one of these selected patients based on genetic testing [27]. The limitations enumerated in the review were similar to ours: different strategies of patient recruitment, the self–assessment of dysfunction instead of standardised methods making studies difficult to compare, and the fact that a reliable diagnosis only emerged with genetic testing after 1993. This shows that during the last decade there has been no substantial progress in this field.

Treatment recommendations released this year contain a section for sexual disorders. They state that in a case of decreased libido, we should consider lowering the dose or substituting the treatment because the cause could be iatrogenic, but they do not explain the procedure if possibly-affecting medications are not taken (i.e. if sexual dysfunction occurs in a not-previously treated patient). For erectile dysfunction – a consultation with an endocrinologist and a specialist in psychosexual disorders is suggested as well as considering symptomatic treatment such as phosphodiesterase 5 inhibitors. For hypersexual behaviour – a psychological approach is recommended, but when associated with violence or social discomfort – neuroleptics and/or SSRI are proposed. If this is not working, then adding/replacing with an anti–androgen under the guidance of a specialist in sexology or endocrinology, or in severe cases a visit to a psychiatrist, is recommended [28].

The guidelines show that sexual dysfunction is no longer a neglected area and is now taken into consideration. However, the focus is still on the most common (hyposexuality, problems with erection) or the most impactful for the patient and his or her family, such as hypersexuality. They are based mostly on good clinical practice instead of randomised studies. Therefore we still need studies on sexual problems and the ways to resolve them in the HD population.

Conflicts of interest: *There is no conflict of interest*

References

1. MACDONALD M. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell. 1993; 72(6): 971–983, doi: 10.1016/0092–8674(93)90585–e.
2. Telenius H, Kremer B, Goldberg YP, et al. Somatic and gonadal mosaicism of the Huntington disease gene CAG repeat in brain and sperm. Nat Genet. 1994; 6(4): 409–414, doi: 10.1038/ng0494–409, indexed in Pubmed: 8054984.
3. Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. Lancet Neurol. 2011; 10(1): 83–98, doi: 10.1016/S1474–4422(10)70245–3, indexed in Pubmed: 21163446.
4. Huntington G. On Chorea. The Medical and Surgical Reporter: A Weekly Journal. 1872; 26(15): 317–21.
5. Dunn KM, Croft PR, Hackett GI. Sexual problems: a study of the prevalence and need for health care in the general population. Fam Pract.

1998; 15(6): 519–524, doi: 10.1093/fampra/15.6.519, indexed in Pubmed: 10078790.
6. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM–IV). SpringerReference. , doi: 10.1007/springerreference_179660.
7. Fedoroff JP, Peyser C, Franz ML, et al. Sexual disorders in Huntington's disease. J Neuropsychiatry Clin Neurosci. 1994; 6(2): 147–153, doi: 10.1176/jnp.6.2.147, indexed in Pubmed: 8044036.
8. Fava M, Rankin M. Sexual functioning and SSRIs. J Clin Psychiatry. 2002; 63 Suppl 5: 13–6; discussion 23, indexed in Pubmed: 11964136.
9. Clayton A, Ramamurthy S. The impact of physical illness on sexual dysfunction. Adv Psychosom Med. 2008; 29: 70–88, doi: 10.1159/000126625, indexed in Pubmed: 18391558.
10. Craufurd D, Thompson JC, Snowden JS. Behavioral changes in Huntington Disease. Neuropsychiatry Neuropsychol Behav Neurol. 2001; 14(4): 219–226, indexed in Pubmed: 11725215.
11. Kolenc M, Kobal J, Podnar S. Male sexual function in presymptomatic gene carriers and patients with Huntington's disease. J Neurol Sci. 2015; 359(1–2): 312–317, doi: 10.1016/j.jns.2015.11.015, indexed in Pubmed: 26671134.
12. Kolenc M, Kobal J, Podnar S. Female Sexual Dysfunction in Presymptomatic Mutation Carriers and Patients with Huntington's Disease. Journal of Huntington's Disease. 2017; 6(2): 105–113, doi: 10.3233/jhd–160224.
13. Aldaz T, Nigro P, Sánchez–Gómez A, et al. Non–motor symptoms in Huntington's disease: a comparative study with Parkinson's disease. J Neurol. 2019; 266(6): 1340–1350, doi: 10.1007/s00415–019–09263–7, indexed in Pubmed: 30834978.
14. Aziz NA, Anguelova GV, Marinus J, et al. Autonomic symptoms in patients and pre–manifest mutation carriers of Huntington's disease. Eur J Neurol. 2010; 17(8): 1068–1074, doi: 10.1111/j.1468–1331.2010.02973.x, indexed in Pubmed: 20192977.
15. World Health Organization. ICD–10 Version:2016 [Internet]. 2016 [cited 2019 Dec 19]. Available from:. https://icd.who.int/browse10/2016/en.
16. Kirkwood SC, Su JL, Conneally P, et al. Progression of symptoms in the early and middle stages of Huntington disease. Arch Neurol. 2001; 58(2): 273–278, doi: 10.1001/archneur.58.2.273, indexed in Pubmed: 11176966.
17. Reininghaus E, Reininghaus B, Fitz W, et al. Sexual behavior, body image, and partnership in chronic illness: a comparison of Huntington's disease and multiple sclerosis. J Nerv Ment Dis. 2012; 200(8): 716–720, doi: 10.1097/NMD.0b013e318261410f, indexed in Pubmed: 22850308.
18. Simpson JA, Lovecky D, Kogan J, et al. Survey of the Huntington's Disease Patient and Caregiver Community Reveals Most Impactful Symptoms and Treatment Needs. J Huntingtons Dis. 2016; 5(4): 395–403, doi: 10.3233/JHD–160228, indexed in Pubmed: 27983566.
19. Dominguez JM, Hull EM. Dopamine, the medial preoptic area, and male sexual behavior. Physiol Behav. 2005; 86(3): 356–368, doi: 10.1016/j.physbeh.2005.08.006, indexed in Pubmed: 16135375.
20. Argiolas A, Melis MR. Central control of penile erection: role of the paraventricular nucleus of the hypothalamus. Prog Neurobiol. 2005; 76(1): 1–21, doi: 10.1016/j.pneurobio.2005.06.002, indexed in Pubmed: 16043278.
21. Markianos M, Panas M, Kalfakis N, et al. Plasma testosterone in male patients with Huntington's disease: relations to severity of illness and dementia. Ann Neurol. 2005; 57(4): 520–525, doi: 10.1002/ana.20428, indexed in Pubmed: 15786456.
22. Ho AK, Robbins AOG, Barker RA. Huntington's disease patients have selective problems with insight. Mov Disord. 2006; 21(3): 385–389, doi: 10.1002/mds.20739, indexed in Pubmed: 16211608.
23. Hoth KF, Paulsen JS, Moser DJ, et al. Patients with Huntington's disease have impaired awareness of cognitive, emotional, and functional abilities. J Clin Exp Neuropsychol. 2007; 29(4): 365–376, doi: 10.1080/13803390600718958, indexed in Pubmed: 17497560.
24. Sitek EJ, Thompson JC, Craufurd D, et al. Unawareness of deficits in Huntington's disease. J Huntingtons Dis. 2014; 3(2): 125–135, doi: 10.3233/JHD–140109, indexed in Pubmed: 25062855.
25. Sitek EJ, Sołtan W, Wieczorek D, et al. Self–awareness of motor dysfunction in patients with Huntington's disease in comparison to Parkinson's disease and cervical dystonia. J Int Neuropsychol Soc. 2011; 17(5): 788–795, doi: 10.1017/S1355617711000725, indexed in Pubmed: 21729402.
26. Mitchell KR, Jones KG, Wellings K, et al. Estimating the Prevalence of Sexual Function Problems: The Impact of Morbidity Criteria. J Sex Res. 2016; 53(8): 955–967, doi: 10.1080/00224499.2015.1089214, indexed in Pubmed: 26605494.
27. Schmidt EZ, Bonelli RM. Sexuality in Huntington's disease. Wien Med Wochenschr. 2008; 158(3–4): 78–83, doi: 10.1007/s10354–007–0477–8, indexed in Pubmed: 18330523.
28. Bachoud–Lévi AC, Ferreira J, Massart R, et al. International Guidelines for the Treatment of Huntington's Disease. Front Neurol. 2019; 10: 710, doi: 10.3389/fneur.2019.00710, indexed in Pubmed: 31333565.

REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54, no. 4, pages: 312–322
DOI: 10.5603/PJNNS.a2020.0062

ISSN 0028–3843

A practical approach to adult-onset white matter diseases, with illustrative cases

Tasneem F. Hasan[1], Philip W. Tipton[2], Kenneth A. Vatz[6], Suzanne M. Brown[3], Neeharika Thottempudi[7], Prasuna Kamireddi[8], Paldeep S. Atwal[9], Zbigniew K. Wszolek[2], William D. Freeman[2, 4, 5]

[1]Department of Neurology, Ochsner Louisiana State University Health Sciences Center, Shreveport, Louisiana, United States
[2]Department of Neurology, Mayo Clinic, Jacksonville, Florida, United States
[3]Department of Nursing, Mayo Clinic, Jacksonville, Florida, United States
[4]Department of Critical Care Medicine, Mayo Clinic, Jacksonville, Florida, United States
[5]Department of Neurosurgery, Mayo Clinic, Jacksonville, Florida, United States
[6]Department of Neurology, Community Health, Chicago, Illinois, United States
[7]Department of Neurology, University of Texas Medical Branch, Galveston, Texas, United States
[8]Department of Neurology, West Virginia University School of Medicine, Morgantown, West Virginia, United States
[9]Department of Medical Genomics, Atwal Clinic, Jacksonville, Florida, United States

ABSTRACT

Aim. To evaluate five illustrative cases and perform a literature review to identify and describe a working approach to adult-onset white matter diseases (WMD).

State of the art. Inherited WMD are a group of disorders often seen in childhood. In adulthood, progressive WMDs are rare, apart from the common nonspecific causes of hypertension and other cerebrovascular diseases. The pattern of WMDs on neuroimaging can be an important clue to the final diagnosis. Due to the adoption of a combined clinical-imaging-laboratory approach, WMD is becoming better recognised, in addition to the rapidly evolving field of genomics in this area.

Clinical implications. While paediatric WMDs have a well-defined and literature-based clinical-laboratory approach to diagnosis, adult-onset WMDs remain an important, pathologically diverse, radiographic phenotype, with different and distinct neuropathologies among the various subtypes of WMD. Adult-onset WMDs comprise a wide collection of both acquired and inherited aetiologies. While severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) neurological complications are emerging, we are as yet unaware of it causing WMD outside of post-anoxic changes. It is important to recognise WMD as a potentially undefined acquired or genetic syndrome, even when extensive full genome testing reveals variants of unknown significance.

Future directions. We propose a combined clinical-imaging-laboratory approach to WMD and continued exploration of acquired and genetic factors. Adult-onset WMD, even given this approach, can be challenging because hypertension is often comorbid. Therefore, we propose that undiagnosed patients with WMD be entered into multicentre National Organisation for Rare Diseases registries to help researchers worldwide make new discoveries that will hopefully translate into future cures.

Key words: adult-onset, genetic analysis, magnetic resonance imaging, white matter disease, white matter hyperintensities, COVID-19

(*Neurol Neurochir Pol 2020; 54 (4): 312–322***)**

Address for correspondence: William D. Freeman, Department of Neurology, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224, USA, e-mail: freeman.william1@mayo.edu

Introduction

White matter diseases (WMD) are a group of brain disorders characterised by either abnormal myelin development (hypomyelination) or a loss of acquired myelin (demyelination). While WMD can be of metabolic origin, the involvement of gene coding for proteins (genetic origin) has been strongly implicated [1].

Furthermore, the widespread use of magnetic resonance imaging (MRI) of the brain has increased the recognition of adult-onset WMD, and the recognition of WMD has similarly paralleled that of multiple sclerosis [2]. Classic inherited WMD must be distinguished from WMD due to acquired causes, such as inflammatory or toxic processes, autoimmune diseases, infections, neoplasms, and WMD, seen in 50–98% of elderly patients, presumably due to small vessel disease [3]. While there are increasing reports of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing neurological complications, we are as yet unaware of it causing WMD [4–6]. Furthermore, Köhler et al. [7] and Lynch et al. [8] have recently published comprehensive reviews on the diagnosis, categorisation, and in some cases, treatment of WMD.

We here present five challenging illustrative cases that demonstrate the complexity and difficulty of investigating adult-onset WMDs, especially those of unknown aetiology, and we set out a structured approach to diagnosis.

Case 1: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

A 46-year-old man presented to our institution for a second opinion on a pituitary tumour. His medical history was notable for headaches and cognitive decline, including slowed processing speed. The patient was told he might have multiple sclerosis in addition to the pituitary tumour and was unclear about his underlying condition. His neurological examination showed no evidence of visual impairment, despite the pituitary tumour. His family history was notable for the death of his father and brother from possible stroke. MRI of the brain showed distinct anterior temporal pole WMD, highly suggestive of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Fig. 1) [9].

The neuro-ophthalmology and neurosurgery consultants felt that his pituitary tumour was incidental, and recommended the investigation of other causes of his headache and cognitive impairment. The patient agreed to undergo genetic evaluation and counselling. A commercial single gene test for a *NOTCH3* gene mutation was positive, thus confirming a diagnosis of CADASIL [10]. The patient underwent risk factor modification and education for his mild systemic hypertension and obstructive sleep apnoea, and his family was advised to seek outpatient genetic counselling for their daughter.

Case 2: unknown WMD

A 75-year-old right-handed white woman with a history of hypertension, hyperlipidemia, and osteoporosis was followed over 11-years in our neurology clinic for intermittent progression of numbness and tingling of her left upper and lower extremities, as well as cognitive decline with subsequent inability to perform activities of daily living. She also reported dizziness (dysequilibrium), multiple falls, and left visual field difficulty, but no hearing loss. The patient had an unremarkable birth history, and no history of neurological milestone delays or dysmorphic features. She denied a history of tobacco, alcohol, or recreational drug use. Her home medications included simvastatin 20 mg daily, aspirin 325 mg daily, and multivitamins. She had no known family history of WMD. On neurological examination, she was alert and oriented, with intact speech and cranial nerves. Neuropsychological testing revealed cognitive difficulties characterised by impairment in executive function, visuospatial skills, and visuoconstruction. Auditory attention, verbal learning and memory, and language remained essentially intact.

On confrontational field testing, a progression from left quadrantanopia to left homonymous hemianopia was noted and confirmed on formal perimetry. Serial funduscopic examinations

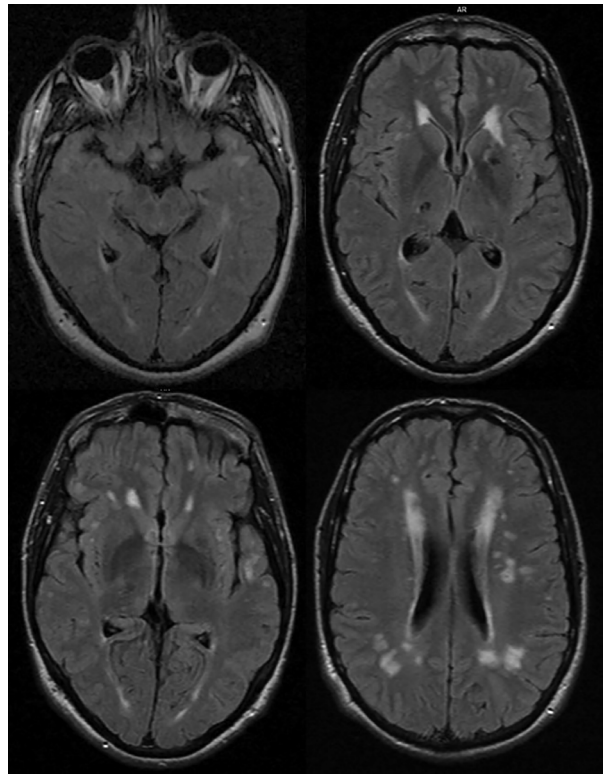


Figure 1. Case 1: T2 FLAIR MRI of the brain. Imaging shows hyperintensities in the anterior temporal pole concerning for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

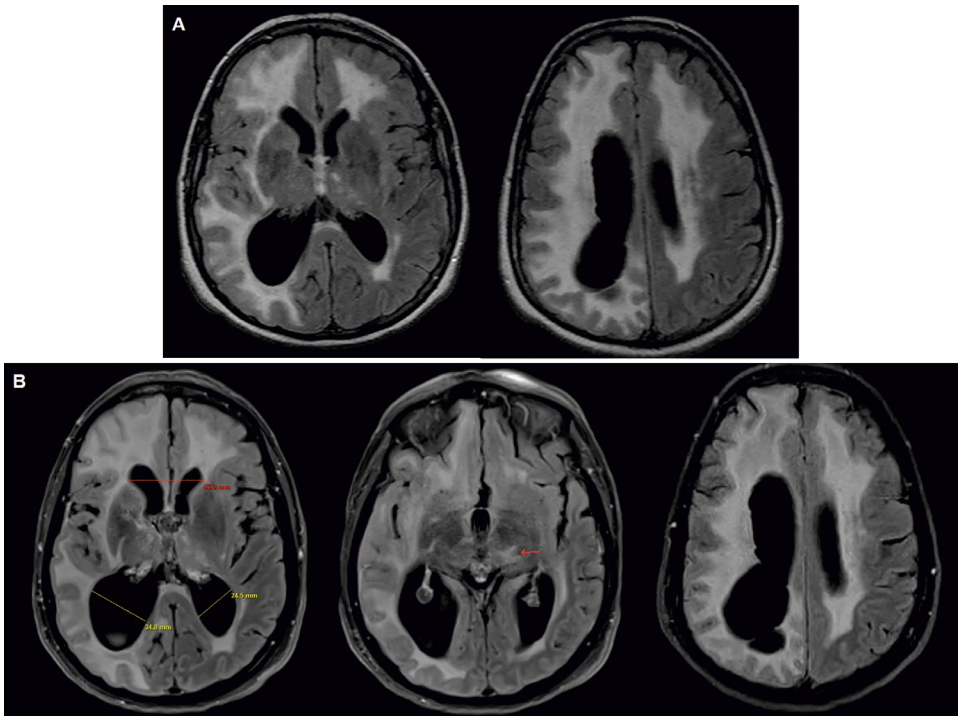


Figure 2. Case 2: T2 FLAIR MRI of the brain. **A.** Imaging from 2006 demonstrates large areas of confluent hyperintensities involving the white matter of the bilateral cerebral hemispheres, right > left. Associated volume loss is greater on the right, with moderate enlargement of the right lateral ventricle, particularly posteriorly. **B.** Imaging from 2014 demonstrates stable volume loss (bifrontal ventricular horns [Evan's index] 43.0 mm; right posterior lateral ventricle 34.8 mm; left posterior lateral ventricle 24.5 mm) and confluent cerebral white matter disease, right > left, with thalamic hyperintensities (red arrow)

were unremarkable. She gradually developed postural instability, left spastic hemiparesis (Medical Research Council grade 4/5), and brisk left-sided reflexes (3+) with a left Babinski sign. Myoclonus and Hoffman and Tromner signs were absent. There was diminished pin-prick sensation, vibration, and proprioception in the left upper and lower extremities, with a positive Romberg sign and the presence of pseudoathetoid movements. Fine motor movements were diminished, and left-sided dysmetria and ataxic gait were noted. Orthostatic blood pressure testing was negative and autonomic function appeared to be normal.

In 2006, T2 fluid-attenuated inversion recovery (FLAIR) MRI of the brain revealed diffuse large confluent white matter hyperintensities with abnormal signal intensity in the bilateral thalami with right hemisphere brain volume loss and moderate enlargement of the right lateral ventricle (ex vacuo), consistent with WMD (Fig. 2A). Despite a progression in symptoms, imaging in 2014 demonstrated stable volume loss (bifrontal ventricular horns [Evan's index] 43.0 mm; right posterior lateral ventricle 34.8 mm; left posterior lateral ventricle 24.5 mm) and confluent cerebral WMD, right > left, with thalamic hyperintensities (red arrow) (Fig. 2B)[11]. Magnetic resonance spectroscopy demonstrated a decrease in all major metabolites (e.g. N-acetyl aspartate, choline, and creatine) consistent with nonspecific neuronal loss. A fluorodeoxyglucose PET scan of the brain showed globally decreased metabolism in the right hemisphere. Cervical, thoracic, and lumbar MRI were unremarkable. Comprehensive testing, including a battery of tests for inherited WMD, was negative (Tab. 1). Based on the available clinical, laboratory, genetic, and imaging data, the patient was diagnosed with WMD of unknown aetiology.

While this case is unusual, it demonstrates that even with advanced imaging and the most up-to-date genetic and laboratory repertoires, cases of WMD of unknown aetiology still exist that may be the result of sporadic genetic mutation. In these cases, it is important to follow the patient's neurological condition over time and continue to search for important clues in the family history or other factors. Similar to the management of other neurodegenerative diseases, it is necessary to recognise the degree of neurological impairment and to prescribe rehabilitative services, such as physical and occupational therapy to prevent falls.

Case 3: 'Chasing the dragon' leukoencephalopathy

A 42-year-old man with a history of opiate addiction presented to the emergency department with coma and hypoxemic respiratory arrest. He required transient intubation and mechanical ventilation, and was given naloxone intravenously. Upon wakening, he was able to follow commands and was

Table 1. Case 2 – Unknown WMD: negative comprehensive testing results

Type of Testing	Specific Tests
Routine labs	• Comprehensive metabolic panel • Vitamin B12 • Folate • Methylmalonic acid • Homocysteine • Thyroid profile
Autoimmune	• Cytoplasmic antineutrophil cytoplasmic antibodies • Perinuclear antineutrophil cytoplasmic antibodies • Anti–double-stranded DNA • Rheumatoid factor • Antiphospholipid antibody • Thyroid peroxidase antibody
Infection	• Human immunodeficiency virus • Herpes simplex virus • Human T-cell lymphotropic virus • Whipple disease • Syphilis • St. Louis encephalitis • Varicella-zoster virus • Epstein-barr virus • Cytomegalovirus • West Nile virus • John Cunningham virus • Lyme disease • Brucella
Mitochondrial/genetic	• Normal-to-low venous lactate levels excluded mitochondrial disorder • Comprehensive leukodystrophy/leukoencephalopathy and mitochondrial DNA genetic testing† • Whole-exome sequencing revealed a variant of undetermined significance in gene *TRPA1*
Inherited WMD‡	• Metachromatic leukodystrophy (arylsulfatase A, urine sulfatides) • Tay-Sachs disease (hexosaminidase A) • Peroxisomal disorders (long-chain fatty acids) • Adrenoleukodystrophy (very long-chain fatty acids) • CADASIL (*NOTCH3*) • Childhood ataxia with central hypomyelination or vanishing WMD (*EIF2B1-5*) • Hereditary diffuse leukoencephalopathy with axonal spheroids (*CSF1R*) • Krabbe disease (galactosylceramidase) • Organic acidemia (urine organic acid analysis)
Additional testing	• EMG/NCV: mild neuropathy • EEG: delta slowing with occasional sharp activity in the right temporal and parietal regions; no evidence of electrographic seizures • Lumbar puncture: negative for inflammatory causes; negative for oligoclonal bands and immunoglobulin G index; negative paraneoplastic panel • Visual- and brainstem auditory–evoked response tests were normal

CADASIL — cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CSF1R — colony stimulating factor 1 receptor; DNA — deoxyribonucleic acid; EEG — electroencephalogram; EIF2B1-5 — eukaryotic translation initiation factor 2b; EMG - electromyography; NCV — nerve conduction velocity; NOTCH3 — neurogenic locus notch homolog protein 3; TRPA1 — transient receptor potential ankyrin 1; WMD — white matter disease

†Genes assessed by this test: *ABAT, ABCD1, ACOX1, ADAR, ADK, AIMP1, ALDH3A2, APOA1BP, APOPT1, ARCN1, ARSA, ASPA, ASXL2, AUH, B3GALNT2, BCL11B, C20ORFZ, C8ORF38, CCDC88A, CLCN2, CLN6, COL4A1, COX15, CSF1R, CTNS, CYP27A1, DARS, DARS2, EARS2, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, FA2H, FAM126A, FBXLA, FKRP, GALC, GFAP, GJC2, GPR56, HEPACAM, HSPD1, HTRA1, ITPA, KCNT1, L2HGDH, LMNB1, MARS2, MLC1, MLYCD, MPV17, MRPS22, MTFMT, MTTP, NDUFA1, NDUFA10, NDUFA11, NDUFA12, NDUFA2, NDUFA9, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFB3, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NSUFS8, NDUFV1, NDUFV2, NOTCH3, NUBPL, OMG, PAH, PC, PHGDH, PSAP, PTEN, PUS3, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, SCP2, SDHA, SDHAF1, SDHB, SLC1A2, SLC1A4, SLC16A2, SLC25A12, SLCBA9, SNORD118, SNRPB, SON, SOX10, STXBP1, TACO1, TARS2, TBCD, TMTC3, TREM2, TREX1, TUBB4, TUFM, TYMP, TYROBP, VARS2*

‡Sjögren-Larsson syndrome, adult polyglucosan body disease, leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation, neuronal ceroid-lipofuscinosis, megalencephalic leukoencephalopathy with subcortical cysts, merosin-deficient congenital muscular dystrophy, molybdenum cofactor deficiency, sulfide oxidase deficiency, L-2 hydroxyglutaric aciduria, propionic acidemia, adult-onset Canavan disease, and urea cycle deficits were low on the differential

subsequently extubated and discharged home. However, after returning home, his wife reported that he became somnolent with intermittent apnoeic episodes overnight. His family brought him back to the ED and he was again unresponsive. He was reintubated and admitted to the intensive care unit and extubated a few days later. The patient, however, remained cognitively impaired, and over the next 30 days developed a progressive decline in neurological function, including mild parkinsonism, poor short-term memory and concentration, and behavioural changes including disinhibition and hypersexuality. Delayed MRI of the brain showed diffuse white matter abnormalities (Supplemental Fig. 1A). Laboratory testing for congenital leukoencephalopathies was negative, including arylsulfatase A and galactosylceramidase, which excluded adult-onset metachromatic leukodystrophy and Krabbe disease, respectively. While the patient's clinical condition and MRI findings gradually improved over the next six months (Supplemental Fig. 1B), he never returned to his prior normal neurological baseline.

The patient's family revealed that he had been inhaling heroin vapour, a practice known as "chasing the dragon" which can cause acute toxic (or spongiform) leukoencephalopathy due to leukotoxins [12–14]. Given the opioid epidemic in the United States, this condition could become increasingly prevalent. Coenzyme Q10 has been proposed as a potential therapeutic agent, along with ongoing anti-opioid efforts to reduce disease incidence [15].

Case 4: WMD with axonal spheroids and pigmented glia

A 37-year-old woman presented with an 11-month history of progressive gait dysfunction that had begun with a tendency for her left foot to turn in when walking. This progressed to considerable balance difficulties. At our first evaluation, her neurological examination was notable only for mild ataxia involving the left arm and leg. She had a family history of similar symptoms that appeared to be dominantly inherited paternally. Laboratory testing of metabolic, haematological, autoimmune, rheumatological, infectious, and neoplastic entities were unremarkable, as was her cerebrospinal fluid (CSF) profile. Formal neuropsychological testing showed mild cognitive impairment with deficits in complex attention, processing speed, and fine motor speed. Non-contrast computed tomography (CT) of the head showed bilateral frontoparietal atrophy without calcifications. MRI of the brain showed severe cortical atrophy of the parietal lobes, and to a lesser extent, the frontal lobes, as well as periventricular and subcortical hyperintensities on T2 FLAIR sequence (Fig. 3).

At follow-up 12-months later, she reported difficulty with multi-tasking, spelling, and performing mental calculations. She was also experiencing slurred speech, worsening balance, and difficulty using her left hand, which would move involuntarily. Notwithstanding these difficulties, she remained independent with her activities of daily living. Neurological examination demonstrated dysarthria and left-sided predominant apraxia, ataxia, and spasticity that severely affected her gait. Genetic testing demonstrated a pathologic mutation in the *CSF1R* gene.

CSF1R is a tyrosine kinase receptor and is the causative gene for axonal spheroids and pigmented glia, also known as *CSF1R*-related leukoencephalopathy. More than 70 mutations have been shown to disrupt the function of *CSF1R* in the brain microglia, leading to their dysfunction [16]. Brain biopsy was previously the only means of diagnosing this disease; however, genetic testing has now removed the need for such an invasive procedure. Axonal spheroids with pigmented glia is currently considered to be a progressive incurable WMD, though case studies have suggested that haematopoietic stem cell transplantation may be beneficial [17, 18]. Although the mechanism of this treatment is not entirely understood, it is thought that haematopoietic stem cell transplantation may lead to replenishment of a healthy microglial population.

Case 5: WMD from COVID-19 post-anoxic encephalopathy

A 70-year-old man developed COVID-19 pneumonia and progressive hypoxaemia requiring intubation, sedation, and mechanical ventilation. He developed adult respiratory

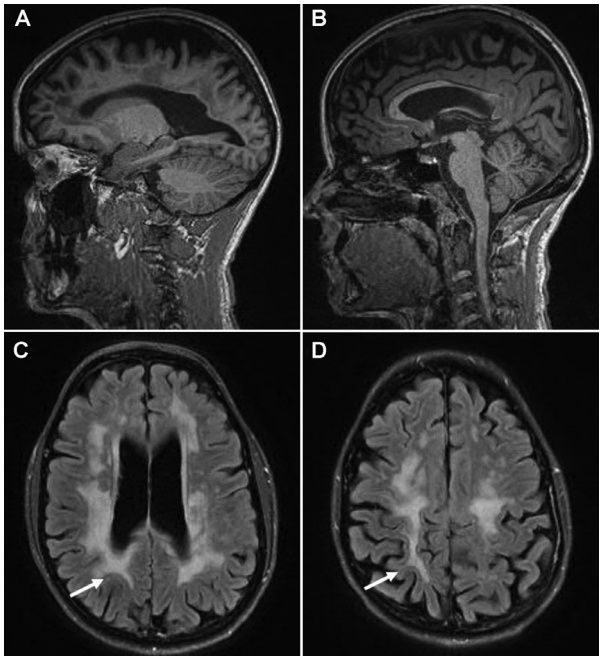


Figure 3. Case 4: MRI of the brain. **A.** Sagittal T1 MRI shows predominantly parietal and frontal lobe cortical atrophy with ex vacuo ventriculomegaly, and **B.** thinning of the corpus callosum. **C.** and **D.** Axial T2 FLAIR MRI shows hyperintensities in the periventricular and subcortical regions, with sparing of the cortical U-fibres (arrows)

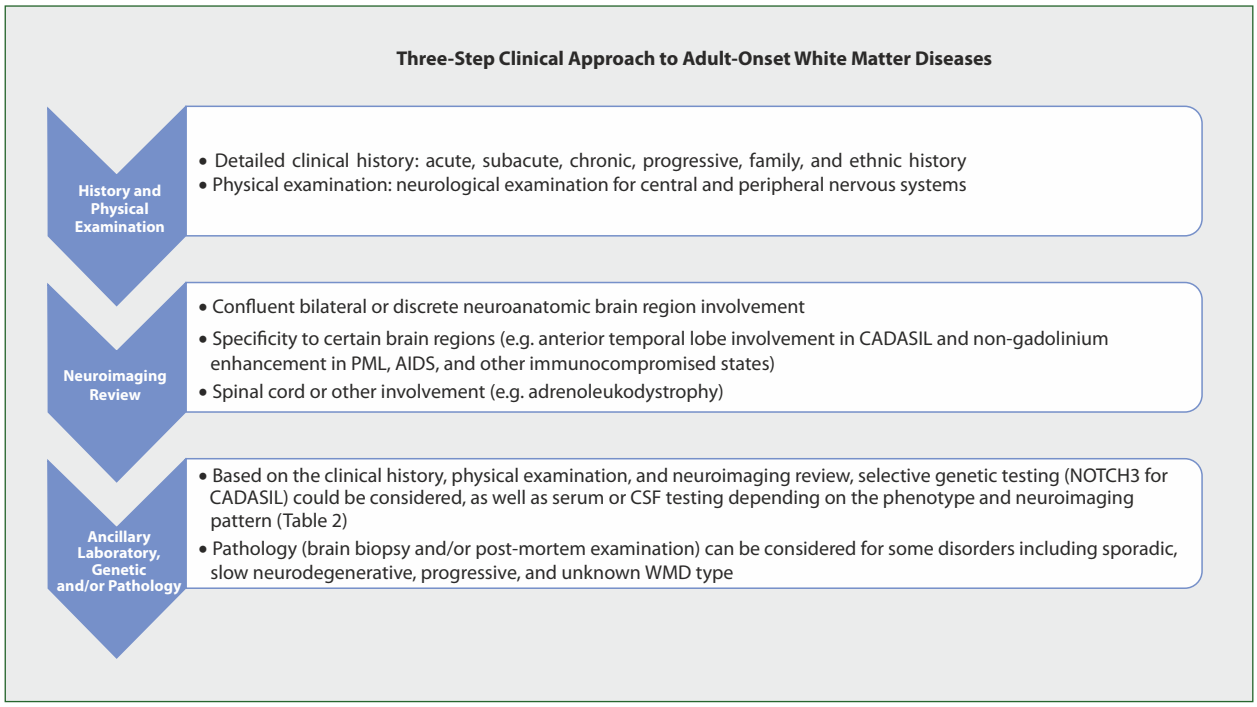


Figure 4. Three-step clinical approach to adult-onset white matter diseases.
AIDS — acquired immunodeficiency syndrome; CADASIL — cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CSF — cerebrospinal fluid; NOTCH3 — neurogenic locus notch homolog protein 3; PML — progressive multifocal leukoencephalopathy; WMD - white matter disease

distress syndrome and multiorgan failure including renal failure and critical illness myopathy on electromyography. He eventually received a tracheostomy after his nasopharyngeal COVID-19 test was negative and developed SARS-CoV-2 IgG antibodies. After a month of hospitalisation, he was transported to a chronic care facility for rehabilitation, but suffered unresponsiveness and severe hypoxia (pulse oximeter in the 70s) despite increasing his fractional inspired oxygen (FiO^2). Arterial blood gas showed an acute severe acidosis, with pH of 6.95, $PaCO^2$ of 135, and PaO^2 of 95 on 100% FiO^2. He later developed left facial focal twitching; electroencephalogram confirmed generalised periodic discharges. Non-contrast CT head imaging showed hypodense frontal white matter with a subtle loss in grey-white matter differentiation (Supplemental Fig. 2A). T2 FLAIR MRI of the brain showed severe bilateral hyperintensities in the subcortical and cortical white matter, particularly in the left occipital cortical regions, consistent with global hypoxic-brain injury (Supplemental Fig. 2B). Susceptibility weighted imaging (SWI) showed diffuse microhaemorrhages (Supplemental Fig. 2C). Given his overall poor prognosis, palliative care was discussed with his family.

This case demonstrates a straightforward post-hypoxic cause of white matter changes similar to cardiac arrest, which is a direct neuronal injury to the cortex, white matter neurons, and astrocytes. However, the emergence of COVID-19 cases of demyelinating disease have also been reported similar to multiple sclerosis with gadolinium enhancement [19]. This patient's MRI of the brain and cervical and thoracic spine with and without contrast failed to reveal any contrast enhancement. Multiple microhaemorrhages seen on SWI have also been reported in COVID-19, and may represent an underlying microvasculopathy of the disease. In one of the largest neuroimaging studies on COVID-19, 35% of patients had non-specific white matter changes noted on CT and/or MRI. Some patients were also noted to have acute cerebrovascular, hypoxic, and post-ictal changes on neuroimaging [20].

Given the global prevalence of COVID-19, and assuming the 35% baseline WMD changes seen on neuroimaging, these changes may in fact reflect small vessel disease secondary to chronic hypertension. However, clinicians should be aware of other autoimmune/demyelinating variants where the history and imaging are supportive of it.

Discussion

WMDs comprise an array of clinical, genetic, and pathophysiologically distinct entities, including acquired progressive diseases such as demyelinating disorders and nonspecific cerebrovascular WMD seen with hypertension, diabetes mellitus, and renal dysfunction (Tab. 2). Some cases of WMD may represent an undefined genetic syndrome or variants of unknown significance, which are areas on extensive full genome testing

Table 2. Adult- and paediatric-onset white matter disease

Inherited adult-onset WMD					
Disorder	**Genetic inheritance**	**Lab diagnosis**	**Gene mutation**	**Clinical features**	**MRI (T1, T2, FLAIR) increased signal**
MLD†	AR	ARSA enzyme	ARSA	• Behavioural and psychiatric changes • Cognitive decline and gait disturbance • Peripheral neuropathy	• Diffuse, symmetric WMH (T2, FLAIR) • Abnormal periventricular myelin (T2, FLAIR) • Sparing of subcortical U-fibres • T1 increased signal
CADASIL	AD	Genetic testing	NOTCH3	• Atypical migraine; recurrent ischaemic events • Cognitive decline	• Nodular to diffuse periventricular WMH • Anterior temporal lobe WMH (T2, FLAIR) and prolonged T1 and T2 relaxation times
HDLS	AD	Molecular genetic testing	CSF1R	• Behavioural changes, ataxia, seizures • Pyramidal and extrapyramidal signs	• Bilateral, asymmetric, confluent WMH (T2, FLAIR) • Frontal predominance
Krabbe disease‡	AR	GALC enzyme	GALC	• Cognitive decline and gait disturbance • Peripheral neuropathy • Vision loss	• Centrum semiovale, periventricular, and deep subcortical WMH (T2, FLAIR)
X-ALD	X-linked	VLCFA measurement	ABCD1	• Dementia, ataxia, spastic paraparesis • Neurogenic bladder, bowel dysfunction, sexual dysfunction, peripheral neuropathy	• Occipital predominance for WMH (T2, FLAIR) • Splenium of corpus callosum and posterior limb of internal capsule involvement • Spinal cord atrophy
VWM	AR	CSF asialotransferrin	*EIF2B1-5*	• Ataxia, spastic paraparesis • Cognitive decline, depression	• Diffuse WMH especially infratentorial (T2, FLAIR) • Marked diffuse atrophy of brain with *ex vacuo* ventriculomegaly, cerebellum, and corpus callosum
Tay-Sachs disease	AR	β-HEXA enzyme	*HEXA*	• Psychosis, mood disorders • Cognitive decline	• Severe cerebellar atrophy
Acquired adult-onset WMD					
Disorder	**Aetiological factors**	**Lab diagnosis**		**Clinical features**	**MRI (T2 FLAIR) findings**
Acute toxic leukoencephalopathy from heroin vapour inhalation 'Chasing the dragon'	Inhalation of heroin vapour and 'leukotoxins'	Urine toxicology/ /microscopy - spongiform leukoencephalopathy		• Pseudobulbar speech, ataxia • Pyramidal tract signs, hyperactive reflexes • Stretching spasms, akinetic mutism, central pyrexia	• Diffuse, symmetric WMH • Cerebellum, posterior cerebrum, and posterior limbs of the internal capsule involvement • Posterior-anterior supratentorial white matter gradient
Acute toxic leukoencephalopathy from methamphetamine use or khat	Methamphetamine abuse and recently khat, a similar drug	Urine toxicology/ /microscopy – spongiform leukoencephalopathy		• Mental deterioration, seizures, nystagmus, focal neurological deficits • Catatonic state or 'khatatonia' from khat, an amphetamine-like substance	• Diffuse, bilateral, symmetrical lesions in the subcortical white matter and corpus callosum • Sparing of the U-fibres and basal ganglia • Reversal of findings after discontinuation of drug

→

Table 2 cont. Adult- and paediatric-onset white matter disease

PML from JC Virus or HIV/AIDS	Acquired	Lumbar puncture/ /brain biopsy		• Mental deterioration, vision loss, speech difficulty • Ataxia, paralysis, seizures	• Multifocal, bilateral, asymmetrical lesions involving the subcortical and periventricular white matter • Supratentorial lesions • Parieto-occipital predominance • U-fibres may be involved
Hypertension--induced RPLS	Acquired	Blood pressure measurement		• Altered mental status, headache • Abnormal visual perception • Seizures	• Reversible white matter lesions • Parieto-occipital predominance
Paediatric-onset WMD					
Disorder	**Genetic inheritance**	**Lab diagnosis**	**Gene mutation**	**Clinical features**	**MRI (T2 FLAIR) findings**
Alexander Disease	AD	Molecular genetic testing	*GFAP*	• Dysphagia, dysarthria, dysphonia • Spastic paraplegia, palatal myoclonus, tremor • Autonomic dysfunction	• Diffuse, symmetric WMH involving the frontoparietal regions • Atrophy of the medulla and upper cervical cord
Canavan Disease	AR	Urine N-acetyl aspartic acid levels	*ASPA*	• Macrocephaly, lack of head control • Hypotonia	• Diffuse, symmetric WMH in the subcortical areas • Bilateral globus pallidus involvement
PMD	X-linked	Genetic testing	*PLP1*	• Ataxia, spasticity, hypotonia • Cognitive decline	• Diffuse WMH, with cerebellum and brain stem involvement

ABCD1 — peroxisomal ABC half-transporters ALDP; AD — autosomal dominant; AIDS — acquired immunodeficiency syndrome; AR — autosomal recessive; ARSA — arylsulfatase A; ASPA — aspartoacylase; CADASIL — cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CSF — cerebrospinal fluid; CSF1R — colony stimulating factor 1 receptor; EIF2B1-5 — eukaryotic translation initiation factor 2B; FLAIR — fluid-attenuated inversion recovery; GALC — galactosylceramidase; GFAP — glial fibrillary acidic protein; HDLS — hereditary diffuse leukoencephalopathy with neuroaxonal spheroids; HEXA — hexosaminidase; HIV — human immunodeficiency virus; JC — John Cunningham; MLD — metachromatic leukodystrophy; MRI — magnetic resonance imaging; NOTCH3 — neurogenic locus notch homolog protein 3; PLP1 — proteolipid protein 1; PMD — Pelizaeus-Merzbacher Disease; PML — progressive multifocal leukoencephalopathy; RPLS — reversible posterior leukoencephalopathy syndrome; VLCFA — very long chain fatty acid; VWM — vanishing white matter disease; WMH — white matter hyperintensity; X-ALD — x-linked adrenoleukodystrophy
†Late infantile MLD characterised by weakness hypotonia, dysarthria, spasticity, seizures, compromised vision and hearing; Juvenile MLD characterised by decline in school performance, behavioural problems; MRI changes are similar to adult disease
‡Paediatric-onset Krabbe Disease characterised by progressive neurological deterioration, muscle hypertonicity, irritability, and peripheral neuropathy

not known to be associated with certain diseases [1, 13, 21–24]. Variants of unknown significance are challenging since they might or might not represent actual genetic pathogenicity to the patient's condition [25]. In rare or sporadic gene mutations, there may not be an adequate number of global cases to know whether the gene variant of unknown significance in question is or is not related. While MRI and advanced genetic testing aid in the diagnosis of WMD, atypical cases of unknown aetiology present a continuing challenge.

We recommend a systematic approach to these patients. We have drawn up several steps to increase the likelihood of reaching an accurate diagnosis (Fig. 4).

Step 1: Detailed history and neurological examination

A methodical approach to WMD is critical to establish an aetiological diagnosis. We suggest a process consisting of a detailed history and a comprehensive neurological examination with neuropsychological testing.

The detailed history should include a family history or a pedigree to better understand the patterns of inheritance (e.g. autosomal dominant, autosomal recessive, X-linked, or sporadic) in efforts to obtain cost-effective genetic screening. Family history is thus helpful in diagnosing inherited WMDs. Nonetheless, patients often provide an incomplete family history, limiting the sensitivity of potential selected genetic testing. Also, family history is not just pedigree-based, but requires detailed investigation into the ethnic background. For example, asking about a particular ethnic history of Ashkenazi Jewish (neuronal ceroid lipofuscinosis), Asian-Indian, or Turkish (Behçet syndrome) descent may help to differentiate specific forms of leukoencephalopathy [1]. The demographics of Case 2 revealed no such ethnic association.

In addition, it is important to obtain where possible a pregnancy and perinatal history, as white matter abnormalities and hypomyelination can result from exposure to alcohol, methamphetamine, and cocaine. [26–29]

Neurological signs and symptoms, including peripheral neuropathy, cerebellar ataxia, spastic weakness, and dystonic dyskinetic movements, which may be found in specific forms of WMD [1], should be explored because they may provide additional information to the diagnosis. Progressive unilateral

symptoms in the presence of drug-resistant focal epilepsy and cognitive decline raises the possibility of Rasmussen encephalitis. The absence of one or a group of symptoms does not exclude WMD [1]. Case 2 presented with various symptoms, but tests for specific forms of WMD were negative.

The COVID-19 pandemic has emerged with increasing reports of devastating diencephalic encephalitis. While WMD might be occurring from this disease, we are unaware of any formal study. COVID-19 neurological manifestations reported to date include: central nervous system manifestations (dizziness, headache, stroke, epileptic seizures, and impaired consciousness secondary to acute encephalopathy, encephalitis, and necrotising haemorrhagic encephalopathy); peripheral nervous system manifestations (impairment of taste, smell, and vision, and peripheral neuropathy); and skeletal muscular injury manifestations including rhabdomyolysis and myalgia [4, 6]. The neurological manifestations of COVID-19 according to one study depends on the severity of the overall disease burden, and there are reports of the virus having neurotropism. We are therefore uncertain as to whether the novel coronavirus causes WMD. This is likely to be an area that warrants study.

Step 2: Careful review of the neuroimaging patterns of WMD

Careful review of the neuroimaging patterns of WMD is important. MRI of the brain is fundamental in the diagnostic workup of WMDs and reliably classifies WMD by identifying distinct structural pattern involvement specific to a disease entity [30, 31]. An MRI algorithm has been discussed [32] and subdivides MRI characteristics according to 1) prominent T2-hyperintensity and T1-hypointensity WMD, further subdivided into confluent and multifocal patterns, and 2) hypomyelination with mild T1 hyperintensity and T2 hyperintensity, T1 isointensity, or mild T1 hypointensity, further subdivided into peripheral or no peripheral nervous system involvement.

MRI discriminators have also been defined [32] and help to differentiate confluent and isolated patterns from multifocal ones. While inherited WMDs often present with bilateral, symmetric, and confluent MRI patterns, acquired cases demonstrate a multifocal, isolated, and asymmetric pattern; however, these disease-specific patterns may sometimes overlap (e.g. the bilateral, symmetric, and confluent pattern of human immunodeficiency virus / acquired immunodeficiency syndrome [HIV/AIDS] encephalopathy). In patients older than 18-months, other MRI discriminators help differentiate T2-hyperintensities due to delayed myelination or permanent hypomyelination from other forms of WMD and help localise confluent patterns to the frontal, parieto-occipital, periventricular, subcortical, or posterior fossa regions. Furthermore, while an MRI algorithm may be helpful in the diagnosis of WMD, the MRI brain findings in Case 2 remained stable despite progressive symptoms, thus impeding our efforts to make an aetiological diagnosis.

The pattern of WMD, combined with the clinical history, will help guide the approach to a more advanced laboratory or genetic testing. Abrupt, stroke-like, or multiple sclerosis-like attacks are completely different from a slowly progressive WMD. Nonspecific WMD patterns associated with uncontrolled hypertension and renal failure, which are amenable to education and risk factor management, should be identified and differentiated from specific, adult-onset, acquired WMDs. These include acute toxic WMDs from methamphetamine use and the inhalation of heroin vapour (e.g. chasing the dragon leukoencephalopathy), HIV/AIDS, progressive multifocal leukoencephalopathy from John Cunningham (JC) virus, and remote multiple sclerosis.

Since the COVID-19 pandemic onset, there has been a rapid increase in the number of studies reporting the neuroimaging findings of SARS-CoV-2 given the reports of neural tissue tropism. In patients with COVID-19, non-contrast CT head imaging has demonstrated symmetric hypoattenuation within the bilateral medial thalami with negative CT angiogram and venogram, while on T2 FLAIR MRI of the brain, hyperintensities have been reported within the bilateral medial temporal lobes and thalami with evidence of diffuse microhaemorrhages on SWI [33]. Based on these preliminary reports, a 'diencephalic encephalitis' pattern seems to suggest a severe viral attack on these deep brain structures.

As described above, neuroimaging in COVID-19 patients have shown a prevalence of 35% of non-specific white matter changes, and clinicians should be aware that demyelinating WMD variant could be underreported. Other reported findings on MRI of the brain in COVID-19 patients include cortical signal abnormalities on FLAIR, cortical diffusion restriction, leptomeningeal enhancement, and cortical blooming artifact [34].

Step 3: Ancillary laboratory testing, genetic testing, and pathology

As illustrated in the cases above, some patients with WMD can be diagnosed simply by means of Steps 1 and 2 (detailed history, neurological examination, and review of neuroimaging). However, as in Case 1, selected genetic testing for *NOTCH3* gene mutation can yield a definitive diagnosis of CADASIL. While single-gene tests or whole genome sequencing can be considered, we generally recommend performing these in conjunction with a medical geneticist; if a genetic disorder is discovered, genetic counselling is often needed for the patient and offspring. Furthermore, optical coherence tomography (OCT) and OCT-angiography can be useful in measuring vessel density and thickness in the early detection of CADASIL white matter changes [35, 36].

Progressive multifocal leukoencephalopathy due to JC virus is an important differential diagnosis in immunocompromised adults. JC virus PCR in CSF is typically high enough to form the majority of diagnoses, albeit negative in rare cases [37]. On the other hand, while isolated case reports have

indeed detected SARS-CoV-2 RNA in the CSF [38], other studies have been unable to isolate the virus and have only found an elevated total protein count, despite having a positive nasal swab and in the presence of neurological symptoms and/or positive neuroimaging [5, 34, 39].

Brain biopsy has been proposed in some cryptogenic WMD cases, but only yields a diagnosis 29-65% of the time, although this figure can be as high as 78% when a more discrete or localised lesion is identified on neuroimaging [40]. Brain biopsy in patients with WMD may be useful when the clinical state is deteriorating, when all tests have failed to provide a diagnosis, or when a treatable condition is suspected.

For progressive, neurodegenerative cases of WMD of unknown cause, autopsy remains the standard criterion for postmortem diagnosis [41–44]. It can better inform the offspring and guide family planning, contribute to our scientific understanding of WMD, and lead to better treatments. In Case 2, after multiple discussions with our patient about a brain biopsy, the patient refused to proceed given the uncertainty that a biopsy would yield a treatable diagnosis. The patient and her family understood that a final diagnosis after death via autopsy could be definitive, and they agreed to that approach.

We propose that undiagnosed patients with WMD be entered into multicentre National Organisation for Rare Diseases registries to help researchers across the globe make new discoveries that will hopefully translate into future cures.

Conclusion

While paediatric WMDs historically have a well-defined and literature-based clinical-laboratory approach to diagnosis, adult-onset WMD remains an important yet pathologically diverse radiographic phenotype, with different and distinct neuropathologies among the various subtypes of WMD.

We propose a three-step clinical approach to adult-onset WMD: 1) detailed history collection, including family and ethnic history, and neurological examination; 2) careful review of neuroimaging patterns; and 3) selective consideration of laboratory, genetic, and pathological means of diagnosis.

The combined clinical-imaging-laboratory approach to adult-onset WMD must continue to evolve if we are to shed more light on these conditions, and discover better therapies for cerebral WMDs.

Conflicts of interest: *The authors have no conflict of interest to report.*

Funding: *This publication was prepared without any external source of funding.*

Data availability statement: *Data that supports the findings of this study is available from the corresponding author upon request.*

Author contributions: *Dr Hasan contributed to conceptualisation, formal analysis, project administration, resources, supervision, visualisation, writing, and critical revision. Dr Tipton contributed to formal analysis, resources, visualisation, and critical revision. Dr Vatz contributed to formal analysis, project administration, resources, supervision, visualisation, and critical revision. Ms Brown contributed to critical revision. Dr Thottempudi contributed to critical revision. Dr Kamireddi contributed to critical revision. Dr Atwal contributed to critical revision. Dr Wszolek contributed to critical revision. Dr Freeman contributed to conceptualisation, formal analysis, project administration, resources, supervision, visualisation, and critical revision.*

References

1. Ahmed RM, Murphy E, Davagnanam I, et al. A practical approach to diagnosing adult onset leukodystrophies. J Neurol Neurosurg Psychiatry. 2014; 85(7): 770–781, doi: 10.1136/jnnp-2013-305888, indexed in Pubmed: 24357685.
2. Costello DJ, Eichler AF, Eichler FS. Leukodystrophies: classification, diagnosis, and treatment. Neurologist. 2009; 15(6): 319–328, doi: 10.1097/NRL.0b013e3181b287c8, indexed in Pubmed: 19901710.
3. Xiong YY, Mok V, Wong A, et al. Age-related white matter changes. J Aging Res. 2011; 2011(1): 617927–57, doi: 10.4061/2011/617927, indexed in Pubmed: 21876810.
4. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020 [Epub ahead of print], doi: 10.1001/jamaneurol.2020.1127, indexed in Pubmed: 32275288.
5. Al Saiegh F, Ghosh R, Leibold A, et al. Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. J Neurol Neurosurg Psychiatry. 2020; 91(8): 846–848, doi: 10.1136/jnnp-2020-323522, indexed in Pubmed: 32354770.
6. Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. Rev Neurol. 2020; 70(9): 311–322, doi: 10.33588/rn.7009.2020179, indexed in Pubmed: 32329044.
7. Köhler W, Curiel J, Vanderver A. Adulthood leukodystrophies. Nat Rev Neurol. 2018; 14(2): 94–105, doi: 10.1038/nrneurol.2017.175, indexed in Pubmed: 29302065.
8. Lynch DS, Wade C, Paiva AR, et al. Practical approach to the diagnosis of adult-onset leukodystrophies: an updated guide in the genomic era. J Neurol Neurosurg Psychiatry. 2019; 90(5): 543–554, doi: 10.1136/jnnp-2018-319481, indexed in Pubmed: 30467211.
9. O'Sullivan M, Jarosz JM, Martin RJ, et al. MRI hyperintensities of the temporal lobe and external capsule in patients with CADASIL. Neurology. 2001; 56(5): 628–634, doi: 10.1212/wnl.56.5.628, indexed in Pubmed: 11245715.
10. Hack R, Rutten J, Lesnik O, et al. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al., editors. GeneReviews [Internet]. Seattle, WA: University of Washington. Seattle, WA: University of Washington, Seattle. ; 2000.
11. Toma AK, Holl E, Kitchen ND, et al. Evans' index revisited: the need for an alternative in normal pressure hydrocephalus. Neurosurgery. 2011; 68(4): 939–944, doi: 10.1227/NEU.0b013e318208f5e0, indexed in Pubmed: 21221031.
12. Bartlett E, Mikulis DJ. Chasing "chasing the dragon" with MRI: leukoencephalopathy in drug abuse. Br J Radiol. 2005; 78(935): 997–1004, doi: 10.1259/bjr/61535842, indexed in Pubmed: 16249600.
13. Singh R, Saini M. Toxic leucoencephalopathy after 'chasing the dragon'. Singapore Med J. 2015; 56(6): e102–e104, doi: 10.11622/smedj.2015094, indexed in Pubmed: 26106246.

14. Filley CM, Kleinschmidt-DeMasters BK. Toxic leukoencephalopathy. N Engl J Med. 2001; 345(6): 425–432, doi: 10.1056/NEJM200108093450606, indexed in Pubmed: 11496854.
15. Alambyan V, Pace J, Miller B, et al. The Emerging Role of Inhaled Heroin in the Opioid Epidemic: A Review. JAMA Neurol. 2018; 75(11): 1423–1434, doi: 10.1001/jamaneurol.2018.1693, indexed in Pubmed: 29987325.
16. Konno T, Yoshida K, Mizuno T, et al. Clinical and genetic characterization of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia associated with CSF1R mutation. Eur J Neurol. 2017; 24(1): 37–45, doi: 10.1111/ene.13125, indexed in Pubmed: 27680516.
17. Eichler FS, Li J, Guo Y, et al. CSF1R mosaicism in a family with hereditary diffuse leukoencephalopathy with spheroids. Brain. 2016; 139: 1666–72.
18. Mochel F, Delorme C, Czernecki V, et al. Haematopoietic stem cell transplantation in CSF1R-related adult-onset leukoencephalopathy with axonal spheroids and pigmented glia. J Neurol Neurosurg Psychiatry. 2019; 90(12): 1375–1376, doi: 10.1136/jnnp-2019-320701, indexed in Pubmed: 31213485.
19. Zanin L, Saraceno G, Panciani PP, et al. SARS-CoV-2 can induce brain and spine demyelinating lesions. Acta Neurochir (Wien). 2020; 162(7): 1491–1494, doi: 10.1007/s00701-020-04374-x, indexed in Pubmed: 32367205.
20. Mahammedi A, Saba L, Vagal A, et al. Imaging in Neurological Disease of Hospitalized COVID-19 Patients: An Italian Multicenter Retrospective Observational Study. Radiology. 2020 [Epub ahead of print]: 201933, doi: 10.1148/radiol.2020201933, indexed in Pubmed: 32437313.
21. Renaud DL. Adult-Onset Leukoencephalopathies. Continuum (Minneap Minn). 2016; 22(2 Dementia): 559–578, doi: 10.1212/CON.0000000000000303, indexed in Pubmed: 27042908.
22. Tavazzi E, White MK, Khalili K. Progressive multifocal leukoencephalopathy: clinical and molecular aspects. Rev Med Virol. 2012; 22(1): 18–32, doi: 10.1002/rmv.710, indexed in Pubmed: 21936015.
23. McKinney AM, Kieffer SA, Paylor RT, et al. Acute toxic leukoencephalopathy: potential for reversibility clinically and on MRI with diffusion-weighted and FLAIR imaging. AJR Am J Roentgenol. 2009; 193(1): 192–206, doi: 10.2214/AJR.08.1176, indexed in Pubmed: 19542414.
24. Lee SY, Dinesh SK, Thomas J. Hypertension-induced reversible posterior leukoencephalopathy syndrome causing obstructive hydrocephalus. J Clin Neurosci. 2008; 15(4): 457–459, doi: 10.1016/j.jocn.2006.12.019, indexed in Pubmed: 18249121.
25. Garrett LT, Hickman N, Jacobson A, et al. Family Studies for Classification of Variants of Uncertain Classification: Current Laboratory Clinical Practice and a New Web-Based Educational Tool. J Genet Couns. 2016; 25(6): 1146–1156, doi: 10.1007/s10897-016-9993-2, indexed in Pubmed: 27422780.
26. Cloak CC, Ernst T, Fujii L, et al. Lower diffusion in white matter of children with prenatal methamphetamine exposure. Neurology. 2009; 72(24): 2068–2075, doi: 10.1212/01.wnl.0000346516.49126.20, indexed in Pubmed: 19369643.
27. Donald KA, Roos A, Fouche JP, et al. A study of the effects of prenatal alcohol exposure on white matter microstructural integrity at birth. Acta Neuropsychiatr. 2015; 27(4): 197–205, doi: 10.1017/neu.2015.35, indexed in Pubmed: 26022619.
28. Fryer SL, Schweinsburg BC, Bjorkquist OA, et al. Characterization of white matter microstructure in fetal alcohol spectrum disorders. Alcohol Clin Exp Res. 2009; 33(3): 514–521, doi: 10.1111/j.1530-0277.2008.00864.x, indexed in Pubmed: 19120066.
29. Lebel C, Warner T, Colby J, et al. White matter microstructure abnormalities and executive function in adolescents with prenatal cocaine exposure. Psychiatry Res. 2013; 213(2): 161–168, doi: 10.1016/j.pscychresns.2013.04.002, indexed in Pubmed: 23769420.
30. van der Knaap MS, Breiter SN, Naidu S, et al. Defining and categorizing leukoencephalopathies of unknown origin: MR imaging approach. Radiology. 1999; 213(1): 121–133, doi: 10.1148/radiology.213.1.r99se01121, indexed in Pubmed: 10540652.
31. van der Knaap MS, Valk J, de Neeling N, et al. Pattern recognition in magnetic resonance imaging of white matter disorders in children and young adults. Neuroradiology. 1991; 33(6): 478–493, doi: 10.1007/BF00588038, indexed in Pubmed: 1780048.
32. Schiffmann R, van der Knaap MS. Invited article: an MRI-based approach to the diagnosis of white matter disorders. Neurology. 2009; 72(8): 750–759, doi: 10.1212/01.wnl.0000343049.00540.c8, indexed in Pubmed: 19237705.
33. Poyiadji N, Shahin G, Noujaim D, et al. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. Radiology. ; 2020: 201187.
34. Kandemirli SG, Dogan L, Sarikaya ZT, et al. Brain MRI Findings in Patients in the Intensive Care Unit with COVID-19 Infection. Radiology. 2020 [Epub ahead of print]: 201697, doi: 10.1148/radiol.2020201697, indexed in Pubmed: 32384020.
35. Fang XJ, Yu M, Wu Y, et al. Study of Enhanced Depth Imaging Optical Coherence Tomography in Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy. Chin Med J (Engl). 2017; 130(9): 1042–1048, doi: 10.4103/0366-6999.204935, indexed in Pubmed: 28469098.
36. Nelis P, Kleffner I, Burg MC, et al. OCT-Angiography reveals reduced vessel density in the deep retinal plexus of CADASIL patients. Sci Rep. 2018; 8(1): 8148, doi: 10.1038/s41598-018-26475-5, indexed in Pubmed: 29802397.
37. Rahmlow M, Shuster EA, Dominik J, et al. Leflunomide-associated progressive multifocal leukoencephalopathy. Arch Neurol. 2008; 65(11): 1538–1539, doi: 10.1001/archneur.65.11.1538, indexed in Pubmed: 19001176.
38. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis. 2020; 94: 55–58, doi: 10.1016/j.ijid.2020.03.062, indexed in Pubmed: 32251791.
39. Espinosa PS, Rizvi Z, Sharma P, et al. Neurological Complications of Coronavirus Disease (COVID-19): Encephalopathy. Cureus. 2020; 12(3): e7352, doi: 10.7759/cureus.7352, indexed in Pubmed: 32328364.
40. Gilkes CE, Love S, Hardie RJ, et al. Brain biopsy in benign neurological disease. J Neurol. 2012; 259(5): 995–1000, doi: 10.1007/s00415-012-6455-0, indexed in Pubmed: 22361977.
41. Koga S, Roemer SF, Kasanuki K, et al. Cerebrovascular pathology presenting as corticobasal syndrome: An autopsy case series of "vascular CBS". Parkinsonism Relat Disord. 2019; 68: 79–84, doi: 10.1016/j.parkreldis.2019.09.001, indexed in Pubmed: 31621626.
42. Moghekar A, Kraut M, Elkins W, et al. Cerebral white matter disease is associated with Alzheimer pathology in a prospective cohort. Alzheimers Dement. 2012; 8(5 Suppl): S71–S77, doi: 10.1016/j.jalz.2012.04.006, indexed in Pubmed: 23021624.
43. Rost NS, Sadaghiani S, Biffi A, et al. Setting a gold standard for quantification of leukoaraiosis burden in patients with ischemic stroke: the Atherosclerosis Risk in Communities Study. J Neurosci Methods. 2014; 221: 196–201, doi: 10.1016/j.jneumeth.2013.10.009, indexed in Pubmed: 24459720.
44. Gouw AA, Seewann A, Vrenken H, et al. Heterogeneity of white matter hyperintensities in Alzheimer's disease: post-mortem quantitative MRI and neuropathology. Brain. 2008; 131(Pt 12): 3286–3298, doi: 10.1093/brain/awn265, indexed in Pubmed: 18927145.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54, no. 4, pages: 323–328
DOI: 10.5603/PJNNS.a2020.0042

ISSN 0028–3843

Pentosidine, advanced glycation end product, in acute ischaemic stroke patients with and without atrial rhythm disturbances

Marta Leńska-Mieciek[1], Grażyna Korczak-Kowalska[2,3], Katarzyna Bocian[2], Urszula Fiszer[1]

[1]Department of Neurology and Epileptology, Centre of Postgraduate Medical Education, Warsaw, Poland
[2]Department of Immunology, Faculty of Biology, University of Warsaw, Warsaw, Poland
[3]Department of Clinical Immunology, Transplantation Institute, Medical University of Warsaw, Warsaw, Poland

ABSTRACT

Atrial fibrillation (AF) and atherosclerotic disease are independent risk factors for acute ischaemic stroke (AIS). The optimal biological marker which could allow differentiation between AF and non-AF AIS patients is still not available.

Aim of the study. Aim of the present study was to investigate the role of pentosidine as a potential biological marker for AF in an AIS patient group.

Materials and methods. Sixty-three acute ischaemic hemispheric stroke patients were recruited and divided into two groups according to the presumed underlying mechanism: with or without atrial rhythm disorders. Ten healthy volunteers were a reference group for serum level of pentosidine. Carotid artery ultrasound was performed, and common carotid artery stiffness and intima-media thickness were measured. Serum levels of pentosidine and selected routine biochemical risk factors for atherosclerosis (cholesterol and its lipoprotein fractions, homocysteine) were examined.

Results. A higher serum level of pentosidine was observed in patients without atrial fibrillation (1,509 ± 485.13pmol/ml); a statistically significant difference was observed compared to the reference group (1,041.52 ± 411.17pmol/ml; p = 0.01), but not the AF patients (1,438.19 ± 495.97pmol/ml; p = 0.59). No significant difference in the non-AF group compared to the AF group for carotid intima-media thickness (IMT)/stiffness and pentosidine serum level was recorded.

Conclusions and clinical implications. A higher serum level of pentosidine was observed in AIS patients without atrial fibrillation compared to the healthy volunteers. According to the results of the present study, no difference between these patients in the selected risk factors of atherosclerosis were observed. Further studies are needed to identify a reliable marker of AF that would bring added value to the standard diagnostic workup after acute ischaemic stroke.

Key words: acute ischaemic stroke, atrial fibrillation, pentosidine, carotid ultrasound

(*Neurol Neurochir Pol 2020; 54 (4): 323–328***)**

Introduction

Atrial fibrillation (AF) and atherosclerotic disease are independent risk factors for acute ischaemic stroke (AIS) [1–3]. In 20–25% of AIS cases, no causative factor can be found in routine tests. There is a need for biomarkers that are capable of identifying them. In recent years, a number of trials have studied the potential biological markers of AF. Four groups can be differentiated: markers of inflammation (e.g. pentraxin-3, neutrophil-to-lymphocyte ratio); markers of fibrosis (e.g. galectin-3, TGF-b1, matrix metalloproteinase – 9, growth/differentiation factor – 15); markers of hormonal activity (e.g. N-terminal prohormone, fibroblast growth factor – 23); and others (e.g. circulating procoagulant microparticles, asymmetric dimethylarginine, microRNA) [4, 5].

Address for correspondence: Marta Leńska-Mieciek, Department of Neurology and Epileptology, Centre of Postgraduate Medical Education, Warsaw, Poland, e-mail: martalenska@wp.pl

Atherosclerosis is characterised by intramural thickening of the sub-intima, and therefore, the carotid intima-media thickness (IMT) is now used as a marker of subclinical atherosclerosis [6–11]. A popular hypothesis is that oxidative stress promotes atherogenesis by accelerating glycation, and leads to the accumulation of advanced glycation end products (AGEs), which increase tissue stiffness and reduce elasticity [12–14]. Pentosidine is a well-characterised natural AGE that is used as a biomarker for AGE production.

Finding an optimal, biological marker for AF would be of great importance for stroke patients.

Aim of study

The aim of the present study was to investigate the role of pentosidine as a potential biological marker for AF in an AIS patient group.

Materials and methods

Over 27 months, 73 participants were recruited into the study by neurologists working in the Department of Neurology. The study group included 63 patients with hemispheric AIS, all of whom were treated at the stroke unit, plus 10 healthy volunteers (reference group for serum level of pentosidine). Hemispheric stroke was diagnosed based on the hemispheric syndrome. Age-matched staff family members were enrolled as the healthy controls. The inclusion criteria to the study group were as follows: (1) a patient with AIS, who (2) was able to provide informed consent. The exclusion criteria were: (1) a diagnosis other than AIS responsible for the neurological syndrome and (2) a refusal or inability to give informed consent. The 63 stroke patients were divided into two groups, according to the presumed underlying mechanism i.e. with and without atrial rhythm disorders. AF was diagnosed in 22 patients (the AF group). Patients were allocated to this group if there was a history of AF or if AF was observed during 24 hours of ECG monitoring (a standard test during hospitalisation). The 41 remaining stroke patients, who did not have heart rhythm disorders, were assigned to the non-AF group.

Carotid artery ultrasound was performed using the MYLAB 70 platform, with linear array transducer LA 522. IMT was measured at the posterior wall of the right and left CCAs, 10 mm from the carotid bifurcation. CCA-IMT was measured with Mylab 70 (Esaote) using the software-guided technique RF-Quality Intima Media Thickness (QIMT, Esaote). A region of interest was superimposed on the B-mode image. The mean of the IMT values was continuously calculated by the system and displayed on the left side of the image. The IMT values were expressed in micrometres. An example of the CCA-IMT measurement is shown in Figure 1. Common carotid artery stiffness was assessed using the Automatic Quality Arterial Stiffness (QAS) calculation, measuring the modification of arterial diameter between systolic and diastolic phases. The distensibility coefficient (DC), compliance coefficient (CC; ratio between variations in arterial cross-sectional area and blood pressure), and pulse wave velocity [PWV — time taken for a pressure pulse to travel between two set points] kPA-1 were calculated. The α and β stiffness parameters were calculated as follows:

$$\alpha = A \times \ln(ps/pd)/\Delta A,$$

where A — diastolic area, ΔA — change of area in systole, ps — systolic pressure, pd — diastolic pressure); and

$$\beta = D \times \ln(ps/pd)/\Delta D,$$

where D — diastolic diameter, ΔD — change of diameter in systole, ps — systolic pressure, pd — diastolic pressure [15, 16].

All measurements of carotid stiffness were performed in the supine position by the same experienced neurosonologist (M.L.), both on the right and left common carotid arteries.

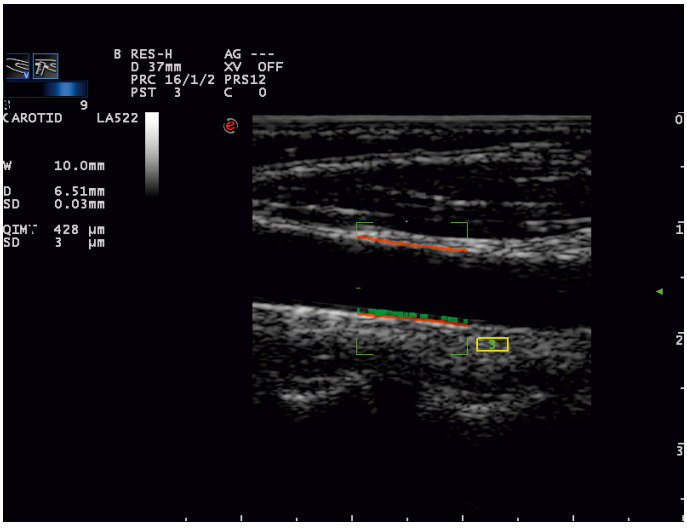


Figure 1. Common carotid artery intima-media thickness measurement using software-guided RF-Quality Intima Media Thickness (QIMT, Easote)

For each patient, the systolic and diastolic brachial pressure was specified.

Routine biochemical risk factors for atherosclerosis, including the blood serum level of cholesterol and its lipoprotein fractions (high- and low-density lipoprotein; HDL and LDL, respectively), homocysteine and pentosidine were examined. All serum-level parameters were measured using standard laboratory practices within 72 hours of the onset of ischaemic stroke. The serum level of pentosidine was measured using a Human Pentosidine ELISA Kit (CUSABIO, Wuhan, China).

Characteristics of the study population were recorded and compared using the Student's t-test, Mann–Whitney U test, Kendall's tau-b test and Pearson's chi-squared test. All statistical analyses were performed using PAWS Statistic 18 (SPSS). P<0.05 was considered statistically significant.

The local Ethical Committee approved the study.

Results

A total of 31 men and 32 women participated in the study: 22 AF patients (six men and 16 women; mean age: 76.82 years; age range: 61 to 90), and 41 non-AF patients (25 men and 16 women; mean age: 72.49 years; age range: 44 to 91). Four men and six women were included in the reference group (mean age: 71.8 years; age range: 66 to 78). The characteristics of each group are set out in Table 1.

A higher serum level of pentosidine was reported in the non-AF patients. A statistically significant difference compared to the reference group (p = 0.01), but not to the AF patients, was observed.

Although the distribution of males and females differed across the AF and non-AF groups, no statistically significant difference between men and women, in terms of any of the measured parameters, was observed within the groups. A higher serum level of triglycerides in men in the non-AF, compared to the AF, group was observed (p = 0.008), but this was not the case for women. In both the AF and non-AF patient groups, the level of HDL cholesterol was higher (p = 0.016) and the CRP was lower (p = 0.04) in women than in men (Tab. 2).

No statistically significant difference in the non-AF group compared to the AF group for DC, CC, PWV, IMT, α and ß stiffness and pentosidine serum level was recorded. Total cholesterol, triglycerides and LDL cholesterol serum levels tended to be higher in the non-AF group compared to the AF group, but a statistically significant difference between the two was recorded only for triglycerides (p = 0.034).

No correlation between DC, CC, PWV, α and ß stiffness and pentosidine serum level was noted.

Ten out of 63 patients (16%) suffered with diabetes mellitus (four in the AF group). Forty-four out of 63 (70%) patients were diagnosed with arterial hypertension (13 in the AF group), and none with renal insufficiency. No statistically significant difference in pentosidine serum level between diabetes mellitus patients (mean: 1,601 ± 540 pmol/ml) and patients without such a diagnosis (mean: 1,462 ± 478 pmol/ml; p = 0.41) was recorded. No statistically significant difference in pentosidine serum level between patients with arterial hypertension (mean: 1,534 ± 488 pmol/ml) and patients without such a diagnosis (mean: 1,379 ± 475 pmol/ml; p = 0.22) was noted.

There was no correlation between patient age and pentosidine serum level in the group of 63 patients (p = 0.70, r = -0.5), or in the AF group (p = 0.81, r = 0.05), or in the non-AF group (p = 0.64, r = -0.07).

Discussion

The present study provides a comparison of pentosidine serum level in non-AF and AF AIS patients. Little is known about the relationship between AGEs and AIS. A high serum level of pentosidine has been previously shown to be indicative of a poor prognosis 30 days after acute stroke and to be associated with branch atheromatous disease among small vessels occlusion [17, 18].

According to the results of the present study, no difference in serum level of pentosidine in non-AF and AF patients was noted. A higher serum level of pentosidine was reported in the non-AF patients, but there was a statistically significant difference compared only to the relatively small reference group (p = 0.01). There was no significant difference in the level of pentosidine between AF and healthy controls, but this is likely to have been caused by the sample size. The point estimates and SD in AF and non-AF groups are very similar. The p value of 0.06 indicates a clear tendency. Recent studies have shown higher subcutaneous content of AGEs in patients with subclinical atheromatous disease than in subjects without disease. No difference in serum level of pentosidine was reported between patients with and patients without generalised atheromatous disease [19]. Further studies are necessary to explore this for the AIS patients, and to establish reference values for serum level pentosidine in healthy controls.

The results of the present study showed no difference in carotid artery stiffness/IMT in AIS patients with and without AF. This confirms previous reports that increased IMT is associated with an increased stroke risk in AF patients [20]. Common carotid IMT, in the absence of cardiovascular risk factors, is strongly related to age [21]. In the present study, the age of patients in both groups was comparable. Increased carotid IMT is associated also with blood pressure variability, obesity and overweight [22, 23]. These factors were not analysed in our study and they could interfere with the results. Mean IMT has been shown to be significantly correlated with systemic atherosclerotic change and PWV to predict the onset of stroke in hypertensive patients [24]. That was not confirmed in the present study, but hypertension was not an exclusion criterion in our study and patients with hypertension were included both in the AF and the non-AF groups. No difference in carotid artery stiffness/IMT in AIS patients with

Table 1. General characteristics of study groups (AF, non-AF, and healthy volunteers)

Mean values	AF patients (n = 22)	SD	Non-AF patients (n = 41)	SD	Healthy volunteers (n = 10)	SD	p value for difference AF vs non-AF	p value for difference AF vs healthy volunteers	p value for difference non-AF vs healthy volunteers
Age (years)	76.8	8.8	72.5	12.0	71.8	4.0	0.17	0.08	0.39
Total cholesterol (mg/dl)	167.1	35.5	184.9	55.4	192.5	70.5	0.26	0.60	0.88
Triglycerides (mg/dl)	89.5	27.8	133.0	94.6	108.2	51.1	0.03	0.55	0.53
HDL cholesterol (mg/dl)	43.7	9.9	39.7	9.8	64.2	23.0	0.15	< 0.01	< 0.001
LDL cholesterol (mg/dl)	105.5	34.9	125.8	66.5	106.6	60.8	0.24	0.38	0.18
CRP (mg/dl)	11.2	11.2	13.9	13.8	6.5	13.0	0.64	< 0.001	< 0.0001
Homocysteine (mg/dl)	17.8	9.8	16.7	6.9	17.0	4.3	0.71	0.70	0.42
α stiffness stroke side	6.4	3.6	8.0	6.5	10.3	6.8	0.37	0.09	0.26
β stiffness stroke side	13.1	7.2	16.2	13.0	20.9	13.6	0.37	0.09	0.27
α stiffness non-stroke side	8.6	5.6	7.8	5.6	6.0	2.5	0.41	0.30	0.70
β stiffness non-stroke side	17.5	11.2	15.8	11.2	12.3	5.1	0.43	0.30	0.70
α stiffness mean	7.5	4.2	7.9	4.6	8.2	4.3	0.83	0.73	0.90
β stiffness mean	15.3	8.4	16.0	9.2	16.6	8.7	0.83	0.73	0.90
PWV stroke side (ms-1)	8.8	2.5	9.6	3.7	10.7	3.7	0.48	0.19	0.35
PWV non-stroke side (ms-1)	10.1	3.2	9.4	3.2	8.3	1.8	0.29	0.12	0.37
PWV mean (ms-1)	9.5	2.5	9.5	2.8	9.5	2.5	0.96	0.98	0.99
CC stroke side (mm2kPa-1)	0.8	0.3	0.8	0.6	0.7	0.5	0.52	0.17	0.40
CC non-stroke side (mm2kPa-1)	0.6	0.4	0.8	0.5	0.9	0.4	0.13	0.05	0.40
CC mean (mm2kPa-1)	0.7	0.3	0.8	0.5	0.8	0.4	0.74	0.92	0.90
IMT stroke side (μm)	800.2	157.1	799.3	182.3	789.7	77.4	0.64	0.50	0.59
IMT non-stroke side (μm)	791.0	165.3	791.6	141.9	748.8	127.7	0.57	0.48	0.34
IMT mean (μm)	795.6	121.5	795.4	139.6	769.2	81.9	0.97	0.78	0.58
Pentosidine (pmol/ml)	1,438	496	1,509	485	1,041	411	0.59	0.06	0.01

CRP — C-reactive protein; HDL — high density lipoprotein; AF — atrial fibrillation

Table 2. Characteristics of study groups (AF, non-AF, and healthy volunteers) according to sex

Mean values	AF patients (n = 22)	SD	p value for difference women vs men	Non -AF patients (n= 41)	SD	p value for difference women vs men	AF+ non-AF patients (n = 63)	SD	p value for difference women vs men	Healthy volunteers (n = 10)	SD	p value for difference women vs men	p value for difference AF vs non-AF
Triglycerides (mg/dl)													
Women	95.0	27.8	0.14	114.1	53.0	0.31	104.5	42.8	0.19	104.8	48.5	0.81	0.21
Men	75.0	24.1		145.2	113.0		131.6	105.4		113.2	62.0		< 0.01
HDL cholesterol (mg/dl)													
Women	45.4	9.9	0.18	42.6	10.4	0.13	44.0	10.1	0.02	75.2	23.2	0.06	0.43
Men	39.0	9,0		37.8	9.2		38.0	9.02		47.7	9.4		0.77
CRP (mg/dl)													
Women	10.6	12.3	0.69	10.9	10.9	0.26	10.7	11.4	0.04	2.5	1.1	0.40	0.96
Men	12.98	8.3		15.9	15.3		15.3	14.1		12.6	20.5		0.65
Pentosidine (pmol/ml)													
Women	1,357	4,137	0.22	1,660	448	0.11	1,508	451	0.69	945	506	0.39	0.06
Men	1,655	666		1,413	492		1,460	526		1,186	184		0.32

HDL — high density lipoprotein; LDL — low density lipoprotein; CRP — C-reactive protein; PWV — pulse wave velocity; CC — compliance coefficient; IMT — intima-media thickness; AF — atrial fibrillation

and without AF, as shown in the present study, supports the previous reports that higher carotid IMT and greater arterial stiffness are associated with higher AF incidence, and play a role in AF aetiopathogenesis [25].

Although several interesting and potentially important relationships have been established in the present study, it does face some limitations: a relatively small group of patients, an overrepresentation of non-AF stroke patients, an uneven sex distribution in groups, and the method of AF/non-AF group allocation. The exclusion criterion "refusal or inability to give informed consent" was responsible for the relatively low number of patients recruited to the study. All patients with aphasia and critical illness, who were unable to provide informed consent, were excluded from the study. Currently, only 1/6 cases of stroke is attributed to AF. This is the reason for the overrepresentation of non-AF stroke patients in our study. Patients were allocated to the AF group either if there was a history of AF or if AF was registered during 24 hours of ECG monitoring. The detection of AF depends on the time of ECG monitoring [26], and is five times higher in 30-day event-triggered recording than when conventional 24-hour monitoring is used. One method of AF screening is an external miniaturised recorder with an adhesive electrode. This method enables the detection of AF in 12.3% of patients with stroke of unknown source during four weeks of monitoring [27]. This means that, potentially, in five patients from the presented non-AF group, AF would be revealed during four weeks of ECG monitoring. Implantable cardiac monitors may be recommended for some patients with AIS. Precise criteria for that procedure could enable the detection of AF in approximately 30% of patients [28].

Conclusions

Serum level of pentosidine was higher in non-AF patients, but it did not differentiate between AF and non-AF patients.

Cholesterol/LDL and carotid IMT correlate in patients without atrial fibrillation.

There was no difference in risk factors of atherosclerosis in the AF group compared to the non-AF group.

Funding source: *This study was financially supported by the Center of Postgraduate Medical Education, Warsaw, Poland (project number 501-1-14-16-13). The funding body had no role in the design or conduct of the study, nor in the collection, management, analysis, or interpretation of the data. The funding body had no involvement in the preparation, review, or approval of the manuscript in which the findings of the study were reported.*
Conflicts of interest: *None*

References

1. Deb P, Sharma S, Hassan KM. Pathophysiologic mechanisms of acute ischemic stroke: An overview with emphasis on therapeutic significan-

ce beyond thrombolysis. Pathophysiology. 2010; 17(3): 197–218, doi: 10.1016/j.pathophys.2009.12.001, indexed in Pubmed: 20074922.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991; 22(8): 983–988, doi: 10.1161/01.str.22.8.983, indexed in Pubmed: 1866765.
3. Falk E. Pathogenesis of Atherosclerosis. Journal of the American College of Cardiology. 2006; 47(8): C7–C12, doi: 10.1016/j.jacc.2005.09.068.
4. Szegedi I, Szapáry L, Csécsei P, et al. Potential Biological Markers of Atrial Fibrillation: A Chance to Prevent Cryptogenic Stroke. Biomed Res Int. 2017; 2017: 8153024, doi: 10.1155/2017/8153024, indexed in Pubmed: 28785588.
5. Ardhianto P, Yuniadi Y. Biomarkers of Atrial Fibrillation: Which One Is a True Marker? Cardiol Res Pract. 2019; 2019: 8302326, doi: 10.1155/2019/8302326, indexed in Pubmed: 31061732.
6. Bonomini F, Tengattini S, Fabiano A, et al. Atherosclerosis and oxidative stress. Histol Histopathol. 2008; 23(3): 381–390, doi: 10.14670/HH-23.381, indexed in Pubmed: 18072094.
7. Cowdry EV. Arteriosclerosis: A survey of problem. New York: MacMillan; 1933 [Introduction.
8. Crowther MA. Pathogenesis of atherosclerosis. Hematology Am Soc Hematol Educ Program. 2005: 436–441, doi: 10.1182/asheducation-2005.1.436, indexed in Pubmed: 16304416.
9. O'Leary DH, Bots ML. Imaging of atherosclerosis: carotid intima-media thickness. Eur Heart J. 2010; 31(14): 1682–1689, doi: 10.1093/eurheartj/ehq185, indexed in Pubmed: 20542989.
10. Stein JH, Korcarz CE, Hurst RT, et al. American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. 2008; 21(2): 93–111; quiz 189, doi: 10.1016/j.echo.2007.11.011, indexed in Pubmed: 18261694.
11. Bruno RM, Bianchini E, Faita F, et al. Intima media thickness, pulse wave velocity, and flow mediated dilation. Cardiovasc Ultrasound. 2014; 12: 34, doi: 10.1186/1476-7120-12-34, indexed in Pubmed: 25148901.
12. Li H, Horke S, Förstermann U. Vascular oxidative stress, nitric oxide and atherosclerosis. Atherosclerosis. 2014; 237(1): 208–219, doi: 10.1016/j.atherosclerosis.2014.09.001, indexed in Pubmed: 25244505.
13. Yamagishi Si, Maeda S, Matsui T, et al. Role of advanced glycation end products (AGEs) and oxidative stress in vascular complications in diabetes. Biochim Biophys Acta. 2012; 1820(5): 663–671, doi: 10.1016/j.bbagen.2011.03.014, indexed in Pubmed: 21440603.
14. Goldin A, Beckman JA, Schmidt AM, et al. Advanced glycation end products: sparking the development of diabetic vascular injury. Circulation. 2006; 114(6): 597–605, doi: 10.1161/CIRCULATIONAHA.106.621854, indexed in Pubmed: 16894049.
15. Cecelja M, Chowienczyk P. Role of arterial stiffness in cardiovascular disease. JRSM Cardiovasc Dis. 2012; 1(4), doi: 10.1258/cvd.2012.012016, indexed in Pubmed: 24175067.
16. Kubozono T, Ohishi M. Prognostic Significance of Regional Arterial Stiffness for Stroke in Hypertension. Pulse (Basel). 2015; 3(2): 98–105, doi: 10.1159/000381795, indexed in Pubmed: 26587458.
17. Ikeda T, Maruyama K, Ito N, et al. Serum pentosidine, an advanced glycation end product, indicates poor outcomes after acute ischemic stroke. J Stroke Cerebrovasc Dis. 2012; 21(5): 386–390, doi: 10.1016/j.jstrokecerebrovasdis.2010.10.004, indexed in Pubmed: 21111635.
18. Ikeda T, Maruyama K, Ito N, et al. High serum pentosidine in branch atheromatous disease among small vessels occlusion. J Neurosurg Sci. 2019; 63(4): 388–393, doi: 10.23736/S0390-5616.16.03628-6, indexed in Pubmed: 26899301.
19. Sánchez E, Betriu À, Yeramian A, et al. ILERVAS project, ILERVAS Project:. Skin Autofluorescence Measurement in Subclinical Atheromatous Disease: Results from the ILERVAS Project. J Atheroscler Thromb. 2019; 26(10): 879–889, doi: 10.5551/jat.47498, indexed in Pubmed: 30842389.
20. Bekwelem W, Jensen PN, Norby FL, et al. Carotid Atherosclerosis and Stroke in Atrial Fibrillation: The Atherosclerosis Risk in Communities Study. Stroke. 2016; 47(6): 1643–1646, doi: 10.1161/STROKEAHA.116.013133, indexed in Pubmed: 27217511.
21. Gori N, Anania G, Stefani L, et al. Carotid Intima-Media Thickness in Master Athletes. Asian J Sports Med. 2015; 6(2): e22587, doi: 10.5812/asjsm.6(2)2015.22587, indexed in Pubmed: 26448832.
22. Chen Y, Xiong H, Wu D, et al. Relationship of short-term blood pressure variability with carotid intima-media thickness in hypertensive patients. Biomed Eng Online. 2015; 14: 71, doi: 10.1186/s12938-015-0059-8, indexed in Pubmed: 26204889.
23. Schiel R, Beltschikow W, Radón S, et al. Increased carotid intima-media thickness and associations with cardiovascular risk factors in obese and overweight children and adolescents. Eur J Med Res. 2007; 12(10): 503–508, indexed in Pubmed: 18024257.
24. Kawai T, Ohishi M, Takeya Y, et al. Carotid plaque score and intima media thickness as predictors of stroke and mortality in hypertensive patients. Hypertens Res. 2013; 36(10): 902–909, doi: 10.1038/hr.2013.61, indexed in Pubmed: 23823172.
25. Chen LY, Leening MJG, Norby FL, et al. Carotid Intima-Media Thickness and Arterial Stiffness and the Risk of Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study, Multi-Ethnic Study of Atherosclerosis (MESA), and the Rotterdam Study. J Am Heart Assoc. 2016; 5(5), doi: 10.1161/JAHA.115.002907, indexed in Pubmed: 27207996.
26. Gladstone DJ, Dorian P, Spring M, et al. EMBRACE Steering Committee and Investigators, EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014; 370(26): 2467–2477, doi: 10.1056/NEJMoa1311376, indexed in Pubmed: 24963566.
27. Lumikari TJ, Putaala J, Kerola A, et al. Continuous 4-week ECG monitoring with adhesive electrodes reveals AF in patients with recent embolic stroke of undetermined source. Ann Noninvasive Electrocardiol. 2019; 24(5): e12649, doi: 10.1111/anec.12649, indexed in Pubmed: 31045315.
28. Farkowski MM, Karliński MA, Kaźmierczak J, et al. Statement by a Working Group conceived by the Polish National Consultants in Cardiology and Neurology addressing the use of implantable cardiac monitors in patients after ischaemic embolic stroke of undetermined source. Neurol Neurochir Pol. 2019; 53(3): 181–189, doi: 10.5603/PJNNS.a2019.0018, indexed in Pubmed: 31145466.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54, no. 4, pages: 329–336
DOI: 10.5603/PJNNS.a2020.0044

ISSN 0028–3843

Cardiac autonomic modulation in drug-resistant epilepsy patients after vagus nerve stimulation therapy

Victor Constantinescu[1], Daniela Matei[1], Irina Constantinescu[2], Dan Iulian Cuciureanu[1]

[1]University of Medicine and Pharmacy, Iasi, Romania

[2]Department of Neurology, Regional Hospital of Orléans, Orléans, France

ABSTRACT

The positive effect of vagus nerve stimulation (VNS) in patients with drug-resistant epilepsy is considered to be mediated by the afferent pathways of the vagus nerve, but the efferent pathways may influence the cardiac autonomic activity.

Aim of the study. To assess the effects of VNS on cardiac autonomic modulation in epilepsy patients, over three months of neurostimulation.

Clinical rationale for the study. Linear and non-linear heart rate variability (HRV) analysis can provide information on the sympathovagal balance and reveal particularities of the central control of the autonomic cardiovascular function.

Materials and Methods. Using Biopac Acquisition System, we analysed HRV parameters in resting condition and during sympathetic and parasympathetic activation tests in five patients with drug-resistant epilepsy, who underwent VNS procedure.

Results. During the sympathetic and vagal activation tests, all five patients presented normal responses of cardiac autonomic activity, reflected in RMSSD, HFnu and LF/HF dynamics in both HRV evaluations. No bradycardia, cardiac arrhythmia or orthostatic hypotension was registered during the two evaluations.

Conclusions. Our results indicate that VNS appears not to alter the cardiac autonomic function after three months of neurostimulation. HRV analysis is a useful tool for evaluating cardiac autonomic modulation in epilepsy patients during VNS therapy.

Clinical Implications. Patients with decreased HRV should be periodically monitored. Cardiac changes in patients with epilepsy are important because of the additional risk of arrhythmias mediated through the autonomic dysfunction.

Key words: drug-resistant epilepsy, vagus nerve stimulation, cardiac autonomic modulation, heart rate variability, linear and non-linear analysis

(*Neurol Neurochir Pol 2020; 54 (4): 329–336***)**

Introduction

Since vagus nerve stimulation (VNS) was approved as a therapeutic approach for the treatment of refractory epilepsy, the search has been ongoing for nonpharmacological modulation of the autonomic nervous system (ANS) for different pathological conditions. The advantage of VNS therapy has also been evaluated for drug-resistant depression, heart failure, hypertension, and cardiac arrhythmias [1, 2].

The precise mechanism of neuromodulation exerted by the VNS is still a matter of debate. 80% of the fibres of the vagus nerve are afferent pathways to the central nervous system. Only 20% are efferent pathways, some of them reaching the cardiovascular system [3]. The afferent pathways of the vagus nerve play an essential role in the neuromodulation process, influencing the interplay of various cortical networks probably involved in epileptogenic activity [4, 5]. The activation of the vagal efferent pathways concerns the sinoatrial node and the cardiac conduction system [2, 4]. Consequently, it may decrease the heart rate and reduce atrioventricular conduction and excitability of the His bundle.

Research dedicated to VNS's impact on cardiac rhythm has yielded contradictory results. A minor increase in sympathetic cardiovascular modulation without significant haemodynamic

Address for correspondence: Daniela Matei, University of Medicine and Pharmacy, Universitatii street No 16, 700115 Iasi, Romania, e-mail: dvm2202@yahoo.com

effects, probably related to the activation of sympathetic pathways from the brainstem, has been reported [3]. Cardiac bradyarrhythmia is a rare complication during ongoing VNS therapy [6]. An increase in cardiac vagal modulation appears to play a cardioprotective role against sudden death [7].

Heart rate variability (HRV) describes the variations between consecutive heartbeats, known as RR intervals, on ECG recordings. Frequency-domain analysis allows the assessment of the global variation of a biologic signal, divided into its different spectral components [8]. The presence of different frequency spectra can be attributed to the modulation of the ANS on cardiovascular activity [9–11]. Time-domain indices of HRV evaluate the amount of variability in measurements of the interbeat interval. Mechanisms involved in cardiovascular regulation interact with each other in a non-linear manner [12, 13]. Non-linear dynamics can be evaluated with the help of chaos theory, offering a more detailed perspective of the HRV. Fractal methods assess the scaling exponent of the signal which indicates the presence of fractal properties, or self-similarity of beat-to-beat intervals — the RR intervals on the ECG recordings [14]. Entropy measures have been widely used in HRV analysis, assessing the irregularity and complexity of HRV [15].

The rationale for implementing the analysis of the non-linear dynamics of HRV is thus to better understand the mechanisms of cardiac autonomic control. It has been demonstrated that alteration of fractal properties precedes the onset of fatal cardiac arrhythmias [16], as the increased regularity and the loss of complexity in the heart rate signal is related to the dysregulation of cardiac autonomic control [17, 18]. A decreased HRV was initially shown to be predictive of mortality in the elderly population [19]. Moreover, in epilepsy patients, it appears to be associated with an increased risk of sudden unexpected death (SUDEP) [20]. Therefore, HRV analysis may identify patients with autonomic dysregulation at risk of fatal cardiac arrhythmias [20].

The same group of patients was previously assessed using Multiple Trigonometric Regressive Spectral analysis, using a different analytical approach [21]. The actual evaluation based on Fast Fourier Transform provides, in addition to the spectral power analysis, the non-linear appraisal of the HRV. Since this has not been previously described [21], we considered it worthy of further analysis.

Clinical rationale for the study

The clinical rationale of this study was to assess the effects of VNS on cardiovascular autonomic function in different physiological conditions in drug-resistant epilepsy patients, over three months of neurostimulation. The results of the study may be clinically useful for detecting a cardiac activity adjustment in the analysed epilepsy patients, and may contribute to better understanding of the effect of VNS on the autonomic cardiac activity.

Methods

ECG recordings of the first five patients with drug-resistant epilepsy who underwent VNS procedure, in our department, were analysed. In these patients, seizure control was not obtained within two years of multiple antiepileptic drug treatment. Epilepsy surgery was not a viable option in any of the five patients. Each patient had an ECG recording before VNS procedure and after three months of neurostimulation, during ON and OFF periods of the stimulation. All patients were monitored with prolonged EEG and ECG recordings before and after the autonomic tests (including night EEG), which excluded clinical or infraclinical seizures.

A standardised protocol consisting of a resting state ECG recording followed by four autonomic activation tests, each lasting for five minutes, was applied. Standardised conditions imposed the following criteria: ECG recording at the same time range after 30 minutes of clinostatism rest, in the absence of noise, at a constant temperature of 22°C, without previous physical activity or the ingestion of beverages containing caffeine. The four autonomic activation tests were performed in the same sequence in all patients, as follows: deep breathing, standing, hand-grip and Valsalva manoeuvre. To remove the respiratory influence on the heart rate, the patients followed a paced breathing pattern at 15 cycles per minute, as described in other studies [22]. During the deep breathing test, a complete deep inhale and exhale lasted 10 seconds, six complete cycles per minute, to emphasise the vagal activation. The following sympathetic activation tests were performed: the standing test and the hand-grip test, consisting of a three-minute isometric contraction of the fist, using a dynamometer. BIOPAC® acquisition system was used for the ECG recording. AcqKnowledge software version 3.9.1.6 eliminated artifacts of the recorded signal. HRV analysis was performed using Kubios HRV software version 2.2 (Biosignal Analysis and Medical Imaging Group, University of Eastern Finland). HRV parameters were analysed using Fast Fourier Transform. A minimum of 256 RR intervals on the ECG were analysed for each recording.

The following HRV time-domain parameters were analysed: Root Mean Square of the Successive Differences (RMSSD), the proportion of pairs of successive RR intervals that differ by more than 50 ms to the total number of NN intervals (pNN50), the standard deviation of the so-called normal-to-normal NN interval that reflects all the cyclic components responsible for variability in the period of recording (SDNN), the mean RR interval, and the heart rate [9]. The frequency-domain analysis referred to the following spectral components: VLF (very low frequency power, 0.02–0.04 Hz), LF (low frequency power, 0.04–0.15 Hz) and HF (high frequency power, 0.15–0.4 Hz). These parameters were expressed in absolute values (ms^2), and in relative values calculated as a percentage (%) to total power. Given the complex mechanisms that seem to influence the values of the VLF spectrum (i.e. thermoregulatory mechanisms, activity of the renin-angiotensin-aldosterone system) [9,

10], we analysed the normalised units (nu) for the LF and HF spectrum, which excluded from calculation VLF values, and the LF/HF ratio (the ratio of absolute LF power to HF power). RMSSD, pNN50, HF and HFnu parameters are considered to be markers of parasympathetic autonomic control on the heart rate [9, 10].

The following HRV parameters were considered for the non-linear analysis: SD1, SD2, SampEn (Sample Entropy), ApEn (Approximate Entropy), DFA α1 and DFA α2 (Detrended Fluctuation Analysis α1 and α2). When analysing the Poincaré graph, SD1 shows the short-term variability of a chronological series, while SD2 is the second component of the ellipse formed from the point cloud (which has as abscissa and ordinate two consecutive R-R values from the ECG recording) and it illustrates the long-term variability of the biological signals [23]. SD1 represents the standard deviation of the Poincaré plot and is graphically perpendicular to the line-of-identity, while SD2 is along the line-of-identity. SD1 is considered a parameter that reflects the influence of parasympathetic tone on the control of the sinus node, being an expression of the rapid changes of the RR interval, since the vagal effects on the sinus node manifest faster than those mediated by the sympathetic nervous system [24, 25]. ApEn measures the 'disorder' in the heart rate signal and quantifies the regularity and complexity of the chronological series [26]. SampEn is a more constant measure derived from ApEn [27], which quantifies the complexity of the signal in short time segments [28], low values of SampEn indicating a greater similarity between successive RR in chronological series [29]. Detrended Fluctuation Analysis (DFA) is an evaluation method of the statistical 'self-affinity', assessing the regularity and complexity of the biosignals [27, 30, 31] when the RR interval is analysed. Values of the scalar exponent α that are higher than 1 illustrate an increase in regularity and a decrease in signal complexity in the chronological series [28, 29], with an increased self-correlation power, constantly associated with pathological conditions [32, 33]. α1 represents the short-range scaling exponent, while α2 represents the long-range scaling exponent [14].

We referred mainly to the SD1, SampEn, ApEn and DFA α1 parameters, as our ECG recordings lasted five minutes.

All five patients underwent left laterocervical stimulation of the vagus nerve and had no cardiovascular comorbidities or cardiovascular medication. The output current of stimulation was 2 mA for the first, third and fourth patients, 1.5 mA for the second patient, and 1 mA for the fifth patient. The frequency of stimulation was set at 30Hz for all five patients, while pulse width (500 μsec), duty cycle (10%), ON time period (30 seconds) and OFF time period (5 minutes) was identical for all patients.

Biological parameters (blood pressure, oxygen saturation, renal and hepatic function and blood electrolytes) were within the normal range for all five patients. The antiepileptic medication was unchanged either in the three months before the first ECG recordings or between the two HRV tests. Blood pressure was measured in supine and orthostatic position for each patient after both evaluations.

Patients were recruited from the neurological department, and all patients were duly informed according to the study protocol and consented to the assessment in accordance with ethical principles. This study was carried out in accordance with the Helsinki Declaration.

For the statistical analysis of data, taking into consideration the small sample size, series normalisation was very difficult. Applied comparative tests were specific to the characteristics of the analysed parameters. A value of $p < 0.05$ was considered significant. GraphPad Prism software version 6.07 was used for the analysis and graphical presentation of the data.

Description of patients

The first patient, a 33-year-old female, was diagnosed with focal epilepsy (left anterior temporal epilepsy) and secondarily generalised seizures. The clinical symptoms were rotatory vertigo, breathing difficulties, facial flush, dreamy state, and generalisation. Brain MRI showed no abnormalities. The patient was being medicated with three antiepileptics: lamotrigine, levetiracetam and oxcarbazepine.

The second patient, a 34-year-old female, presented focal epilepsy (left insular epilepsy) with secondarily generalised seizures. The clinical symptoms were nausea, dyspnoea, abnormal sensation of retrosternal pain, burning heat restricted to the perioral area, and anarthria. No epilepsy-related brain MRI abnormalities were found. The patient was under treatment with valproic acid and levetiracetam.

The third patient, a 34-year-old female, had been diagnosed with focal epilepsy (right insular epilepsy) and secondarily generalised seizures (rotatory vertigo, facial flush, sense of unreality, and subsequent generalisation) at the age of 22. No epilepsy-related brain MRI abnormalities. Patient under treatment with levetiracetam and oxcarbazepine.

The fourth patient, a 29-year-old female, presented multifocal epilepsy with secondarily generalised seizures (onset features: vertigo, sweating and motor unilateral symptoms, motor aphasia and generalisation). Brain MRI showed parietal and occipital gyration abnormalities. Pharmacological treatment consisted of lamotrigine, levetiracetam and carbamazepine.

The fifth patient, a 31-year-old male, presented left insular focal epilepsy with secondarily generalised seizures (retrosternal ascending heat, hypersalivation and post-ictal psychomotor agitation with hetero-aggressive behaviour). Left insular atrophy with frontoparietal extension was revealed on cerebral MRI. Antiepileptic medication consisted of valproate and oxcarbazepine.

Results

The first patient presented a sympathetic predominance on the heart rate control, as indicated by RMSSD, pNN50, HFnu and LF/HF values in resting state (Tab. 1). After the autonomic

activation tests, the patient displayed an appropriate response of the cardiac autonomic regulation, as marked by the values of HFnu and LF/HF. Parasympathetic activation tests increased the HRV, illustrated by DFAα1 values (Tab. 1). There was no significant difference concerning the dynamic of HFnu and LF/HF parameters in response to activation tests in the two HRV evaluations (Fig. 1). After three months of neurostimulation, an improvement in HRV was noticed, as shown by an increase of ApEn and SampEn during standing test, hand-grip test and Valsalva manoeuvre (Fig. 1).

The second patient presented normal responses to parasympathetic and sympathetic activation tests, reflected in HFnu, LF/HF and RMSSD values during challenge, in both HRV evaluations. A decrease in the HRV after sympathetic activation tests in both evaluations was seen regarding DFA α1 values (Fig.1).

The third patient presented appropriate responses to parasympathetic and sympathetic activation tests mirrored in the dynamics of HFnu and LF/HF ratio in both HRV evaluations. DFAα1 presented similar values after three months of neurostimulation (Fig.1).

The fourth patient presented normal dynamic of the HFnu and LF/HF ratio in response to autonomic activation tests, similar in both HRV assessments. During sympathetic activation tests, there was a shift to sympathetic predominance, seen in LF/HF values, correlated with a low HRV after three months of neurostimulation, revealed by DFAα1 values (Fig.1).

For the fifth patient, during the first evaluation, the Valsalva manoeuvre determined an increase of vagal modulation and of the HRV, illustrated by the values of RMSSD, pNN50, HFnu, SD1 and DFAα1 (Tab. 1). During the second evaluation, deep breathing test induced an increase in the parasympathetic control over the heart rate (higher RMSSD, HFnu values, lower LF/HF ratio), compared to resting state, highlighting a normal response to the vagal activation test. ApEn and SampEn illustrated similar responses to the activation tests in both HRV evaluations (Fig. 1).

All five patients presented an increase of vagal modulation after parasympathetic activation tests, specifically at the Valsalva manoeuvre ($p < 0.05$), during the first HRV evaluation (T1) and after deep breathing test during the second HRV evaluation (T2), as shown by the RMSSD values (Fig. 2). LF/HF ratio decreased after deep breathing test ($p < 0.05$) and Valsalva manoeuvre during the first HRV evaluation. The same dynamic of the LF/HF values was observed during the second HRV evaluation, with increased values after standing and hand-grip tests ($p < 0.05$) (Fig. 2). HFnu presented increased values after deep breathing test ($p < 0.05$) during the first HRV evaluation. Similar features were observed at the second HRV evaluation, with an increment of the HFnu values after deep breathing test and a decrease after sympathetic activation tests ($p < 0.05$), reflecting a regular response of the heart rate to sympathetic and parasympathetic modulation (Fig. 2). SDNN values presented a similar dynamic as RMSSD in response to the autonomic tests. Mean RR values were correlated to the heart rate values during the four autonomic tests (Tab. 1).

No patient presented orthostatic hypotension, defined as a decrease of at least 20 mmHg in systolic blood pressure or of at least 10mmHg in diastolic blood pressure, after a three--minutes standing test, performed after ECG recording, incurred after the two HRV evaluations. During autonomic evaluations and the prolonged ECG recordings, no cardiac arrhythmias were identified for the five patients. Furthermore, the patients did not recall seizure-related symptoms during the current hospitalisation. During the autonomic tests performed, including the deep breathing test, the patients were not monitored by EEG, but no seizure was observed by the examiner or reported by the patient.

Discussion

The cortical neuromodulation exerted by VNS therapy involves brain structures related to autonomic regulation, such as the prefrontal region, thalamus and amygdala [34]. Recent findings indicate that activated vagal afferents initiate centrally mediated reflexes that inhibit parasympathetic efferent outflows to the heart [35], without consequent bradycardia, a clinical feature not found in our five patients after VNS therapy. Efferent vagal fibres do not directly synapse with cardiomyocytes, but rather with the intrinsic cardiac nervous system, acting as a buffer in modulating the commands to the cardiomyocytes [35]. The intrinsic cardiac nervous system comprises a complex network of ganglia and its neurons that can independently operate or connect with its complement structures of the autonomic pathways in the spinal cord, brainstem or cortex, in order to balance the intracardiac reflexes [35].

Periodic VNS may effectively modulate heart rate dynamics. A phenomenon of pharmacological tolerance has been described, in which both vagus nerve and the autonomic nervous network adapt to periodic stimulation [3].

Epilepsy and seizures can have dramatic effects on cardiac function, through the ANS. While some authors have concluded that VNS seems not to change decreased HRV in drug-resistant epilepsy patients [35], others have reported that VNS improves HRV shortly after implantation via the extensive innervation of the vagus nerve into the sinoatrial and atrioventricular nodes [3, 8, 36]. However, cardiac autonomic dysfunction related to VNS in epilepsy patients is rare (0.1%) [37–39].

The originality of our study consists of using the autonomic activation tests (Ewing tests) and the analysis of non-linear HRV parameters besides time- and frequency-domain parameters for describing the cardiac autonomic response after sympathetic and parasympathetic challenge in patients with drug-resistant epilepsy, three months after vagal stimulation. Non-linear parameters have been used to analyse and predict the behaviour of biological phenomena. These parameters

Table 1. Heart rate variability (HRV) parameters for the five patients

Test 1/ /Test 2	HR	Mean RR	SDNN	RMSSD	pNN50	LF (nu)	HF (nu)	LF/HF	SD1	ApEn	SampEn	DFAα1
RS Patient 1	90/91	671/660	39/31	13/15	0.6/0.5	84.8/77.4	14.7/22.5	5.74/3.4	16/10	1.2/1.1	1.3/1.3	1.1/1.4
DB Patient 1	92/87	653/685	48/36	66/45	1.7/0.5	36.5/44.6	56.4/55	0.64/0.8	46.8/32	1.1/1	1.1/1	0.6/1.2
ST Patient 1	92/96	655/632	62/25	77/22	2.1/2.8	69/77	30/22	2.27/3.4	54.5/15	0.8/1.1	0.8/1.1	0.8/1.3
HG Patient 1	92/87	653/683	72/22	86/14	2.7/0.3	70/83.5	29/16.5	2.39/5	60/10.4	0.8/1.1	0.7/1.6	0.7/1.5
VA Patient 1	92/93	659/642	69/35	77/14	2.6/1	42.7/74.7	57.3/25.2	0.74/2.9	50/10.4	0.7/1	0.7/1	0.6/1.3
RS Patient 2	76/67	793/903	49/67	39/67	12/36	68/54.7	31/45.3	2.4/1.2	28/47	1.1/1	1.6/1.6	1.2/0.9
DB Patient 2	78/73	777/824	72/54	89/53	9.2/14.5	38.7/52.9	60.9/47	0.63/1.1	63/38	1/1	1/1.3	0.9/1.1
ST Patient 2	85/75	711/802	80/58	58/42	4.5/14.5	71/77	28/22	2.53/3.3	41/29	0.7/1	0.6/1.3	1.1/1.2
HG Patient 2	76/76	787/797	40/58	40/44	12.3/15.8	58/78.4	41.7/21.5	1.39/3.6	29/31	1.2/1.1	1.6/1.4	1.1/1.3
VA Patient 2	81/70	740/863	75/57	96/51	6.3/20	41/71	58.7/28.6	0.69/2.4	68/36	0.8/1	0.8/1.4	0.6/1.1
RS Patient 3	89/81	670/735	41/24	20/20	2.4/1.7	73.9/70	26/29.5	2.84/2.3	14/14	1/1.2	1.1/1.7	1.3/1.2
DB Patient 3	90/81	665/740	30/29	20/23	3.6/2.7	50/63.9	50/36	0.99/1.7	14/16	1/1.1	1.1/1.6	1.3/1.2
ST Patient 3	93/86	640/700	19/29	14/22	0.9/2.8	73/78	26/20	2.77/3.8	10/16	1.2/1.1	1.7/1.6	1.3/1.2
HG Patient 3	89/83	673/724	22/32	18/24	0.2/4.4	80/81.8	20/18.2	3.99/4.4	12.7/17	1.2/1	1.7/1.4	1.2/1.4
VA Patient 3	89/78	672/766	39/36	28/29	4.4/7	78/63	21/36	3.6/1.72	20/21	1/1	1.2/1.6	1.4/1.2
RS Patient 4	79/74	755/811	9/16	11/13.9	0.4/0.3	77/76	22/23	3.5/3.2	35/9	0.8/1.1	0.8/1.6	1/1.4
DB Patient 4	76/72	790/823	31/18	28/15	4/1.2	73/52	26.9/47	2.7/1.1	20/11	1/1.1	1.1/1.6	1.2/1.1
ST Patient 4	82/81	737/743	27/25	19/17	2.5/0.9	84/81	15/18	5.5/4.4	14/12	0.9/0.9	1.2/0.6	1.4/1.2
HG Patient 4	81/76	743/787	40/17	37/13	2.5/0.5	73.7/81	26.1/18	2.82/4.3	26/9	0.9/1.2	0.9/1.5	0.5/1.3
VA Patient 4	76/72	792/826	46/32	58/23	2.3/4.9	60.4/71	39.3/28	1.52/2.5	41/16	0.9/1	0.9/1.3	0.9/1.2
RS Patient 5	75/73	805/814	85/43	54/29.9	25/6.9	62/58.3	37/41.7	1.68/1.3	38.8/21	1/1.2	1.2/1.6	1.1/1
DB Patient 5	74/76	811/791	87/88	52/111.5	27/6.8	50.9/43.7	48.9/55	1.04/0.7	36.8/78	1/0.8	1.1/0.7	1.2/0.9
ST Patient 5	81/77	754/782	104/93	59.8/24.6	20.1/5.1	65.2/65.2	34.6/34.8	1.88/1.8	42.3/17	0.8/0.7	0.8/0.5	1.1/1.4
HG Patient 5	75/77	805/776	93/42	57.8/20.2	27.8/2.5	66.1/73.4	33.8/26.5	1.95/2.7	40.9/14	1/1	1.1/1.2	1.1/1.2
VA Patient 5	69/75	883/795	132/46	146/24.2	52.4/4.7	39.2/84.9	60.2/15.1	0.65/5.6	104/17	1.1/1	1.4/1.2	0.8/1.4

HR — heart rate; RR interval — variations between consecutive heartbeats; SDNN — standard deviation of Normal-to-Normal intervals; RMSSD — Root Mean Square of Successive Differences; pNN50 — the proportion of NN50, representing the number of pairs of successive NNs that differ by more than 50 ms, divided by total number of NNs; LF — low frequency power; HF — high frequency power; ApEn — Approximate Entropy; SampEn — Sample Entropy; SD1 – standard deviation of instantaneous beat-to-beat interval variability; DFA – detrended fluctuation analysis

have proved to be good predictors of morbidity and mortality in clinics [40].

Although it is known that drug-resistant epilepsy is associated with significant inhibition of vagal modulation of heart rate and lower HRV [41, 42], the non-linear parameters ApEn, SampEn, SD1 underlined an increase of HRV during the vagal activation tests compared to sympathetic activation tests. DFA α1 confirmed the increase of HRV, especially during the Valsalva test, in all five patients, in the first evaluation. Thus, the non-linear analysis of HRV validated the results from time- and frequency-domain analysis, reflecting the shift in the sympathovagal balance during the autonomic tests.

VNS appears not to disrupt the cardiac autonomic activity, with no significant alteration in HRV parameters during autonomic tests being registered during the ECG recordings. The first and fourth patients presented sympathetic predominance over the heart rate control. The first patient displayed an increase of HRV, while the fourth patient displayed a decrease of HRV requiring further cardiac monitoring. Also, the second patient presented a decrease of HRV after sympathetic activation tests in both evaluations, while the third and the fifth patients kept constant features regarding the non-linear parameters. This observation underlines the importance of non-linear analysis, which may provide useful information about the cardiac autonomic state.

Our results reveal that all patients presented adequate autonomic responses after sympathetic and parasympathetic activation tests, before VNS therapy, and three months after neurostimulation.

Although not necessarily reflecting a novel mechanism, the dynamic autonomic tests provide useful information regarding cardiac regulation. An impaired response to the autonomic challenge reflected by HRV parameters is not only a potential biomarker for monitoring progressive decline of the ANS system regulation, but is also a probable risk factor for sudden unexplained death determined by cardiac arrhythmias in patients with epilepsy [20, 43].

Further studies are needed to assess whether a perpetuation of the sympathetic control and a decreased HRV, observed in some of our patients during sympathetic activation

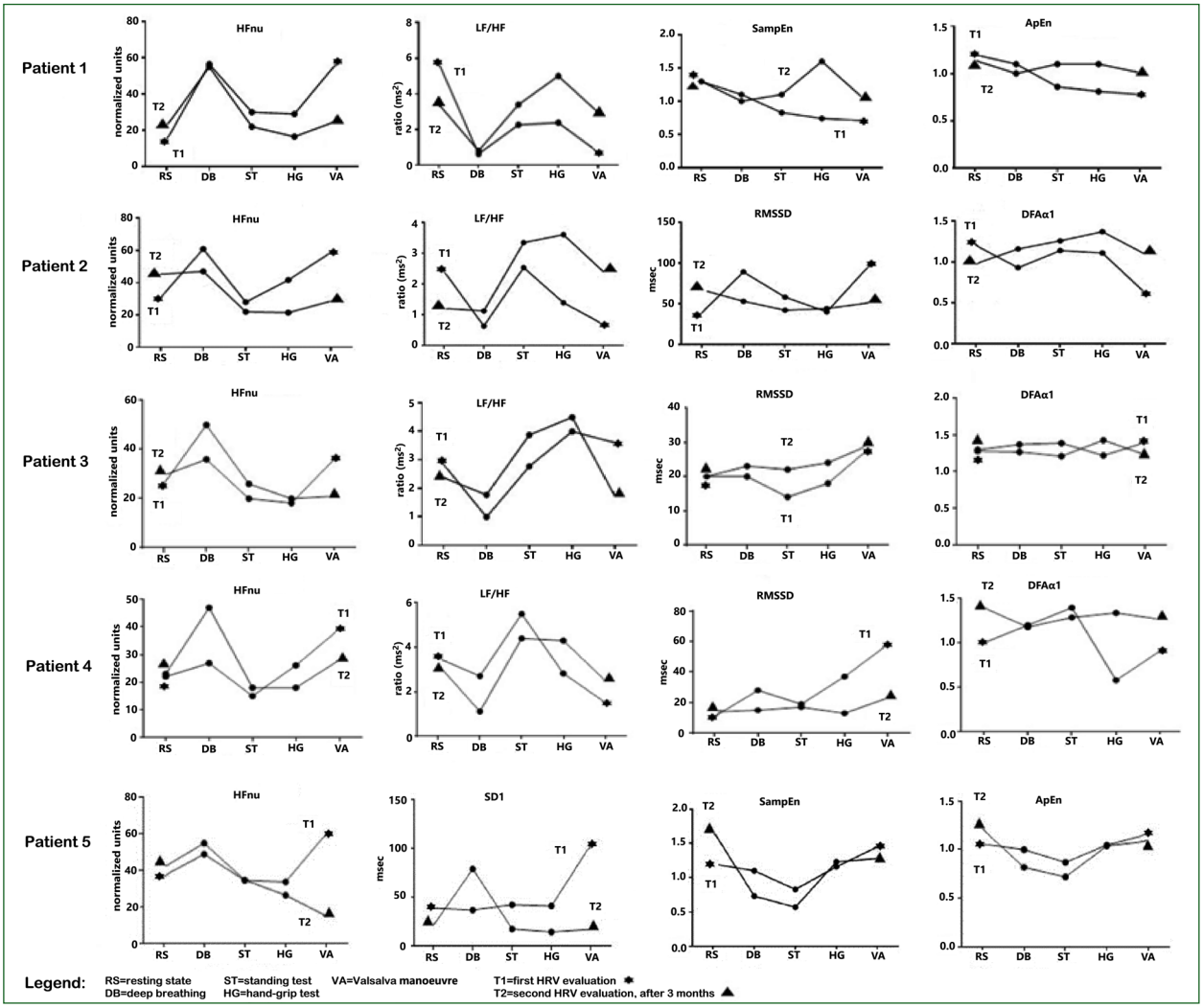


Figure 1. Heart rate variability (HRV) parameters for the five patients

tests, is confirmed in larger populations of drug-resistant epilepsy patients during VNS therapy, and if it might predispose to negative outcomes in patients with concurrent diseases. Currently, there is insufficient data to show how VNS influences different cardiac autonomic activity parameters within 24 hours, implying sleep-wake alternation, including physiological vulnerability periods of cardio-circulatory or respiratory control.

HRV analysis may be included in the current drug-resistant epilepsy patient evaluation. Drug-resistant epilepsy patients who are non-responders to VNS therapy, defined as the lack of an at least 50% seizure reduction after one year of treatment, had significantly lower RMSSD, pNN50, HF, and SD1 than the responders [44]. Thus, presurgical HRV evaluation measurements representing parasympathetic control on heart rate were significantly associated with the responsiveness to VNS [44] and may serve as a marker for the effectiveness of this therapeutic option, although further studies are needed to evaluate this hypothesis.

VNS has been shown to exert antiarrhythmic effects, improve left ventricular function, and reduce mortality in patients with heart failure [45]. The optimum VNS parameters define a stabilised state in which both afferent and efferent fibres are activated in a balanced manner, called 'neural fulcrum' [35]. VNS performed near this neural fulcrum ensures an adequate response to stressors involving both central and peripheral components [35]. It would be of interest to analyse whether reaching this cardiac autonomic balanced state would reduce the risk of fatal cardiac arrhythmia in epilepsy patients.

HRV study could, therefore, provide essential data about the neural fulcrum and could guide the adjustments of VNS parameters for the neurological target as well.

One limit of our study, besides the limited number of patients, is the interfering antiepileptic medication, especially sodium or potassium channel blockers that may alter the depolarisation-repolarisation potentials of the cardiac cells. It is therefore difficult to distinguish the medication-mediated

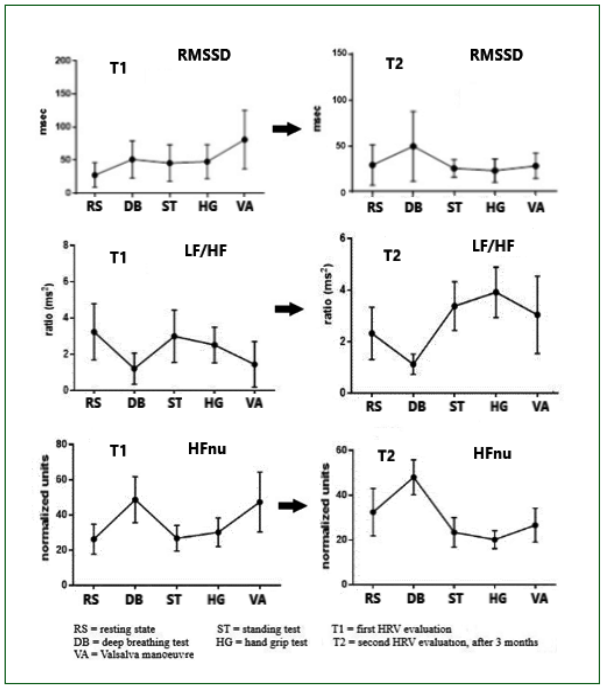


Figure 2. Root Mean Square of the Successive Differences (RMSSD), low frequency power (LF)/ high frequency power (HF) ratio and HFnu dynamics for the five patients

effects from the cardiac dysautonomia present in epilepsy patients.

Clinical implications and future directions

The involvement of ANS in patients with epilepsy has been insufficiently explored, and has produced conflicting results. Epilepsy patients present a risk of sudden unexpected death, autonomic dysfunction being one of the causes. However, the exact mechanism remains unclear. HRV is a useful method to assess the influence of ANS at the cardiac level.

Our results revealed that VNS does not alter the cardiac autonomic responses to the sympathetic and parasympathetic activation tests, having no clinically relevant effects on cardiac autonomic activity at the analysed stimulation threshold.

Patients with decreased HRV should be periodically monitored. Further studies on larger groups of drug-resistant epilepsy patients, and longer follow-up periods, are needed in order to observe the cardiac autonomic response after neurostimulation.

Conflicts of interest

None.

References

1. Lee SW, Kulkarni K, Annoni EM, et al. Stochastic vagus nerve stimulation affects acute heart rate dynamics in rats. PLoS One. 2018; 13(3): e0194910, doi: 10.1371/journal.pone.0194910, indexed in Pubmed: 29590213.
2. Premchand RK, Sharma K, Mittal S, et al. Extended Follow-Up of Patients With Heart Failure Receiving Autonomic Regulation Therapy in the ANTHEM-HF Study. J Card Fail. 2016; 22(8): 639–642, doi: 10.1016/j.cardfail.2015.11.002, indexed in Pubmed: 26576716.
3. Garamendi I, Acera M, Agundez M, et al. Cardiovascular autonomic and hemodynamic responses to vagus nerve stimulation in drug-resistant epilepsy. Seizure. 2017; 45: 56–60, doi: 10.1016/j.seizure.2016.11.018, indexed in Pubmed: 27919011.
4. Henry TR. Therapeutic mechanisms of vagus nerve stimulation. Neurology. 2002; 59: S3–14.
5. Schachter SC, Saper CB. Vagus nerve stimulation. Epilepsia. 1998; 39(7): 677–686, doi: 10.1111/j.1528-1157.1998.tb01151.x, indexed in Pubmed: 9670894.
6. Amark P, Stödberg T, Wallstedt L. Late onset bradyarrhythmia during vagus nerve stimulation. Epilepsia. 2007; 48(5): 1023–1024, doi: 10.1111/j.1528-1167.2007.01023.x, indexed in Pubmed: 17381444.
7. Schomer AC, Nearing BD, Schachter SC, et al. Vagus nerve stimulation reduces cardiac electrical instability assessed by quantitative T-wave alternans analysis in patients with drug-resistant focal epilepsy. Epilepsia. 2014; 55(12): 1996–2002, doi: 10.1111/epi.12855, indexed in Pubmed: 25470430.
8. Bernardi L, Bianchini B, Spadacini G, et al. Demonstrable cardiac reinnervation after human heart transplantation by carotid baroreflex modulation of RR interval. Circulation. 1995; 92(10): 2895–2903, doi: 10.1161/01.cir.92.10.2895, indexed in Pubmed: 7586257.
9. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996; 93(5): 1043–1065, indexed in Pubmed: 8598068.
10. Hilz MJ. Quantitative autonomic functional testing in clinical trials. In: Brown WF, Bolton CF, Aminoff MJ. ed. Neuromuscular function and disease. Basic, clinical and electrodiagnostic aspects. WB Saunders, Philadelphia 2002: 1899–1929.
11. Saul JP, Berger RD, Albrecht P, et al. Transfer function analysis of the circulation: unique insights into cardiovascular regulation. Am J Physiol. 1991; 261(4 Pt 2): H1231–H1245, doi: 10.1152/ajpheart.1991.261.4.H1231, indexed in Pubmed: 1928405.
12. Huikuri HV, Mäkikallio TH, Perkiömäki J. Measurement of heart rate variability by methods based on nonlinear dynamics. J Electrocardiol. 2003; 36 Suppl: 95–99, doi: 10.1016/j.jelectrocard.2003.09.021, indexed in Pubmed: 14716599.
13. Voss A, Kurths J, Kleiner HJ, et al. The application of methods of non-linear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death. Cardiovasc Res. 1996; 31(3): 419–433, indexed in Pubmed: 8681329.
14. Golińska AK. Detrended fluctuation analysis (DFA) in biomedical signal processing: Selected examples. Studies in Logic, Grammar and Rhetoric. 2012; 29: 107–115.
15. Chen C, Jin Yu, Lo IL, et al. Complexity Change in Cardiovascular Disease. Int J Biol Sci. 2017; 13(10): 1320–1328, doi: 10.7150/ijbs.19462, indexed in Pubmed: 29104498.
16. Mäkikallio TH, Koistinen J, Jordaens L, et al. Heart rate dynamics before spontaneous onset of ventricular fibrillation in patients with healed myocardial infarcts. Am J Cardiol. 1999; 83(6): 880–884, doi: 10.1016/s0002-9149(98)01068-6, indexed in Pubmed: 10190403.
17. Mäkikallio TH, Seppänen T, Niemelä M, et al. Abnormalities in beat to beat complexity of heart rate dynamics in patients with a previous

myocardial infarction. J Am Coll Cardiol. 1996; 28(4): 1005–1011, doi: 10.1016/s0735-1097(96)00243-4, indexed in Pubmed: 8837582.
18. Varadhan R, Chaves PHM, Lipsitz LA, et al. Frailty and impaired cardiac autonomic control: new insights from principal components aggregation of traditional heart rate variability indices. J Gerontol A Biol Sci Med Sci. 2009; 64(6): 682–687, doi: 10.1093/gerona/glp013, indexed in Pubmed: 19223607.
19. Tsuji H, Venditti FJ, Manders ES, et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. Circulation. 1994; 90(2): 878–883, doi: 10.1161/01.cir.90.2.878, indexed in Pubmed: 8044959.
20. Myers KA, Bello-Espinosa LE, Symonds JD, et al. Heart rate variability in epilepsy: A potential biomarker of sudden unexpected death in epilepsy risk. Epilepsia. 2018; 59(7): 1372–1380, doi: 10.1111/epi.14438, indexed in Pubmed: 29873813.
21. Constantinescu V, Matei D, Constantinescu I, et al. Heart Rate Variability and Vagus Nerve Stimulation in Epilepsy Patients. Transl Neurosci. 2019; 10: 223–232, doi: 10.1515/tnsci-2019-0036, indexed in Pubmed: 31497318.
22. Budrejko S, Kempa M, Chmielecka M, et al. Analysis of Heart Rate Variability During Head-Up Tilt-Test in Patients with Vasovagal Syncope. Eur J Transl Clin Med. 2018; 1(1): 24–36, doi: 10.31373/ejtcm/92837.
23. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health. 2017; 5: 258, doi: 10.3389/fpubh.2017.00258, indexed in Pubmed: 29034226.
24. Mourot L, Bouhaddi M, Perrey S, et al. Decrease in heart rate variability with overtraining: assessment by the Poincaré plot analysis. Clin Physiol Funct Imaging. 2004; 24(1): 10–18, doi: 10.1046/j.1475-0961.2003.00523.x, indexed in Pubmed: 14717743.
25. Mourot L, Bouhaddi M, Perrey S, et al. Quantitative Poincaré plot analysis of heart rate variability: effect of endurance training. Eur J Appl Physiol. 2004; 91(1): 79–87, doi: 10.1007/s00421-003-0917-0, indexed in Pubmed: 12955518.
26. Peng CK, Havlin S, Stanley HE, et al. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. Chaos. 1995; 5(1): 82–87, doi: 10.1063/1.166141, indexed in Pubmed: 11538314.
27. Corino VDA, Ziglio F, Lombardi F, et al. Detrended Fluctuation Analysis of Atrial Signal during Adrenergic Activation in Atrial Fibrillation. Computers in Cardiology. 2006; 33: 141–144.
28. Yeh RG, Shieh JS, Chen GY, et al. Detrended fluctuation analysis of short-term heart rate variability in late pregnant women. Auton Neurosci. 2009; 150(1-2): 122–126, doi: 10.1016/j.autneu.2009.05.241, indexed in Pubmed: 19464962.
29. Rodriguez E, Echeverria J, Alvarez-Ramirez J. Detrended fluctuation analysis of heart intrabeat dynamics. Physica A. 2007; 384(2): 429–438, doi: 10.1016/j.physa.2007.05.022.
30. Acharya RU, Lim CM, Joseph P. Heart rate variability analysis using correlation dimension and detrended fluctuation analysis. ITBM-RBM. 2002; 23(6): 333–339, doi: 10.1016/s1297-9562(02)90002-1.
31. Absil PA, Sepulchre R, Bilge A, et al. Nonlinear analysis of cardiac rhythm fluctuations using DFA method. Physica A: Statistical Mechanics and its Applications. 1999; 272(1-2): 235–244, doi: 10.1016/s0378-4371(99)00295-2.
32. Germán-Salló Z, Germán-Salló M. Non-linear Methods in HRV Analysis. Procedia Technology. 2016; 22: 645–651, doi: 10.1016/j.protcy.2016.01.134.
33. Pikkujämsä SM, Mäkikallio TH, Sourander LB, et al. Cardiac interbeat interval dynamics from childhood to senescence : comparison of conventional and new measures based on fractals and chaos theory. Circulation. 1999; 100(4): 393–399, doi: 10.1161/01.cir.100.4.393, indexed in Pubmed: 10421600.
34. Fornai F, Ruffoli R, Giorgi FS, et al. The role of locus coeruleus in the antiepileptic activity induced by vagus nerve stimulation. Eur J Neurosci. 2011; 33(12): 2169–2178, doi: 10.1111/j.1460-9568.2011.07707.x, indexed in Pubmed: 21535457.
35. Ardell JL, Rajendran PS, Nier HA, et al. Central-peripheral neural network interactions evoked by vagus nerve stimulation: functional consequences on control of cardiac function. Am J Physiol Heart Circ Physiol. 2015; 309(10): H1740–H1752, doi: 10.1152/ajpheart.00557.2015, indexed in Pubmed: 26371171.
36. Galbarriatu L, Pomposo I, Aurrecoechea J, et al. Vagus nerve stimulation therapy for treatment-resistant epilepsy: a 15-year experience at a single institution. Clin Neurol Neurosurg. 2015; 137: 89–93, doi: 10.1016/j.clineuro.2015.06.023, indexed in Pubmed: 26164349.
37. Ryvlin P, Gilliam FG, Nguyen DK, et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. Epilepsia. 2014; 55(6): 893–900, doi: 10.1111/epi.12611, indexed in Pubmed: 24754318.
38. Stemper B, Devinsky O, Haendl T, et al. Effects of vagus nerve stimulation on cardiovascular regulation in patients with epilepsy. Acta Neurol Scand. 2008; 117(4): 231–236, doi: 10.1111/j.1600-0404.2007.00944.x, indexed in Pubmed: 18005223.
39. Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. J Clin Neurophysiol. 2001; 18(5): 415–418, doi: 10.1097/00004691-200109000-00005, indexed in Pubmed: 11709646.
40. Vanderlei LC, Pastre CM, Hoshi RA, et al. Basic notions of heart rate variability and its clinical applicability. Rev Bras Cir Cardiovasc. 2009; 24(2): 205–217, doi: 10.1590/s0102-76382009000200018, indexed in Pubmed: 19768301.
41. Ronkainen E, Korpelainen JT, Heikkinen E, et al. Cardiac autonomic control in patients with refractory epilepsy before and during vagus nerve stimulation treatment: a one-year follow-up study. Epilepsia. 2006; 47(3): 556–562, doi: 10.1111/j.1528-1167.2006.00467.x, indexed in Pubmed: 16529621.
42. Liu H, Yang Z, Meng F, et al. Deceleration and acceleration capacities of heart rate in patients with drug-resistant epilepsy. Clin Auton Res. 2019; 29(2): 195–204, doi: 10.1007/s10286-018-0569-0, indexed in Pubmed: 30328033.
43. Baysal-Kirac L, Serbest NG, Şahin E, et al. Analysis of heart rate variability and risk factors for SUDEP in patients with drug-resistant epilepsy. Epilepsy Behav. 2017; 71(Pt A): 60–64, doi: 10.1016/j.yebeh.2017.04.018, indexed in Pubmed: 28549245.
44. Liu H, Yang Z, Huang L, et al. Heart-rate variability indices as predictors of the response to vagus nerve stimulation in patients with drug-resistant epilepsy. Epilepsia. 2017; 58(6): 1015–1022, doi: 10.1111/epi.13738, indexed in Pubmed: 28440954.
45. Rousselet L, Le Rolle V, Ojeda D, et al. Influence of Vagus Nerve Stimulation parameters on chronotropism and inotropism in heart failure. Conf Proc IEEE Eng Med Biol Soc. 2014; 2014: 526–529, doi: 10.1109/EMBC.2014.6943644, indexed in Pubmed: 25570012.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54, no. 4, pages: 337–343
DOI: 10.5603/PJNNS.a2020.0054

ISSN 0028–3843

Treatment and management of migraine in neurological ambulatory practice in Poland by indicating therapy with monoclonal anti-CGRP antibodies

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, 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, Lodz, Poland
[4]Department of Neurology, Military Institute of Medicine in Warsaw, Warsaw, Poland
[5]Department of Neurology, Charles Marcinkowski University of Medical Sciences, Poznan, Poland

ABSTRACT

Aim of study. To analyse Polish neurologists' familiarity with the diagnostic criteria for migraine, and how their methods of management of migraine work in daily practice.

Clinical rationale for study. Migraine is a common primary headache disease that causes substantial disability and reduces quality of life. Many migraine patients remain undiagnosed and deprived of treatment. Migraine treatment is problematic, and many patients discontinue preventive treatment, mainly because of a lack of efficacy or adverse effects. Antibodies targeting calcitonin gene-related peptide and its receptor seem to be effective and well-tolerated agents in migraine prevention.

Material and methods. This study was conducted using a computer-assisted web interview conducted with 51 neurologists in Poland, who agreed to participate in the study during a phone call. The questionnaire mainly assessed methods of treatment of migraine patients and diagnostic criteria used in neurological practice.

Results. Only one neurologist listed all of the diagnostic criteria for migraine, and 80% of physicians in their practice used only a part of the migraine diagnostic criteria, usually the migraine without aura criteria. On average, each neurologist had 55 patients under continuous care, seeing roughly 18 patients per month. On average, neurologists estimated that 77% of all patients with migraine had episodic migraine, whereas the rest had the chronic form. Importantly, 40% of patients with chronic migraine received all available preventive treatments without a satisfactory effect. Neurologists could offer monoclonal antibodies that target the CGRP-pathway (i.e. anti-CGRP and anti-CGRP receptor monoclonal antibodies) for the prevention of chronic migraine to about one in three patients with a chronic form of the disease.

Conclusions and clinical implications. Migraine is underdiagnosed and undertreated in Poland. Understanding of the diagnostic criteria for migraine among neurologists is insufficient. Most neurologists in Poland see patients in whom anti-CGRP/R--targeting treatment is indicated.

Key words: migraine, chronic migraine, anti-CGRP

(*Neurol Neurochir Pol 2020; 54 (4): 337–343*)

Introduction

Migraine is a common primary headache disease that causes substantial disability and seriously affects quality of life. Globally, migraine is the second highest cause of years lived with disability, and it is the most common cause for referrals to a neurologist [1, 2]. It is estimated that migraine affects 15–18% of women and 6% of men [3]. However, many people

Address for correspondence: Izabela Domitrz, Department of Neurology, Faculty of Medical Sciences, Medical University of Warsaw, Cegłowska 80 Str., 01-809 Warsaw, Poland, e-mail: izabela.domitrz@wum.edu.pl

with migraine remain undiagnosed; about a quarter of patients with headaches meeting the diagnostic criteria for migraine do not receive a proper diagnosis [4]. In an online survey among Polish adults, 25% had reported migraine symptoms within the previous 12 months, 2.5% had experienced migraine attacks with aura only, 6.4% had experienced migraine attacks without aura, and 16.2% had experienced migraine attacks with or without aura. 37% of people with migraine declared that they had had migraine diagnosed by a physician in the past. 43% of people suffering from migraine attacks received medical advice for their condition; in the majority of cases they were referred to a primary care physician/general practitioner (71%), or slightly less frequently to a neurologist (48%) [5]. Similarly, in a large population study in Poland, 8.5% of participants had migraine; there are no other reliable studies except those quoted here [6].

In the USA, the National Hospital Interview Survey showed that the overall prevalence of migraine or severe headache was 15.3% [7]. Chronic migraine affects 1.4–2.2% of the general population, with a 2.5–6.5-fold greater prevalence among women [8]. Compared to episodic migraine, chronic migraine poses a greater burden for patients and their families and generates three times more healthcare costs. In addition to frequent headaches, patients with chronic migraine often present anxiety, depression, obesity, and disorders of the respiratory, cardiovascular, and gastrointestinal systems [9].

The International Classification of Headache Disorders, 3rd. Edition (ICHD-III) defines chronic migraine as a headache occurring on 15 or more days per month for three months or longer, with features of a migraine headache on eight or more days per month [10]. Some have even suggested that having a migraine headache on eight or more days per month should itself be sufficient to define chronic migraine, because such patients have a disabling disease that requires effective treatment [4, 10, 11].

There are three main aspects to managing migraine: lifestyle changes which include the recognition and avoidance of migraine triggers, the treatment of acute attacks, and preventive treatment. The most common migraine triggers include fasting, alcohol, caffeine withdrawal, or specific foods [12].

Effective treatment, acute and preventive, reduces the risk of progression and improves the outcome in patients with migraine [13].

Acute migraine should be treated pharmacologically, with nonsteroidal anti-inflammatory drugs, triptans, antiemetics, or, less commonly, ergots, all together being the first-line medications [14, 15]. Preventive treatment should be considered in patients with chronic migraine or episodic migraine with frequent attacks, when the frequency or severity of headaches interferes substantially with work, school, or social life. Many drugs are used for preventive treatment, including β-blockers, calcium channel blockers, antidepressants, and anticonvulsants, as well as botulinum toxin, although this last-named is used exclusively in chronic migraine.

Moreover, because calcitonin gene-related peptide (CGRP) is crucially implicated in the pathogenesis of migraine, monoclonal antibodies that target CGRP or its receptor (CGRP-R) have been developed to prevent both chronic and episodic migraine [16, 17]. On average, these agents shorten the duration of migraine by about a week per month [18]. The drugs for preventive treatment are chosen based on the headache pattern, comorbidities, medication tolerability, and patient preferences.

In practice, many patients discontinue classical/pharmacological preventive treatment, mainly because of a lack of efficacy or adverse effects. Thus, there is a need for highly tolerable and effective preventive treatments for migraine [19].

Clinical rationale for this study

Migraine is an underdiagnosed and undertreated disease in Poland. Greater knowledge in the field of migraine diagnosis will help neurologists estimate the number of patients who require treatment, including monoclonal antibodies that target the CGRP-pathway. The aim of this study was to analyse Polish neurologists' familiarity with the diagnostic criteria for migraine and their management preferences for migraine in daily practice, including the latest recommendations.

Materials and methods

In June and July 2019 we conducted a computer-assisted web interview with neurologists in Poland, who had agreed to participate in the study during a phone call.

The inclusion criteria were as follows:

- Specialisation in neurology (board certification)
- Seeing eight or more patients with migraine per month
- Seeing patients with chronic migraine
- Initiating treatment for chronic migraine

The neurologists filled out a questionnaire (spontaneous answer, open-ended question) that assessed:

- Knowledge of the diagnostic criteria for migraine
- Number of patients with episodic or chronic migraine under their care
- Treatment options of episodic and chronic migraine
- Preventive treatment for chronic migraine
- Need for new therapies in migraine
- Knowledge of anti-CGRP and/or anti-CGRP-R monoclonal antibodies.

Results

A total of 51 neurologists, with a mean experience in neurology of 17.2 years, completed the questionnaire. Only one neurologist (~2%) knew the exact definition of, and listed all the diagnostic criteria for, migraine without and with aura. Five (~10%) neurologists listed all the diagnostic criteria for migraine without aura, 80% of physicians in their practice

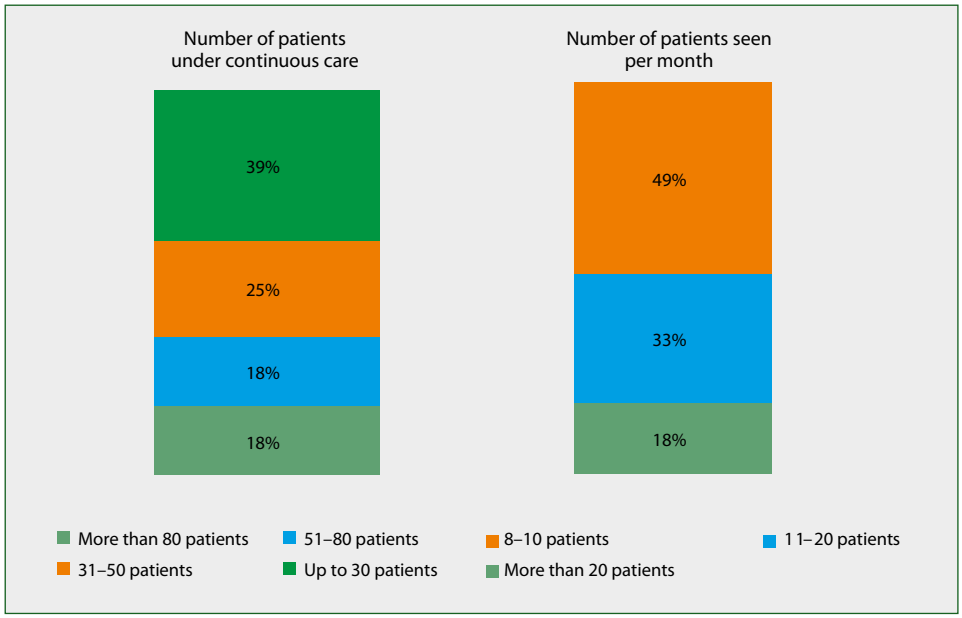


Figure 1. Percentages of neurologists declaring the number of patients under continuous care and the number of patients seen per month

used only a part of the migraine diagnostic criteria, usually migraine without aura criteria, and a large proportion of them (29% of neurologists) listed very limited criteria. Nine (18% of neurologists) did not list any diagnostic criteria for migraine (Fig. S1).

Thirty-six (71%) neurologists provided care to patients with migraine in a public outpatient clinic. Thirty-four (67%) neurologists provided care for patients with migraine in hospital. Figure 1 shows the percentages of neurologists declaring the number of patients under continuous care and the number of patients per month. On average, each neurologist had 55 (median 40) patients under continuous care, seeing a mean of 18 (median 12) patients per month. On average, neurologists estimated that 77% of all patients with migraine had episodic migraine, whereas the rest had chronic migraine.

On average, neurologists estimated that 8% of patients with episodic migraine (which is one patient per month) required sick leave, with a mean absence of four days. Among patients with chronic migraine, 22% required sick leave (which is one patient per month), with a mean absence of seven days.

Treatment for episodic migraine

Each neurologist provided care to an average of 42 patients with episodic migraine. On average, 78% of patients with episodic migraine received prescription drugs, 19% received over-the-counter (OTC) drugs only, and 3% did not receive any drugs. Of patients who received pharmacological treatment, 53% received acute treatment only, 41% received preventive and acute treatment, and 6% received preventive treatment only (Fig. S2).

Thirty-four (67%) neurologists initiated preventive therapy based on the number of days with migraine headaches in a month, with an average of seven days being sufficient to start treatment. Neurologists estimated that, among patients with episodic migraine, 36% overused OTC analgesics and 8% overused triptans.

Treatment for chronic migraine

On average, each neurologist provided care to 13 patients with chronic migraine. Most of these patients (84%) received prescription drugs, 6% received OTC treatment ordered by a neurologist, 9% self-medicated with OTC drugs, and 1% did not receive any drugs. Most patients with chronic migraine (78%) received preventive and acute treatment, 14% received acute treatment only, and 8% received preventive treatment only (Fig. 2).

Twenty-seven neurologists (53%) initiated preventive treatment based on the number of days with a migraine headache in a month, with cut-off values ranging from three to 16 days. Eighteen of them initiated preventive treatment in their patients when the total length of time with a migraine headache in a month was 14-16 days (average > 12 days). Fifteen (29%) neurologists initiated preventive treatment based on the number of days with a headache in a month, and nine of them used the cut-off value of 14-15 days (average > 12 days).

On average, of patients with chronic migraine on preventive treatment, 39% received anticonvulsants, 24% received β-blockers, and 22% received calcium channel blockers (Fig. S3). Among patients with chronic migraine, 54% overused OTC analgesics and 18% overused triptans.

Twenty-nine (57%) neurologists initiated preventive therapy for chronic migraine with anticonvulsants, 19 (37%) with β-blockers, and 18 (35%) with calcium channel blockers. First-line preventive treatment was effective in 64% of patients;

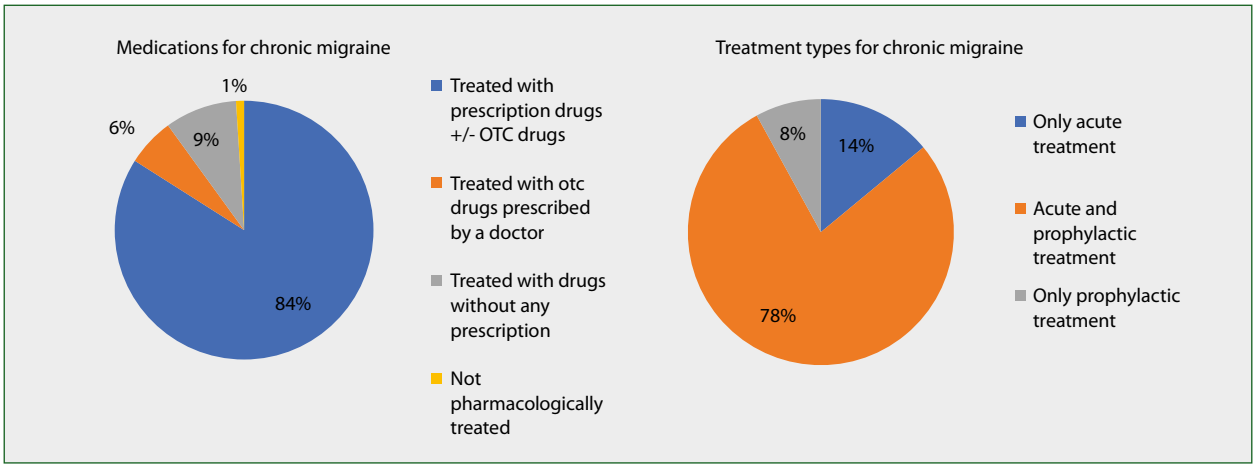


Figure 2. Medications and treatment types for chronic migraine

28% of patients switched to a second-line drug, and 9% discontinued first-line treatment. Thirty-six (71%) neurologists used anticonvulsants as second-line preventive treatment for chronic migraine. Second-line treatment was effective in 58% of patients; 31% of patients switched to a third-line drug, and 11% of patients discontinued second-line treatment. Twenty-four (47%) neurologists used anticonvulsants as third-line preventive treatment; botulinum toxin was prescribed by nine (18%) neurologists. Third-line treatment was effective in 49% of patients; 32% of patients switched to a fourth-line drug, and 19% discontinued third-line treatment. Twenty-seven (53%) neurologists did not try fourth-line preventive treatment, and 36 (70%) did not try fifth-line preventive treatments. Preventive treatment was discontinued due to a lack of effectiveness (34% of patients), patient decision (30%), or adverse effects (19%). On average, each neurologist had about five (40%) patients with chronic migraine, who had received all possible treatments in their opinion. On average, each neurologist could offer anti-CGRP/R-targeting treatment to 4.2 patients i.e. 33% of patients with chronic migraine, and 8% of all patients with migraine. Figure S4 shows the percentages of neurologists declaring the number of patients with chronic migraine who used all possible treatments and the number of patients who could be offered anti-CGRP or anti-CGRP-R treatment.

Forty-one (80%) neurologists were aware that anti-CGRP and/or anti-CGRP-R monoclonal antibodies were available in Poland. Forty neurologists (78%) knew that erenumab was approved in Poland. Four (8%) neurologists declared that eptinezumab was available in Poland, which is not yet true. Nine (18%) neurologists did not know of any anti-CGRP drugs approved in Poland (Fig. S5).

Discussion

In this study, only one neurologist knew the exact diagnostic criteria for migraine with and without aura. Less than a third of the responding neurologists listed some of the diagnostic criteria only for migraine without aura.

It must be underlined that the neurologists participating in this study defined themselves as being those who regularly manage migraine patients and are experts in this field.

Our findings show that knowledge of the diagnostic criteria for migraine among neurologists in Poland is very poor, which can lead to inappropriate treatment.

Our results are only partially in line with previous research, because in that previous research the problem was investigated only in relation to family doctors/primary care physicians. Gultekin et al. found that only one in 10 primary healthcare physicians was able to make a correct diagnosis of migraine [20]. In another study, 70% of patients with primary headache complaints did not receive a correct diagnosis from general practitioners [21]. It seems that educating doctors and patients on migraine symptoms is necessary in order to increase the recognition of migraine and to improve treatment outcomes, including the outcomes of preventive treatment.

In 2016, migraine was ranked as the number one cause of years lived with disability in people aged 15–49, i.e. the sector of society who are the most occupationally active [22]. Patients with chronic migraine have considerably reduced health-related quality of life in physical, mental, and overall health aspects. The impact of migraine on life increases with the number of days on which migraine headaches occur [23].

Indeed, in the internet-based survey by Silberstein et al., headache-related disability, healthcare resource utilisation, and economic burden were found to increase gradually in patients presenting low-, moderate-, and high-frequency migraine, with the highest scores achieved in the chronic migraine subgroup [24].

Lack of effective treatment for migraine leads to frequent physician consultations, thereby generating substantial social and economic costs [25]. In 2017, the National Health Fund in Poland provided services for patients with migraine at

a total cost exceeding 7 million PLN [26]. The costs due to absenteeism (nearly 100,000 days annually) were estimated at nearly 31 million PLN. According to the Social Insurance Institution in Poland, patients with episodic migraine have decreased productivity for 3.3 days quarterly, and those with chronic migraine, for 15.7 days quarterly. In this study, more than 20% of patients with chronic migraine required sick leave that lasted for an average of seven days.

Apart from the aforementioned absenteeism, presenteeism seems to be another, perhaps even more common and significant, problem. It is much more difficult to evaluate and to count the economic consequences of incomplete functioning in the workplace because of a set of symptoms of migraine attack including not only headache but also nausea, vomiting, hyperresponsiveness to light, sound, and smell, as well as avoiding any motor activities. Even though employees are physically at work, they are unable to concentrate, focus on work, and fully perform their duties. They do their jobs ineffectively, and are more likely to make mistakes.

It is clear that the burden of migraine, particularly chronic migraine, is underestimated.

In Poland, perhaps 1% of the general population might have chronic migraine, but fewer than half of those suffering from migraine receive medical help [26, 27].

Effective preventive treatment can reduce the economic costs of migraine. In practice, however, it is difficult to achieve effective migraine prevention. In this study, 40% of patients with chronic migraine received all available preventive treatments, but without a satisfactory result. The main reasons for treatment discontinuation were a lack of effectiveness (61%) and adverse effects (41%). In the International Burden of Migraine Study (IBMS-II), the reasons given for discontinuation were similar (lack of effectiveness ~40%; adverse effects ~40%). These findings indicate that there is a need for tolerable and effective preventive treatments for migraine [19].

The classic preventive oral treatments, including tricyclic antidepressants, β-blockers, calcium channel blockers, and antiepileptics, were not developed specifically for patients with migraine. In contrast, anti-CGRP-pathway monoclonal antibodies target CGRP or its receptor, a key neuropeptide which is implicated in the pathophysiology of migraine. Moreover, these medications (anti-CGRP-pathway monoclonal antibodies) are much better tolerated and have almost no contraindications.

With regard to the most serious adverse events due to some classic migraine prevention therapeutics, such as teratogenicity and liver toxicity, there is currently no evidence that anti-CGRP-pathway monoclonal antibodies would cause such adverse events [28]. The efficacy and safety of four anti-CGRP-pathway monoclonal antibodies have been assessed in groups of both episodic and chronic migraine patients [29–37].

In a phase 3, randomised trial among patients with chronic migraine, the anti-CGRP monoclonal antibody fremanezumab, injected quarterly, reduced the number of headache days by 4.3 ± 0.3 per month and, when injected monthly, by 4.6 ± 0.3 per month, compared to 2.5 ± 0.3 per month in the placebo group ($p < 0.001$ for both comparisons with placebo). Injection-site reactions to the drug were common. The most common adverse event was injection-site pain, which occurred with comparable frequency in all three groups (30%, 26%, and 28%, respectively) [29]. In the FOCUS study among 838 patients after the failure to up to four migraine preventive medication classes, fremanezumab monthly and quarterly reduced the number of days with migraine headache by 3.5 and 3.1 per month compared to placebo respectively ($p < 0.0001$). Fremanezumab was well tolerated, and there were no safety concerns. The FOCUS study showed that patients with difficult-to-treat episodic or chronic migraine, who previously did not respond to up to four preventive medications, can achieve clinically meaningful improvement with fremanezumab [30].

Another anti-CGRP monoclonal antibody, galcanezumab, was assessed in prevention of episodic or chronic migraine in adult patients in three phase 3, randomised, double-blind, placebo-controlled studies: EVOLVE-1 [31], EVOLVE-2 [33], and REGAIN [34].

In the EVOLVE-2 trial, galcanezumab given to episodic migraine patients at a dose of 120 mg or 240 mg monthly reduced the number of days with migraine headache by 2.02 ± 0.27 and 1.90 ± 0.27, respectively, compared to placebo ($p < 0.001$). Injection site pain was the most commonly reported treatment-emergent adverse event [33].

Erenumab, a monoclonal antibody targeting CGRP receptor, was assessed in patients with episodic migraine in the STRIVE trial. While significantly reducing the number of days with migraine (3.2 at a dose of 70 mg and 3.7 at a dose of 140 mg per month compared to 1.8 for placebo, $p < 0.001$), it showed a safety profile similar to that of the placebo [32]. It also proved to be efficacious and well tolerated in chronic migraine patients in a phase 2 clinical trial [35].

Eptinezumab, the only intravenous anti-CGRP monoclonal antibody, was investigated in the PROMISE-1 study in patients with episodic migraine [36], and in the PROMISE-2 study in patients with chronic migraine [37]. In both studies, it proved to be efficacious and well-tolerated.

In conclusion, all four anti-CGRP-pathway drugs appear to be highly successful in both episodic and chronic migraine management, while presenting favourable safety profiles.

Our study showed that each neurologist could offer anti-CGRP-pathway treatment for the preventive treatment of migraine to about four patients, i.e. about a third of patients with chronic migraine and about 10% of all patients with migraine. Of the four anti-CGRP-pathway monoclonal antibodies developed to date, three are approved in Europe/Poland (approved first by FDI, next by EMA), i.e. erenumab, fremanezumab, and galcanezumab. Eptinezumab has not yet been approved in Poland or Europe, but it has received FDA approval [38]. About eight in 10 neurologists were aware that erenumab was available in Poland, but only 6% and 2%

knew of the approval of galcanezumab and fremanezumab, respectively. During the study period, only erenumab was available in Poland; fremanezumab also became available in November 2019.

The cost of anti-CGRP-pathway monoclonal antibodies is considerably higher than that of other drugs used for migraine prevention. However, since monoclonal antibodies targeting CGRP and its receptor have demonstrated strong and consistent efficacy, favourable tolerability, and no safety signals, they can reduce the direct and indirect costs of migraine. Effectiveness, good tolerability, but also convenience of administration and, in our opinion, very high compliance and adherence, are evident advantages of anti-CGRP-pathway monoclonal antibodies. This kind of therapy may represent a valid option for episodic migraine and chronic migraine prevention in patients who are intolerant or who have inadequate response or contraindications to conventional preventive treatments [39]. Importantly, early treatment in patients with high-frequency episodic migraine may prevent progression from episodic to chronic migraine, thus reducing the burden on patients and society.

Conclusions and clinical implications

Migraine is underdiagnosed and undertreated in Poland. The diagnostic criteria for migraine used by neurologists in their practice are insufficient, mainly due to poor knowledge. Increasing migraine recognition will help to establish the number of patients who require treatment, including prevention. Importantly, 40% of patients with chronic migraine receive all available preventive treatments used not only for the prevention of chronic migraine but also for treating episodic migraine, but without a satisfactory result.

Anti-CGRP-pathway monoclonal antibodies are effective and have a favourable safety profile. Most neurologists in Poland see migraine patients in whom anti-CGRP-pathway treatment is both justified and indicated.

Ethical permission: *Ethical approval was not necessary for the preparation of this article.*

Funding: *This research was funded by Teva Pharmaceuticals Polska Sp. z o.o., Poland and was conducted in co-operation with PEX PharmaSequence, Poland.*

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 and sponsored by Teva Pharmaceuticals Polska Sp. z o.o., Poland.

Conflicts of interest: *A.L. is a Teva Pharmaceuticals Polska employee. The authors declare no conflicts of interest. All authors have read and approved the revised manuscript.*

References

1. Goadsby PJ. Bench to bedside advances in the 21st century for primary headache disorders: migraine treatments for migraine patients. Brain. 2016; 139(Pt 10): 2571–2577, doi: 10.1093/brain/aww236, indexed in Pubmed: 27671024.
2. GBD 2016 Neurology Collaborators, GBD 2016 Headache Collaborators. 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. 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.
4. Tepper SJ, Dahlöf CGH, Dowson A, et al. Prevalence and diagnosis of migraine in patients consulting their physician with a complaint of headache: data from the Landmark Study. Headache. 2004; 44(9): 856–864, doi: 10.1111/j.1526-4610.2004.04167.x, indexed in Pubmed: 15447694.
5. 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, International Headache Congress Dublin 05-08; 2019.
6. Stępień A, Prusiński A, Suwała A. Selected epidemiological data on migraine prevalence in Poland. Ból. 2003; 3(4): 9–12.
7. Burch R, Rizzoli P, Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. Headache. 2018; 58(4): 496–505, doi: 10.1111/head.13281, indexed in Pubmed: 29527677.
8. 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.
9. Buse DC, Manack A, Serrano D, et al. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. J Neurol Neurosurg Psychiatry. 2010; 81(4): 428–432, doi: 10.1136/jnnp.2009.192492, indexed in Pubmed: 20164501.
10. The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018; 38(1): 1–211.
11. Chalmer MA, Hansen TF, Lebedeva ER, et al. Proposed new diagnostic criteria for chronic migraine. Cephalalgia. 2020; 40(4): 399–406, doi: 10.1177/0333102419877171, indexed in Pubmed: 31544467.
12. Chądzyński P, Kacprzak A, Domitrz W, et al. Migraine headache facilitators in a population of Polish women and their association with migraine occurrence - preliminary results. Neurol Neurochir Pol. 2019; 53(5): 377–383, doi: 10.5603/PJNNS.a2019.0044, indexed in Pubmed: 31592536.
13. Charles A. The pathophysiology of migraine: implications for clinical management. The Lancet Neurology. 2018; 17(2): 174–182, doi: 10.1016/s1474-4422(17)30435-0.
14. Evers S, Afra J, Frese A, et al. European Federation of Neurological Societies, Members of the task force:. EFNS guideline on the drug treatment of migraine - report of an EFNS task force. Eur J Neurol. 2006; 13(6): 560–572, doi: 10.1111/j.1468-1331.2006.01411.x, indexed in Pubmed: 16796580.
15. Stępień A. Kryteria diagnostyczne i leczenie migreny w oparciu o obowiązujące zalecenia międzynarodowe. Med Dypl. 2011; 9(186): 81–87.
16. Monteith T. Chronic Migraine: Epidemiology, Mechanisms, and Treatment. Chronic Headache. 2018: 37–62, doi: 10.1007/978-3-319-91491-6_4.

17. Weatherall MW. The diagnosis and treatment of chronic migraine. Ther Adv Chronic Dis. 2015; 6(3): 115–123, doi: 10.1177/2040622315579627, indexed in Pubmed: 25954496.
18. Ong JJ, Wei DYT, Goadsby PJ. Recent Advances in Pharmacotherapy for Migraine Prevention: From Pathophysiology to New Drugs. Drugs. 2018; 78(4): 411–437, doi: 10.1007/s40265-018-0865-y, indexed in Pubmed: 29396834.
19. Blumenfeld AM, Bloudek LM, Becker WJ, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). Headache. 2013; 53(4): 644–655, doi: 10.1111/head.12055, indexed in Pubmed: 23458496.
20. Gültekin M, Balci E, İsmaİLOĞULLARI 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.
21. Kernick D, Stapley S, Hamilton W. GPs' classification of headache: is primary headache underdiagnosed? Br J Gen Pract. 2008; 58(547): 102–104, doi: 10.3399/bjgp08X264072, indexed in Pubmed: 18307854.
22. Steiner TJ, Stovner LJ, Vos T, et al. Migraine is first cause of disability in under 50s: will health politicians now take notice? J Headache Pain. 2018; 19(1): 17, doi: 10.1186/s10194-018-0846-2, indexed in Pubmed: 29468450.
23. Blumenfeld AM, Varon SF, Wilcox TK, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). Cephalalgia. 2011; 31(3): 301–315, doi: 10.1177/0333102410381145, indexed in Pubmed: 20813784.
24. Silberstein SD, Lee L, Gandhi K, et al. Health care Resource Utilization and Migraine Disability Along the Migraine Continuum Among Patients Treated for Migraine. Headache. 2018; 58(10): 1579–1592, doi: 10.1111/head.13421, indexed in Pubmed: 30375650.
25. Wang SJ, Fuh JL, Huang SY, et al. Taiwan MAP Study Group. Diagnosis and development of screening items for migraine in neurological practice in Taiwan. J Formos Med Assoc. 2008; 107(6): 485–494, doi: 10.1016/S0929-6646(08)60157-6, indexed in Pubmed: 18583220.
26. Społeczne znaczenie migreny z perspektywy zdrowia publicznego i systemu ochrony zdrowia. Zakład Analiz Ekonomicznych i Systemowych Narodowy Instytut Zdrowia Publicznego – Państwowy Zakład Higieny. 2019: Warszawa.
27. Katarzyńska A, Domitrz I. Codzienny przewlekły ból głowy – historia, epidemiologia, klinika i przyszłość Neurologia i Neurochirurgia Polska. 2009; 43(2): 155–161.
28. 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.
29. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. N Engl J Med. 2017; 377(22): 2113–2122, doi: 10.1056/NEJMoa1709038, indexed in Pubmed: 29171818.
30. Ferrari MD, Diener HC, Ning X, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. Lancet. 2019; 394(10203): 1030–1040, doi: 10.1016/S0140-6736(19)31946-4, indexed in Pubmed: 31427046.
31. Stauffer VL, Dodick DW, Zhang Qi, et al. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. JAMA Neurol. 2018; 75(9): 1080–1088, doi: 10.1001/jamaneurol.2018.1212, indexed in Pubmed: 29813147.
32. Goadsby PJ, Reuter U, Hallström Y, et al. A Controlled Trial of Erenumab for Episodic Migraine. N Engl J Med. 2017; 377(22): 2123–2132, doi: 10.1056/NEJMoa1705848, indexed in Pubmed: 29171821.
33. Skljarevski V, Matharu M, Millen BA, et al. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. Cephalalgia. 2018; 38(8): 1442–1454, doi: 10.1177/0333102418779543, indexed in Pubmed: 29848108.
34. Detke HC, Goadsby PJ, Wang S, et al. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. Neurology. 2018; 91(24): e2211–e2221, doi: 10.1212/WNL.0000000000006640, indexed in Pubmed: 30446596.
35. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017; 16(6): 425–434, doi: 10.1016/S1474-4422(17)30083-2, indexed in Pubmed: 28460892.
36. Ashina M, Saper J, Cady R, et al. Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1). Cephalalgia. 2020; 40(3): 241–254, doi: 10.1177/0333102420905132, indexed in Pubmed: 32075406.
37. Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. Neurology. 2020; 94(13): e1365–e1377, doi: 10.1212/WNL.0000000000009169, indexed in Pubmed: 32209650.
38. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761119s000lbl.pdf (22.02.2020).
39. Negro A, Martelletti P. Patient selection for migraine preventive treatment with anti-CGRP(r) monoclonal antibodies. Expert Rev Neurother. 2019; 19(8): 769–776, doi: 10.1080/14737175.2019.1621749, indexed in Pubmed: 31109209.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54, no. 4, pages: 344–349
DOI: 10.5603/PJNNS.a2020.0045

ISSN 0028–3843

Safety and tolerability of therapeutic plasma exchange in autoimmune neurological diseases — a retrospective single-centre analysis

Agnieszka Gala-Błądzińska[1, 3], Katarzyna Mazur[1], Adam Dębiec[2], Krzysztof Gargasz[3], Halina Bartosik-Psujek[2,3]

[1]Department of Internal Medicine, Nephrology and Endocrinology, St. Queen Jadwiga Clinical District Hospital No2 in Rzeszow, Rzeszow, Poland

[2]Neurology Clinic, St. Queen Jadwiga Clinical District Hospital No. 2 in Rzeszow, Rzeszow, Poland

[3]Medical College of Rzeszow University, Institute of Medical Sciences, Rzeszow, Poland

ABSTRACT

Clinical rationale for study. The sudden onset of autoimmune neurological diseases often threatens life. In such clinical situations, fast, effective and safe treatment is needed. Therapeutic plasma exchange (TPE) is an option in the treatment of autoimmune disorders.

Aim of study. The aim was to assess the tolerability and safety of membrane-based therapeutic plasma exchange (mTPE) in patients with autoimmune neurological diseases.

Materials and methods. A total of 410 TPE treatments were performed in 91 adult patients. The main reasons for performing TPE were: Guillain-Barre syndrome (39.56%), chronic inflammatory demyelinating polyradiculoneuropathy (20.88%), and myasthenia gravis (17.58%).

Results. A total of 183 (44.6%) mTPE treatments were performed without complications. In 18 (19.8%) patients, there were no complications observed in any of the mTPE procedures (a total of 83 procedures). Serious and life-threatening complications occurred during four (0.97%) mTPEs. The most common abnormality in laboratory tests was hypocalcaemia. In patients with a fibrinogen concentration ≥ 2.63 g/L, measured before the second plasmapheresis, coagulation in the TPE filter was more frequently observed ($p = 0.04$).

Conclusions and clinical implications. Our study proves that the use of plasmapheresis conducted by filtration in the treatment of autoimmune neurological diseases is safe and well tolerated.

Key words: autoimmune neurological diseases, therapeutic plasma exchange, efficacy, side effects

(*Neurol Neurochir Pol 2020; 54 (4): 344–349*)

Introduction

Therapeutic plasma exchange (TPE) is a clinical procedure for the replace of plasma, which aims to remove the immune system's extracellular components and the pro-inflammatory agents from the blood. These factors are of key importance in the pathogenesis of many diseases, including those affecting the nervous system. During TPE, the patient's plasma is separated and removed. Along with the patient's plasma, we remove specific, potentially pathogenic factors such as: antibodies (Ag) including alloantibodies, monoclonal protein, circulating immune complexes, complement activation products, cytokines, atherogenic substances, and toxic compounds. TPE is thought to affect the immune system by: improving the function of the reticuloendothelial system; removing inflammatory mediators; changing antigen proportions and antibodies leading to the formation of better soluble immune complexes; and stimulating a lymphocyte

Address for correspondence: Agnieszka Gala-Błądzińska, Dialysis Centre, St. Queen Jadwiga Clinical District Hospital No. 2 in Rzeszów, Lwowska 60 St., 35-301 Rzeszów, Poland, e-mail: agala.edu@gmail.com

Table 1. Indications for PTE in our study, and category and grade recommendations for TPE according to the ASFA [2]

Neurological disorders	Indication	Category	Grade	Number/percentage of treated patients
Acute disseminated encephalomyelitis	Steroid refractory	II	2C	7/7.69
Acute inflammatory demyelinating polyradiculoneuropathy(Guillain-Barre syndrome)	Primary treatment	I	1A	36/39.57
Chronic inflammatory demyelinating polyradiculoneuropathy	Severe relapse or steroid refractory	I	1B	19/20.89
Multiple Sclerosis	Rapidly evolving MS	III	2B	10/10.99
Myasthenia gravis	Moderate-to-severe symptoms	I	1B	16/17.58
Neuromyelitis optica spectrum disorders	Severe relapse or steroid refractory	II	1B	3/3.3

ASFA — American Society for Apheresis

population sensitised to cytotoxic treatment with which the plasma exchange is often associated. TPE also allows for supplementing the deficiencies of specific plasma factors [1–2]. In the current American Society for Apheresis (ASFA) guidelines, therapeutic plasma exchange is recommended for the treatment of 157 conditions. Disorders of the nervous system include 25 disease entities. TPE is most commonly used in Guillain-Barre syndrome (GBS), neuromyelitis optica spectrum disorders (NMOSD), myasthenia gravis (MG), Multiple Sclerosis (MS), and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [2]. Also, in the latest update to the guidelines, two out of six new diseases listed are neurological or possibly involve the nervous system: amyotrophic lateral sclerosis, and POEMS syndrome (POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) [2]. In the ASFA recommendations, indications for TPE are divided into four therapeutic categories, the first being where TPE treatment is the basic and preferred method of therapy, and the fourth category being where the use of TPE is ineffective and may even be harmful. In our dialysis centre, therapeutic plasma exchange is mainly performed in patients with autoimmune neurological diseases.

Clinical rationale for the study

The aim of this study was to assess the tolerability and safety of membrane-based therapeutic plasma exchange (mTPE) in patients with autoimmune neurological diseases.

Materials and methods

Our study involved patients treated with therapeutic plasma exchange for neurological indications between March 2013 and October 2017. In most of the disease entities, the TPE treatment was combined with pharmacotherapy in accordance with current recommendations. The data was assessed retrospectively based on the patients' medical records. The number and percentage of patients treated with TPE classified by category and the ASFA TPE grading recommendations are presented in Table 1 [2].

TPE was performed by filtration (mTPE) using the Gambro Prismaflex apparatus. Vascular access was obtained by introducing a two-lumen vascular catheter into the internal jugular, subclavian or femoral veins using the Seldinger technique. In all cases, cannulas sized 13.5 Fr/15 cm or 13.5 Fr/20 cm were inserted. For the TPE treatments, ready-made sets of capillary tubing and plasma filters from Gambro Prismaflex TPE 2000 were used, and prior to the procedure these were filled with saline and vented. Therapeutic plasma exchange was usually performed every two days. The duration of any single treatment did not exceed four hours. The number and mode of treatments depended on the clinical status of the patient and their underlying condition. On average, patients received both 1,000–1,500 mL of crystalloids (multi-electrolyte fluid, 0.9% NaCl solution) and 1,000–1,500 mL of colloids. The total volume of plasma to be exchanged (EPV) was calculated based on the patient's haematocrit (Hct) level and body weight using the Kaplan formula:

$$EPV = [0.065 \times \text{body weight (kg)}] \times [1\text{-Hct}].$$

Where anticoagulation was required, unfractionated heparin was used, with an initial dose of 50 IU/kg body weight (2,000–3,000 IU on average) followed by a continuous intravenous infusion of unfractionated heparin at a dose of 1,000 IU/hour. In patients showing a severe clinical condition, with an increased risk of bleeding complications, or in the case of repeated problems with plating of the plasma filter, 2–3 activated-clotting time (ACT) measurements were taken at the bedside. ACT values were kept between 90–130 s. The blood flow rate was kept at 100-110 ml/min, and transmembrane pressure (TMP) was within 20–60 mmHg. During mTPE, the patient's vital signs (blood pressure, heart rate using continuous ECG recording, oxygen saturation, frequency and character of breathing, body temperature, state of consciousness) and any possible side effects were closely monitored. In addition, the patient's skin layers were observed for the presence of urticaria or erythema. The technical parameters of the procedure were regularly monitored: TMP, arterial pressure, venous pressure,

ultrafiltration, blood flow, and flow and temperature of substitution fluids.

In accordance with the protocols adopted by our dialysis centre, before the second mTPE, patients' blood counts, prothrombin time expressed as the international normalised ratio (INR), activated partial thromboplastin time (APTT), fibrinogen concentrations, potassium, magnesium, total protein, and serum albumin were each recorded and evaluated.

Complications observed during mTPE were divided using the World Apheresis Association (WAA) categories into mild (self-limiting without treatment), medium (requiring additional drugs during TPE), severe (being the reason for discontinuing the TPE treatment), and death [3].

Statistical analysis

Data was presented as the number of patients (the percentage of the group) for nominal variables, and as a median (lower--upper quartile). Distribution normality was assessed using the Shapiro-Wilk test. Where normality assumptions were not met, the differences between the two groups were tested using the Mann-Whitney U test. The Wilcoxon pairs order test was used to show the effect of the procedure on the patients' conditions. The dependence between the type of substitution fluid and the appearance of a clot in the dialysis set was demonstrated using the Chi-square independence test with the Yetsa correction. For the ROC curve analysis, cut-off values optimizing the Youden index were calculated. The predictability of clotting in the therapeutic plasma exchange kit was determined by the fibrinogen level. Results were statistically significant at $p < 0.05$. The Statistica 13.1 package (StatSoft) was used in the calculations.

Results

Over the course of 56 months, 410 mTPEs were performed in 91 patients aged between 18 and 88 years (mean 53.9). Men comprised 58 of the patients, women 33.

In the group of patients who qualified for mTPE, the following comorbidities were most often observed: hypertension (n = 43; 47.25%), osteoarthritis (n = 17; 18.68%), diabetes or impaired glucose tolerance (n = 12; 13.19%), current or history of cancer (n = 11; 12.1%), hypothyroidism (n = 11; 12.1%), history of Lyme disease (n = 10; 10.9%), and infections of the urinary or respiratory systems (n = 9; 9.89%). Other diseases, such as hypercholesterolemia, chronic kidney disease, peripheral osteoarthritis, vascular damage to the central nervous system, liver damage, obesity, epilepsy, chronic pancreatitis, and atrial fibrillation were observed in less than 10% of patients.

The number of procedures performed in one patient ranged from 1–7 (average 4.5). The patient who underwent one mTPE developed massive allergic symptoms after the albumin solution was transfused. The largest group, consisting of almost 1/3 of the patients treated with mTPE, were those with Guillain-Barre syndrome. Table 1 shows the number and percentage of patients treated for neurological disorders.

A total of 183 (44.6%) mTPE treatments were performed without complications. In 18 (19.8%) patients there were no complications observed in any of the mTPE procedures (a total of 83 procedures). In the remaining patients, at least one mTPE procedure resulted in one or more complications.

We observed mild complications in 44 (48.3%) patients during 80 (19.5%) mTPE procedures, and moderate complications, requiring the administration of additional drugs, in 76 (83.5%) patients during 119 (29%) procedures. Table 2 presents the type, number and percentage of complications during TPE, with their severity measured according to WAA [3]. Of the 96 patients undergoing TPE, three (3.2%) died. Deaths were a consequence of a severe course of the underlying disease (diffuse inflammation of the brain and spinal cord in two patients) or complications of the underlying disease (in one patient a myasthenic crisis with sepsis resulting from massive pneumonia). All deaths occurred long after the end of mTPE treatments, and were not related to the therapeutic plasma exchange.

After analysing the results of tests taken before the second TPE, we prepared Table 3, in which we identified the irregularities found in the test results along with the frequency of their occurrence in the studied population. In addition, it was observed that in patients with fibrinogen concentration ≥ 2.63 g/L, measured before the second plasmapheresis, coagulation in the TPE filter was more frequently observed ($p = 0.04$). The observed regularity is shown in Figure 1. Changes in other blood parameters did not significantly affect the complications associated with the TPE technique.

There was no correlation between age and complications related to mTPE in the study group ($p < 0.05$). No correlation was observed between the conditions that are an indication for TPE and the complications observed during mTPE.

Technical problems with the catheter were observed significantly more frequently in patients with concomitant Lyme disease ($p = 0.005$), and paresthesia during mTPE was more common in patients with vascular CNS damage ($p = 0.05$).

Discussion

Our work is one of few original papers to have summarised the use of therapeutic plasma exchange in neurological disorders [4–6]. The work presented here is the result of a five-year period of conducting therapeutic plasma exchange by the filtration method in our dialysis centre. In our study, most of the indications for TPE were in the first and second categories according to the ASFA recommendations [2].

TPE is an invasive method of treatment and carries a risk of complications, but in most cases these are mild; in our study, their frequency was estimated at 18.6%. This percentage is much higher than in WAA data, in which mild complications occurred in 2.8% of TPE treatments from all indications; although in the WAA report only 17% of patients had neurological disorders [3]. In addition, some of the complications

Table 2. Type, number and percentage of complications with severity according to WAA grading scale in course of TPE treatment

Grading of adverse event	Symptoms/findings	Patients with complications (n/%)	TPE with complications (n/%)
Mild	Hypotension not requiring replacement of pressure amines	31/34.1	64/15.6
	Technical problems with the catheter	13/14.28	16/3.9
Moderate	TMP increase or coagulation in the filter	21/23.98	21/5.12
	Hypotension associated with plasma turning	12/13.2	35/8.5
	Dyspnoea	12/13.2	18/4.4
	Paresthesia	7/7.7	15/3.7
	Chest pain	4/4.4	5/1.2
	Headache	4/4.4	7/1.7
	Back pain (spine)	3/3.3	4/1.0
	Shivers, fever	3/3.3	4/1.0
	Urticaria	3/3.3	3/0.7
	Abdominal pain	1/1.1	1/0.2
	Lower limb pain	1/1.1	1/0.2
	Eye irritation, tears	1/1.1	1/0.2
	Arrythmia — tachycardia	1/1.1	1/0.2
	Arrythmia — bradycardia	1/1.1	1/0.2
	Anxiety	1/1.1	1/0.2
	Nausea, vomiting	1/1.1	1/0.2
Severe	TRALI	1/1.1	1/0.2
	Acute anaphylactic reaction	1/1.1	1/0.2
	Sepsis staphylococcus	1/1.1	1/0.2
	HIT II	1/1.1	1/0.2
Death	–	0	0

HIT II — heparin-induced thrombocytopenia type II; TMP — transmembrane pressure; TRALI — transfusion-related acute lung injury; WAA — World Apheresis Association

Table 3. Irregularities in laboratory tests taken before second TPE

Type of irregularity	Number and percentage of patients (n/%) with laboratory irregularities (n = 78)
Anaemia (Hgb [†] < 12 g/dL for women and < 13.0 g/dL for men)	28/29.17
Leukopenia (leucocytes < 4,000/μ)	1/1.04
Elevated leucocytosis (leukocyte count > 11,000/μ)	41/42.7
Thrombocytopenia (platelet count < 100,000/μ)	14/14.58
Hypokalaemia (serum potassium < 3.5 mml/L)	6/6.25
Hyponatraemia (serum sodium < 135 mmol/L)	21/21.87
Hypocalcaemia (decrease in total serum calcium < 2.25 mmol/L)	49/51.04
Hypomagnesaemia (magnesium concentration < 0.65 mmol/L)	21/21.87
Lowered fibrinogen concentration (< 1.8 g/L)	16/16.66
eGFR [‡] < 60 mL/min/1.73m^2	5/5.2
Reduced total protein levels < 66 g/L	75/96.15
Decreased albumin level < 35 g/L	12/12.5
INR [§] < 0.8 or > 1.2	2/2.08
APTT [¶] < 24 s or > 36 s	10/10.42

[†]Haemoglobin; [‡]estimated Glomerular Filtration Rate; [§]International Normalised Ratio; [¶]Activated Partial Thromboplastin Time

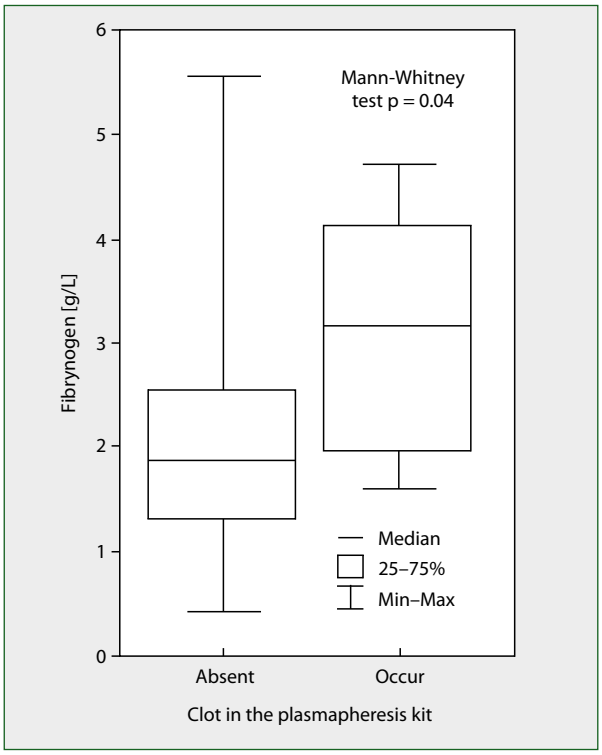


Figure 1. The effect of blood fibrinogen on the presence of clots in a TPE kit

that occur can be included in patients' subjective feelings, such as: pain in various places, paresthesia, or pruritus, and these may actually result from the course of the underlying disease and thus affect the higher rate of TPE complications that we observed.

Our study confirmed the findings of earlier reports that patients who undergo albumin replacement therapy are more likely to have pressure drops during TPE than those in whom FFP was used in the substitution [3]. In our patients, severe life-threatening complications accompanied only four treatments (0.97%). In the WAA report, severe complications after apheresis occurred in less than 1% of cases, which confirms that it is a safe method [3]. The most common abnormalities in laboratory tests were hypocalcaemia caused, inter alia, by the binding of calcium ions by citrate, which is a component of fresh frozen transfusion plasma, or the removal of calcium from the vascular bed as a consequence of the plasma exchanging with liquids that either do not contain, or have a low concentration of, calcium ions. Hypocalcaemia lowers the cell excitability threshold and may be responsible for several tetany and paraesthesia symptoms. During mTPE conducted in our centre, symptoms that may be a consequence of hypocalcaemia were usually slightly intensified, but they could cause the patient discomfort or anxiety. Due to reports of frequent complications in the routine use of calcium carbonate in the prophylaxis of hypocalcaemia accompanying mTPE [3], in 2016 our centre ceased routine calcium substitution. Despite the lack of this, we did not find any increased symptoms that may be related to hypocalcaemia.

In our study, the next most frequently observed abnormality in the laboratory tests, observed in just over 40% of patients, was increased leucocytosis, which is probably related to the higher incidence of infection in this group of patients who were burdened with immune disorders resulting from the primary disease process and numerous co-morbidities. The immunosuppressive treatment used in some patients undergoing TPE treatment, including systemic glucocorticoids, is also important. An important role in the decline in immunity in patients treated with therapeutic plasma exchange is played by the depletion of immunoglobulins and the complement component C3-C4 [3, 7].

All the factors described above help explain the relatively higher frequency of septic complications occurring in this group of patients. We suggest that both laboratory tests and increased and reliable observations of the patient are required to look for signs of infection.

In our study, we observed that if the patient started a second mTPE with a fibrinogen concentration equal to or higher than 2.63 g/L, then he or she was more likely to clot in the filter during mTPE. In addition, it is important that the removal of a significant amount of antithrombin and other anticoagulants from the body can result in venous thromboembolism including pulmonary embolism [2]. Our work is probably the first to draw attention to the value of fibrinogen on the course of the mTPE procedure. In our work, unfractionated heparin was used as an anticoagulant during TPE treatment. However, we are aware of reports in which the authors describe the possibility of using TPE with filtration without using an anticoagulant [7–9]. For instance, Gashti et al. reported a 7.7% incidence of clotting of the filter requiring cartridge/filter replacement, and they suggested that TMP should be closely monitored [8].

The pathogenesis of adverse reactions during TPE should consider the lower efficacy of pharmacotherapy in patients treated with therapeutic plasma exchange. Drugs that are extensively removed during therapeutic plasma exchange include those characterised by low distribution volume and strong protein binding such as: acetylsalicylic acid, cefazolin, ceftriaxone, chlorpropamide, diclofenac, heparin, ibuprofen, valproic acid, warfarin, and thyroxine [10]. Considering the above observations, it is usually recommended that all scheduled drugs should be administered immediately after the therapeutic plasma exchange procedure [11].

Clinical implications

TPE conducted by filtration is relatively safe in the treatment of neurological disorders, and the benefits of its use in autoimmune disease outweigh the risk of complications. Fibrinogen concentration ≥ 2.63 g/L, measured before the second TPE, significantly predisposes to the appearance of clotting

in the TPE kit. Complications observed during TPE may be related to concomitant diseases that are not indications for TPE.

Acknowledgements: *We thank Dr. Łukasz Budziak (St. Queen Jadwiga Clinical District Hospital No2 in Rzeszów) and Maciej Błądziński (Medical College of Rzeszow University) for help in data collection.*

Ethical permission: *Not necessary for the preparation of this article.*

Funding: *This article was prepared without any external source of funding.*

Conflict of interest: *The authors declare no conflict of interest or financial relationship.*

References

1. Sokolov AA, Solovyev AG. Russian pioneers of therapeutic hemapheresis and extracorporeal hemocorrection: 100-year anniversary of the world's first successful plasmapheresis. Ther Apher Dial. 2014; 18(2): 117–121, doi: 10.1111/1744-9987.12067, indexed in Pubmed: 24571429.
2. Padmanabhan A, Connelly-Smith L, Aqui N, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice - Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue. J Clin Apher. 2019; 34(3): 171–354, doi: 10.1002/jca.21705, indexed in Pubmed: 31180581.
3. Mörtzell Henriksson M, Newman E, Witt V, et al. Adverse events in apheresis: An update of the WAA registry data. Transfus Apher Sci. 2016; 54(1): 2–15, doi: 10.1016/j.transci.2016.01.003, indexed in Pubmed: 26776481.
4. Jani-Acsadi A, Lisak RP. Myasthenic crisis: guidelines for prevention and treatment. J Neurol Sci. 2007; 261(1-2): 127–133, doi: 10.1016/j.jns.2007.04.045, indexed in Pubmed: 17544450.
5. Guptill JT, Oakley D, Kuchibhatla M, et al. A retrospective study of complications of therapeutic plasma exchange in myasthenia. Muscle Nerve. 2013; 47(2): 170–176, doi: 10.1002/mus.23508, indexed in Pubmed: 23168720.
6. Weinshenker BG, O'Brien PC, Petterson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann Neurol. 1999; 46(6): 878–886, doi: 10.1002/1531-8249(199912)46:6<878::aid-ana10>3.0.co;2-q, indexed in Pubmed: 10589540.
7. Wood L, Jacobs P. The effect of serial therapeutic plasmapheresis on platelet count, coagulation factors, plasma immunoglobulin, and complement levels. J Clin Apher. 1986; 3(2): 124–128, doi: 10.1002/jca.2920030209, indexed in Pubmed: 3516979.
8. Gashti CN, Andreoli DC, Patel D. Membrane-based therapeutic plasma exchange (mTPE): Technical and clinical experience. J Clin Apher. 2018; 33(1): 38–45, doi: 10.1002/jca.21561, indexed in Pubmed: 28608569.
9. Córdoba JP, Larrarte C, Medina MC. Experience in therapeutic plasma exchange by membrane filtration at an academic center in Colombia: Registry of the first 500 sessions. J Clin Apher. 2015; 30(6): 347–352, doi: 10.1002/jca.21391, indexed in Pubmed: 25708454.
10. Ibrahim RB, Liu C, Cronin SM, et al. Drug removal by plasmapheresis: an evidence-based review. Pharmacotherapy. 2007; 27(11): 1529–1549, doi: 10.1592/phco.27.11.1529, indexed in Pubmed: 17963462.
11. Szczeklik W, Jankowski M, Wegrzyn W, et al. Acute respiratory failure in patients with Guillain-Barré syndrome and myasthenic crisis treated with plasmapheresis in the intensive care unit. Pol Arch Med Wewn. 2008; 118(4): 239–242, indexed in Pubmed: 18575425.

SHORT COMMUNICATION

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54, no. 4, pages: 350–355
DOI: 10.5603/PJNNS.a2020.0053

ISSN 0028–3843

Spinocerebellar ataxia type 6 family with phenotypic overlap with Multiple System Atrophy

Rana Hanna Al-Shaikh[*1], Anna I. Wernick[*2,4], Audrey J. Strongosky[1], Alexandra I. Soto-Beasley[2], Jay A. van Gerpen[1,5], William P. Cheshire[1], Ryan J. Uitti[1], Owen A. Ross[2,3], Zbigniew K. Wszolek[1]

[1]Department of Neurology, Mayo Clinic, Jacksonville, Florida, United States
[2]Department of Neuroscience, Mayo Clinic, Jacksonville, Florida, United States
[3]Department of Clinical Genomics, Mayo Clinic, Jacksonville, Florida, United States
[4]University College London, London, United Kingdom
[5]University of Alabama at Birmingham, Huntsville, Alabama, United States

ABSTRACT

Aim of the study. Multiple system atrophy (MSA) and spinocerebellar ataxia (SCA) share similar symptomatology. We describe a rare occurrence of familial MSA that proved to be SCA6 upon genetic analysis.

Materials and methods. Eighty MSA patients were enrolled in our study; blood samples were collected and genetic screening of the familial case for known SCA loci was performed.

Results. A 68-year-old woman presented with recurrent and severe episodes of light-headedness, imbalance, frequent falls, neck and lower back stiffness, subjective arm and leg weakness, and numbness and tingling in both feet. One year later, her condition had declined; she experienced more falls, worsening instability, again more generalised but still subjective weakness, impaired fine motor movements, slurred speech, difficulty swallowing, episodes of choking, bladder incontinence, and constipation. Clinical suspicion included parkinsonism, MSA, and SCA. The patient was enrolled in our MSA study and was found to have 22 and 12 CAG repeats in *CACNA1A*. The other 79 clinical MSA patients were negative for SCA6 screening.

Conclusions and clinical implications. While MSA and SCA may have similar presentations during early disease stages, the presence of both conditions on the list of differential diagnoses can be a diagnostic dilemma. Further analysis will aid in developing a biomarker to distinguish between the two conditions and guide proper management.

Key words: cerebellum, gait disorders/ataxia, SCA, spinocerebellar ataxia

(*Neurol Neurochir Pol 2020; 54 (4): 350–355*)

Introduction

Multiple system atrophy (MSA) and spinocerebellar ataxia (SCA) share a similar phenotype, largely due to the involvement of cerebellar degeneration present in both conditions, particularly the cerebellar form of MSA [1]. This means that differentiating between the two conditions can be challenging. SCA is an autosomal dominant neurodegenerative condition that affects the cerebellum and spinal cord. More than 45 genetic subtypes of SCA have been identified and listed in the Online Mendelian Inheritance in Man database at the National Centre for Biotechnology Information. Various types of mutations are known to result in SCA [2–4], including polyglutamine CAG repeat expansion. SCA type 6 (SCA6) is caused by a CAG trinucleotide repeat in the *CACNA1A* gene. Possessing 20 to 33 CAG repeats in 1 allele on *CACNA1A* has proven to

[*]Contributed equally to the manuscript.

Presented at the 144th Annual Meeting of the American Neurological Association, St. Louis, Missouri, October 2019.

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

be pathogenic [5–10]. Our genetic analysis demonstrated the presence of SCA6 in one familial patient among our cohort of 80 patients with MSA.

Materials and methods

Standard protocol approval, patient consent, clinical scales/assessments, sample collection

The study was approved by the Mayo Clinic Institutional Review Board, and written informed consent was obtained from all participants. Neurological evaluations were performed by movement disorder specialists at the Mayo Clinic Florida, patients were followed clinically by four of the authors (J.A.V.G., W.P.C., R.J.U., and Z.K.W.), and all office visits and outside records were reviewed. Blood samples were collected from all patients. Eighty patients clinically diagnosed with MSA were recruited and enrolled, beginning in 1999 and extending to the present day. The following data was collected: date of birth, sex, race, age at enrollment, age at disease onset, disease duration, family history of neurological conditions, and past medical history. One patient reported a family history of parkinsonism reminiscent of MSA (Fig. 1, subject III-2), and as a result we screened for several genes to verify whether a genetic condition was indeed present. After obtaining the results, we decided to screen the remainder of the cohort (n = 79). Diagnostic criteria were adopted from the first MSA consensus in 1998, consisting of four main domains: I Autonomic and Urinary Dysfunction, II Parkinsonism, III Cerebellar Dysfunction, and IV Corticospinal Dysfunction, and were updated after the second consensus in 2008 [11, 12].

Magnetic resonance imaging

Neuroradiological studies were performed for the index case (subject III-2). This included magnetic resonance imaging (MRI) scans. All MRI sequences obtained for clinical purposes were reviewed (see Supplemental Fig. 1).

Genetic analysis

Genomic DNA was extracted from whole blood using a FlexSTAR automated extraction machine (AutoGen, Inc) according to the manufacturer's instructions. Whole exome sequencing was performed on our familial MSA patient using an Agilent SureSelect Human All Exon V5+UTRs capture kit, with sequencing performed on an Illumina HiSeq2500 by the Mayo Clinic Genomics Core. Exome data was processed using the Mayo Genome GPS v4.0 pipeline. Functional annotations of variants were performed using ANNOVAR (version 2016Feb01). Genotype calls with GQ < 10 and/or depth (DP) < 10 were set to missing, and variants with ED > 4 were removed from all subsequent analyses. For all analyses, only variants that passed Variant Quality Score Recalibration (VQSR) and with a call rate > 95% were considered, unless otherwise specified. We extracted the identified variants for the SCA-associated genes from the generated VCF using Golden Helix (SNP & Variation Suite v8.8.3); see Supplemental Table 1. In addition, we screened nine SCA genes with known pathogenic repeats/insertions (again see Supplemental Table 1). The regions of interest were amplified (FAM–labelled forward primer) using standard polymerase chain reaction (PCR) protocol, and the PCR products were run out on an agarose gel. The products were diluted based on the intensity of the gel image. GeneScan 400HD ROX dye Size Standard (Applied Biosystems) was then added to the diluted product, which was read on an ABI 3730xl DNA Sequencer (Applied Biosystems). Allelic sizes were analysed using GeneMapper Software 5 (Applied Biosystems). For Sanger sequence validation of pathogenic repeat length, primers were designed for the *CACNA1A* repeat, and the region was amplified using standard PCR protocol and cloned using a TOPO™ TA Cloning™ Kit (Invitrogen). Products were cleaned using Agencourt AMPure XP magnetic beads and the Biomek FXP Dual Arm System (Beckman Coulter, Inc). The same primers were used for sequencing using a BigDye Terminator Cycle Sequencing Kit (Applied Biosystems). The cycle sequence products were cleaned with Agencourt CleanSEQ magnetic beads (Beckman Coulter, Inc) and read on an ABI 3730xl DNA Sequencer. Sequences were then analysed using SeqScape v3.0 (Applied Biosystems) (Fig. 1).

Results

Our proband carried a pathogenic CAG trinucleotide repeat in *CACNA1A*, providing a genetic diagnosis of SCA6 rather than MSA. Genetic analysis revealed 22 CAG repeats on 1 allele and 12 CAG repeats on a second allele of *CACNA1A*; the longer repeat length was confirmed by Sanger sequencing (Fig. 1). Further screening of our clinical MSA series for SCA6 (n = 79) did not identify any other carriers of a pathogenic *CACNA1A* repeat length.

Clinical case description

The patient with SCA6 was a 68-year-old woman with a history of aortic regurgitation, arterial hypertension, and lacunar infarcts who presented with recurrent and severe episodes of light-headedness, gait imbalance, and frequent falls. She did not seem to think that her falls were due to the chronic dizziness, and cardiovascular work up demonstrated aortic regurgitation. She also complained of stiffness in her neck and lower back, weakness beginning in the arms then involving the legs, and numbness and tingling in both feet. She used a walking stick. She noted that her local neurologist had diagnosed her with Parkinson's Disease and administered the regular formulation of carbidopa/levodopa. However she was unable to tolerate it due to numbness, tingling, and experienced no benefit from it.

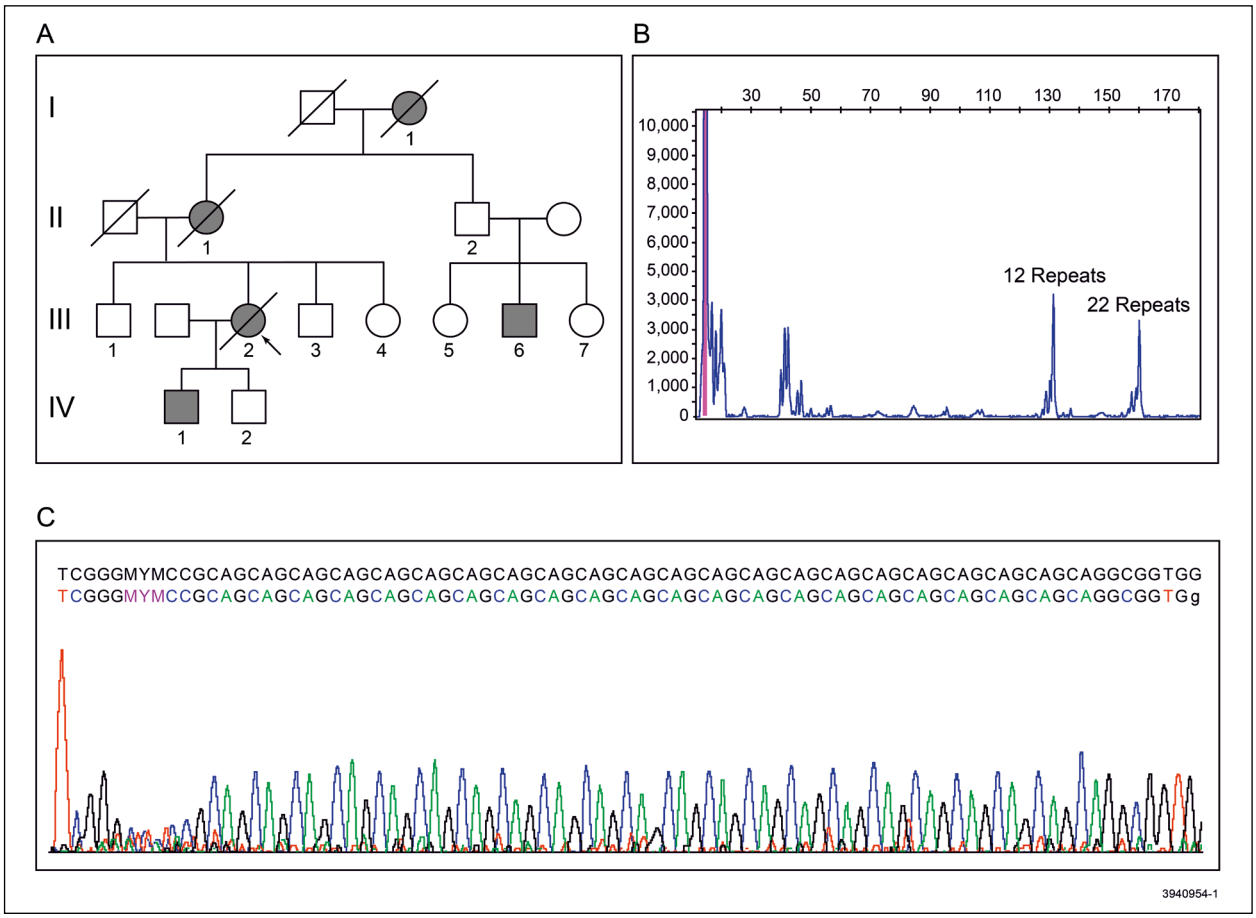


Figure 1. A. Family pedigree of patient with *CACNA1A 22 CAG* repeats on allele 1, and 12 CAG repeats on allele 2. Pathogenic range is 20 to 33 CAG repeats. Squares indicate men, circles indicate women; shaded symbols indicate affected individuals. Arrow indicates proband, and slashed line through symbol indicates deceased individual. Individual IV-1 developed gait impairment and underwent neurological evaluation by his local physician at an outside institution. **B.** Proband (III-2), peaks identified by fluorescent polymerase chain reaction assay, visualised on GeneMapper software, highlighting an expanded repeat. **C.** Proband (III-2), cloning and sequencing confirmed a 22-repeat allele in the *CACNA1A* gene

Her maternal grandmother, mother, and a maternal cousin all experienced gait and speech impairment (Fig. 1).

Neurological evaluation demonstrated nystagmus, slow saccades, reduced upgaze, and square wave jerks. Reduced facial expression and drooling were absent. She required assistance in walking, and her Romberg and pull tests were positive. Stooped posture and tremor were absent. Spasticity and hyperreflexia were present in the lower extremities. Muscle strength was normal in the upper and lower extremities. Two to three beats of non-sustained ankle clonus were present, plantar responses were positive bilaterally. Formal assessment for orthostatic hypotension and autonomic reflex screening were not performed.

Nerve conduction studies of right motor and sensory median and ulnar nerves, right tibial, peroneal and sural nerves, and needle examination of selected right upper and lower extremity muscles were normal. Amantadine was prescribed, 100mg twice a day, and the patient noted a significant improvement in her gait and balance. At her second visit 12 months later, the patient's condition had worsened; she had experienced more falls and she demonstrated worsening of balance, generalised but subjective muscle weakness, impaired fine motor movements, slurred speech, difficulty swallowing, and episodes of choking. She had also developed urinary stress incontinence treated with a pubovaginal sling, as well as constipation. Clinical suspicion included parkinsonism based on her generalised body bradykinesia. Probable MSA was considered based on the presence of urinary dysfunction, parkinsonism with poor levodopa response, and cerebellar dysfunction as per the initial MSA consensus [11]. According to the second consensus, she fulfilled the criteria for possible MSA due to the presence of parkinsonism, cerebellar syndrome, autonomic dysfunction, Babinski sign with hyperreflexia, gait ataxia and postural instability [12]. SCA was added to the list of differentials due to the presence of gait impairment, fine motor dysfunction, in addition to hypophonic and dysarthric speech. A more aggressive trial of carbidopa/levodopa was administered; one half tablet of 25/100 escalated in half-tablet increments each week until reaching 2.5 tablets per dose, three times per day. Total daily dose of levadopa was 750mg. The patient did not report to the clinic after this point.

Table 1. Clinical characteristics of SCA6 and MSA

SCA6	MSA
–	Parkinsonism (bradykinesia and rigidity)
Gait ataxia	Gait ataxia
Nystagmus	–
Postural instability	Postural instability
Dysarthria	Dysarthria
Limb ataxia	–
Truncal ataxia	–
–	Orthostatic hypotension
–	Incontinence
–	Erectile dysfunction
Babinski sign with hyperreflexia	Babinski sign with hyperreflexia
–	Poor response to levodopa

SCA6 — Spinocerebellar ataxia type 6; MSA — Multiple System Atrophy

Head MRI revealed cerebellar atrophy, but no apparent pontine atrophy (Supplemental Fig. 1). The patient died 13 years later.

The autopsy report, performed at another institution, indicated atrophy of the dentate nucleus, substantia nigra, inferior olivary nucleus, and cerebellar cortex. Neuronal loss was evident in the subthalamic nucleus, globus pallidus, substantia nigra, and inferior olivary nucleus. Gliosis was present in the subthalamic nucleus, basal ganglia, globus pallidus, and putamen, and Purkinje cell loss was evident. It is unknown whether α-synuclein was present in brain pathology.

The patient's eldest son (subject IV-1, Fig. 1) developed loss of balance leading to falls at the age of 65; he was evaluated by a local neurologist, exhibited nystagmus and was then diagnosed with SCA6.

Discussion

Familial cases are more rarely encountered in MSA compared to SCA. Some familial forms of MSA have been reported previously in the literature. The first was reported in 1964, although the diagnosis of MSA is questionable considering the lack of pathology and the presence of atypical clinical features [13, 14]. When 157 patients with possible and probable MSA were studied for the presence of family history of neurological conditions, only one was found to carry a family history of MSA [15]. Autosomal dominant inheritance of MSA was reported in a German family [16], and four families were reported to have autosomal recessive MSA [17]. This latter study discussed the presence of pontine atrophy and 'hot cross bun' sign on cranial MRI [17]; however, these findings can also be encountered, albeit infrequently, in patients with SCA types 2 and 3 [17–19]. While the likelihood of a definitive diagnosis of MSA with pontine atrophy and 'hot cross bun' sign is decreased by these findings, it should remain a differential diagnosis given the reported cases of familial MSA.

Cerebellar ataxia, parkinsonism, pyramidal signs, and autonomic dysfunction are signs often shared between MSA and SCA patients [20]; while the first condition is sporadic and the second is a genetic autosomal dominant disease, both fall under spinocerebellar degeneration and exhibit olivopontocerebellar, striatal, and spinal cord involvement [12, 14]. Even with its autosomal dominant genetic disposition, there is a 15–20% chance that SCA may still occur sporadically, more commonly encountered among the trinucleotide forms of SCA [12]. Clinically differentiating between the two conditions can pose a challenge, especially during the early stages [21]. In a review of 203 patients with pathologically confirmed MSA, 110 (54%) displayed cerebellar ataxia, 98 (49%) pyramidal signs, 176 (87%) parkinsonism, and 150 (74%) presented with autonomic failure [22]. Parkinsonism was the most frequently reported form of motor impairment, followed by cerebellar ataxia [22]. Parkinsonism has been previously described in SCA6 patients [23], and one patient presented with parkinsonism and urinary incontinence and was initially diagnosed with MSA [24]. Our patient's initial symptoms included gait impairment, falls, and light-headedness; based on the clinical presentation, both SCA and MSA were considered.

In addition to the overlap in symptomatology (Tab. 1), disease onset tends to occur later in life with both MSA and SCA6 [15, 25]. Mean age at onset for patients with SCA6 is 43 to 52 years (range 19–71) [5]; therefore, as expected, disease progression tends to be slower [6, 26]. This was evident in our patient, whose onset of symptoms occurred at 68 years, with a disease duration of 15 years. Total lifespan remains unaffected in patients with SCA6 [5]. A retrospective analysis investigating disease progression and survival rates among different forms of cerebellar degenerative disorders revealed that the onset of MSA occurs between the ages of 50 and 60, with a median of 56 years [27]. The study concluded that patients with MSA exhibited a faster rate of progression compared to SCA patients. Of note, the majority of the patients with SCA in this study had SCA type 1, type 2, or type 3; patients with SCA6 were not included as a group, given the low sample size (n = 4) [27].

Distinguishing MSA from SCA is difficult in clinical practice due to the phenotypic overlap. Studies have investigated radiological features of MSA and SCA to create a standardised protocol in distinguishing the two conditions [1, 21]. However, MRI findings commonly associated with MSA, such as the 'hot cross bun' sign, hyperintense putaminal rim, and olivopontocerebellar atrophy, can also be encountered with SCA [12, 28]. 'Hot cross bun' sign and middle cerebellar peduncle hyperintensities were highly specific MRI findings in 12 pathologically confirmed MSA cases; they were identified in seven (58.3%) and six (50%) of the 12 respectively [29]. Our patient's MRI findings of cerebellar atrophy and lack of pontine involvement point

toward a pure cerebellar condition. One study used magnetic resonance diffusion kurtosis imaging to monitor and identify pathological alterations in patients with cerebellar MSA or SCA, concluding that diffusion kurtosis imaging can be used when differentiating between the two conditions [1]. Another study measured peripheral neurofilament light levels in patients with MSA or SCA compared to controls, demonstrating a significant increase in neurofilament light levels in those with SCA [30].

Perhaps measuring neurofilament light levels could serve as a method to distinguish between the two conditions in future cases. Early and prompt diagnosis of MSA and SCA can improve prognosis, facilitate for better management and a more precise therapeutic plan [12, 28].

Genetic counselling is offered to all SCA patients and family members. Early detection allows patients planning for pregnancy to seek prenatal genetic testing as well as preimplantation genetic testing [5].

Our study is limited due to the lack of formal orthostatic and autonomic evaluations. However, other signs and symptoms present in our patient still point towards MSA as a possible diagnosis. MSA and SCA can have similar presentations during early stages, and the presence of both conditions on the list of differential diagnoses can be a common dilemma for clinicians. Further analysis will aid in developing a biomarker for longitudinal observations and follow up on potential therapies that undoubtedly will be developed. Genetic analysis is already widely utilised in SCA cases, and it can bring precision to the differential diagnosis.

Clinical implications/future directions

Despite the rare occurrence of MSA and SCA as differentials, reporting such cases is crucial. Their reporting in the literature will provide a stronger incentive to investigate and discover blood and cerebrospinal fluid biomarkers that will assist in future management.

Funding: *This publication was prepared without any external source of funding. Mayo Clinic does not endorse specific products or services included in this article.*

Author contributions: *Dr Hanna Al Shaikh: Organising, co-ordinating with family, study design, data acquisition, data analysis, drafting, and revising the manuscript. Ms. Wernick: Sample processing, laboratory analysis, and variant identification. Mrs. Strongosky: Participant identification and recruitment, co-ordinating family visits, and sample collection. Mrs. Soto-Beasley: Sample processing, laboratory analysis, and variant identification. Dr van Gerpen: Patient care and participant identification. Dr Cheshire: Patient care. Dr Uitti: Patient care. Dr Ross: Genetic testing, analysis and interpretation, study concept, study design, study supervision, and revising the manuscript. Dr Wszolek: Participant identification, study concept, study design, analysis and interpretation of data, study supervision, obtaining funding, and revising the manuscript.*

Disclosures: *Dr Hanna Al Shaikh: Receives funding from the Donald G. and Jodi P. Heeringa Family. Dr Ross: Is partially supported by R01-NS078086, P50-NS072187, U54 NS100693, U54 NS110435, Department of Defense, and the Michael J. Fox Foundation. He is an editorial board member for the American Journal of Neurodegenerative Disease, Frontiers in Neurology: Neurogenetics, and Molecular Neurodegeneration. Dr Wszolek: Is partially supported by the Mayo Clinic Centre for Regenerative Medicine, gifts from The Sol Goldman Charitable Trust, and the Donald G. and Jodi P. Heeringa Family, the Haworth Family Professorship in Neurodegenerative Diseases Fund, and the Albertson Parkinson's Research Foundation. He serves as PI or Co-PI on grants from Abbvie, Inc (M15-562 and M15-563), Biogen, Inc (228PD201), and Biohaven Pharmaceuticals, Inc (BHV4157-206 and BHV3241-301). He serves as PI of the Mayo Clinic American Parkinson's Disease Association Information and Referral Centre. Dr Cheshire, Ms. Wernick, Mrs. Strongosky, Mrs. Soto-Beasley, Dr van Gerpen and Dr Uitti report no disclosures.*

Acknowledgments: *We would like to thank our patient and her family for their co-operation and support for this research study. We would also like to thank our collaborators and partners in the lab for taking the time to verify all blood samples and their continuous efforts in this research endeavour. Mayo Clinic is an American Parkinson's Disease Association (APDA) Information and Referral Centre, an APDA Centre for Advanced Research, and a Lewy Body Dementia Association Research Centre of Excellence. Dr. Wszolek serves as Co-Editor-in-Chief of Neurologia i Neurochirurgia Polska. This manuscript processing was performed by Dr. Sławek, the second Co-Editor-in-Chief of journal.*

References

1. Ito, K. Differentiation Between Multiple System Atrophy and Other Spinocerebellar Degenerations Using Diffusion Kurtosis Imaging. Acad Radiol, 2019. 26(11): p. : e333–e339.
2. Hanna Al Shaikh R, Caulfield T, Strongosky AJ, et al. TRIO gene segregation in a family with cerebellar ataxia. Neurol Neurochir Pol. 2018; 52(6): 743–749, doi: 10.1016/j.pjnns.2018.09.006, indexed in Pubmed: 30279051.
3. Fujioka S, Sundal C, Wszolek ZK. Autosomal dominant cerebellar ataxia type III: a review of the phenotypic and genotypic characteristics. Orphanet J Rare Dis. 2013; 8: 14, doi: 10.1186/1750-1172-8-14, indexed in Pubmed: 23331413.
4. Whaley NR, Fujioka S, Wszolek ZK. Autosomal dominant cerebellar ataxia type I: a review of the phenotypic and genotypic characteristics. Orphanet J Rare Dis. 2011; 6: 33, doi: 10.1186/1750-1172-6-33, indexed in Pubmed: 21619691.
5. Casey, H.L. and C.M. Gomez, Spinocerebellar Ataxia Type 6, in GeneReviews((R)), M.P. Adam, , Editors. 1993: Seattle. (WA).
6. Buijsen RAM, Toonen LJA, Gardiner SL, et al. Genetics, Mechanisms, and Therapeutic Progress in Polyglutamine Spinocerebellar Ataxias. Neurotherapeutics. 2019; 16(2): 263–286, doi: 10.1007/s13311-018-00696-y, indexed in Pubmed: 30607747.
7. Ishikawa K, Tanaka H, Saito M, et al. Japanese families with autosomal dominant pure cerebellar ataxia map to chromosome 19p13.1-p13.2 and are strongly associated with mild CAG expansions in the spinocerebellar ataxia type 6 gene in chromosome 19p13.1. Am

J Hum Genet. 1997; 61(2): 336–346, doi: 10.1086/514867, indexed in Pubmed: 9311738.
8. Shizuka M, Watanabe M, Ikeda Y, et al. Molecular analysis of a de novo mutation for spinocerebellar ataxia type 6 and (CAG)n repeat units in normal elder controls. Journal of the Neurological Sciences. 1998; 161(1): 85–87, doi: 10.1016/s0022-510x(98)00270-6.
9. Mariotti C, Gellera C, Grisoli M, et al. Pathogenic effect of an intermediate-size SCA-6 allele (CAG)(19) in a homozygous patient. Neurology. 2001; 57(8): 1502–1504, doi: 10.1212/wnl.57.8.1502, indexed in Pubmed: 11673601.
10. Yabe I, Sasaki H, Matsuura T, et al. SCA6 mutation analysis in a large cohort of the Japanese patients with late-onset pure cerebellar ataxia. Journal of the Neurological Sciences. 1998; 156(1): 89–95, doi: 10.1016/s0022-510x(98)00009-4.
11. Gilman S, Low PA, Quinn N, et al. Consensus statement on the diagnosis of multiple system atrophy. Journal of the Neurological Sciences. 1999; 163(1): 94–98, doi: 10.1016/s0022-510x(98)00304-9.
12. Gilman, S., , Second consensus statement on the diagnosis of multiple system atrophy. Neurology, 2008. 71(9): p. : 670–6.
13. Lewis, P., Familial Orthostatic Hypotension. Brain, 1964. 87: p. : 719–28.
14. Quinn N. Multiple system atrophy–the nature of the beast. J Neurol Neurosurg Psychiatry. 1989; Suppl: 78–89, doi: 10.1136/jnnp.52.suppl.78, indexed in Pubmed: 2666581.
15. Soma, H., , Heredity in multiple system atrophy. J Neurol Sci, 2006. 240(1-2): p. : 107–10.
16. Wüllner U, Abele M, Schmitz-Huebsch T, et al. Probable multiple system atrophy in a German family. J Neurol Neurosurg Psychiatry. 2004; 75(6): 924–925, doi: 10.1136/jnnp.2003.025155, indexed in Pubmed: 15146018.
17. Hara K, Momose Y, Tokiguchi S, et al. Multiplex Families With Multiple System Atrophy. Archives of Neurology. 2007; 64(4): 545, doi: 10.1001/archneur.64.4.545.
18. Bürk K, Skalej M, Dichgans J. Pontine MRI hyperintensities ("the cross sign") are not pathognomonic for multiple system atrophy (MSA). Mov Disord. 2001; 16(3): 535, doi: 10.1002/mds.1107, indexed in Pubmed: 11391754.
19. Murata Y, Yamaguchi S, Kawakami H, et al. Characteristic magnetic resonance imaging findings in Machado-Joseph disease. Arch Neurol. 1998; 55(1): 33–37, doi: 10.1001/archneur.55.1.33, indexed in Pubmed: 9443709.
20. Yeh TH, Lu CS, Chou YH, et al. Autonomic Dysfunction in Machado-Joseph Disease. Archives of Neurology. 2005; 62(4): 630, doi: 10.1001/archneur.62.4.630.
21. Kim, M., , Differential value of brain magnetic resonance imaging in multiple system atrophy cerebellar phenotype and spinocerebellar ataxias. Sci Rep, 2019. 9(1): p. ; 17329.
22. Wenning GK, Tison F, Shlomo Yb, et al. Multiple system atrophy: A review of 203 pathologically proven cases. Movement Disorders. 1997; 12(2): 133–147, doi: 10.1002/mds.870120203.
23. Park H, Kim HJ, Jeon BS. Parkinsonism in spinocerebellar ataxia. Biomed Res Int. 2015; 2015: 125273, doi: 10.1155/2015/125273, indexed in Pubmed: 25866756.
24. Frequency Analysis and Clinical Characterization of Spinocerebellar Ataxia Types 1, 2, 3, 6, and 7 in Korean Patients—Correction. Archives of Neurology. 2003; 60(9): 1256, doi: 10.1001/archneur.60.9.1256.
25. Murata Y, Kawakami H, Yamaguchi S, et al. Characteristic magnetic resonance imaging findings in spinocerebellar ataxia 6. Arch Neurol. 1998; 55(10): 1348–1352, doi: 10.1001/archneur.55.10.1348, indexed in Pubmed: 9779664.
26. Ashizawa T, Öz G, Paulson HL. Spinocerebellar ataxias: prospects and challenges for therapy development. Nat Rev Neurol. 2018; 14(10): 590–605, doi: 10.1038/s41582-018-0051-6, indexed in Pubmed: 30131520.
27. Klockgether T, Lüdtke R, Kramer B, et al. The natural history of degenerative ataxia: a retrospective study in 466 patients. Brain. 1998; 121 (Pt 4): 589–600, doi: 10.1093/brain/121.4.589, indexed in Pubmed: 9577387.
28. Li M, Ma Q, Zhao X, et al. Dilemma of multiple system atrophy and spinocerebellar ataxias. J Neurol. 2018; 265(12): 2764–2772, doi: 10.1007/s00415-018-8876-x, indexed in Pubmed: 29700645.
29. Massey LA, Micallef C, Paviour DC, et al. Conventional magnetic resonance imaging in confirmed progressive supranuclear palsy and multiple system atrophy. Mov Disord. 2012; 27(14): 1754–1762, doi: 10.1002/mds.24968, indexed in Pubmed: 22488922.
30. Wilke C, Bender F, Hayer SN, et al. Serum neurofilament light is increased in multiple system atrophy of cerebellar type and in repeat-expansion spinocerebellar ataxias: a pilot study. J Neurol. 2018; 265(7): 1618–1624, doi: 10.1007/s00415-018-8893-9, indexed in Pubmed: 29737427.

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54, no. 4, pages: 356–357
DOI: 10.5603/PJNNS.a2020.0051

ISSN 0028–3843

DBS patient with diagnosed Non-Hodgkin's Lymphoma: is radiation therapy safe?

Łukasz Milanowski, Amy L. Grassle, Ryan J. Uitti

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

(*Neurol Neurochir Pol 2020; 54 (4): 356–357*)

Dear Editors,

We read with great interest the excellent article by Schinwelski et al. [1]. The authors described two patients with Parkinson's Disease (PD) with implanted deep brain stimulation (DBS) who required radiation therapy (RT) due to different malignancies.

Both patients were in their sixties and had been diagnosed with PD in their forties. At the time of qualification for DBS, the first patient was diagnosed with prostate cancer during hormonotherapy, stable on urological examination and biochemical markers (PSA - prostate specific antigen). However, a year after diagnosis, the same patient developed brain metastases, a distinctly unusual site for metastatic prostate cancer. RT (to pelvis and brain) did not cause damage to the DBS system; however, due to disease progression and urosepsis, the patient died at the age of 67.

The second patient was treated with DBS after a diagnosis of breast cancer. Eight years after DBS therapy, she had a recurrence of breast cancer and RT was conducted. No impact on the DBS system was observed. The DBS systems were active during all RT procedures performed in both patients [1].

The authors also discussed previously reported cases of RT use in patients treated with DBS [1]. While DBS of the subthalamic nucleus and globus pallidus internus was approved in 2002 for PD therapy, only four other cases of RT use in this context have been reported [2]. Mazdai et al. [3] described a patient treated with DBS for severe PD who underwent RT to the head and neck. Another study reported a patient with bilateral DBS who underwent RT for a left upper lung tumour [4]. The irradiated areas in the two other cases were brain metastases [5, 6]. In all cases described, no negative impact on DBS system was observed.

The conclusion drawn from this experience, albeit based on rare cases, is that RT appears safe in the context of DBS.

More studies have been performed with pacemakers and implantable cardioverter defibrillators (PM/ICD). Patients with PM/ICD undergoing RT do not require supplementary device evaluations in PM/ICD clinic as per manufacturers' instructions [7]. As the impact of RT on such devices is more dependent on beam energy than on a total dose of radiation, limiting photon beam energy to 10 MV or less is recommended where possible. The frequency of PM/ICD malfunction is about 3% and consists mainly of device resets, rarely requiring replacement [8].

Between 1995 and 2020, more than 2,000 DBS procedures were performed in the Departments of Neurology and Neurosurgery at the Mayo Clinic in Jacksonville, Florida.

We would like to present a case report of a patient treated with DBS who had cancer and for whom RT was considered as one treatment option. Our patient, a 68-year-old man, had contended with PD symptoms for more than 20 years, with the condition having been heralded by resting tremor in the left hand. Bilateral DBS was performed to combat motor fluctuations characterised by intolerable levodopa-induced dyskinesia, with good response. Four years after DBS therapy, the patient developed an enlarged lymph node near the clavicle, which was subsequently resected with histopathology confirming non-Hodgkin's lymphoma. Different treatment options were considered, including RT; however, the patient was initially treated with chemotherapy.

This case, we believe, is the first reported instance of non-Hodgkin's lymphoma in a patient treated with DBS. We believe that RT can be considered in our patient, and in others similarly affected. The topic of DBS and the incidence of cancer and subsequent implications for therapy is relatively unchartered, and requires further study.

Acknowledgements: *L.M. is supported by the Polish National Agency for Academic Exchange Iwanowska's Fellowship PPN/IWA/2018/1/00006/U/00001/01.*
Conflict of interest: *None*

Address for correspondence: Ryan J. Uitti, Dept. of Neurology, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224, USA, e-mail: Uitti@mayo.edu

References

1. Schinwelski MJ, Dulski J, Łuczak W, et al. Radiation therapy in patients with implanted deep brain stimulation. Neurol Neurochir Pol. 2020 [Epub ahead of print], doi: 10.5603/PJNNS.a2020.0033, indexed in Pubmed: 32285432.
2. Smilowska K, Bloem BR, Esselink RAJ, et al. Keep calm and beam on? Unmet needs in radiotherapy and deep brain stimulation. Parkinsonism Relat Disord. 2020; 71: 15–16, doi: 10.1016/j.parkreldis.2020.01.005, indexed in Pubmed: 31955127.
3. Mazdai G, Stewart DP, Hounsell AR. Radical radiation therapy in a patient with head and neck cancer and severe Parkinson's disease. Clin Oncol (R Coll Radiol). 2006; 18(1): 82–84, doi: 10.1016/j.clon.2005.09.009, indexed in Pubmed: 16477925.
4. Borkenhagen JF, Morris ZS, Hoberg JR, et al. Delivery of definitive dose external beam radiation in close proximity to an implanted deep brain stimulator. Pract Radiat Oncol. 2014; 4(5): 294–297, doi: 10.1016/j.prro.2013.10.003, indexed in Pubmed: 25194097.
5. Guy JB, Levy A, Malkoun N, et al. Preventing radiotherapy-induced side effects on deep brain stimulators: the need for a multidisciplinary management. Br J Neurosurg. 2014; 28(1): 107–109, doi: 10.3109/02688697.2013.801395, indexed in Pubmed: 23692069.
6. Kotecha R, Berriochoa CA, Murphy ES, et al. Report of whole-brain radiation therapy in a patient with an implanted deep brain stimulator: important neurosurgical considerations and radiotherapy practice principles. J Neurosurg. 2016; 124(4): 966–970, doi: 10.3171/2015.2.JNS142951, indexed in Pubmed: 26315009.
7. Munshi A, Agarwal JP, Pandey KC. Cancer patients with cardiac pacemakers needing radiation treatment: a systematic review. J Cancer Res Ther. 2013; 9(2): 193–198, doi: 10.4103/0973-1482.113348, indexed in Pubmed: 23771357.
8. Zaremba T, Jakobsen AR, Søgaard M, et al. Radiotherapy in patients with pacemakers and implantable cardioverter defibrillators: a literature review. Europace. 2016; 18(4): 479–491, doi: 10.1093/europace/euv135, indexed in Pubmed: 26041870.

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54, no. 4, pages: 358–359
DOI: 10.5603/PJNNS.a2020.0052

ISSN 0028–3843

Reply to the Letter to the Editors: DBS patient with diagnosed Non-Hodgkin's lymphoma: is radiation therapy safe?

Michał J. Schinwelski[1], Jarosław Dulski[2,3], Wojciech Łuczak[4], Witold Libionka[5,6], Tomasz Mandat[7], Jarosław Sławek[2,3]

[1]Neurocentrum-MiwoMed — Neurological Clinic, Gdansk, Poland
[2]Neurology Department, St. Adalbert Hospital, Gdansk, Poland
[3]Neurological and Psychiatric Nursing Department, Medical University of Gdansk, Gdansk, Poland
[4]Oncology and Radiotherapy Department, Oncology Centre of Gdynia, Gdynia, Poland
[5]Neurosurgery Department, M. Kopernik Hospital, Gdansk, Poland
[6]Department of Neurobiology of Muscle, Faculty of Rehabilitation and Kinesiology, Gdansk University of Physical Education and Sport, Gdansk, Poland
[7]Department of Neurosurgery, Maria Sklodowska-Curie Memorial Oncology Centre, Warsaw, Poland

(*Neurol Neurochir Pol 2020; 54 (4): 358–359*)

We thank Drs. Milanowski, Grassle and Uitti for their interest in our article [1]. We agree that it is important to report every new patient who requires radiation therapy (RT) with implanted deep brain stimulation (DBS). As the number of DBS patients with concomitant cancer continues to rise, the influence of RT on those patients should be analysed.

At the time of qualification for DBS, both of our patients had cancer histories: the first patient had been diagnosed with prostate cancer and was undergoing hormone therapy, stable on urological examination and biochemical markers; the second patient had a history of left-sided mastectomy due to breast cancer. Such patients may be considered as being at risk if they were to encounter future RT. Important factors determining the risk of harmful interference from RT to DBS include the incidence of specific cancer type and its localisation. The reported DBS patient with non-Hodgkin's lymphoma affecting the lymph node in the vicinity of the internal pulse generator (IPG) represents an important clinical dilemma [2]. This neoplasm is listed by the American Cancer Society as being one of the most common cancers in the United States, and RT is a viable treatment option [3]. Other common cancers that may interfere with the DBS system, especially with pulse generators that are usually placed in the infraclavicular region, include lung and breast cancer. The latter was the culprit in our second patient, in whom RT of the left subclavian area with 15 MV photons and a dose of 20 Gy in five fractions was carried out (Fig. 1). The maximal estimated radiation dose for left IPG was 1.7 Gy. In a case report by Brokenhagen et al., the maximal radiation dose for IPG was over 48 Gy.

Broader experience with pacemakers and implantable cardioverter defibrillators (PM/ICD) has shown that the impact of RT on a device depends on the beam energy rather than on the total dose of radiation [4]. In the two aforementioned cases, the maximal recommended beam energy (< 10MV) and maximal recommended radiation dose were far exceeded, but fortunately no complications from IPG were observed. The surgical relocation of IPG is an option for minimising its exposure for RT [5], but possible malignant DBS withdrawal syndrome associated with acute cessation or failure of the DBS device must be considered [6]. In addition, maintaining neurostimulation during an RT procedure is crucial to avoid unwanted involuntary movements such as the head tremor in the case reported by Mazdai et al. [7].

In summary, despite the lack of structured studies, RT has been safely delivered in all patients with DBS reported thus far. Nonetheless, further multidisciplinary efforts should be made so as to ascertain the safety and feasibility of radiotherapy in patients with implanted DBS.

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

Address for correspondence: Michał J. Schinwelski, Neurocentrum-MiwoMed — Neurological Clinic, Gdansk, Poland, e-mail: szyna777@gmail.com

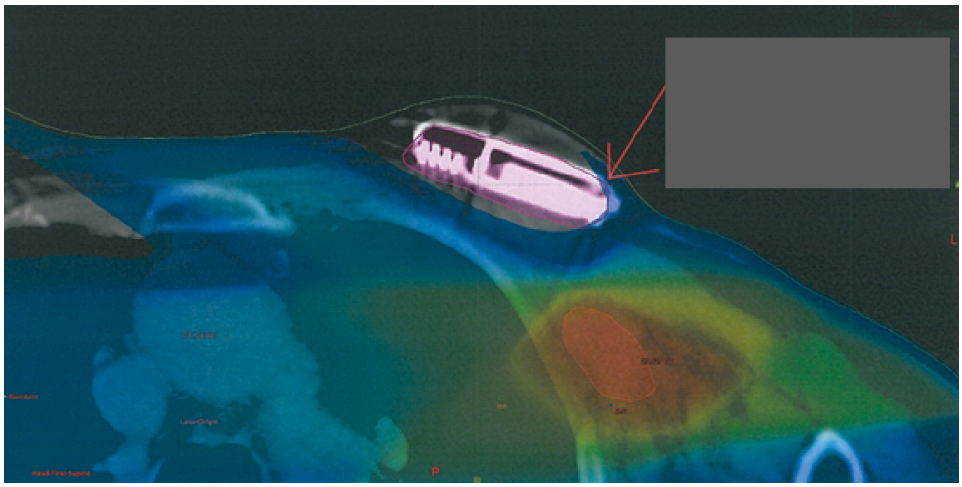


Figure 1. Planning of radiotherapy of breast cancer near pulse generator in Patient 2. Maximal estimated radiation dose for left internal pulse generator (IPG) was 1.7 Gy [1]

References

1. Schinwelski MJ, Dulski J, Łuczak W, et al. Radiation therapy in patients with implanted deep brain stimulation. Neurol Neurochir Pol. 2020; 54(3): 280–283, doi: 10.5603/PJNNS.a2020.0033, indexed in Pubmed: 32285432.
2. Milanowski L, Grassle AL, Uitti RJ, et al. DBS Patient With Diagnosed Non-Hodgkin Lymphoma: Is Radiation Therapy Safe? *Neurol Neurochir Pol. 2020; 54(4): 356–357, doi: 10.5603/PJNNS.a2020.0051, indexed in Pubmed: 32677029.*
3. Key Statistics for Non-Hodgkin Lymphoma. www.cancer.org (24 August 2019).
4. Zaremba T, Jakobsen AR, Søgaard M, et al. Radiotherapy in patients with pacemakers and implantable cardioverter defibrillators: a litera-ture review. Europace. 2016; 18(4): 479–491, doi: 10.1093/europa-ce/euv135, indexed in Pubmed: 26041870.
5. Son BC, Kim JS, Park WC, et al. Management of Pulse Generators in a Breast Cancer Patient with in Situ Subthalamic Nucleus Deep Brain Stimulation. J Neurol Surg A Cent Eur Neurosurg. 2019; 80(3): 223–227, doi: 10.1055/s-0038-1677518, indexed in Pubmed: 30708388.
6. 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.
7. Mazdai G, Stewart DP, Hounsell AR. Radical radiation therapy in a patient with head and neck cancer and severe Parkinson's disease. Clin Oncol (R Coll Radiol). 2006; 18(1): 82–84, doi: 10.1016/j.clon.2005.09.009, indexed in Pubmed: 16477925.