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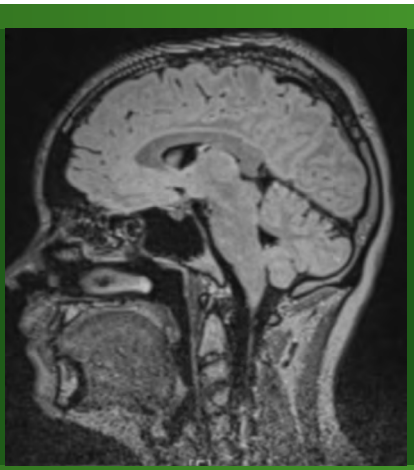

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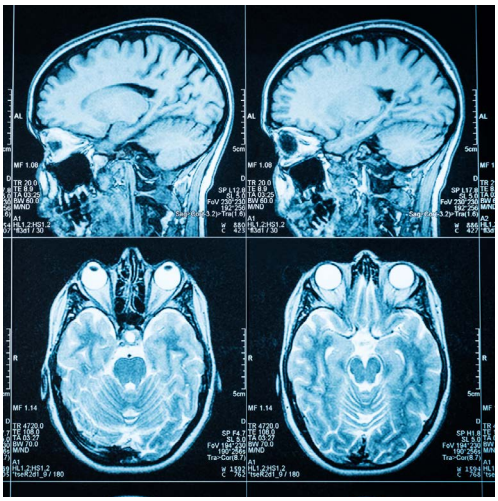

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Neurologia i Neurochirurgia Polska also known under the name of *Polish Journal of Neurology and Neurosurgery (PJNNS)* is a premier research and educational platform of the Polish Neurological Society and Polish Society of Neurosurgeons. It has a long 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.

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Cover photo: Paulina Fonderska et al. Midline sagittal T2-weighted MRI: typical lesions in corpus callosum (see figure on apage 143)

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EDITORIAL NOTE

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Editor's Thank You to Our Authors and Reviewers

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, Poland

In 2021, the Polish Journal of Neurology and Neurosurgery (Neurologia i Neurochirurgia Polska) continued to make progress as measured by all bibliometric indicators. The total number of submissions in 2021 was 270 items, with an acceptance rate of 34%. In six issues, the Journal published 8 Invited Editorials, 4 Invited Review Articles, 18 Review Articles, 30 Research Papers, 5 Short Communications, 2 Technical Notes, and 17 Letters to the Editors. Issues 2 and 6 included Leading Topic sections bringing together manuscripts on a similar subject accompanied by an Invited Editorial written by the Leading Topic section editor.

The three most downloaded and the three most viewed articles from 2021 are presented in Table 1 [1–5]. The Invited Review by Nojszewska et al. came first in both categories [1]. This manuscript provided a statement by a Working Group of the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society on COVID-19 mRNA vaccines in patients with multiple sclerosis.

We thank all authors who submitted articles to our Journal. However, the success of the Journal also depends on engagement and critical assessment of these submitted works. Thus, we are very much indebted to all our 124 national and international reviewers. We are especially grateful to those reviewers who provided multiple reviews over the course of the year. Table 2 names the Journal's reviewers for 2021.

Table 1. Three most downloaded and three most viewed articles published in 2021 by the Polish Journal of Neurology and Neurosurgery (Neurologia i Neurochirurgia Polska)

Three most downloaded articles	Downloads*
1. Nojszewska M., Kalinowska A., Adamczyk-Sowa M. et al. COVID-19 mRNA vaccines (Pfizer-BioNTech and Moderna) in patients with multiple sclerosis: a statement by a working group convened by the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society. Neurol Neurochir Pol 2021; 55(1):8–11.	5,109
2. Yiannopoulou K.G., Papagiannis G.I., Triantafyllou A.I. et al. Neurological and neurourological complications of electrical injuries. Neurol Neurochir Pol 2021; 55(1):12–23.	2,270
3. Stępień A. , Kozubski W., Rożniecki J.J. et al., Migraine treatment recommendations developed by an Expert Group of the Polish Headache Society, the Headache Section of the Polish Neurological Society, and the Polish Pain Society. Neurol Neurochir Pol 2021; 55(1):33–51.	2,155
Three most viewed articles	**Views***
1. Nojszewska M., Kalinowska A., Adamczyk-Sowa M. et al., COVID-19 mRNA vaccines (Pfizer-BioNTech and Moderna) in patients with multiple sclerosis: a statement by a working group convened by the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society. Neurol Neurochir Pol 2021; 55(1):8–11.	5,864
2. Gueye T., Dedkova M, Rogalewicz V. et al., Early post-stroke rehabilitation for upper limb motor function using virtual reality and exoskeleton: equally efficient in older patients. Neurol Neurochir Pol 2021; 55(1):91–96.	4,473
3. Czarnowska A., Brola W., Zajkowska O. et al., Clinical course and outcome of SARS-CoV-2 infection in multiple sclerosis patients treated with disease-modifying therapies — the Polish experience. Neurol Neurochir Pol 2021; 55(2):212–222.	2,702

*Reporting date: April 14, 2022

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

Table 2. Alphabetical list of those who provided the Polish Journal of Neurology and Neurosurgery (Neurologia i Neurochirurgia Polska) with reviews in 2021*

1.	Monika Adamczyk-Sowa	63.	Tomasz Mandat
2.	Shan Ali	64.	Elizabeth Mauricio
3.	Wojciech Ambrosius	65.	**Maria Mazurkiewicz-Bełdzińska**
4.	Yasuhiko Baba	66.	James F. Meschia
5.	Magdalena Badura-Stronka	67.	Erik Middlebrooks
6.	Naci Balak	68.	**Łukasz Milanowski**
7.	Anna Barczak	69.	Dagmara Mirowska-Guzel
8.	Krzysztof Barć	70.	Maciej Mrugala
9.	Huseyin Berk Benek	71.	Marcin Mycko
10.	Monika Białecka	72.	Monika Nojszewska
11.	Magdalena Boczarska-Jedynak	73.	Przemysław Nowacki
12.	Magdalena Bosak	74.	Marta Nowakowska-Kotas
13.	Daniel Broderick	75.	Katarzyna Nowomiejska
14.	Sławomir Budrewicz	76.	Stanisław Ochudło
15.	Krzysztof Bujarski	77.	**Ashley Pena**
16.	Kaisorn Chaichana	78.	Ronald Pfeiffer
17.	William P. Cheshire	79.	Ewa Pilarska
18.	Kamil Chwojnicki	80.	Anna Pokryszko-Dragan
19.	Michael Cordes	81.	Andrzej Potemkowski
20.	**Victor Constantinescu**	82.	Anna Potulska-Chromik
21.	Anna Członkowska	83.	Mercedes Prudencio
22.	Elliot Dimberg	84.	Maciej Radek
23.	**Izabela Domitrz**	85.	Daniel Ręcławowicz
24.	**Jarosław Dulski**	86.	**Radosław Rola**
25.	Stephen English	87.	Owen Ross
26.	**Olga Fermo**	88.	Iwona Rościszewska-Żukowska
27.	Anteneh Feyissa	89.	Monika Rudzińska-Bar
28.	Urszula Fiszer	90.	Beth Rush
29.	Andrzej Friedman	91.	Danuta Ryglewicz
30.	Shinsuke Fujioka	92.	Anna Sarnowska
31.	Dariusz Gąsecki	93.	Iwona Sarzyńska-Długosz
32.	Jonathan Graff-Radford	94.	Martin Sawicki
33.	Sanjeet Grewal	95.	Marek Sąsiadek
34.	Michael Heckman	96.	Michał Schinwelski
35.	Ernest Matthew Hoffman	97.	Krzysztof Selmaj
36.	Josephine Huang	98.	Wendy Sherman
37.	Ewa Iżycka-Świeszewska	99.	Elizabeth Shuster
38.	Dariusz Jaskólski	100.	Mariusz Siemiński
39.	Robert Jech	101.	**Halina Sienkiewicz-Jarosz**
40.	Wolfgang Jost	102.	Małgorzata Siger
41.	Sergiusz Jóźwiak	103.	**Emilia Sitek**
42.	Maciej Juryńczyk	104.	**Joanna Siuda**
43.	**Alicja Kalinowska-Łyszczarz**	105.	Matej Skorvanek
44.	**Bartosz Karaszewski**	106.	**Michał Sobstyl**
45.	Aleksandra Karbowniczek	107.	Paweł Sokal
46.	Michał Karliński	108.	Mariusz Stasiołek
47.	**Radosław Kaźmierski**	109.	Barbara Steinborn
48.	Kathleen Kennelly	110.	Jacek Szczygielski
49.	Wojciech Kloc	111.	Stanisław Szlufik
50.	Shunsuke Koga	112.	Tomasz Szmuda
51.	Takuya Konno	113.	Katarzyna Śmiłowska
52.	Anna Kostera-Pruszczyk	114.	Pille Taba
53.	Magdalena Koszewicz	115.	Paweł Tacik
54.	**Dariusz Koziorowski**	116.	William Tatum
55.	Magdalena Krygier	117.	**Philip Tipton**
56.	Anna Krygowska-Wajs	118.	Jakub Ubysz
57.	Ewa Krzystanek	119.	**Ryan Uitti**
58.	Iwona Kurkowska-Jastrzębska	120.	Robert Wharen
59.	Mariusz Kwarciany	121.	Grzegorz Witkowski
60.	Anetta Lasek-Bal	122.	Jacek Zaborski
61.	Tomasz Litwin	123.	Beata Zakrzewska-Pniewska
62.	Alfonso S. Lopez Chiriboga	124.	Daniel Zielonka

*Names of reviewers who completed three or more reviews in 2021 appear in green color

References

1. Nojszewska M, Kalinowska A, Adamczyk-Sowa M, et al. COVID-19 mRNA vaccines (Pfizer-BioNTech and Moderna) in patients with multiple sclerosis: a statement by a working group convened by the Section of Multiple Sclerosis and Neuroimmunology of the Polish Neurological Society. Neurol Neurochir Pol. 2021; 55(1): 8–11, doi: 10.5603/PJNNS.a2021.0016, indexed in Pubmed: 33555604.
2. Yiannopoulou KG, Papagiannis GI, Triantafyllou AI, et al. Neurological and neurourological complications of electrical injuries. Neurol Neurochir Pol. 2021; 55(1): 12–23, doi: 10.5603/JNNS.a2020.0076, indexed in Pubmed: 33026644.
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5. Czarnowska A, Brola W, Zajkowska O, et al. Clinical course and outcome of SARS-CoV-2 infection in multiple sclerosis patients treated with disease-modifying therapies - the Polish experience. Neurol Neurochir Pol. 2021; 55(2): 212–222, doi: 10.5603/PJNNS.a2021.0031, indexed in Pubmed: 33856686.

INVITED REVIEW ARTICLE

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Central nervous system autopsy — a neuropathological procedure based on multidisciplinary pathoclinical cooperation

Aleksandra Sejda[1], Teresa Wierzba-Bobrowicz[2], Dariusz Adamek[3], Jacek Gulczyński[4], Sławomir Michalak[5], Wiesława Grajkowska[6], Ewa Iżycka-Świeszewska[7]

[1]Pathomorphology Department, Collegium Medicum, University of Warmia and Mazury, Olsztyn, Poland
[2]Department of Neuropathology, Institute of Psychiatry and Neurology, Warsaw, Poland
[3]Department of Pathology, Jagiellonian University Medical College, Krakow, Poland
[4]Department of Pathology and Neuropathology, Medical University of Gdansk, Poland
[5]Department of Neurology, Division of Neurochemistry and Neuropathology, Poznan University of Medical Science, Poznan, Poland
[6]Department of Pathology, Children's Memorial Health Institute, Warsaw, Poland
[7]Department of Pathology and Neuropathology, Medical University of Gdansk, Poland

ABSTRACT

Introduction: Neuropathological brain and spinal cord post mortem examination is a distinct procedure that still plays an important role in modern medicine. In front of increasing amounts of clinical and genetic data, together with important developments in the field of neuroimaging, the Polish Association of Neuropathologists have updated their recommendations regarding central nervous system (CNS) examination. These guidelines are aimed at neuropathologists, pathologists and clinicians.

Aim of the study: Presentation of the outlined recommendations as their goal is to improve the quality, informativity, and cost effectiveness of CNS post mortem examinations. A comprehensive study of the literature was conducted to provide a clinical background of neuropathological autopsy. There are numerous open questions in neuroscience, and new strategies are required to foster research in CNS diseases. These include the challenge of organizing brain banks tasked with managing and protecting detailed multidisciplinary information about their resources. Complex neuropathological analyses of post mortem series are also important to assess the effectiveness of diagnostics and therapy, identify environmental impact on the development of neurological disorders, and improve public health policy. The recommendations outline the need for collaboration between multiple specialists to establish the proper diagnosis and to broaden knowledge of neurological disorders.

Key words: brain and spinal cord dissection, guidelines, neuropathology, pathoclinical cooperation

(*Neurol Neurochir Pol 2022; 56 (2): 118–130*)

Introduction

Central nervous system (CNS) post mortem neuropathological examination is a comprehensive medical examination performed in order to identify the cause of death, verify the clinical diagnosis, confirm the morphological background of the clinically discovered primary disease, identify any secondary or concomitant changes in the brain and/or spinal cord, and reconstruct the course of disease events [1–3]. The neuropathological post mortem is important for doctors and other medical staff, as well as for administration as it helps with monitoring the quality of health services by verifying

Address for correspondence: Ewa Iżycka-Świeszewska, Department of Pathology and Neuropathology, Medical University of Gdansk, Dębinki 1 Str., 80–211 Gdańsk, Poland; e-mail: ewa.izycka-swieszewska@gumed.edu.pl

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the adopted diagnostic and therapeutic procedures. In addition, it allows the detection of infectious, toxic, genetically determined, environmental and occupational diseases, and often indicates an aetiological factor [4]. An additional aim of the CNS dissection is the maintenance of the principles of good clinical practice and the long-term development of neuroscience [2, 5, 6].

Despite enormous progress in medicine, in many cases it is still not possible to make an unambiguous diagnosis during hospitalisation and to determine the causes of a patient's death, and complete correctly death report. Additionally, as shown by correlation analyses of clinical and sectional diagnoses, in about 15-30% of cases there are incompatibilities even in hospitalised patients examined in detail [3, 7]. Neuroimaging has become a basic diagnostic tool used in modern neurology; however, its accuracy is still insufficient [8]. Therefore, the neuropathological autopsy remains in many cases the final means of establishing a clinical diagnosis in many situations [9]. Despite this, a significant decrease in the number of referrals for post mortem examinations of the CNS has been observed in recent years. This is mainly due to financial constraints, changes in clinical attitudes to autopsy in general, and limited access to professional neuropathological diagnostics. In recent decades, there has been a decline in interest in the specialisation of neuropathology, resulting in a decreasing number of qualified personnel [10]. Recently, post mortem brain magnetic resonance imaging (MRI) has become a powerful bridge between clinical phenotypes and histopathological findings [11]. However, this procedure requires special protocols, is available only in selected centres, and has specific indications. The next modern method is virtopsy - a multidisciplinary post mortem virtual examination, mostly used in forensic medicine to perform minimally invasive, observer-independent, objective case investigation, with good documentation quality [12].

A neuropathological post mortem is either an element of a general autopsy examination, including external and internal examination of body organs with taking samples for histopathological examination, or constitutes a separate examination performed in a pathomorphology facility or in a neuropathology lab. It depends mostly on the degree of reference of the medical centre, and the availability of specially trained staff and sophisticated equipment. General pathologists are trained to deal with typical and the more frequently occurring clinical cases. Every unusual situation should be consulted by a qualified neuropathologist in a particular medical centre. Performing a CNS autopsy correctly requires substantial preparation with a thorough knowledge of neuroanatomy, the location of functionally significant structures, the specific topography of pathological processes, and the need to correlate with the overall neurological picture [2, 13].

During the post mortem neuropathological examination, recommended standard and selected samples from macroscopically changed regions are taken from the different structures, depending on the clinical and pathological picture. These are then taken to a laboratory for tissue processing and ultimately subjected to microscopic assessment. This may require special additional histochemistry, immunohistochemistry or genetic testing [14–16]. There may also be a need for biochemical, microbiological and/or toxicological examination of specimens and/or cerebrospinal fluid [9, 17].

A neuropathological post mortem examination should be conducted based on the relevant guidelines with due diligence, and its results compiled within a specified period to correlate with *in vivo* clinical and neuroimaging data [1, 9, 18].

Clinical background

Historically, most brain diseases, among others Parkinson's Disease, multisystem atrophy, Alzheimer's Disease and amyotrophic lateral sclerosis, were defined and understood based on their clinical course against the background of macroscopic and microscopic CNS examination [19–21]. Rapidly expanding knowledge in neuroscience has brought about changing conceptions regarding multiple neurological diseases. However, in order to verify them, morphological and genetic analyses are still necessary. There is a real need for neuroimaging-neuropathological correlations before, and in parallel with, developing radiological methods, specific contrast media, metabolic and functional imaging. For example, pathological investigation of regions with signal MRI abnormalities and healthy controls has helped to improve MRI imaging and its interpretation in multiple sclerosis diagnosis and treatment [22]. The next illustrative conclusion of such correlations is that post mortem brain analysis of the regions reflecting MRI changes in amyotrophic lateral sclerosis showed a relationship between signal changes and the underlying pathophysiology [23]. Moreover, several conditions might be under-recognised when clinical tests and neuroimaging results are the only factors taken into consideration in establishing a final diagnosis. Thus, the proper treatment, prognosis, and even some global health system statistics and decisions, might be being assessed and incorrectly evaluated [24, 25].

In numerous clinical entities, especially in neurodegenerative diseases, careful assessment of post mortem data has expanded the concepts of their pathobiology, and may even have been crucial in research concerning therapeutic target finding and implementation of clinical trials [25, 26]. Modern classifications of several groups of neurological diseases, such as leukodystrophies, are founded on complex correlations of clinical course, sequential neuroimaging, pathological findings (including identifying deposits of abnormal proteins) and molecular characteristics [27]. In addition, only careful neuropathological investigations are able to reveal different co-pathologies in examined brains, especially in age-related diseases and dementia [28]. The severity of cognitive impairment in Alzheimer's Disease (AD) has been found to be associated with the distribution, quality and quantification of several pathological findings [25]. Similarly in Parkinson's

Disease, clinical heterogeneity corresponds to different spatio-temporal and quantitative pathological phenotypes [26]. In recent years, new drugs and therapies have been developed which have substantially extended patient lifespans in numerous entities. In such cases, morphological changes in CNS are not well known. Finally, simulated brain stereotactic biopsy from autopsied brains could help to establish diagnostic algorithms which might be used for proper intravital diagnosis, but also for monitoring changes, including those caused by disease-modifying therapies [6, 29].

Brain tissue analysis is becoming more important and more interesting in general medicine, psychiatry, oncology and in infectious diseases (Zika virus, COVID-19), deciphering pathophysiology and consequences of many disorders. Moreover, for a deeper understanding of different diseases, as new research techniques have become more widespread, brain tissue samples should be available for neuroscience research [5, 30–33]. To summarise, much remains to be learned about the clinical phenotypes and corresponding pathological changes in neural tissue, and some risk or protective factors in heterogenic conditions need to be recognised.

What is today crucial for a more effective research of neurological diseases in front of the decreased autopsy rate is the formation of systemic brain banks, together with the collection of comprehensive clinical data. In human brain banks, post mortem and biopsied brain samples are collected, preserved and distributed for histological, pathological, and molecular research [34, 35]. Such collections are maintained in many countries and by many institutions, including for instance the US's Harvard Brain Tissue Resource Centre, the UK Brain Bank Network and the Netherlands Brain Bank. There are also more specific collections of selected diseases such as The Mount Sinai School of Medicine Alzheimer's Disease and Schizophrenia Brain Bank in New York [36]. The BrainNet Europe consortium unites 19 countries with the aim of resolving the significant ethical and legal issues and providing bioethical principles to establish brain biobanking in Europe [37]. In 2018, at the Institute of Psychiatry and Neurology (IPiN) in Warsaw, a Digital Brain project (No. POPC.02.03.01-00.0042/18) was begun with the digitalisation of the resources of the Department of Neuropathology. More than 5,000 formalin-fixed brains and spinal cord samples, with paraffin blocks, microscopic specimens and clinical documentation, have been collected there since 1953.

The collection of human brain tissue is essential in order to recognise new entities, as well as to explain clinical manifestations of diseases [38, 39]. The newly recognised type of dementia, limbic-predominant age-related TDP-43 encephalopathy, is an excellent example of the practical utility of such research and collaboration [32, 38]. Another aspect of biobanking includes the transmission of research conducted on well-designed animal models into human tissue, since most of these studies require validation on large brain post mortem cohorts [39].

Clinical, epidemiological, radiological and genetic studies combined with neuropathological analyses of large post mortem series are also important to guide public health policy, and minimise neurotoxicity and the environmental impact on the development of neurological disorders [40]. The focus on interdisciplinary approaches in order to maintain the high quality of these studies should be mentioned. Greater standardisation of brain post mortems is fundamental for extending the current knowledge of brain diseases [1, 3]. The Association of Polish Neuropathologists, which gathers specialists in the fields of pathomorphology, neuropathology, neurology, neurosurgery and neurosciences, has recently updated its guidelines for post mortem examination of the central nervous system. These guidelines are aimed at the medical community, with the goal of updating the rules of conduct, emphasising the usefulness, promotion and revitalisation of CNS post mortems, and determining the cost-effectiveness and specificity of the procedure. It also indicates the need for functioning reference centres in the field of neuropathology. Presenting guidelines corresponds to regulations of Ministry of Health and Polish Society of Pathologist.

Recommendation overview for CNS autopsy

General and neuropathological post mortems should be performed in a dissecting room equipped with a standard set of tools and additional devices, with the safety and personal protection measures necessary when handling biological material and in the possible presence of high-risk infectious diseases. If a high-risk factor is known, precautions should be taken that are appropriate for the disease entity e.g. the skull should be opened, after covering inside a closed bag, using an oscillating saw under a wet towel, so as to reduce the formation of aerosol in patients with Creutzfeldt-Jakob Disease or COVID-19. Depending on the clinical diagnosis, either only the brain might be removed from the body, or the brain plus the spinal cord.

A general autopsy is performed at the request of a clinician, by a qualified physician who is either a specialist in the area of pathomorphology, or a resident under the supervision of a specialist. A neuropathological section should ideally be performed by a specialist in the field of neuropathology or a physician with experience in the evaluation of neuropathological tissue material. A lab technician performs preparatory, cleaning and sanitary activities regarding the body of the deceased and the post mortem room, and during the operation, auxiliary activities related to the removal of the brain and/or spinal cord, under the supervision and on the orders of the physician in charge.

Referral for an autopsy (autopsy card) is an internal document compliant with the health service's procedures and legal provisions, containing the following data: name, address, telephone number of the unit directing the procedure, patient identification data, data regarding the patient's stay in hospital

including the date of admission to hospital, date and time of death, final clinical diagnosis, neuroimaging results and clinical resume, date of referral for post mortem, and finally the details, signature and stamp of the physician who made the referral. The medical history should be delivered before the general post mortem and be available for the neuropathological examination. It is highly recommended that the physician attend the autopsy.

Scope of post mortem examination of brain and spinal cord

A classical autopsy should encompass three body cavities, i.e. the skull, chest and abdominal cavity. Examinations of only the brain are allowed in cases of patients with CNS diseases, when the diagnostic tests performed during the patient's life have not revealed changes in other organs [3]. It is recommended to make photographic documentation, and/or select and describe changes in the CNS scheme. If it is technically possible, the section should be registered with a voice recorder and/or video camera, as well as hospital integrative systems [1].

The stages of the neuropathological examination during a general and neuropathological post mortem include external examination of the head and surrounding tissues, in situ examination, removal of the brain and possibly removal of the spinal cord, and their macroscopic examination including taking samples for histopathological and other tests [2, 40].

The technique of removing the brain and spinal cord includes several steps which have been described in detail in other publications. If cerebrospinal fluid needs to be taken, this procedure should be performed before removing the brain and/or spinal cord from the body [41].

In special cases, CNS can be evaluated actually during the post mortem, but normally this should be done after fixation in neutral buffered (pH 7.0-7.2) 10% formalin for approximately 2-3 weeks. In certain special situations, short fixation is allowed, wherein it is recommended to make several sections and fix them in a flat position so as not to disturb the architecture. The brain should be put in a container filled with fixative in order to avoid deformation. The amount of fixative used should be 5-6 litres for the entire brain; it is recommended to change the fixative weekly. Brain samples should be fixed in a separate container with an appropriate amount of neutral buffered formalin (10 times the volume of the samples). Some pathological changes are visible in the brain only after complete or partial fixation. In these situations, without full brain fixation, significant problems can arise in terms of a proper macroscopic assessment [1, 4, 17].

Brain cutting is most frequently performed according to Spielmeyer's method, starting with separation of the arachnoid mater and vessels of the circle of Willis, maintaining their arrangement and branches. The brainstem and cerebellum should be cut on the border with the cerebral peduncles. The brainstem should be cut off at the level of the substantia nigra and separated from the cerebellum by cutting the cerebellar peduncles, then the bottom of the fourth ventricle should be assessed. Cerebellar hemispheres should be cut through horizontally along the transverse groove. Midbrain, pons and medulla should be cut in the frontal plane into slices, c.0.5 cm thick. Next, whole cerebral hemispheres should be sliced in the frontal plane into intervals of 1-1.5 cm, starting from the frontal pole. To obtain parallel cutting planes, it is advantageous to use a glass plate, which should be applied to both hemispheres before the next cross-section, preventing their deformation. If the spinal cord is removed, it should be cut transversely to the long axis at intervals of 1 cm through the centre of the segment. All the slides should be arranged on an even flat surface, followed by proceeding to description, macroscopic assessment, photographic documentation, and collection of samples [1, 4, 15].

The macroscopic description should include the weight of the brain, its general appearance (i.e. symmetry, deformations, the presence of herniation, oedema, the ratio of gyri to grooves, cortical atrophy) and the appearance of meninges (including the sinuses of dura mater), epidural spaces with particular emphasis on the presence of haemorrhages, assessment of cranial nerves, vascularisation (anatomical variants of vascularisation, malformation, degree of atherosclerosis) and the ventricular system (symmetry, content). In individual frontal sections, the structure, colour, coherence and outline of the cortex, white matter, hippocampus, basal ganglia, thalamus, insular cortex, midbrain, pons, medulla, cerebellum and spinal cord, as well as blurring of the boundary between the cortex and white matter, should all be assessed [1, 42].

Rules for collecting samples for histopathological examination

During a neuropathological autopsy, the brain is classified as either macroscopically normal or abnormal.

The term 'normal brain' refers to situations where the neurological history is negative, neuroimaging was normal or not performed, and the brain is macroscopically without pathological changes. Sections should be taken then from the frontal lobe with cingulate gyrus, superior and middle temporal gyri, parietal lobes, occipital gyri, putamen and globus pallidus, hippocampus, thalamus, periventricular white matter, midbrain, pons, cerebellar cortex with dentate nucleus (minimum 11 samples). If necessary, additional samples might be taken from available cervical spinal cord segments, intervertebral ganglia, medulla, mamillary bodies or other basal ganglia.

An 'abnormal brain' is a brain that is macroscopically altered or taken from patients with described neurological symptoms, with changes described in neuroimaging examinations, and from oncological patients, as well as in cases without an established cause of death.

In the case of a normal brain, the samples might be taken from the brain without previous fixation. In fact, a post-fixation examination of an abnormal brain and spinal cord is recommended. Before performing the section of the fixed material, the brain should be rinsed under a gentle stream of cold running water for 1-2 hours.

The examination of 'abnormal brains' should always be considered in conjunction with medical history and neuroradiological imaging studies. Macroscopic examination should be performed according to general principles, with particular emphasis on the location of pathological changes and the implementation of appropriate photographic documentation or marking changes on cross-sectional views. In particular cases, the entire examination should be performed in a medical reference centre.

Samples from an 'abnormal brain' should be taken from macroscopically changed regions and, depending on the disease entity, clinical symptoms and the results of neuroimaging diagnostics should be collected in accordance with the algorithm of neuropathological diagnostics of a given disease entity [6, 13–15, 18, 19, 21, 22].

Specimens from both normal and abnormal brains should be marked with consecutive letters of the alphabet, e.g. right frontal lobe A, left parietal B, midbrain C etc. and put into separate cassettes (marked with the case number and a letter corresponding to a particular structure). All samples should be then fixed in cassettes for about 24 hours, undergo routine histotechnological processing, and stained using the basic method i.e. haematoxylin-eosin (H&E), and, if necessary, special histochemical, immunohistochemical or ultrastructural and molecular tests can then be performed [18, 43]. Specimens should be evaluated by a neuropathologist or pathologist.

Ancillary studies

Histochemical staining enables the identification and location of tissue and cellular components (proteins, enzymes, carbohydrates, microorganisms) based on their chemical structure [44]. The most commonly used techniques for neuron evaluation are cresyl violet stain and silver impregnation methods such as Bielschowsky or Bodian stains. Myelin sheaths are usually demonstrated by Spielmeyer, luxol fast blue or its variation, Kluver-Barrera stain. Congo red dye is used for amyloid depositions. Microorganisms are mostly visualised by PAS and Grocott staining [14, 16, 17, 43].

Immunohistochemistry is a method of detecting specific tissue antigens in microscopic sections using antibodies directed at sought-for elements/pathological proteins in tissues [45]. There are numerous antibodies used in diagnostic neuropathology including glial fibrillary acidic protein (GFAP), which is a marker of astrocytes, synaptophysin, S-100, neurofilament markers, LCA, CD68 of microglia, or EMA of meningeal cells [17, 18, 43]. Other highly specialised, non-commercial, and scientific antibodies are available only in dedicated centres in Poland and elsewhere.

In certain cases, molecular tests are performed where it may be necessary to secure fresh frozen material at an appropriate temperature. However, many genetic analyses can also be performed on material routinely preserved in paraffin blocks after fixing in formalin [17]. Molecular diagnosis is nowadays often essential for neuropathological examination. There are several clinicopathological entities where it is necessary to perform molecular tests and genetic diagnostics such as inherited/familial diseases, leukodystrophies, storage and metabolic disease, mitochondrial encephalopathies, neuromuscular disorders or triple nucleotide repeat disorders, etc. [27, 46, 47]. Moreover, molecular identification of various infectious agents may be necessary [48].

Securing and preparing material for microbiological, ultrastructural and toxicological tests should be consulted with the appropriate microbiology/toxicology/forensic laboratory in order to avoid pre-analytical errors. For instance, ultrastructure tests require the use of a fixative other than formalin, usually 2-5% glutaraldehyde [1].

Principles of sample collection for histopathological examination in basic clinical and pathological entities

The number and types of samples (tissue sections) taken, and methods used, differ and can be individually variable; it can be as high as 40-50 in complex or coexisting diseases. Figures 1 and 2 set out the most important anatomical sites of sample acquisition. The general rules for collecting samples in the most common CNS disease entities are presented below. In all examples, the samples should be taken as complementary to the basic one referred to as 'normal brain' and described above.

Vascular damage — CNS hypoxia/ischaemic and haemorrhagic stroke

In the case of ischaemia of the CNS, sections should be taken, depending on the clinically predicted cause, from the area(s) most sensitive to hypoperfusion (i.e. hippocampus, cerebellar cortex, thalamus, midbrain), as well as watershed areas of cerebral and spinal vascular arteries (superior and middle frontal gyrus, superior and middle temporal gyrus, cingulate cortex, occipital gyri, putamen with globus pallidus, T4 vertebra). In addition, in the case of a macroscopically visible mass effect, additional samples from the pons, midbrain and medulla oblongata should be taken [15, 18, 49].

In order to assess vascular changes in the course of a haemorrhagic or ischaemic stroke, a detailed macroscopic assessment is necessary, looking for cerebral venous sinus thrombosis, vascular malformations, aneurysms in the circle of Willis area and in the initial sections of the anterior, middle and posterior arteries; the atherosclerosis degree should be assessed. In addition, samples from the macroscopically visible

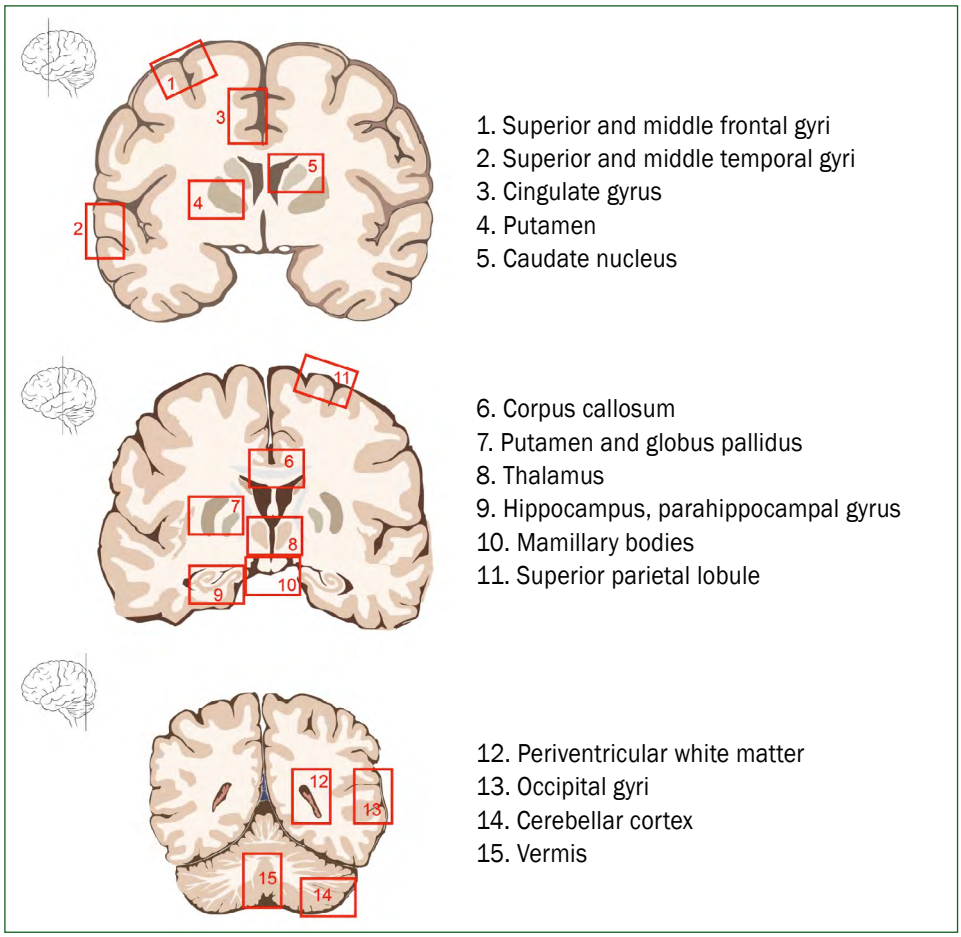

Figure 1. Scheme of sample acquisition according to anatomical localisation of most frequently injured sites in cerebrum

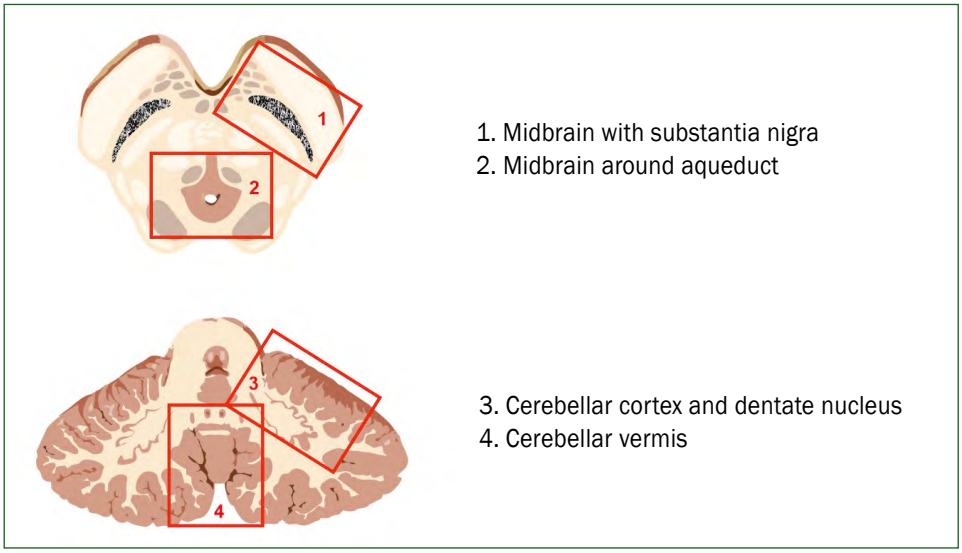

Figure 2. Scheme of sample acquisition according to anatomical localisation of most frequently injured sites in cerebellum and brainstem

haemorrhagic and/or ischaemic focus should be taken each time to assess vascular lesions in the course of small vessel disease. Similarly, if a disease of large or small vessels is suspected, appropriate samples should be taken specific for each kind of disorder. In the case of lacunar stroke associated with hypertension and/or diabetes, samples should be taken from the globus pallidus, putamen and pons [18, 50–52].

To sum up, in total, a minimum of 11 sections (superior and middle frontal gyrus, superior and middle temporal gyrus, cingulate cortex, occipital gyri, putamen with globus pallidus, hippocampus, cerebellar cortex, thalamus, midbrain, and pons) should be taken for the assessment of ischaemic and haemorrhagic injuries without a clinical suspicion of a specific vascular disease. Table 1 shows the additional sample collection according to the most common CNS vascular pathologies [14, 15, 18, 50, 51, 81, 82].

Encephalitis, Infectious/ Inflammatory conditions

In case of viral, bacterial, parasitic or autoimmune encephalitis, taking into account the macroscopic image, numerous samples should be taken from sites typical for a given infective agent. In the absence of pathogen identification, as a minimum, samples should be taken from the cortex of both hemispheres (always including those from the medial areas of both temporal lobes with hippocampi), from deep white and periventricular white matter, and from several levels of the brainstem, cerebellum, basal ganglia, paravertebral ganglia, meninges, and pituitary gland. This comprises a minimum of 11 sections, even up to 40 sections with strict topographic marking. Molecular or microbiological methods can be used on the samples to detect specific infective agents [14, 15, 18, 43].

Neurodegenerative diseases

Neurodegenerative diseases (NDs) constitute a heterogenous group of CNS diseases characterised by progressive neurological deficits associated with neuronal damage in specific anatomical areas, often accompanied by aggregation of incorrectly folded proteins [18, 21, 53]. Depending on the type of damaged and/or excessively stored protein and intracellular inclusions, observed mainly in neurons, but also in glial cells, among NDs we can distinguish tauopathies (most commonly Alzheimer's Disease, corticobasal degeneration, progressive supranuclear palsy, frontotemporal dementia and parkinsonism linked to chromosome 17), alpha-synucleinopathies (Parkinson's Disease, dementia with Lewy bodies, multiple system atrophy), trinucleotide repeat disorders (Huntington's Disease, spinocerebellar ataxia, Friedrich's ataxia, spinal muscular atrophy), prion diseases (Creutzfeldt-Jakob Disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome), and others [18, 54, 55]. In addition, in Alzheimer's Disease there are amyloid deposits made of amyloid beta, and in various subtypes of frontotemporal dementia there are intracellular inclusions of FUS proteins, TDP-43 or ubiquitin [56, 57]. In rarer NDs, such as amyotrophic lateral sclerosis, cytoplasmic inclusions (Bunina bodies) are present, consisting of the TDP43 protein, and in neurodegeneration with brain iron accumulation there are iron deposits mainly in the basal

Table 1. Recommended sample collection in common vascular disease of central nervous system (CNS)

Distinct vessel disease	Samples
Small vessel disease	
Cerebral amyloid angiopathy	Midfrontal and inferior temporal gyrus (leptomeninges, superficial cerebral cortex with subcortical white matter)
	Calcarine cortices
	Angular gyrus
	Cerebellar cortex
	Hippocampus
Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis)	White matter
	Watershed areas
	Subcortical areas
	Cortical areas
Primary angiitis of CNS	Samples from leptomeninges (especially nondominant frontal lobe)
	Superficial cerebral cortex
CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)	Periventricular and deep white matter
	Temporal lobe
	Corpus callosum
	Basal ganglia
	External capsule
	Brain stem
	It is recommended to secure and fix at least one fresh sample in glutaraldehyde for ultrastuctural examination
	Skin samples
Chronic hypertension	Putamen
	Thalamus
	Globus pallidus
	Lobar deep white matter
	Cerebellum
	Pons
Large vessel disease	
Takayasu's arteritis	Aortic arch
	External and internal carotid arteries
	Cerebral arteries
Giant cell arteritis	Temporal arteries
	Vertebral arteries
Fibromuscular dysplasia	Internal carotid arteries
	Vertebral arteries
Moyamoya syndrome	Circle of Willis
	Internal carotid arteries and its branches
	Anterior cerebral arteries
	Middle cerebral arteries

Scheme mentioned below is in addition to basic sample collection in ischaemic/haemorrhagic disease. Large vessel disease section include samples which should be taken from particular vessel wall

ganglia [23, 58]. Many, more or less typical, changes are connected to other entities.

The minimum 13 samples for the diagnosis of the most common neurodegenerative diseases include the middle frontal gyrus, cingulate cortex, superior and middle temporal gyrus, hippocampus with hippocampal gyrus and entorhinal cortex, superior parietal lobule, putamen with globus pallidus, midbrain, substantia nigra, pons, caudate nucleus, cerebellar vermis, cerebellar cortex with dentate nucleus, and medulla oblongata [18, 19, 59].

In the case of AD, a neuropathological assessment is performed according to the CERAD protocol (Consortium to Establish a Registry for Alzheimer's Disease), which assumes a semi-quantitative assessment of the number of senile plaques and neurofibrillary degeneration based on the examination of three neocortical areas [24, 54]. Neuropathological staging of neurodegenerative disorders should be made according to Braak, the six-step scale depending on topographic distribution of neurofibrillary tangles [60]. In cases of other neurodegenerative diseases, samples should be taken in accordance with guidelines for specific clinical pathological units based on the literature [13, 23, 26, 60]. Table 2 sets out information about sample collection in the most important neurodegenerative disorders [18, 60–63].

Apart from the routine H&E stain, the sections are subjected to additional procedures. Most frequently, histochemical tests are performed to assess the degree of myelination and to detect senile plaques, neurophil threads, and neurofibrillary degeneration in specific areas (Bielschowsky silver staining/Yamamoto's modification). In addition, depending on the type of dementia, immunohistochemical tests are performed to detect alpha-synuclein, Tau protein, amyloid beta, ubiquitin or PrP in prion diseases [13, 18, 56, 63, 64].

In the diagnosis of motoneuron diseases, samples are taken from each level of the spinal cord, peripheral nerves (good accessibility is to be found on the ankle halfway between the Achilles tendon and the lateral ankle, and the preferred fixation is in a buffered solution of glutaraldehyde) and muscles (sternocleidomastoid muscle, diaphragm, lumbar muscles) [19]. In neuromuscular diseases (myopathies, mitochondrial diseases, genetically determined diseases), necessary samples include proximal and distal limb muscles and the corresponding peripheral nerves, depending on the clinical picture. It must be remembered that in muscle and nerve diseases, the material often needs to be fixed fresh, or it requires special fixation and preparation. Therefore, before collecting the material, it is advisable to contact an appropriate referential centre [1, 65].

Leukodystrophies and metabolic diseases

Leukodystrophies constitute a group of about 100 genetically conditioned diseases involving white matter. In the case of brain post mortem of a patient with a diagnosed or suspected leukodystrophy, in addition to specimens typical for a normal brain, samples should be taken from subcortical and periventricular white matter of brain and cerebellum hemispheres, especially from macroscopically changed places and those described in the MRI as abnormal. However, a crucial role in metabolic disease diagnosis is played by molecular tests, as most of them are defined as genetically determined diseases with individual profiles [27, 66].

Epilepsy

In cases of patients with a history of epileptic seizures, especially with no known cause of death and a suspicion of sudden unexpected death in epilepsy (SUDEP), it is advisable to take samples from both hippocampi with entorhinal cortex, cingulate cortex, parahippocampal gyrus, middle temporal gyrus, middle frontal gyrus, caudate nucleus, putamen, globus pallidus, thalamus, cerebellar vermis, cerebellar hemispheres with dentate nucleus, and macroscopically visible lesions (minimum 12 samples) [67, 68].

Endogenous and exogenous encephalopathies

Endogenous encephalopathies constitute damage to the CNS in course of diseases of internal organs, e.g. cardiovascular, kidney, digestive or liver diseases, and paraneoplastic changes. Exogenous encephalopathies are most often caused by external factors such as vitamin deficiency, intoxication or poisoning, as well as injuries caused by environmental factors (about 8 extra samples, depending on the type of encephalopathy) [14, 18].

The most common exogenous injurious agent for CNS is alcohol. In patients with a history of alcohol dependence syndrome, taking into account clinical data and macroscopic images, additional samples should include corpus callosum, cerebellar hemispheres with cerebellar vermis (its upper and lower parts), mammillary bodies, periaqueductal grey matter, periventricular region, pons, and medulla oblongata [18, 69, 70].

Foetal and neonatal brain post mortem

Foetal and neonatal brain post mortem is a special type of neuropathological examination. The provided medical documentation, apart from assessing the condition of the newborn and complications in the perinatal period, should be supplemented by information on the course of pregnancy, the mother's diseases, and any possible pathologies occurring in siblings or family [71]. In cases where it is necessary to assess the karyotype, material for cytogenetic testing should be taken, preferably from underarm skin. The scope of the procedure depends strictly on the foetal age.

Removal of the brain should begin with a cut around the skull, from the ear, through the occiput to the other ear, laterally to the neck area and towards the spine. Such a cut allows better access to the cervical spine in order to detect the presence of meningeal herniation, as well as to collect cerebrospinal fluid from the spinal canal. After removing

Table 2. Detailed sample collection in particular neurodegenerative disorders

Type of neuro-degeneration disease	Samples
Tauopathies	
Alzheimer's Disease (AD)	For Consortium to Establish a Registry for Alzheimer's Disease protocol diagnosis of AD
	Superior and middle temporal gyri
	Middle frontal gyrus
	Inferior parietal lobule
	Anterior cingulate gyrus
	Amygdala
	Hippocampus and entorhinal cortex
	Midbrain with substantia nigra
	For Braak stages determination (according to BrainNet Europe Consortium)
	Occipital cortex including calcarine fissure and peristriate/parastriate region
	Superior and middle temporal gyri
	Posterior hippocampus at level of lateral geniculate nucleus
	Anterior hippocampus at level of uncus
Progressive supranuclear palsy	Midbrain with substantia nigra, periaqueductal grey matter and red nucleus
	Pons with locus coeruleus
	Subthalamic nucleus
	Globus pallidus
	Striatum
	Hippocampus
	Medulla with inferior olivary nucleus
	Dentate nucleus of cerebellum
	Frontal cortex
Corticobasal degeneration	Superior frontal gyri
	Superior parietal lobule
	Superior temporal gyrus
	Hippocampus with entorhinal cortex
	Amygdala
	Striatum
	Globus pallidus
	Thalamus
	Subthalamic nucleus
	Midbrain with substantia nigra, tectum and red nucleus
	Pons with locus coeruleus
	Medulla with inferior olivary nucleus
	Dentate nucleus of cerebellum
Frontotemporal dementia and parkinsonism linked to chromosome 17	Frontal and temporal cortex
	Caudate nucleus
	Putamen
	Globus pallidus
	Amygdala
	Hippocampus
	Cerebellar cortex
	Midbrain
	Pons
Unified Staging System for Lewy Body disorders (Dementia with Lewy bodies, PD, AD)	Olfactory bulb
	Medulla at level of IXth and Xth cranial nerves
	Pons at level of locus coeruleus
	Midbrain at level of IIIrd cranial nerve
	Amygdala through its midpoint
	Transentorhinal area adjacent to amygdala
	Anterior cingulate gyrus
	Middle temporal gyrus
	Inferior parietal lobule
	Middle frontal gyrus
Other alpha-synucleinopathies	
Multiple system atrophy	Putamen
	Globus pallidus
	Pons
	Midbrain with substantia nigra
	Medulla with inferior olivary nucleus
	Caudate
Trinucleotide Repeat Diseases	
Huntington's Disease	For Vonsattel staging evaluation samples from three brain levels:
	CAP level (caudate, accumbens, putamen anterior to rostral globus pallidus)
	Level of globus pallidus
	Tail of caudate nucleus (with hippocampus) at level of lateral geniculate body
Frontotemporal lobar degeneration (FTLD)	Middle frontal gyrus
	Superior temporal gyrus
	Parietal lobe
	Hippocampus
	Cingulate gyrus
	Striatum
	Medulla

→

the scalp, measure the fontanelle, assess its tension, and examine the cranial bones. Next, open the cranial cavity by making cuts along the cranial bone suture lines, starting from the anterior fontanelle region forward and backward, and then elliptically along the base of the skull. At this stage, the presence of intracranial bleeding and the appearance and continuity of the dura mater are assessed. An incision of the cerebral falx is then made and both hemispheres of the brain are removed. The removal of the cerebellum takes place after cutting the cerebellar tentorium. The cervical spinal cord should be cut through the foramen magnum as deeply as possible [41, 72].

After removing the entire brain, it should be weighed and placed in a container filled with a fixative solution for c.7-20 days. This is particularly important when hydrocephalus, intracerebral bleeding or holoprosencephaly are suspected. In a situation where early post mortem lesions are suspected, attempts can be made to fix the brain inside the skull by injecting formalin solution into the subdural space with a syringe and a small amount into the ventricular system through the posterior commissure. After this time, macroscopic and microscopic assessments should be performed, paying particular attention to the presence of malformations, perinatal injuries, and prematurity complications (germinal matrix haemorrhage, periventricular leukomalacia). The hemispheres of the brain, brainstem and cerebellum should be cut serially in the frontal plane into slices no larger than 1cm in diameter [1, 71, 72].

Where there is clinical suspicion of neonatal hypoxia, a minimum of 10 samples should be taken from the cerebral cortex and periventricular white matter of both hemispheres, deep grey matter (thalamus, basal ganglia), hippocampus, midbrain, pons, medulla oblongata at the level of the olivary bodies, and cerebellum with dentate nucleus [73]. If congenital malformations are found, it is recommended to collect a large number of specimens from different brain regions, depending on the types of malformation present.

If it is necessary to perform a spinal cord section, removal of the spinal cord and its assessment are performed as would be the case in adults, usually from an anterior approach [1, 4, 71].

Brain autopsy in suspected prion disease

Particular caution is needed when performing a brain post mortem if prion disease is suspected, since the central nervous system has the highest degree of infectivity in prion diseases [59]. Post mortems and the processing of non-decontaminated tissues should take place in a laboratory with a biosafety level of 2 or higher [74]. Tools should be disposable or, if this is not possible, they should be decontaminated [75]. Before the brain is fixed, at least one brain fragment from the frontal cortex and cerebellum should be taken to obtain fresh frozen material for biochemical and genetic testing [59].

The neuropathological autopsy in this particular case is carried out routinely. Recommended specimens for collection are one fragment of the frontal, parietal, occipital and temporal cortex, hippocampus, basal ganglia, thalamus, midbrain, cerebellum and medulla oblongata, since the distribution of lesions can be of different intensities in different CNS regions (minimum 10 samples). In selected specimens, immunohistochemistry detecting the pathological form of prion protein (PrPSc) should be performed. Since most of the available anti-PrP antibodies do not allow the pathological isoform to be distinguished, a procedure combining an autoclave with dipping the specimens in a 96% solution of formic acid can be utilised, or the proteinase K protocol [76–78].

Particular caution should be exercised if a variant of Creutzfeldt-Jakob Disease (vCJD) is suspected, because in addition to the nervous system, high infectivity also affects the lymphatic system and blood. In the case of palatine tonsil biopsy, which is used as a diagnostic method when vCJD is suspected, one should proceed similarly as in the case of brain biopsy [76].

Other CNS diseases

Besides the ones mentioned above, there are numerous CNS conditions such as tumours or demyelinating diseases which affect nervous tissue. Post mortems in these particular cases should be performed individually according to the specific protocols usually in place regarding clinical data and radiological examination.

Forensic autopsy

Due to significant differences in the performance of forensic autopsy of the brain, they should be carried out by a forensic doctor in consultation with a neuropathologist. The scope of such a post mortem is determined by the relevant recommendations in forensic medicine [79]. A forensic autopsy is performed when there is a reasonable suspicion that death did not occur due to natural causes, but rather with the participation of third parties, or to ensure that the cause of death was natural. Autopsy is carried out at the request of the prosecutor's office or the court when there is a suspicion of homicide, as well as in cases of violent death. The most common neuropathological issues in forensic medicine are post-traumatic CNS changes, intoxication, as well as vascular and hypoxic changes. Due to the purpose of a forensic examination, individualised methods of opening the skull and securing tissue material are often used [79, 80].

Post mortem neuropathological examination protocol and quality control

According to Regulation of the Minister of Health (Dz.U. 2015 poz. 2069., DZ. URZ. Min. Zdr. 2021.75) the result of the brain and spinal cord post mortem examination is described in the post mortem protocol, containing the data of the patient and the referring department, clinical diagnosis, a macroscopic neuropathological diagnosis together with a macroscopic description, and the result of the histopathological examination with additional methods and conclusions from the examination. A complete post mortem report should be available to the unit commissioning the post mortem within 30 days in cases of average diagnostic difficulty, and within 60 days in complicated cases [83]. Sometimes, the case requires consultation or additional tests at another centre, and this prolongs the process.

Tissue material collected during the section and the brain fixed in formalin should be stored for a minimum of three months from the issuing of the protocol (in units without an archive of formalin specimens). The storage period of paraffin blocks and microscope slides should be consistent with the relevant Regulation of the Minister of Health regarding storage of medical records (Dz. U. 2015 poz. 2069).

The results of the neuropathological post mortem examination, the final summary of which is contained in the post mortem protocol, should be discussed at appropriate consultation meetings (e.g. neurological meetings, in-hospital mortality conferences) giving the opportunity to discuss clinical diagnoses with pathological data and thus correctly diagnose the cause of death, also for the purposes of administration. In addition, the functioning of existing neuropathological reference centres should be supported, and consideration should be given to the creation of multicentre pathoclinical databases in the field of neurology and neuropathology for statistical purposes, environmental research, and genetic counselling.

As part of ensuring the high quality neuropathological services, it is recommended in pathomorphology/neuropathology centres to follow the recommendations/procedures of the hospital, the Polish Society of Pathologists, and the Association of Polish Neuropathologists. Every major pathomorphology facility, if it does not employ a neuropathologist, is advised to train, or enable the training of, a selected doctor in the field of neuropathology. It is recommended that in difficult cases material be sent for consultative examination by a qualified neuropathologist.

Conclusions and future directions

The guidelines discussed above have been developed by the Polish Association of Neuropathologists, comprising neuropathologists, neurologists and pathomorphologists dealing with this subject matter and having experience in the field of brain and spinal cord post mortems. The proposed standards are based on our own experience and good practice, the recommendations of scientific societies from European Union countries and the United States, as well as the available literature. The recommendations are aimed at standardising the procedures regarding post mortem examinations of the brain and spinal cord, the handling of tissue material and the method of formulating protocols and results of this examination in Poland. The guidelines also define the basis for pathoclinical and administrative cooperation, and introduce the current standard and quality control tool of neuropathological post mortems.

Due to constantly evolving neuroscientific research, it is necessary to correlate clinical diagnosis with brain tissue examination as well as to introduce standards for proper post mortem evaluation of CNS.

Therefore, we emphasise the necessity of conducting brain autopsies in clinical context, the formation of brain banks, the elaboration of standardised diagnostic protocols, and the creation of on-line databases and continuous education of medical staff.

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Ambiguities in blood pressure management in acute ischaemic stroke

Maria Kamieniarz-Mędrygał[1], Radosław Kaźmierski[2, 3]

[1]Department of Neurology, S. T. Dąbrowski Hospital in Puszczykowo, Poland
[2]Department of Neurology and Cerebrovascular Disorders, Poznan University of Medical Sciences, Poznan, Poland
[3]Department of Neurology, University of Zielona Gora, Zielona Gora, Poland

ABSTRACT

Introduction: Blood pressure management in acute ischaemic stroke is crucial. Here we highlight uncertainties surrounding haemodynamic management in acute ischaemic stroke on the basis of current guidelines and the data available from recent studies. This review provides practical treatment options and suggestions for future research.

State of the art: The U-shaped relationship between baseline blood pressure value and patients' functional outcome or death is well established. Nonetheless, there is scant evidence for the benefits of early pharmacological intervention. Current guidelines differentiate blood pressure targets on the basis of implemented reperfusion treatment and allow blood pressure reduction in certain clinical situations. However, there is a substantial lack of evidence to guide management during acute stroke.

Clinical implications: Taking into account several aspects of blood pressure management can improve stroke care, although they are not included in current guidelines. To make an optimal decision as to whether to intervene regarding blood pressure, it is important to consider dehydration, recanalisation status, blood pressure variability, and autoregulation state as measured by novel imaging techniques.

Future directions: Further trials considering patient-specific factors with the use of continuous monitoring of blood pressure, as well as neurovascular imaging, are needed to resolve the current ambiguities.

Key words: blood pressure, ischaemic stroke, acute management, revascularisation

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Introduction

Stroke is the third or, according to the World Health Organisation, perhaps even the second leading cause of death, and the third leading cause of disability worldwide [1–3]. Population-based studies in high-income countries show a consistent pattern of an increasing incidence of stroke at age < 60 years over the last few decades, whereas the incidence has actually declined in older age groups. The absolute incidence, however, is increasing [4]. In 2017, the Polish National Study concerning acute ischaemic stroke epidemiology showed that the crude and the standardised prevalence was 189.95 and 130.43 per 100,000 inhabitants, respectively [5].

Hypertension is one of the most critical risk factors for ischaemic stroke. In a recent (2020) study from West Pomerania, the ischaemic stroke patients who died, compared to those who survived, had hypertension about twice as often (OR = 2.57 in the univariable model; OR = 1.85 in the adjusted model, respectively) [6]. If we consider gender, women suffered from hypertension more often than men (78.3% *vs.* 70.1%) [7].

The high prevalence of hypertension among stroke patients is also clear from data on antihypertensive drug usage in hospitals — they were administered in 79.9% of first-ever stroke patients and in 84.4% of recurrent stroke patients in Poland [8].

Major progress in stroke management has been made since reperfusion therapies were first introduced into clinical

Address for correspondence: Maria Kamieniarz-Mędrygał, S. T. Dąbrowski Hospital in Puszczykowo, Józefa Ignacego Kraszewskiego 11 Str., 62-041 Puszczykowo, Poland; e-mail: maria.kamieniarz@gmail.com

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practice. Intravenous thrombolysis (IVT) was implemented in 1995 in several randomised clinical trials (RCTs) and has proved effective in preventing poor outcomes in eligible patients with acute ischaemic stroke (AIS) [9, 10]. However, according to clinical trials, the administration of alteplase has resulted in recanalisation from 10% to 50% of patients [11–13]. A novel reperfusion technique, endovascular thrombectomy (EVT), has turned out to be much more effective in patients with large vessel occlusion (LVO), with results even exceeding 70% reperfusion rates [14].

As a result, EVT has become the gold standard of care in AIS. Unfortunately, a meta-analysis of 1,287 patient outcomes revealed that only 46% of participants who went through EVT had achieved functional independence at 90 days after their stroke — despite high rates of recanalisation [14]. This relatively low percentage of patients reaching functional independence has prompted the search for other factors that could improve patients' clinical outcome.

As a result, blood pressure (BP) in AIS has attracted major interest. Hypertensive response is a common phenomenon seen in stroke patients. However, it remains unclear whether it is a harmful reaction with potentially negative effects or a protective mechanism aiming to maintain cerebral blood flow. Proper control of BP in AIS is critical to the safe introduction of either IVT or EVT. The widely used American Heart Association/American Stroke Association (AHA/ASA) guidelines on haemodynamic management in reperfusion therapies propose stringent upper BP thresholds. When these are exceeded, causal treatment is contraindicated [15]. In contrast to the 'fixed to the threshold' attitude, recent studies have introduced a more personalised approach. Choosing a strict BP target for all patients may not take sufficiently into account patient-specific factors affecting cerebral perfusion after stroke. Maintaining the same BP threshold can lead to frequent episodes of hypoperfusion and hyperperfusion in vulnerable ischaemic tissue.

Hence in BP management a certain balance is needed to achieve the optimal values in order to avoid the risk of injury with further ischaemia or reperfusion syndrome.

Thus, the aim of this study was to discuss the uncertainties surrounding haemodynamic management in AIS on the basis of the currently applied guidelines and data drawn from recent studies.

State of the art

Current guidelines propose active lowering of BP in AIS patients in two clinical situations [15]. Firstly, in patients with BP ≥ 185/110 who are eligible for either IVT or EVT. In either case, it is recommended to maintain BP below the threshold of 180/105 mmHg after the procedures regardless of whether reperfusion was successful. There is a significant difference in the strength of the recommendation for each procedure (Class I for IVT and Class 2a/2b for EVT).

The second clinical situation in which the guidelines suggest active lowering of BP occurs in patients ineligible for reperfusion therapies with BP ≥ 220/120 mmHg or with pre-existing comorbid conditions (e.g. preeclampsia, acute coronary event, aortic dissection, acute heart failure). Unlike the upper threshold, the lower threshold of BP is not defined. Importantly, the present recommendations on BP management in EVT are not based on evidence from randomised trials. In fact, they are largely extrapolated from IVT trials [10] as well as retrospective studies [16]. There is a notable lack of evidence-based proofs to guide BP management during AIS and revascularisation therapies.

Ambiguities

Whether to treat elevated BP in AIS has long been a matter of debate [17, 18]. Recent trials have brought new insights to this subject. ENCHANTED and RIGHT-2 were both large RCTs designed to assess the efficacy of BP reduction [19, 20]. ENCHANTED was an international randomised, open-label, blinded-endpoint trial of 2,227 patients with acute stroke. RIGHT-2 was a multicentre ambulance-based, randomised, sham-controlled, phase III trial with masked outcome assessment designed to assess the safety and efficacy of glyceryl trinitate (GTN) in a hyperacute stroke population.

The two trials have provided high level evidence that aggressive reduction of BP in hyperacute ischaemic stroke does not improve the functional outcome. Both studies were performed in patients eligible for thrombolysis therapy. In the setting of IVT, it is unknown whether and when recanalisation occurs. A sudden drop in BP in the pre-reperfusion period may increase the ischaemic area and could be the reason for the negative results in the abovementioned studies. Besides, the differences in systolic blood pressure (SBP) between treatment and control groups in both trials were fairly small (5–6 mmHg), which is relevantly low and its impact on cerebral perfusion is debatable. Additionally, the inclusion criteria were broad, which may have affected the findings.

However, there are several aspects regarding BP management that were not specified in the guidelines that one may take into account when deciding whether or not to interfere with BP in AIS. We consider these in the following paragraphs.

Hypovolemia and dehydration

It is stated in the guidelines that both hypotension and hypovolemia should be adjusted while aiming to maintain systemic perfusion levels necessary to support organ function [15]. Hypovolemia may reduce cerebral perfusion and increase the infarct core in ischaemic stroke and perihaematomal ischaemia in intracerebral haemorrhage. The post-hoc analysis of the PASS trial has proved low baseline SBP in patients with AIS to be associated with an increased risk of in-hospital mortality and complications, particularly heart failure, gastrointestinal bleeding, and sepsis [21]. Nevertheless, a clearly defined

cut-off for low BP in AIS patients is lacking. Dehydration is a common phenomenon in AIS and is independently associated with poor clinical outcomes [22, 23]. Managing high BP with the use of antihypertensives may lead to precipitous drops in BP. Billington et al. assessed the impact of dehydration on the haemodynamic effects of antihypertensive treatment and prognosis in the ENOS trial [24]. There were no differences in terms of neurological impairment or in rates of reported hypotension, hypertension or headache by day 7, and no differences in neurological status at three months in those randomised to GTN compared to no GTN, or in those randomised to stop vs continue their pre-stroke antihypertensives. Lowering BP was safe in dehydrated patients, and triggered no precipitous changes in BP, thus supporting hypertensive management in acute stroke patients with blood markers of dehydration. Whether rehydration of dehydrated acute stroke patients has the potential to improve clinical outcome requires further trials.

Autoregulation-guided management

Cerebral autoregulation is a protective mechanism to maintain cerebral blood flow (CBF) despite changes in cerebral perfusion pressure. In normotensive patients, in the case of mean arterial pressure (MAP) fluctuations between 70 and 150 mmHg, CBF remains constant through vasoconstriction and vasodilation. Ischaemic symptoms in the central nervous system of a normotensive person start on average when the MAP at the level of the circle of Willis is 40-50 mmHg in a vertical position, and 45–55 mmHg in a supine position [25].

In patients with chronic hypertension, MAP values of autoregulation are higher, making these patients susceptible to hypoperfusion during hypotensive episodes [26]. Exceeding the specified ranges of MAP leads to a risk of harm due to uncontrolled changes in CBF. The existence of cerebral autoregulation in acute stroke plays a crucial role in the maintenance of a stable blood flow in the ischaemic penumbra and in the avoidance of excessive hyperperfusion [26, 27].

Therefore, potential fluctuations in autoregulatory compliance should be considered in the management of BP in the acute period following stroke. There is a lack of consistency across different studies, and different measurement modalities have been proposed for the assessment of cerebral autoregulation, such as near-infrared spectroscopy (NIRS) and transcranial Doppler ultrasounds (TCD).

Petersen et al. performed a single-centre, prospective cohort study in which the autoregulatory function was measured by interrogating changes in NIRS-derived oxygenation in response to changes in MAP [28]. The percentage of time when MAP exceeded the upper limit of autoregulation, or decreased below the lower limit of autoregulation, was calculated for every patient. Time above fixed systolic BP thresholds was computed in a similar fashion. Every 10% increase in time spent above the upper limit of autoregulation was associated with a 1.9-fold increase in the odds of shifting towards a worse outcome on the modified Rankin Scale (mRS) at 90 days. Likewise, patients with haemorrhagic transformation of AIS spent more time above the upper limit of autoregulation. The authors proved that exceeding individual and flexible thresholds of autoregulation is associated with haemorrhagic transformation and overall worse functional outcome, even after adjusting for important prognostic covariates in stroke. They did not find this association when applying a fixed BP threshold, even when stratifying by reperfusion status [28].

TCD in AIS can provide information on cerebral vascular recanalisation, CBF status, and fluctuations in intracranial pressure, by measuring the blood flow velocity of the major intracranial arteries. Adding continuous BP measurement offers a method with a high temporal resolution feasible for bedside evaluation of cerebral autoregulation. TCD is widely used in stroke units at the bedside, and hence its use in BP management is easy to implement in clinical practice. Chen et al. performed a prospective trial including 95 AIS patients who were randomly divided into a TCD-guided group (TCB) and a non-TCD-guided group (NBC) [29]. They were monitored by TCD for 72 h after EVT. In the TBC group, BP and intracranial pressure were controlled under TCD monitoring using peak systolic velocity and pulsatility index target values of the middle cerebral artery (MCA). The management was performed according to a BP-lowering scheme, a BP-raising scheme, and an intracranial pressure-lowering scheme. The NBC were controlled according to the guidelines. The incidence rates of early neurological deterioration (END) and 3-month mortality in the TBC group were lower than those in the NBC group when TCD parameters were abnormal.

According to this study, when TCD show blood flow deceleration, BP should be elevated under the guidance of TCD monitoring. When TCD show an augmentation of intracranial pressure, the process of decreasing intracranial pressure should be guided by TCD monitoring. The authors hypothesised that the precise control of BP according to individual CBF parameters under TCD monitoring will change cerebral perfusion, reduce the risk of END, and improve prognoses and outcomes. An approach featuring autoregulation-based BP management seems reasonable, although further randomised trials are required.

Type of reperfusion therapy

Several trials have proved the U-shaped relationship between BP and outcome in AIS, with extreme values of BP having prognostic significance for disability and death [30, 31]. The recent post-hoc analysis of the MR CLEAN trial identified a U-shaped relationship between baseline SBP and good functional outcomes, with a nadir at 120 mmHg and a 21% increase in the relative risk of haemorrhage for every 10 mmHg above this value [32]. Nonetheless, clinical situations with patients ineligible for reperfusion therapies, those who received IVT, or both IVT and EVT, are entirely different and should be considered individually.

Although reperfusion therapies are nowadays widely available, there are still patients who are ineligible for either IVT or EVT, most frequently because of exceeding the therapeutic time window. Recent trials have lengthened the time for endovascular treatment up to 16 or even 24 hours [33, 34]. However, the prerequisite for applying EVT in this longer window is the use of imaging techniques which are not readily accessible, leading to the exclusion of some patients. The most recent guidelines recommend SBP to be maintained at a level of < 220 mmHg in the absence of IVT/EVT and < 180 mmHg after IVT/EVT, further highlighting that the usefulness of induced hypertension in patients with acute ischaemic stroke is not well established [15]. The results concerning permissive hypertension are divergent.

Bang et al. presented the effects of multicentre RCT in which for patients with noncardioembolic AIS ineligible for revascularisation therapy, therapeutic-induced hypertension was safe and increased the probability of early neurological improvement and long term independence (class III evidence) [35]. In this study, phenylephrine was administered intravenously to increase the SBP up to 200 mmHg. More patients in the intervention group experienced asymptomatic haemorrhagic transformation on follow-up MRI than in the control group. Interestingly, the effect of induced hypertension was also observed both in patients with large and small artery occlusions. The authors suggested a therapeutic SBP threshold of 180 mmHg in order to achieve beneficial effects. They also implied that the higher response than in former studies might have been the result of a higher therapeutic BP threshold than previously applied.

For instance, in Nasi et al.'s randomised single-centre controlled trial, patients without reperfusion therapies were divided into three groups: low (140–160 mmHg, median 153), medium (161–180, median 163 mmHg), and high (181–200 mmHg, median 178 mmHg) BP thresholds [36]. There was no difference in outcome among the three groups, but the greatest frequency of symptomatic intracerebral haemorrhage (sICH) was found in patients allocated to the higher range target. In logistic regression analysis, the probability of good outcome at day 90 was greater in the medium group compared to the high group (OR = 2.8). Perhaps the use of specific drugs is of more importance than previously thought (in the first trial, phenylephrine was the only drug, while in the second study different drugs, including oral and intravenous, were used). Additionally, the BP target should be more strictly respected (in Nasi et al.'s study in the high BP threshold group, the median BP was only 178 mmHg). In order to sustain adequate brain perfusion pressure, permissive hypertension may be beneficial in nonrecanalised patients. Individual differences in patient-specific factors may influence systemic and cerebral haemodynamics in the response to cerebral hypoperfusion and therapeutic-induced hypertension. Further RCTs assessing the safety and efficacy of permissive hypertension are required.

In the case of patients after recanalisation therapies, high BP appears to be detrimental and should probably be avoided [37–39]. Previous studies have displayed high BP after IVT to be linearly associated with haemorrhagic complications and worse outcomes [40–42]. Therefore, maintaining BP < 185/110 mmHg before IV rt-PA administration and < 180/105 mmHg for the first 24 hours after IVT appear to be valid. Special caution should be exercised in the use of antihypertensives and sudden BP declines after IVT. In the analysis of the NINDS trial, patients treated with antihypertensives had more abrupt BP drops and worse clinical outcomes at three months compared to hypertensive patients who were not treated with pharmacological drugs [40].

For patients undergoing EVT treatment, there is considerably less data concerning BP management. We know exactly when the vessel is recanalised in EVT. However, we do not know when or whether it comes to reperfusion in IVT. For that reason, the same BP targets for each reperfusion therapy might not apply. Uncertainties concern accurate BP management before, during, and after the EVT procedure with regard to the recanalisation effect (successive recanalisation TICI 2b/3 or ≤ 2a).

Post-hoc analysis of the MR CLEAN study showed that baseline BP does not affect the safety of EVT in patients with proximal LVO [32]. Apart from the ESCAPE trial, all pivotal trials introducing EVT have excluded patients with BP above 185/110 mmHg (as such patients were potential candidates for rt-PA), though the conclusions from these studies are limited [33, 34, 43–46].

It is justified in patients after rt-PA administration eligible for thrombectomy to maintain BP below 180/105 mmHg to mitigate the risk of haemorrhage. In patients eligible to endovascular treatment only, the current guidelines suggest that maintaining BP ≤ 185/110 mmHg before the procedure is "reasonable" [15]. Nevertheless, the benefits of BP lowering in the pre-reperfusion time are uncertain and are not supported by the literature [32, 47]. In another study, BP reduction before recanalisation was associated with larger infarct volumes and worse functional outcomes at discharge and at 90 days [48]. The MR CLEAN post-hoc study showed that a decrease in MAP during the intervention under general anaesthesia (GA) compared to baseline BP was associated with a worse outcome. On the other hand, analysis of the SIESTA trial has shown that there is no association between BP parameters (SBP, diastolic blood pressure (DBP), MAP) from baseline to the different phases of intervention (i.e. preintervention, prerecanalisation, postrecanalisation and postintervention) and NIHSS score at 24 h after thrombectomy [47]. Nor was there any association between BP drops and 3-month mRS outcome.

Secondary analysis of data from the GOLIATH trial, in which patients were randomised to undergo endovascular therapy with GA or conscious sedation (CS), examined the relationship between variables related to blood pressure and adverse neurological outcome [49]. There were no statistically

significant associations between BP-related variables and adverse neurological outcomes. In both the GOLIATH and SIESTA trials, strict BP thresholds were applied: SBP ≥ 140 mmHg and MAP ≥ 70 mmHg according to the recommendations from the Society for Neuroscience in Anaesthesiology and Critical Care [50] and the study by Whalin at al. [51], who reported poor outcomes below this threshold. Such predefined treatment targets of SBP and MAP may explain the neutral results in GOLIATH and SIESTA. In contrast, patients included in the MR CLEAN study [32] were presented with median admission BP of 140 mmHg, meaning that 50% of included patients had admission BP levels lower than the minimum level recommended by the Society of Neuroscience in Anaesthesiology and Critical Care [50].

The significance of the type of anaesthesia during EVT has also been a matter of debate. Although retrospective studies have reported worse outcomes with GA and it being associated with hypotension and unstable haemodynamics [51, 52], analysis of three recent randomised trials [47, 49, 53] all investigating peri-interventional management in patients divided into groups of GA and CS, has reported no difference in the primary outcome parameters (90 days 0–2 mRS and NIHSS at 24 h) between groups. The currently ongoing MASTERSTROKE study, assesing two hemodynamic targets during EVT from the beginning of anesthesia to the moment of recanalisation, might provide an interesting perspective. The pilot trial showed no differences in early neurological improvement, all-cause mortality at 90 days, intraoperative complications or intracerebral haemorrhage rates between patients in two BP target groups (130–150 mmHg and 160–180 mmHg) [54].

The subsequent aspect of BP management during EVT is the post-reperfusion time. Studies show that BP drops spontaneously shortly after successive reperfusion therapy and BP decline is not associated with a worse outcome, whereas in non-recanalised patients, BP drops to the same levels but after a longer time [55, 56].

The guidelines recommend maintaining BP after EVT below the level of 180/105 mmHg. However the expert opinion in EVT is to lower BP to 140/90 mmHg in patients with successful reperfusion, aiming to prevent cerebral haemorrhage and reperfusion injury as it was conducted in the DAWN trial [57]. Recent studies seem unanimous in concluding that higher BP values 24 hours after thrombectomy are associated with worse functional outcomes (Tab. 1) [37, 38, 58–60]. However, an association between BP parameters and haemorrhagic complications is less evident [37, 60]. In the groups of patients with successive reperfusion, achieving BP < 160/90 mmHg during the first 24 h post-EVT was independently associated with a lower likelihood of 3-month mortality compared to the group with higher maximum BP values [37]. In successfully recanalised patients, haemorrhagic complications were observed at lower mean values of maximum SBP [38]. In theory, permissive hypertension may benefit patients with non-recanalised LVO by maintaining cerebral perfusion pressure through the

Table 1. Observational studies examining impact of blood pressure during first 24 hours after mechanical thrombectomy in acute ischaemic stroke

Study	Patients and study therapeutic targets	BP parameter	Main findings
Goyal et al. [37]	All: n = 217; TICI ≥ 2b: n = 145	SBP, DBP mean	10 mmHg increment in max SBP associated with lower likelihood of functional independence (OR = 0.7, CI 0.56–0.87, p = 0.001) and higher odds of mortality (OR = 1.49, CI 1.18–1.88, p = 0.001) Achieving BP < 160/90 mmHg in patients with TICI ≥ 2b is associated with lower mortality (p = 0.01, OR = 0.08) No difference in max SBP in patients with or without sICH in whole cohort or in group with TICI ≥ 2b
Mistry et al. [38]	All: n = 228; TICI ≥ 2b: n = 156	SBP, DBP, MAP max, min, mean	Max SBP correlated with worse 90-day outcome (OR = 1.02, CI 1.01–1.03, p = 0.004) and haemorrhagic complications (OR = 1.02, CI 1.01–1.04, p = 0.002) In patients with TICI ≥ 2b, max SBP correlated with worse mRs (OR = 1.02, CI 1.00–1.03, p = 0.01) and severity of haemorrhagic complications (OR = 1.02, CI 1.00–1.03,p = 0.05) Correlation between haemorrhagic complications and max SBP (OR = 1.05, CI 1.01–1.1, p = 0.01) and max MAP (OR = 1.06, CI 1.01–1.11, p = 0.02) in patients with TICI < 2b
Cernik et al. [60]	All: n = 690; TICI ≥ 2b: n = 551	SBP, DBP max, mean	Patients with mRs 0–2 had a lower median of SBP (p < 0.0001) and a median of max SBP (p < 0.0001) compared to those with mRs 3–6 Similar results were found in group with TICI ≥ 2b (p < 0.0001) No significant difference in SBP levels between those with good and poor outcome in patients with TICI < 2b No difference in rate of sICH between patients with median SBP < 140 and ≥ 140 mmHg
Goyal et al. [61]	TICI < 2b: n = 88	SBP, DBP max, min	Max SBP (OR = 0.55, CI 0.39–0.79, p = 0.001) and min SBP (OR = 1.64, CI 1.04–2.6, p = 0.033) were associated with odds of functional independence (mRs 0–2) Min SBP (OR = 0.65, CI 0.47–0.9, p = 0.009) and max DBP (OR = 1.61, CI 1.1–2.36, p = 0.014) were associated with mortality No difference between max SBP and DBP and occurrence of sICH

DBP — diastolic blood pressure; MAP — mean arterial pressure; mRs — modified Rankin scale; SBP — systolic blood pressure; sICH — symptomatic intracerebral haemorrhage; TICI — thrombolysis in cerebral infarction scale

Table 2. Observational studies examining impact of blood pressure variability after mechanical thrombectomy in acute ischaemic stroke

Study	N	BP parameters	Results	
			Primary outcome	sICH
Mistry et al. [72]	443	SBP, DBP SD, CV, ARV, SV, rSD	All BPV indices were significantly higher in patients with poor outcome or death Highest tertile of SBP variability predicted poor outcome (OR 1.8–3.5, all $p < 0.05$) BPV was lowest in patients who did not receive any intravenous medications ($p < 0.001$)	No association between BPV and sICH
Bennett et al. [73]	182	SBP, DBP, MAP SD, CV, SV	SBP indices at 0–24, 0–48 and 0–72 h were associated with a 1-point increase in follow up mRs (OR 2.3–4.38, $p < 0.002$) Systolic SV was best predictor of a 1-point increase in mRS (OR 2.63–3.23, all $p < 0.007$) No consistent association between DBP or MAP and outcome was observed	No association between BPV and sICH

ARV — average real variability; BPV — blood pressure variability; CV — coefficient of variation; DBP — diastolic blood pressure; MAP — mean arterial pressure; mRS — modified Rankin Scale; rSD — residual standard deviation; SBP — systolic blood pressure; SD —standard deviation; sICH — symptomatic intracerebral haemorrhage; SV — successive variation

collaterals. However, this notion is contradicted by studies that have shown an association between high SBP and DBP and an increased likelihood of 3-month mortality and poor outcome [60, 61]. The study authors concluded that future larger studies should examine the potentially beneficial effect of permissive hypertension following EVT in subgroups of patients with sufficient collaterals status and high ASPECTS scores.

Blood pressure variability

The importance of blood pressure variability (BPV) in ischaemic stroke patients has been a matter of debate for the last 20 years. This can be defined as beat-to-beat variability, 24-hours variability, day-to-day variability, or over the longer term — visit-to-visit variability.

Studies show that higher BPV is associated with worse long-term outcomes and mortality after acute stroke [56, 62, 63]. The study by Minhas et al. [64] enrolling over 8,000 ischaemic stroke patients indicated that coefficient of variation (CV) SBP over 24 hours after acute onset had a significant linear association with unfavourable shift in 90 days mRS. By contrast, results regarding short-term outcomes or recurrent stroke are conflicting [65, 66]. However, there is no consensus regarding the most reliable haemodynamic parameter (SBP, DBP, MAP or pulse pressure (PP)) and the variability index or as to the exact thresholds which exceeding might result in an unfavourable outcome [67, 68].

A meta-analysis of the long-term prognostic significance of BPV was attempted by Appiah et al., but unfortunately the methodological heterogeneity of the assayed studies and their incomplete reporting made this impossible [68]. Nonetheless, in the studies considered, the most frequently used BPV parameters were CV, successive variation (SV), standard deviation (SD), and the difference maximum-minimum. The main haemodynamic parameters measured were SBP and MAP. The relevance of PP fluctuations in AIS has been underexplored. Sparse studies show that PP variability, more than SBP variability, is associated with worse outcome after stroke [66, 69]. PP as a pulsatile component of BP and a presumed marker of stiffness may better describe haemodynamic changeability [70].

The association between BPV and outcome has been better reported in studies enrolling patients after reperfusion [62, 63, 71–73] or BP-lowering therapies [63]. In patients after IVT, BP changes were independently associated not only with outcome, but also with sICH and death [62, 71]. Some studies have demonstrated that the impact of BPV on outcome varied depending on the recanalisation status, with a significant association observed only in the non-recanalised group [56, 74]. Similar results have been achieved in groups of patients after EVT, although an association between BPV and sICH is lacking (Tab. 2) [72, 73]. A decline in blood pressure before recanalisation has been associated with larger volumes and worse functional outcomes for patients affected by an LVO stroke [48]. Apart from recanalisation status, it seems that the collateral circulation might be of importance concerning BPV and outcome. In Chang's study, most BPV parameters remained significant in predicting early deterioration and poor 3-month outcomes in patients with poor collateral circulation [75], whereas no significant association was found between BPV parameters and clinical outcomes in patients with good collateral circulation. Interestingly, in the same study, most BPV parameters were significantly higher in patients with internal carotid artery (ICA) occlusion than in those with MCA occlusion. The explanation may be decreased baroreceptor reflex in patients with ICA occlusion that causes sympathetic overactivity inducing high BPV.

Future directions

There is scarce evidence about managing BP in AIS, and this provides researchers with extensive opportunities for further studies. We recommend considering the following aspects in future trials:

1. BP management in peri-reperfusion time

- The significance of baseline BP in EVT and pre-reperfusion permissive hypertension is uncertain, and requires further research.
- There is a substantial need for RCTs of optimal BP management in peri-procedural time of endovascular treatment. In studies concerning intra-procedural BP management, pre- and post-reperfusion time intervals should be differentiated and considered separately.
- Analysis should distinguish between patients with different recanalisation statuses, since each group may have disparate BP requirements.

2. Neurovascular monitoring/imaging
   - Imaging techniques, e.g. TCD, may be of some value in precise BP control according to blood flow parameters, but further research is necessary.
   - The importance of compliance with collaterals and BP management is not yet determined, and should be further studied.
3. Euvolemia as a therapeutic target
   - The role of rehydration of dehydrated acute stroke patients in improving clinical outcomes needs further trials.
4. Blood pressure variability
   - Future RCTs investigating BPV reduction after reperfusion therapies are needed to assess their utility as a novel therapeutic target after stroke.
   - BPV should be measured in the short term (minutes and hours) and in the longer term (day-by-day and visit-to-visit) and include different BPV parameters.
   - Authors should provide detailed information about their study populations and the employed BP regulation during the observation time, including the class of medications used, so as to enable future meta-analysis.

Conclusions

BP management is an important and challenging aspect of care in acute stroke patients. Although the U-shaped association between BP values during the acute period and functional outcome has been verified, no benefits have been found of active BP correction. The current guidelines differentiate BP targets on the basis of employed reperfusion treatment, and allow BP reduction in only a few clinical situations.

However, topical literature shows that personalised, autoregulation-based BP targets, compared to static systolic BP thresholds, might be of greater value in order to achieve the best functional outcome and avoid detrimental events. The optimal BP goal may exist, but it is questionable whether a one-size-fits-all approach is reasonable. Future trials considering patient-specific factors with the use of continuous BP and neurovascular monitoring may provide some answers.

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Susac's syndrome diagnostic difficulties — the neurological point of view

Paulina Fonderska[1], Joanna Tomalka-Kochanowska[1], Jan Kochanowski[1, 2], Izabela Domitrz[1, 2]

[1]Department of Neurology, Bielański Hospital, Warsaw, Poland
[2]Department of Neurology, Faculty of Medical Science, Medical University of Warsaw, Poland

ABSTRACT

Susac's syndrome is a rare microangiopathy affecting small vessels of the retina, inner ear and brain. It is characterised by a triad of symptoms: encephalopathy, visual defects, and sensorineural hearing loss. The disease is probably caused by an autoimmune process. Diagnosis is based on the typical symptoms, brain MRI, and, most importantly, fluorescein angiography. It is important to distinguish between Susac's syndrome and multiple sclerosis or migraine with aura, because misdiagnosis leads to the wrong treatment. To date, no detailed guidelines for the treatment of Susac's syndrome have been developed. Immunosuppression seems to be effective. It must be remembered that early and aggressive treatment is crucial, and that delays in diagnosis, and as a result in treatment implementation, worsen the prognosis.

Key words: Susac's syndrome, microangiopathy, MS, headache, encephalopathy, BRAO

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Introduction

Susac's syndrome (SuS) is a rare microangiopathy characterised by a triad of symptoms: encephalopathy of varying severity, visual disturbances due to branch retinal artery occlusion, and sensorineural hearing loss. It was 1979 when the disease entity was first described by Susac [1], and in 1986, it was named after him. To date, almost 500 cases of this disease among patients of both sexes aged between 2.5 [2] and 72 [3] years have been described worldwide, although it most frequently affects young women. The majority of patients are aged between 21 and 41 years, and the female-to-male ratio is 3:1 [4]. No differences in incidence among different races have been observed [5]. Suggestions of more frequent occurrences during spring and summer have appeared in the literature [6, 7].

The full triad of symptoms appears from the beginning of the disease in less than 15% of patients [7], which creates huge diagnostic challenges. The time elapsed from the first symptoms until the appearance of the fully developed syndrome can reach six months or more [8].

Etiopathogenesis

So far, the causes of this disease have not been fully understood, but most authors incline to the hypothesis that it is based on an autoimmune process which results in damage to the endothelial cells in precapillary arterioles of the brain, retina and inner ear. It was believed that anti-endothelial cell antibodies (AECA) played an important role. A study using Western blots, indirect immunofluorescence and flow cytometry has detected AECA in sera of SuS patients [9]. Recently, researchers demonstrated oligoclonal expansion of terminally differentiated activated cytotoxic CD8+ T cells (CTLs). Their study has identified CD8+ T-cell-mediated endotheliopathy to be a key disease mechanism in SuS, and this highlights therapeutic opportunities [10].

Changes occur in vessels < 100 um in size and include: necrosis of endothelial cells, thickening of the basement membrane, infiltration of inflammatory cells, and accumulation of complement deposits in the arterial wall (C4d and C3d). All these changes lead to the occlusion of the affected vessel and, as a consequence, the formation of microischaemia in the

Address for correspondence: Paulina Fonderska, Department of Neurology, Bielański Hospital, 80 Cegłowska St, 01-809 Warsaw, Poland; e-mail: p.fonderska@wp.pl

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affected organs, which leads to clinical manifestations in the form of the aforementioned triad of symptoms [11].

A study has tested the hypothesis of a genetic basis to SuS. In the light of current research, it is impossible to identify a gene responsible for this syndrome. The theory of a common background with known monogenic small vessel diseases has also been ruled out [12].

Diagnostic criteria

In 2016, Kleffner et al. [13] presented proposed diagnostic criteria for Susac's syndrome based on data collected from case reports published from 1990-2016: 1) Brain involvement:— symptoms: cognitive impairment and/or behavioural change and/or focal symptoms and/or new nature of headache;— typical changes in brain MRI — hyperintense, small, diffuse, circular lesions; at least one in corpus callosum on T2 images (or FLAIR);2) Retinal involvement:— BRAO or AWH in retinal fluorescein angiography or characteristic symptoms of retinal branch ischaemia in fundoscopy/SD-OCT examination; 3) Vestibulocochlear involvement:— symptoms: new onset or change in tinnitus and/or hearing loss and/or peripheral vertigo;— hearing loss confirmed by audiogram; vestibular vertigo supported by specific diagnosis.

On this basis, two categories of diagnostic accuracy have been distinguished: The first is a d efinite diagnosis of Susac's syndrome — this requires the fulfillment of all three criteria along with subcriteria; The second is a probable diagnosis of Susac's syndrome — this requires two out of the three diagnostic criteria to be met [13].

The limitation of these presented criteria, as indicated by the authors [13], is the fact that the full triad of symptoms only rarely manifests at the beginning of the disease. Nevertheless, these criteria can be very helpful in deciding when to implement aggressive treatment, or when to perform watchful waiting.

Encephalopathy

Headache is the most common first symptom of Susac's syndrome, and it may appear six months before other symptoms. The headaches are migraine-like (and mimic migraine attacks) or oppressive in nature, and are likely to result from the affection of leptomeningeal vessels [14]. However, headache, although the most common symptom of SuS, is also present in many other diseases, often of a far more mundane nature. Hence, a very extensive differential diagnosis is necessary.

In the next stages, encephalopathy develops, which may include: cognitive impairment, memory impairment, confusion, and mood disturbances. Neuropsychiatric symptoms are also quite characteristic, which can dominate in nearly 75% of patients [15]. There is no one cognitive-behavioural picture typical for SuS [16]. Cognitive-behavioural global impairment usually depends on brain damage location and its volume [16]. In the available literature, there are only a few report cases to have included a neuropsychological assessment. At first, patients and also their environment most often observe psycho-motor slowness, fatigue, attention deficits, and memory disturbances of varying severity. In order to achieve a detailed assessment of the nature of the deficits, selected neuropsychological tests seem to be very useful e.g.: the Wechlsler Adult Intelligence Scale-revised (WAIS-R) for evaluation of intellectual functioning; the Addenbrooke's Cognitive examination-III (ACE-III); the Rivermead Behavioural Memory Test (RBMT-III); the Behavioural Assessment of Dysexecutive Syndome (BADS); the Dysexecutive Questionnaire (DEX); and the Hospital Anxiety and Depression Scale (HADS).

The major limitation of these tests is the lack of standardisation in many languages. The tests reveal a limitation of visual-spatial abilities and executive functions (impaired planning, set shifting and new problem-solving ability), and reduced efficiency of logical reasoning [16, 17]. Additionally, behavioural disorders in the form of inadequate reactions and emotional lability are noteworthy. There have also been episodes of depression, hypomania, anxiety disorders, and panic attacks [17, 18]. Symptoms partially resolve with treatment, but very often recovery is incomplete and difficult to predict.

In the course of Susac's syndrome, focal symptoms such as paresis, paraesthesia, speech disorders, and cerebellar symptoms may be involved in the pathological process. Seizures have also been observed.

Brain MRI is the test of choice in the diagnosis of Susac's syndrome. This allows the visualisation of the typical, small, snowball-like lesions in the corpus callosum, visible in T2 images. They mimic demyelinating lesions and can lead to a misdiagnosis of multiple sclerosis (MS). They can be located throughout the whole corpus callosum, but usually they occupy its centre, and less so its peripheral parts. Over time, the described lesions change and begin to resemble holes, best visible in T1 images mainly within the splenium of the corpus callosum [19].

Additionally, typical, small, multifocal lesions in white matter are visible and they are located subcortical, periventricular, in the centrum semiovale and also in the internal capsule. In the acute phase, they enhance in 70% of cases. Grey matter, basal ganglia and thalamus affections have been observed in 70% of cases, cerebellum in 52%, and brainstem in 33% [14, 20]. Leptomeningeal enhancement is present in one in three patients [21]. In the MRI test, affection of the cranial nerves has not been observed [4]. After acute onset of the disease, atrophy of the whole brain, cerebellum and corpus callosum develops [20]. The number and size of lesions detectable in conventional brain MRI does not correlate with the severity of the encephalopathy symptoms or clinical status, which has led researchers to look for different ways to present tissue damage.

Diffusion Tensor Imaging is a non-invasive and sensitive technique that allows structural impairment of the fibre

integrity to be revealed on the basis of the normal values for fractional anisotrophy (FA). Using this test, Kleffner et al. demonstrated a reduction of FA, particularly in the prefrontal white matter and in the genu of the corpus callosum [22, 23]. Damage in the genu of the corpus callosum seems to be specific for Susac's syndrome [14].

Computed tomography usually shows no significant abnormalities at the beginning of the disease. However, as it progresses, it can reveal atrophy of the cerebral cortex [24].

The result of cerebral arteriography is almost always normal, because the affected precapillary arterioles (< 100 um) are out of scope of arteriography [7].

For every patient with suspected Susac's syndrome, a cerebrospinal fluid (CSF) examination should also be performed in order to exclude other diseases. In most patients, a mild pleocytosis with usually not more than 20 cells/uL and increased protein level to 2g/L is observed [25]. Oligoclonal bands can be detected in about 15% of patients, and this can produce a mistaken diagnosis of MS rather than Susac's syndrome. Their presence does not exclude the diagnosis of Susac's syndrome [26]. However, their absence can be helpful in differentiating Susac's syndrome from multiple sclerosis [14].

EEG testing, while contributing little to the diagnosis of Susac's syndrome, is often performed at the very beginning of a neurological evaluation. EEG findings usually show generalised slowing and frontal intermittent rhythmic delta activity (FRIDA) [27], which is typical for encephalopathy, but not characteristic (especially in younger people).

Visual disturbance

Visual disturbances mostly result from branch retinal artery occlusion (BRAO). The type of presented symptoms depends on the location and the extent of diseased vessels within the retina [11]. Occupation of peripheral arteries may be asymptomatic without any irregularities in fundoscopic exam [28]. With more intense lesions, patients most often report reduced visual acuity, scintillating scotomas, photopsia and visual field defects [29], and even complete blindness. These visual symptoms can be wrongly interpreted as visual aura of migraine with aura.

Fundoscopic findings show narrowing or complete occlusion of the branch retinal artery and small punctuate yellow-white arterial wall plaques (Gass plaques, named after J. Don Glass, who was the first to describe them in idiopathic BRAO). Gass plaques are present not only in Susac's syndrome, they can also be found in toxoplasmosis, primary vitreoretinal lymphoma, arterial macroaneurysms, and acute retinal necrosis [30].

The most helpful, and very often confirmatory, test in diagnosing Susac's syndrome is fluorescein angiography. Abnormalities seen in the examination are pathognomonic for Susac's syndrome and include segmental arterial wall hyperfluorescence (AWH) with dye leakage [7, 29]. Changes

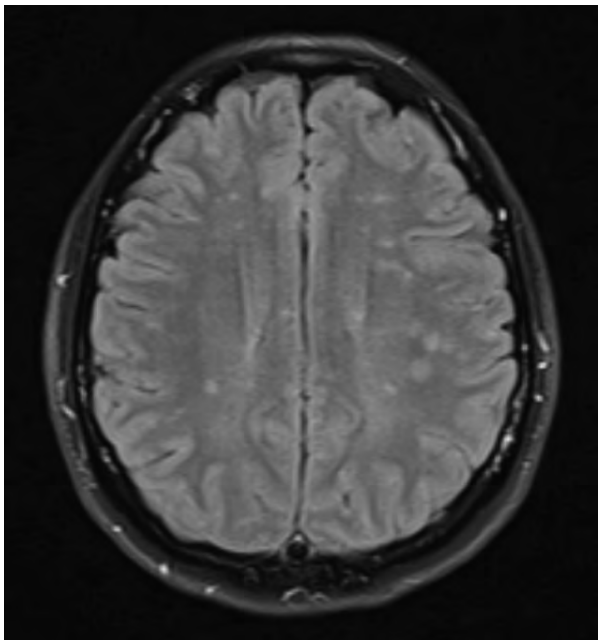

Figure 1. T2-weighted MRI: multifocal lesions in white matter

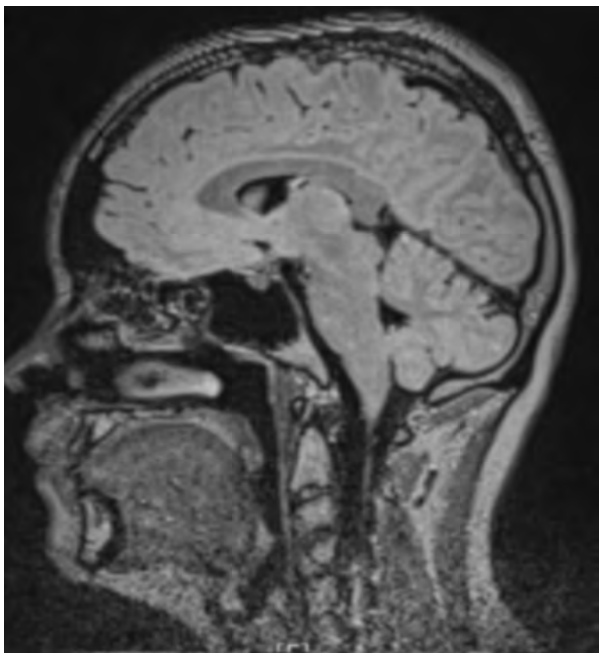

Figure 2. Midline sagittal T2-weighted MRI: typical lesions in corpus callosum

are located unilaterally or bilaterally and may completely disappear over time [14].

A recent addition as a valuable diagnostic tool is optical coherence tomography (OCT). This method allows the illustration of the posterior part of the eyeball — retina and optic nerve. In the study performed by Ringelstein et al., which included 17 patients with SuS, significantly reduced average retinal nerve fibre layer thickness (RNFLT) was revealed in

68% of patients. Additionally, a pattern of scattered changes is very characteristic within the inner retina. In OCT, areas with severe thinning are adjacent to normal areas.

The described phenomenon allows for a clear differentiation between Susac's syndrome and the relapsing-remitting form of multiple sclerosis [31, 32].

Depending on the stage of the disease, both fluorescein angiography and optical coherence tomography provide specific, complementary information.

Hearing loss

Hearing loss often has a very abrupt onset and rapidly progressing course. It can appear one day in one ear, and take over the other ear within as little as a couple of days. Losses in the range of low and medium frequencies are typical, although disturbances in receiving high tones may also appear. Sensorineural hearing loss coexists with preserved acoustic reflexes [33]. Tinnitus and vertigo are frequent accompanying symptoms, which may also precede hearing impairment.

Hearing loss results from the occlusion of the cochlear and semicircular canals precapillary arterioles [3]. Although changes seen in an audiometric examination are very typical, they are not characteristic for Susac's syndrome, and can be observed in different disease entities.

It is worth mentioning the fact that hearing loss, unlike other symptoms, is very often irreversible, and cochlear implantation may be necessary [6].

Other symptoms

Some authors have shown that other organs such as muscle and skin can also be affected by the disease process. In some cases, additional symptoms such as muscle aching or skin rash have appeared. Muscle biopsies performed on patients reporting such symptoms have shown swollen endothelial cells that occluded some small arterioles [34] and foci complement deposits within their walls [35].

Turc et al. [36] reported the case of a young man with skin involvement in the course of Susac's syndrome in the form of livedo racemosa of the flanks and feet. Biopsy showed occlusion in several dermal arterioles due to the presence of thrombus in their lumen, endothelial cells swelling, and mild perivascular lymphocytic infiltrate [36]. The obtained results are identical to the changes observed in the brain or muscles, and this may be confirmation that Susac's syndrome is an autoimmune disease involving small arteries [14].

In 2013, Allmendinger et al. [37] presented a single case of a middle-aged man with the syndrome of cauda equine in the course of Susac's syndrome. A performed spinal MRI showed diffuse lumbosacral nerve root enhancement [37]. In the available literature, there are no other case reports confirming the coexistence of this type of symptoms with Susac's syndrome.

Differential diagnosis

In a differential diagnosis, first of all multiple sclerosis and acute disseminating encephalomyelitis (ADEM) should be considered. The presence of lesions in the centre of the corpus callosum speaks for a diagnosis of Susac's syndrome, as do the typical round shape of lesions, grey matter involvement, or leptomeningeal enhancement. In MS, the lesions are ovoid and are sometimes called Dawson's fingers [14], and in cerebrospinal fluid most commonly oligoclonal bands are present.

A proper distinction between multiple sclerosis and Susac's syndrome is crucial because treatment with interferon beta (commonly used in treating MS) can exacerbate SuS [38].

When the first symptom is a headache in young people, there is often a misdiagnosis of migraine. Accompanying visual disturbances, periodically occurring paraesthesia or other focal deficits can be treated as migraine aura, which additionally hinders the proper differentiation of the disease. A particular type of migraine that may cause additional diagnostic difficulties is vestibular migraine. This connects vertigo and headache. Some patients report mild, transient hearing loss and visual distortions [39]. These symptoms are also quite frequent for SuS.

Therefore, for every patient with a headache (especially a migraine-like feature), every new, additional symptom (auditory, visual, and/or encephalopathic) should raise suspicions and result in referral of the patient for further diagnostics towards Susac's syndrome [40].

Cerebral venous and sinus thrombosis (CVST) is another disease where headache is the predominant symptom. As with SuS, it affects typically young adults, mainly females, which can lead to misdiagnosis [41]. CVST has a lot of varying clinical manifestations similar to SuS, but it is important to remember that the treatment differs significantly.

Also noteworthy in the differential diagnosis is spontaneous intracranial hypotension (SIH), which is dominated by headaches that intensify after standing upright. The orthostatic nature might become less obvious over time, and may become a chronic daily headache. In published case series, hearing change was present in about 70% of patients. In at least 50% of cases, headache was associated with nausea/vomiting and cochlear-vestibular signs. Additionally, mood disorders such as anxiety and depression have been observed [42]. These symptoms can also imitate SuS. The key to diagnosis seems to be establishing the initial, orthostatic, nature of the headache. It is also important to remember that hearing loss should be regarded as a vascular problem.

Treatment

To date, no detailed guidelines for the treatment of Susac's syndrome have been developed. The proposed regimens are based on the assumption that the essence of the disease is an autoimmune process, and thus the treatment should be immunosuppressive. Based on the case reports published so far,

the key seems to be early, aggressive and long-term treatment in order to protect against the recurrence of symptoms [14].

Most authors recommend starting treatment with high doses of steroids, administered intravenously, 1,000 mg of methylprednisolone for five days, and then orally at 1mg/kg body weight, with a gradual reduction under clinical control. This makes a correct diagnosis difficult, because such treatment is also helpful in MS relapse.

In severe cases, intravenous immunoglobulins also seem to be effective [43]. In the event of the recurrence of symptoms after steroid therapy or aggressive onset of the disease, high doses of cyclophosphamide, administered every four weeks [44], should be considered, or another immunosuppressive drug such as mycophenolate mofetil, rituximab or tacrolimus. Plasmapheresis treatments also seem worth considering [26].

Long-term treatment is clouded by the greatest uncertainty. It is very difficult to predict the individual course of the disease, and thus determine the appropriate time at which to cease treatment. It seems that any attempt to change the treatment should be carried out under the supervision of ophthalmological, audiological, neuropsychiatric and imaging examinations [45]. Regardless of the severity of the disease, treatment should usually last at least two years [46].

Prophylactic use of anticoagulants and acetylsalicylic acid is ineffective [47]. It is important to state that the vasoconstrictive agents used in migraine are contraindicated.

Prognosis

In most of the described cases, the disease is monophasic and self-limiting. However, there are relapses, as well as chronic and progressive courses [48]. Symptoms can return, even after many years of remission [49]. The severity of symptoms is also variable. They can be mild, moderate, severe or extremely severe; fatal cases are to be found in the literature [50, 51].

The course of the disease is individual for each patient, and it is difficult to predict the prognosis for a given patient, especially at the beginning of the disease. That is why early and aggressive immunosuppressive treatment is indicated. This prevents the emergence of new symptoms, and also reduces persistent deficits. In spite of treatment, some patients experience residual neurological symptoms, permanent hearing loss, and persistent cognitive impairment. There have also been persistent, mostly asymptomatic, changes in eye fluorescein angiography. Moreover, even with treatment, fatal cases may occur. There are published report cases of two women who died despite intensive immunosuppressive therapy (the first of them 12 weeks [50] after the onset of symptoms, and the second after seven months [51]).

Our experience

In our department, we diagnosed Susac's syndrome in a 23-year-old patient who had not been chronically treated so far. The first noticeable symptom was a sudden hearing loss in the left ear, accompanied by tinnitus and dizziness. After a thorough interview, it turned out that a few months earlier there had also been headaches of moderate intensity. The patient was then consulted by a laryngological specialist and treated with steroids, and then with a hyperbaric chamber, with partial improvement. About two weeks later, there was a 15-minute episode of aphasia and right-sided hemi-paraesthesia. At that time, an MRI of the head was performed, which showed small, multifocal lesions visible in T2 images, located in white matter in both hemispheres of the brain and in the corpus callosum. Differential diagnosis was performed in our department. We made a lumbar puncture, and in the cerebrospinal fluid were 7 cells/uL and an increased protein level to 78 mg/L. Oligoclonal bands were not detected in the CSF. EEG showed normal baseline function with a series of slow waves. Susac's syndrome was suspected, and therefore a 5-day course of methylprednisolone at a dose of 1,000 mg/day was prescribed, which resulted in a reduction of tinnitus and a subjective improvement in hearing. Then we referred the patient for ophthalmological consultation in order to perform fluorescein angiography. This examination confirmed branch retinal artery occlusion and dye leakage through the walls of the retinal vessels. Before the diagnosis was completed, hearing loss occurred in the right ear. Plasmapheresis was performed on the patient, which gave an improvement. Eventually, we diagnosed Susac's syndrome and introduced long-term treatment with mycophenolate mofetil.

Conclusions

Susac's syndrome is a disease that is still not fully understood and is often overlooked in the diagnostic process. In addition, during the first stage of the disease it is often misdiagnosed. Among young women, the first symptoms are often misread as migraine-like symptoms or MS-like symptoms. A major limitation in fully understanding the disease is its very rare occurrence. Most of the available information is based only on individual case reports or analyses of small groups of patients.

It must be underlined that early and aggressive treatment is crucial, and that delays in diagnosis of this disease, and as a result in the implementation of treatment, worsen the prognosis.

As our own experience shows, before making the correct diagnosis, a patient will have come into contact with various specialists: a laryngologist, a neurologist and/or an ophthalmologist. That is why it is so important to spread the knowledge published so far among doctors of all specialisations, in particular neurologists, ophthalmologists, and laryngologists, but also radiologists and general practitioners.

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Platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio may reflect differences in PD and MSA-P neuroinflammation patterns

Natalia Madetko[1], Bartosz Migda[2], Piotr Alster[1], Paweł Turski[3], Dariusz Koziorowski[1], Andrzej Friedman[1]

[1]Department of Neurology, Medical University of Warsaw, Poland
[2]Department of Paediatric Radiology, Medical University of Warsaw, Poland
[3]Students' Scientific Association of the Department of Neurology, Medical University of Warsaw, Poland

ABSTRACT

Aim of the study. To assess the usefulness of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in evaluating the inflammatory process in alpha-synucleinopathies.

Clinical rationale for the study. The role of neuroinflammation in PD and MSA pathogenesis is indisputable. However, there is no method available in everyday use that would enable its evaluation. We suggest that NLR and PLR, as non-specific parameters of inflammation, due to its approachability could be helpful in the assessment of inflammatory activity in alpha-synucleinopathies in everyday clinical practice.

Material and methods. 98 patients with a clinical diagnosis of PD, 28 with MSA-P, and 99 healthy age-matched controls, were included in the study. Blood samples were analysed in order to count neutrophil and lymphocyte rates and, subsequently, NLR and PLR. The obtained parameters were compared between the groups. Results were statistically analysed.

Results. Our results indicate that patients with PD have higher values of NLR and PLR compared to controls. For MSA-P, only NLR was significantly higher in relation to the control group. There were no statistically significant differences between patients with PD and MSA-P in relation to NLR and PLR values. There was a positive average correlation between NLR and disease duration for MSA-P patients.

Conclusions. NLR and PLR values are significantly higher in alpha-synucleinopathies (MSA-P and PD) in relation to a control group. In PD patients, both NLR and PLR values are significantly higher in relation to a control group, whereas in patients with MSA-P, only NLR is significantly increased. The observed differences may reflect distinct neuroinflammatory patterns present in these entities.

Clinical implications. NLR and PLR are features of peripheral inflammation. Their specificity is relatively low, although increased values suggest possible inflammatory pathogenesis of clinical entities. NLR is based on the observations that in chronic and acute diseases the neutrophil rate has a tendency to rise, while the lymphocyte rate tends to decline. This aspect of inflammatory processes has been primarily evaluated in Intensive Care Units. PLR is a marker presenting changes in platelet and lymphocyte counts caused by acute inflammatory or prothrombotic states. Different values of NLR and PLR in PD and MSA-P compared to healthy controls suggest that in these two alpha-synucleinopathies, different patterns of neuroinflammation might be present. The role of inflammation in the differential diagnosis of parkinsonian syndromes remains unexplored.

Key words: PD, MSA-P, alpha-synucleinopathy, NLR, PLR, inflammation

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Address for correspondence: Natalia 1Madetko, Department of Neurology, Medical University of Warsaw, Kondratowicza Str. 8, 03–242 Warsaw, Poland; e-mail: natalia.madetko@wum.edu.pl

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Introduction

Parkinson's Disease (PD) and Multiple System Atrophy (MSA) are progressive neurodegenerative disorders classified pathologically as alpha-synucleinopathies. PD was first described by James Parkinson in 1817 [1] and has been the subject of scientific interest ever since. Even so, the exact mechanism responsible for the process remains unclear. There are many theories concerning the pathogenesis of the disease. There is no doubt that mutations in several genes cause autosomal dominant or recessive forms of Parkinson's Disease. Many papers considering epigenetic abnormalities, exposure to toxins, oxidative stress, metabolic changes, telomere shortening, dysfunction of cellular proteolytic and mitochondrial system, or cardiovascular factors causing ischaemia, as potential causes of PD can be found in the literature [2–10]. Some studies have suggested that PD could be considered to be a prion-like disease [11]. Of all the discussed possible factors leading to PD pathology, the neuroinflammatory theory seems to be one of the most plausible.

It remains unclear, whether the prolonged inflammation in the cause or an effect of neurodegeneration, but the presence of this process is beyond doubt [12, 13]. It has been stated that chronic neuroinflammatory process and microglial activation play crucial roles in the neurodegeneration observed in PD [14, 15]. Chronic neuroinflammation can lead to blood-brain-barrier damage that opens the door to central nervous system (CNS) infiltration by peripheral immune system cells and chemokines. This process can activate glial cells, T-cells and mast cells in the CNS, leading to increased neuroinflammation, which becomes chronic and results in neuronal loss. Mutual activation of inflammation in the CNS and peripheral immune cells leads to the release of neurotoxic molecules and exacerbates neurodegeneration [16]. Pro-inflammatory cytokines and chemokines prompt oxidative stress and damage to dopaminergic neurons [17].

Microglial activation seen as reactive oxygen species (ROS) synthesis is directly increased by α-synuclein, and this activity is even more severe in the case of mutated α-synuclein forms compared to the wild type [18]. Moreover, microglial-mediated inflammation (nuclear factor kappa-B and mitogen-activated protein kinase pathways) may be initiated by soluble α-synuclein when it binds to microglial TLR surface receptors [19, 20]. Inflammation initiated in microglia causes the activation of astrocytes and, *inter alia*, the upregulation of nitric oxide (NO) production [21]. A high concentration of NO causes α-synuclein aggregation [22] and promotes protein accumulation due to a decrease in proteasome activity [23]. This pathological cycle may be responsible for the prolonged neuroinflammation and progressive neurodegeneration seen in PD. In PD, neuroinflammation can be described as having a snowball-like effect with inflammatory activity gradually increasing over time.

MSA is often misdiagnosed as PD, especially the variant with predominant parkinsonism (MSA-P) and mainly in the early stages of the disease. Neuroinflammation is an important feature of MSA pathology, and can be observed as micro- and astrogliosis with increased proinflammatory cytokine levels [24]. Intensity of neuroinflammatory process is restricted to white matter regions due to the impact of oligodendrocytes containing α-syn inclusions [24]. MSA animal models indicate that the inflammatory response is more intense compared to a PD model, which may suggest that increased inflammation in MSA from its early stages is responsible for its more aggressive clinical course [25].

Animal models of MSA indicate that neuroinflammation has an early, pre-symptomatic, onset with explicit response of myeloid cells with proliferative and phagocytic activity in areas with more pronounced alpha-synucleinopathy [24]. In later stages of the disease, proliferation and activity of myeloid cells decreases to a lesser but continuant proinflammatory level [24].

These findings indicate a specific pattern of neuroinflammation characterised by very severe inflammatory response at the onset of the disease. Widespread microglial activation in the early stages of MSA-P has also been described in humans [26]. Data concerning the intensity of peripheral inflammation in the course of MSA remain ambiguous [27, 28].

There are several methods of assessing neuroinflammation activity *in vivo*, featuring mainly neuroimaging with the use of specific radiotracers, e.g. [^{18}F]-FEPPA PET [29] or 11C-PK11195 PET [30]. However, these methods are not available in everyday clinical practice. Finding evidence for connections between neuroinflammation and peripheral inflammation may provide a solution to this challenge [31], as there is data supporting the interrelationship of the peripheral inflammatory response and neuroinflammation, meaning that the activity of one should reflect the activity of the other.

Neutrophil-to-lymphocyte ratio (NLR) is a parameter which was introduced in 2001 by Zahorec [32]. The value of NLR is calculated by dividing the number of neutrophils by the number of lymphocytes. The purpose of evaluating this parameter was to examine patients affected by systemic inflammation who were in a critical condition [32]. It was interpreted as a simple non-specific tool. Since the introduction of NLR, many researchers have verified the usefulness of this parameter in various diseases, not only those directly related to inflammatory involvement.

The role of NLR in Parkinson's Disease has been assessed in several papers; in the study by Moghaddam et al. [33], the authors verified an association between NLR and striatal binding ratios in DaT SPECT. The study showed that increased NLR is concomitant with a decrease in the striatal binding ratio and more pronounced motor impairment [33]. One of the studies interpreted NLR to be a possible marker of peripheral neuroinflammation in differentiating PD from progressive supranuclear palsy (PSP) [34]. The increase of NLR in PD has also been associated with a loss of neural connections [35]. The

abnormalities were observed within cingulum bilaterally, body and left crus of fornix and corticospinal tract bilaterally [35]. An earlier work was based on the comparison of NLR in two variants of PD — the akinetic-rigid and the tremor-dominant [36]. This did not reveal any significant differences. To date, no study has evaluated NLR in the context of MSA.

Platelet-to-lymphocyte ratio (PLR) is calculated by dividing the number of platelets by the number of lymphocytes obtained from the same blood sample. As platelets are involved in peripheral inflammatory response, PLR is a parameter reflecting the level of inflammation. In the literature, this has mainly been discussed in the context of cardiovascular events [37], rheumatic diseases [38], cancer [39], and mental disorders [40]. This parameter has been assessed as a potential tool in differentiating PD from essential tremor [41], but there have been no papers considering this parameter in the context of MSA.

The aim of this study was to assess the intensity of peripheral inflammation in PD and MSA-P compared to healthy controls. We decided to use non-specific parameters, i.e. NLR and PLR, in order to evaluate the usefulness of tools available in everyday clinical practice.

Clinical rationale for the study

Neuroinflammation as an important factor involved in PD and MSA pathogenesis has been widely discussed in recent literature. It is possible that different patterns of ongoing neuroinflammatory process are responsible for its different clinical course and prognosis. However, the methods used in research facilities for neuroinflammation evaluation are not commonly available in everyday clinical practice.

The aim of this study was to assess whether NLR and PLR, as non-specific widespread parameters reflecting peripheral inflammation, could contribute to the diagnosis of PD/MSA and describe differences of inflammation intensity in PD/MSA and healthy age-matched populations. The results of our study could introduce a feasible tool into clinical practice, and generate a discussion regarding a possible correlation between, and the implications of, central and peripheral inflammation in the pathogenesis of alpha-synucleinopathies.

Material and methods

This study was based on a retrospective analysis of blood samples taken from patients with a clinical diagnosis of either Parkinson's Disease or Multiple System Atrophy who were hospitalised in the Department of Neurology at the Medical University of Warsaw, Poland. Diagnoses were made according to the current criteria [42, 43]. The results of the control group were based on the routine examination of blood samples taken in the University's Department of Occupational Medicine. This study was approved by the Ethics Committee of Warsaw Medical University (AKBE151/2020).

Study participants did not suffer from any condition that could affect peripheral inflammation or blood count. The study included 98 patients with PD (43 females, 55 males, aged 39 to 85 years, mean 63), 28 patients with MSA-P (18 females, 10 males, aged 48 to 78, mean 61), and 99 healthy controls (58 females, 41 males, aged 37 to 86, mean 57). Disease duration ranged from 1-6 years for MSA and 2-20 years for PD. All patients were treated with levodopa (medications combined with benserazide or carbidopa); daily dose ranged from 150 to 1,450 mg for MSA patients (c.850 mg average) and from 400 to 2,100 mg for PD patients (c. 1,100 mg average). Less than 15% of patients with PD included in the study received low doses of ropinirole — maximum 4 mg. No changes in drug dosage were made before taking the blood sample. The minimum duration of treatment at a fixed dose was 10 weeks. Other medications in the analysed population included: donepezil, low doses of pyridostigmine (due to constipation), levothyroxine, and metformin.

The exclusion criteria were: age under 35, active infection, chronic inflammatory disease, neoplasm, haematopoietic abnormalities, drug use (including parkinsonian treatment) affecting blood count, diabetes, and significant cardiovascular disorders. Patient data was obtained by analysing their medical records. NLR and PLR ratios were compared between the groups.

The results were statistically analysed using the Shapiro-Wilk test, the Kruskal-Wallis ANOVA test with pairwise multiple comparison of mean ranks (PMCMR) in post-hoc analysis, and Spearman's correlation. p values < 0.05 were considered to be statistically significant.

Statistical analysis

All calculations were performed using Statistica software (version 13.1 Dell. Inc. Statsoft). Data distribution was assessed with a Shapiro-Wilk test. All results were expressed as medians with interquartile range. As the analysed data did not have a normal distribution, for group comparison we used Kruskal-Wallis ANOVA. Pairwise multiple comparison of mean ranks (PMCMR) was used for post-hoc analysis. Spearman's correlation coefficient was used to check the dependence of potential changes in NLR and PLR with disease duration for patients with PD and MSA-P.

Results

The WBC levels were within the normal range for all the subjects analysed (4–10 $*10^3$/ul).

Basic and subgroup analysis

Median values with interquartile range (Q1-Q3) of assessed parameters for whole groups and subgroups are set out in Table 1.

Table 1. Descriptive statistics of study group, PD, MSA-P, PD+MSA-P subgroups and control group

	Whole group (n = 225)		PD (n = 98)		MSA-P (n = 28)		MSA-P + PD (n = 126)		Control (n = 99)	
	Median	Q1–Q3	Median	Q1-Q3	Median	Q1–Q3	Median	Q1–Q3	Median	Q1–Q3
Age	60	54–66	62.5	54–71	62	54–67	62	54–70	59	54–63
Disease duration	–	–	9	6–12	4	3–5	7	5–10	–	–
Neutrophils	$3.6*10^3$	$2.8–4.7*10^3$	$3.6*10^3$	$2.8–4.7*10^3$	$4.3*10^3$	$3.7–5.1*10^3$	$3.8*10^3$	$2.9–4.8*10^3$	$3.4*10^3$	$2.7–4.6*10^3$
Lymphocytes	$1.9*10^3$	$1.5–2.3*10^3$	$1.7*10^3$	$1.4–2.1*10^3$	$1.8*10^3$	$1.4–2.2*10^3$	$1.7*10^3$	$1.4–2.1*10^3$	$2.1*10^3$	$1.8–2.5*10^3$
Platelets	$234*10^3$	$197–275*10^3$	$229*10^3$	$193–261*10^3$	$216.5*10^3$	$187.5–272*10^3$	$227.5*10^3$	$193–268*10^3$	$239*10^3$	$198–285*10^3$
NLR	2.01	1.44–2.65	2.2	1.54–3.04	2.12	1.77–3.27	2.2	1.6–3.04	1.72	1.31–2.26
PLR	124.59	95.24–160.75	134.49	100–179.29	124.43	10^3.89–160.08	130.23	101.58–177.69	111.76	89.82–148.35

Q1–Q3 — interquartile range

The PD patients had higher median values of NLR and PLR compared to controls, 2.2 vs 1.72 and 134.49 vs 111.76, respectively ($p < 0.05$, Tab. 2).

For MSA-P patients only, median of NLR was significantly higher in relation to the control group, 2.12 vs 1.72 ($p < 0.05$, Tab. 2).

Unfortunately, there were no statistically significant differences between patients with PD and MSA-P in relation to NLR and PLR values.

Spearman correlation

There was a positive average correlation between NLR and disease duration for MSA-P patients Rs = 0.5 ($p < 0.05$, Tab. 3). For PD patients, Rs values were low Rs < 0.1 ($p > 0.05$, Tab. 3).

Discussion

Studies looking into NLR as a potential parameter measuring inflammatory activity in PD have shown inconsistent results. Inci et al. [34] and Ataç Uçar et al. [36] reported no statistical difference in NLR values between PD and healthy controls, although Akıl et al. [44] observed a significantly higher NLR level in PD compared to a healthy population. This study proves that both NLR and PLR are significantly increased in a PD group compared to a control group.

The differences in the obtained results in the abovementioned studies might be explained by the size of the examined populations —the larger the studied group, the more pronounced were the differences in the NLR values observed. In a recently published paper analysing data obtained from 453 PD patients and 436 controls, it was also proven that NLR is significantly higher in PD patients, although this paper did not describe PLR [45]. NLR has been found to correlate with white matter changes in PD [46], which suggests that it may, at least partially, reflect inflammatory and degenerative processes ongoing in the CNS. Some papers have proved that significantly increased peripheral inflammatory indices are correlated with the akinetic-rigid PD phenotype, whereas low peripheral inflammation markers are characteristic for patients with the tremor-dominant or mixed phenotypes [47].

In our study, increased NLR and PLR values distinguished PD and MSA-P from healthy controls and indicated the inflammatory process involved in disease pathogenesis, although for MSA-P patients, only the NLR value was sensitive enough. In MSA-P, the level of lymphocytes was not significantly higher than in PD. This resulted in the fact that the difference between the level of lymphocytes among MSA-P patients and the control group was much less pronounced than between PD and controls. This, combined with the relatively low number of platelets, was the cause of significant differences between PLR in PD patients and controls. This observation was not maintained in the comparison of MSA patients and controls. On the other hand, a high increase of neutrophils compared

Table 2. Comparison of PD, MSA-P, and control groups

	PD vs MSA-P *vs.* control	PD vs control	MSA-P *vs.* control	PD *vs.* MSA-P
	p*	p**	p**	p**
Age	0.0041	0.0034	1.0000	0.3079
Neutrophils	0.1047	0.9812	0.1064	0.4420
Lymphocytes	< 0.001	< 0.001	0.0487	1.0000
Platelets	0.2990	0.5719	0.6631	1.0000
NLR	< 0.001	< 0.001	0.0176	1.0000
PLR	0.0127	0.0105	0.4868	1.0000

p* — p-value for Kruskal-Wallis ANOVA; p** — p-value for pairwise multiple comparison of mean ranks (post-hoc test); in red are marked statistically significant p-values < 0.05

Table 3. Correlations between PD, MSA-P, and disease duration

	PD (n = 98)	MSA-P (n = 28)
	disease duration Rs	disease duration Rs
Neutrophils	–0.17	0.47
Lymphocytes	–0.11	–0.01
Platelets	0.00	0.10
NLR	–0.08	0.50
PLR	0.07	–0.06

Rs — Spearman correlation coefficient; in red are marked Rs values with p < 0.05

to controls resulted in the fact that the comparison of NLR between MSA-P and controls showed significant differences, whereas in PLR the significance of differences was not confirmed. The tendency towards increased levels of neutrophils in MSA-P may be influenced by the differences in neuroinflammatory pattern of PD and MSA. Based on previous studies regarding cytokine profiling in the prefrontal cortex of PD and MSA patients, it has been shown that increased mRNA levels of GSK3β are observed in MSA but not in PD [48]. GSK3β is a relevant factor in the inhibition of AMP-activated protein kinase (AMPK). GSK3β inhibition of AMPK is an enhancer of lipopolysaccharide inflammatory responses resulting in stimulation of neutrophils [49]. The role of platelets in neurodegeneration is currently being widely discussed in the literature; due to neurotransmitters like γ-aminobutyric acid (GABA), glutamate, serotonin, epinephrine, dopamine, and histamine which are present in platelets cytoplasm or exosomes, these cells are thought to act as messengers connecting the CNS to the peripheral environment [50]. It is known that platelets release serotonin when exposed to glycolipid structures specific for neurons and astrocytes' lipid rafts [51], and this phenomenon occurs as a response to blood-brain-barrier damage and promotes neuroinflammation, *inter alia* in neurodegeneration [52]. According to Rydbirk et al. [48], there are no statistically significant differences in PDGF levels between PD and MSA, and therefore a disparity in platelet number should not be expected.

Another possible explanation for partially similar results of NLR and PLR obtained from patients with PD and MSA-P may lie in different inflammatory patterns. Taking into account the pace of deterioration and the previously described inflammatory patterns, it is possible that analysed parameters are similar due to inflammation in MSA fading over the course of time and incompletely developed neuroinflammation in middle-stage PD.

We hypothesise that the curves showing the severity of inflammation over time run in opposite directions, only to converge in the intermediate period of the diseases. Initially, the severity of inflammation should be much higher in MSA, while in late-stage PD, the severity of inflammation should exceed that seen in late-stage MSA. However, our theory requires verification. This hypothesis was not directly confirmed by our results, but they were obtained with the use of non-specific parameters of inflammation, and recent research concerning this issue suggests a multicausal background to this phenomenon. Kouli et al. [53] proved that at the earliest stages of PD there is a reduction in terminally differentiated effector memory (TEMRA) lymphocyte T CD8+ population compared to healthy controls. A study by Csencsits-Smith et al. [54] revealed that in MSA the dynamics of neuroinflammation acceleration measured by levels of serum cytokine secretion is four times greater than in PD, which could explain faster progression.

However, due to the fact that the neuroinflammatory processes present in the pathogenesis of both the diseases under discussion is complex and includes multiple variables, it is very difficult to exactly determine which components of the immune system play the dominant role. Increased parameters of peripheral inflammation may be used as one of the biomarkers of alpha-synucleinopathies, among others, in non-invasive assessments [55].

To the best of our knowledge, this is the first study to assess NLR or PLR in MSA.

The fundamental limitation of this study is its retrospective character, which precluded an assessment of genetic features of included patients or other markers of the inflammatory process. All patients included in the study remain alive, and therefore all diagnoses were made according to current diagnostic criteria without neuropathological confirmation.

NLR and PLR are non-specific parameters, although their assessment could be useful in everyday clinical practice. The exact mechanism of a possible association between peripheral inflammation and neuroinflammation must be further explored.

Therefore, it seems crucial to search for more specific parameters reflecting neuroinflammatory intensity that are accessible in everyday use. This is a topic that requires further investigation.

Conclusions

NLR and PLR values are significantly higher for alpha-synucleinopathies (MSA-P and PD) compared to a control group.

In PD patients, both NLR and PLR values are significantly higher compared to a control group, whereas in patients with MSA-P only, NLR is significantly higher.

NLR and PLR values do not help differentiate PD from MSA-P patients.

NLR and PLR values suggest the presence of different patterns of ongoing inflammation in PD and MSA-P.

Clinical implications/future directions

This study has identified a possible role of the everyday use of laboratory tests in the clinical diagnosis of PD and MSA-P. Our obtained results contribute to the discussion considering neuroinflammation and its possible peripheral markers in the context of alpha-synucleinopathies. This study highlights the need to search for accessible tools facilitating the management and diagnosis of Parkinson's Disease and Multiple System Atrophy. To the best of our knowledge, this is the first paper evaluating PLR in the context of atypical parkinsonian syndrome; this parameter should be assessed in patients with atypical parkinsonian syndromes, as previously published studies have shown interesting results in the context of peripheral inflammation markers [56].

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Factors that may delay disappearance of trigeminal neuralgia after percutaneous balloon compression

Wenming Lv[1, 2], Wenjing Hu[3], Lingyi Chi[1], Liangwen Zhang[4]

[1]Department of Neurosurgery, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China
[2]Department of Neurosurgery, First People's Hospital of Ningyang County, Tai'an, Shandong, China
[3]Shandong First Medical University and Shandong Academy of Medical Sciences, Tai'an, Shandong, China
[4]Department of Neurosurgery, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, China

ABSTRACT

Introduction. We set out to explore the factors that may affect delayed disappearance (DD) of trigeminal neuralgia (TN) after percutaneous balloon compression (PBC).

Material and methods. PBC was undergone by 221 patients with TN (95 male, 126 female) aged 33–89 years (mean 65). Delayed disappearance after surgery occurred in 59 patients. Follow-up continued until pain disappeared.

Results. A total of 221 patients, with an overall effective rate of 98.19%, including 59 patients with DD (26.70%), 158 patients with non-DD (71.49%), and four patients without relief, were included in this study. The time of delayed disappearance ranged from two to 30 days after surgery, with an average of c.9 days. Factors related to delayed disappearance included symptom duration (≥ 8 years), history of radiofrequency thermocoagulation, diabetes mellitus, herpes zoster, pain involving V2, and non-pear-shaped balloon. These were independent influencing factors ($p < 0.05$).

Conclusions. PBC is a safe and effective surgical method for treating TN. Delayed disappearance is a common phenomenon after surgery, and is influenced by many factors.

Key words: percutaneous balloon compression, trigeminal neuralgia, delayed disappearance, symptom duration

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Introduction

At present, the treatment methods for trigeminal neuralgia (TN) mainly include drug therapy, microvascular decompensation (MVD), radiofrequency thermocoagulation (RFT), and percutaneous balloon compression (PBC). PBC is mainly suitable for elderly patients with ineffective oral drugs, multi-branch pain, and poor surgical tolerance. It has the advantages of minimal trauma, high safety, and rapid effect.

However, pain may not disappear immediately after PBC surgery. Clinically, the phenomenon where pain does not disappear immediately after surgery, but gradually disappears during observation after surgery, is known as 'delayed disappearance' (DD). Nerve tissue undergoes sequential pathological changes after the ganglion is compressed by the balloon. When the filling pressure in the balloon is maintained for a period of time, most nerve cells are mechanically damaged. However, pathological changes do not occur, which may be the pathological basis of delayed disappearance. To date, no studies have reported on delayed disappearance in patients with TN who underwent PBC surgery.

Therefore, our study examined 59 patients with delayed disappearance of TN treated using PBC in our department. For the first time in this study we have examined related factors such as symptom duration, concomitant diseases, and balloon shape, to further explore the influencing factors of delayed disappearance, thus inferring the prognoses for patients and so guiding clinical work.

Address for correspondence: Liangwen Zhang, Shandong Provincial Hospital Affiliated to Shandong University, 324 Jingwu Weiqi Road, Jinan, 250021, Shandong Province, China; e-mail: zhangliangwen1221@163.com; co-corresponding author: Lingyi Chi

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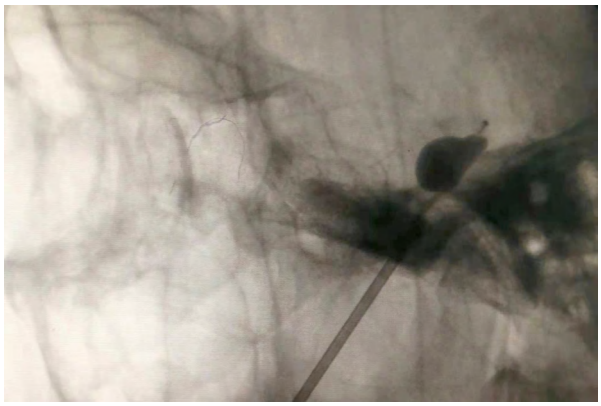

Figure 1. Pear-shaped balloon in situ. Pear-shaped balloon formed in Meckel's cave during percutaneous balloon compression (PBC) surgery

Table 1. Compression time

Time (min)	Number of patients (%)
3	39 (17.65)
4	143 (64.70)
5	39 (17.65)

Variables are presented as n (%) for nominal data; mean ± SD or continuous data (average: 4 min); SD — standard deviation

Table 2. Barrow Neurological Institute (BNI) pain intensity scale score

Score	Definition
I	No pain, no medication
II	Occasional pain, not requiring medication
III	Some pain, adequately controlled with medication
IV	Some pain, not adequately controlled with medication
V	Severe pain/no pain relief

Material and methods

Material

A total of 221 patients who underwent PBC in our department from January 2018 to June 2021, and who were willing to be followed up after their surgery, were recruited as research participants. This study was approved and implemented by the Hospital Ethics Committee, and all patients who participated provided signed informed consent.

The inclusion criteria were: (1) medical history, symptoms and signs, and brain computed tomography and magnetic resonance imaging results that all met the International Headache Society (IHS)-II (2008) and IHS-III (2013) diagnostic criteria for TN [1, 2]; and (2) oral carbamazepine invalid or serious adverse reactions.

Patients were excluded if: (1) they could not tolerate general anaesthesia, had dysfunction of the heart, lungs, liver, kidneys, or other vital organs, or had an obvious neurological impairment; or (2) had secondary TN; or (3) their medical records or follow-up information were incomplete.

Methods

Patients were placed in a supine position, and Hartel's puncture technique was performed after successful induction of general anaesthesia [3]. Under the fluoroscopic guidance of a C-arm machine (Ziehm 8000, Germany), the needle was inserted 3 cm outside the angle of incidence, and a No. 14 needle was inserted into the opening of the foramen ovale. A 4-F Fogarty catheter, connected to the T-joint, was slowly introduced into Meckel's cave along the puncture path. Next, 0.4–0.8mL gadolinium diamine was injected to inflate the balloon to achieve a pear-like shape (Fig. 1). The compression continued for 3–5 min (average: 4 min, Tab. 1). The contrast agent in the balloon was evacuated, and then the catheter and puncture needle were pulled out. The puncture port was compressed for 10 min before a sterile dressing was applied. Patients were followed up postoperatively via telephone or outpatient visits. This follow-up continued until the pain disappeared.

Observation indices and effect evaluation

(1) The time taken for pain symptoms to disappear, to be relieved, or to recur was recorded. The Barrow Neurological Institute (BNI) pain score was used to create an efficacy score (Tab. 2). "Immediate disappearance of pain" after surgery referred to a pain score of Grade I after the patient awoke from anaesthesia. "Delayed disappearance" (DD) was defined as when the patient's BNI score gradually changed to Grade I from the first postoperative day. "Non-improvement of postoperative pain" meant that the pain did not change, or was even aggravated, in the period between recovery from anaesthesia and the follow-up visit.

(2) The number of cases of intraoperative and postoperative complications (inhibitory reactions of the trigeminal nerve, facial numbness, facial hypoesthesia, masticatory-muscle weakness, tinnitus, diplopia, keratitis, herpes labialis, headache, cerebral haemorrhage, and blindness) was recorded.

(3) Any factors possibly related to delayed disappearance (including age, symptom duration, sex, side, history of RFT, MVD, concomitant disease, pain involving V2, balloon volume, compression time [≤ 4 min], and shape) were evaluated.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 26.0 software was used for analysis, and the enumeration data was analysed using a χ^2 test. Multivariate logistic regression analysis was performed on the basis of single-factor analysis to screen for independent risk factors and $p < 0.05$ was considered statistically significant.

Results

Demographic data and clinical characteristics

A total of 221 patients with TN underwent PBC, performed by the same neurosurgeon in the Neurosurgery Department of Qilu Hospital, from January 2018 to June 2021. Table 3 shows the demographic data and clinical characteristics of the patients.

Overall effect and complications of PBC for TN

A total of 221 patients were analysed with an overall effective rate of 98.19%, including 59 patients with delayed disappearance (26.70%), 158 patients with non-delayed disappearance (71.49%), and four patients without relief (1.81%) (Tab. 4). There were many complications during and after PBC. The incidence of inhibitory reaction of the trigeminal nerve during surgery was 97.3%. The most common postoperative complications were: facial numbness, masticatory-muscle weakness, tinnitus, diplopia, and keratitis, which occurred at rates of 76.9%, 28.1%, 14.5%, 11.8%, and 10.4%, respectively (Tab. 5).

Analysis of delayed disappearance time and influencing factors

The duration of postoperative pain in the delayed disappearance group ranged from two to 30 days (Tab. 6), and the average duration of delayed disappearance was c.9 days. In univariate logistic regression analysis, symptom duration (≥ 8 years), MVD, RFT, hypertension, diabetes mellitus, herpes zoster, pain involving V2, and non-pear-shaped balloon were all statistically significant ($p < 0.05$) as set out in Tab. 7. Multivariate logistic regression analysis showed that symptom duration (≥ 8 years), RFT, diabetes mellitus, herpes zoster, pain involving V2, and non-pear-shaped balloon were independent factors for recurrence ($p < 0.05$) as set out in Tab. 8.

Discussion

PBC surgery, an effective treatment for TN, is mainly suitable for elderly patients with ineffective oral drugs, multi-branch pain, and poor surgical tolerance. Percutaneous balloon compression (PBC) is based on the principle that the balloon selectively compresses the damaged myelinated nerve fibres that conduct pain in Meckel's cave, preserving the motor branches of the trigeminal nerve [4], and closing the trigger switch of the pain conduction pathway of the trigeminal nerve to eliminate pain. The statistical rates of immediate disappearance after PBC surgery in China and abroad vary significantly, ranging from approximately 74% to 100% [5–8]. The incidence of delayed disappearance has been described as 9.31–19%, which was different from our findings in the present study. However, the average duration of delayed disappearance was approximately nine days, which was consistent with the research by Li Zaiyu et al. [9] in China [5, 9, 10].

Table 3. Demographic characteristics of 221 patients

Sex	
M	95
F	126
Age (range; years)	65 (33–89)
< 40	2 (0.9%)
41–50	12 (5.4%)
51–60	35 (15.9%)
61–70	65 (29.4%)
71–80	80 (36.2%)
> 80	27 (12.2%)
Symptom duration (range; years)	8 (0.04–50)
Distribution by side	
Left	79 (35.7%)
Right	142 (64.3%)
Trigeminal division	
V_1	4 (1.8%)
V_2	76 (34.4%)
V_3	12 (5.4%)
V_{1+2}	57 (25.8%)
V_{1+3}	2 (0.9%)
V_{2+3}	40 (18.1%)
V_{1+2+3}	30 (13.6%)
Previous failed procedures	
Microvascular decompression	74
Radiofrequency thermocoagulation	60
Percutaneous balloon compression	3
Glycerol gangliolysis	2
Therapeutic effect of drugs	
No response to medical treatment	110
Multiple side effects of drugs	75
Concomitant disease	
Hypertension	79
Diabetes mellitus	43
Coronary heart disease	25
Cerebral infarction	23
Herpes zoster	116
Chronic bronchitis	5
Sequelae of cerebral haemorrhage	2
Others (MS etc.)	9

Variables are presented as n (%) for nominal data, M — male; F — female; MS — multiple sclerosis

Percutaneous balloon compression (PBC) is prone to causing complications such as inhibition of the trigeminal nerve reaction during surgery, postoperative facial numbness,

Table 4. Barrow Neurological Institute (BNI) pain grades of 221 patients after percutaneous balloon compression (PBC)

BNI pain grade	Preoperatively of PBC, number of patients (%)	Immediately after PBC, number of patients (%)	During postoperative period, number of patients (%)
I	0	158 (71.5)	217 (98.2)
II	0	27 (12.2)	0
III	21 (9.5)	28 (12.7)	1 (0.4)
IV	65 (29.4)	8 (3.6)	3 (1.4)
V	135 (61.1)	0	0
Total	221 (100)	221 (100)	221 (100)

This table reflects changes in numbers and percentages of pain in different grades before and after PBC. Variables are presented as n (%) for nominal data

Table 5. Complications of 221 patients during/after percutaneous balloon compression (PBC) (n/%)

Complication	Number of patients (%)
Inhibitory reactions of trigeminal nerve	215 (97.3)
Cardiac arrest	15 (6.8)
Facial numbness	17 (76.9)
Severe facial hypoesthesia	26 (11.8)
Paresthesia	14 (6.3)
Masticatory-muscle weakness	62 (28.1)
Tinnitus	32 (14.5)
Diplopia	26 (11.8)
Keratitis	23 (10.4)
Labial herpes	18 (8.1)
Headache	2 (0.9)

Number and percentage of complications during or after PBC, variables are presented as n (%) for nominal data

paresthesia, and masticatory-muscle weakness. Because Meckel's cave, where the semilunar segment of the trigeminal nerve is located, is adjacent to the oculomotor, trochlear, abducens, and vestibular nerves and other structures, it is common for patients to experience diplopia, keratitis, tinnitus, and other complications due to excessive balloon filling. Most inhibitory reactions of the trigeminal nerve are transient, with an incidence as high as 97.3% in this study. The incidences of postoperative complications, such as facial numbness, paresthesia, and masticatory-muscle weakness, and their recovery times, which have been reported in many articles both in China and abroad, may be related to factors such as the size of Meckel's cave, the volume and shape of the balloon, and the compression time of the balloon [11, 12].

At present, there is a lack of research on factors influencing delayed disappearance after PBC surgery in China and abroad. Therefore, the focus of this study was to include many factors affecting delayed disappearance. Our study has confirmed for the first time in the world that symptom duration (≥ 8 years), RFT, diabetes mellitus, herpes zoster, pain involving V2, and non-pear-shaped balloon are factors affecting delayed disappearance after PBC surgery.

It is surprising that symptom duration (≥ 8 years) was a significant factor in our results. We believe that the longer the course of TN, the more obvious the nerve compression. After mechanical damage is caused by PBC, it will take a period of time for the trigeminal nerve to adapt to the damage and for the neuroelectrophysiology to return to normal [5]. Yadav et al. [6] confirmed that the delay to cure in patients with facial spasm after surgery positively correlated with the length of the course of the disease, and even reported a formula to calculate that delay to cure. This would seem to demonstrate the delayed repair of cranial nerves after mechanical injury.

Radiofrequency thermocoagulation (RFT) utilises a difference in temperature tolerance between different nerve fibres of the trigeminal nerve to selectively destroy fine fibres that transmit pain while preserving the coarse fibres for transmitting touch, which have relatively high thermal resistance. Observation of nerve injury under the microscope after radiofrequency thermocoagulation is characterised by thermosetting degeneration, necrosis, fracture of the adventitia and nerve fibres, complete destruction of the myelin sheath and axonal structure of nerve fibres, and charring to varying degrees of connective tissues such as blood vessels [13, 14]. At present, there is a lack of basic research on nerve fibre repair after treatment of TN with RFT. We speculate that the 'scar' after the repair of the adventitia and nerve fibres delays the conduction of electrical signals.

Diabetic peripheral nerve disease occurs in approximately two-thirds of patients with diabetes, and neuropathic pain is induced by sensory hyperalgesia due to increased intracellular glycated end products, increased activities of inflammatory cytokines and aldose reductase, oxidative stress, and other factors [15, 16].

Urban et al. conducted research on the involvement of the trigeminal nerve and facial nerve in patients with diabetes. They found that 60% of cases had distal symmetrical sensory nerve multiple lesions; using electrophysiological examination, they also found that a high-glucose environment would affect the function of the trigeminal nerve [17, 18]. This indicates

Table 6. Timetable of delayed pain disappearance (days)

Number	Duration of DD	Number	Duration of DD	Number	Duration of DD
1	5	21	10	41	30
2	9	22	7	42	2
3	3	23	5	43	5
4	13	24	21	44	5
5	12	25	2	45	12
6	20	26	5	46	21
7	3	27	7	47	3
8	7	28	7	48	6
9	5	29	4	49	7
10	3	30	10	50	7
11	10	31	7	51	7
12	12	32	21	52	10
13	7	33	30	53	4
14	30	34	10	54	12
15	10	35	5	55	7
16	3	36	6	56	2
17	8	37	30	57	2
18	5	38	3	58	14
19	2	39	2	59	3
20	3	40	21	-	-

DD — delayed disappearance

Table 7. Univariate logistic regression analysis for delayed pain disappearance (DD)

Variable	DD (n/%)	No DD (n/%)	P
Age (≥ 65years)	40 (27.0)	108 (73.0)	0.938
Sex: M	27 (29.3)	65 (70.7)	0.542
Symptom duration (≥ 8 years)	33 (40.2)	49 (59.8)	**0.001**
Microvascular decompression	28 (37.8)	46 (62.2)	**0.006**
Radiofrequency thermocoagulation	39 (65.0)	21 (35.0)	**0.000**
Concomitant disease			
Hypertension	32 (40.5)	47 (59.5)	**0.001**
Diabetes mellitus	19 (44.2)	24 (55.8)	**0.000**
Cerebral infarction	10 (43.5)	13 (56.5)	0.064
Coronary heart disease	8 (22.9)	27 (77.1)	0.568
Herpes zoster	58 (50.0)	58 (50.0)	**0.000**
Left side	19 (24.1)	60 (75.9)	0.434
Involvement of V2	58 (29.1)	141 (70.9)	**0.002**
Balloon volume (≤ 0.4ml)	26 (28.0)	67 (72.0)	0.827
Compression time (≤ 4min)	26 (28.3)	66 (71.7)	0.501
'Non-pear-shaped' balloon	36 (72.0)	14 (28.0)	**0.000**

Statistically significant values are given in bold, and $p < 0.05$ was considered a statistically significant difference

Table 8. Multivariate logistic regression analysis for delayed pain disappearance

Variable	OR	95% CI	P
Symptom duration (≥ 8 years)	5.092	1.527-16.975	**0.008**
Microvascular decompression	0.220	0.051-1.760	**0.179**
Radiofrequency thermocoagulation	32.500	3.239-326.064	**0.003**
Hypertension	3.244	0.901-11.684	**0.072**
Diabetes mellitus	4.012	1.758-13.645	**0.048**
Herpes zoster	125.302	11.716-1,340.075	**0.000**
Involvement of V2	29.069	2.112-400.058	**0.012**
'Non-pear–shaped' balloon	5.174	1.493-17.931	**0.010**

Statistically significant values are given in bold, and $p < 0.05$ was considered a statistically significant difference; OR — odds ratio; CI — confidence interval; P — probability; V2 — maxillary nerve (the 2nd branch of trigeminal nerve)

that continuous cytokine stimulation in patients with diabetes is likely to be the influencing factor for the occurrence, aggravation, delayed disappearance, and recurrence of TN. At the same time, another result of our study (which has been received by 'World Neurosurgery') confirmed that there was a correlation between postoperative recurrence of TN and

delayed disappearance, and that diabetes was a non-independent factor for recurrence.

Herpes zoster is neurotropic and can hide in the neurons of the posterior roots or ganglia of the nerves for years, or even decades. The reasons for delayed disappearance caused by the reactivation of herpes virus after PBC may be related to the following factors [19]: 1) the trigeminal nerve was damaged during surgery, and the irritation led to virus propagation; 2) the resistance and immunity of the patient decreased due to surgery, and the herpes virus in the semilunar ganglion of the trigeminal nerve was induced and activated; 3) the herpes zoster membrane ruptured to form an erosion or secondary suppurative infection, or even cause herpes zoster meningitis; and 4) surgical stimulation caused dissolution of chromatin in the trigeminal nerve ganglion cells, exudation of serous fluid under the stratum corneum, and generation of facial blisters. After antiviral treatment the pain symptoms of the patient resolve, along with the disappearance of herpes.

The expanded saccule directly and mechanically damaged the myelinated nerve fibres and nerves, and blocked the blood supply to the semilunar ganglion of the trigeminal nerve by pulling and pressing Meckel's cave, thus promoting fibre demyelination and pain conduction inhibition. There are more independent branches and anastomotic branches in the blood supply system of the maxillary branch (V2) of the trigeminal nerve than there are in V1 and V3 [20]. Therefore, in theory, patients with TN involving V2 are more likely to have delayed disappearance during PBC treatment.

A balloon that is pear-shaped is considered to be the key to the effectiveness and reduction of complications after PBC surgery [21, 22]. The shape of the balloon is closely related to its location and insertion process. Poor location of a balloon can lead to a non-pear-shaped balloon morphology during surgery and influence the postoperative effect [23]. The compression effect of the non-pear-shaped balloon on the semilunar segment of the trigeminal nerve was worse than that of the pear-shaped balloon, and more recovery time was needed. This might be because of the insufficient effective contact area of balloon compression or the delay of vascular injury caused by mechanical traction.

Future directions

We have confirmed, for the first time, that symptom duration (≥ 8 years), history of RFT, diabetes mellitus, herpes zoster, pain involving V2, and a non-pear-shaped balloon are independent influencing factors. This allows us to better judge the recovery time of patients after PBC surgery to verify the effect of the surgery and give patients a reasonable explanation of their condition.

Limitations

The sample size of this study was small, and other possible contributory factors (e.g. intra-balloon pressure, Meckel's cave size) were not analysed. There is a lack of basic research on delayed disappearance after PBC, and there was a lack of evidence to support hypotheses in our discussion.

Conclusion

Influenced by many factors, delayed disappearance is a common phenomenon after surgery. Because of the existence of delayed disappearance, we suggest waiting at least one month after surgery before judging whether PBC is invalid.

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Mechanical thrombectomy in COVID-19-associated ischaemic stroke: patient characteristics and outcomes in a single-centre study

Katarzyna Sawczyńska[1, 2], Paweł Wrona[1, 2], Tomasz Kęsek[2], Marcin Wnuk[1, 2], Robert Chrzan[3, 4], Tomasz Homa[5], Roman Pułyk[1, 2], Jeremiasz Jagiełła[1, 2], Tadeusz Popiela[3, 4], Agnieszka Słowik[1, 2]

[1]Department of Neurology, Jagiellonian University Medical College, Krakow, Poland
[2]Department of Neurology, University Hospital in Krakow, Poland
[3]Department of Radiology, Jagiellonian University Medical College, Krakow, Poland
[4]Department of Radiology, University Hospital in Krakow, Poland
[5]University Hospital in Krakow, Poland

ABSTRACT

Introduction. The aim of this study was to assess the clinical profiles and outcomes of patients with confirmed COVID-19 infection and acute ischaemic stroke (AIS) treated with mechanical thrombectomy (MT) at the Comprehensive Stroke Centre (CSC) of the University Hospital in Krakow.

Clinical rationale for the study. COVID-19 is a risk factor for AIS and worsens prognosis in patients with large artery occlusions. During the pandemic, the global number of MT has dropped. At the same time, studies assessing outcomes of this treatment in COVID-19-associated AIS have produced divergent results.

Material and methods. In this single-centre study, we retrospectively analysed and compared the clinical profiles (age, sex, presence of cardiovascular risk factors, neurological deficit at admission), stroke size (measured using postprocessing analysis of perfusion CT with RAPID software), time from stroke onset to arrival at the CSC, time from arrival at the CSC to groin puncture, treatment with intravenous thrombolysis, length of hospitalisation, laboratory test results, and short-term outcomes (measured with Thrombolysis in Cerebral Infarction scale, modified Rankin Scale and National Health Institute Stroke Scale) in patients with AIS treated with MT during the pandemic. A comparison between patients with and without concomitant SARS-CoV2 infection was then performed.

Results. There were no statistically significant differences between 15 COVID (+) and 167 COVID (–) AIS patients treated with AIS with respect to clinical profiles ($p > 0.05$), stroke size ($p > 0.05$) or outcomes (NIHSS at discharge, 8.1 (SD = 7.1) vs. 8.8 (SD = 9.6), $p = 0.778$, mRS at discharge 2.9 (SD = 2) vs. 3.1 (SD = 2.1), $p = 0.817$, death rate 6.7% vs. 12.6%, $p = 0.699$). There was a significant difference between patients with and without COVID-19 concerning time from arrival at the CSC to groin puncture [104.27 (SD = 51.47) vs. 97.63 (SD = 156.94) min., $p = 0.044$] and the length of hospitalisation [23.7 (SD = 11.9) vs. 10.5 (SD = 6.9) days, $p < 0.001$].

Conclusion. In AIS patients treated with MT, concomitant SARS-CoV2 infection did not affect the outcome. Our observations need to be confirmed in larger, and preferably multicentre, studies.

Key words: acute ischaemic stroke, COVID-19, mechanical thrombectomy, large artery occlusion

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Address for correspondence: Katarzyna Sawczynska, Department of Neurology, Jagiellonian University Medical College, 2 Jakubowskiego Str., 30–688 Krakow, Poland; e-mail: katarzyna.sawczynska@gmail.com

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Introduction

The majority of hospitalised patients with SARS-CoV2 experience neurological symptoms of varying severity [1]. COVID-19 is proven to be a risk factor for acute ischaemic stroke (AIS) [2]. AIS in patients with a SARS-CoV2 infection is associated with a more severe neurological deficit and higher in-hospital mortality [3]. The incidence of AIS in patients with COVID-19 is estimated at around 1.5%, although this percentage is higher among critically ill patients [4].

Mechanical thrombectomy (MT) is an endovascular method of stroke treatment that has revolutionised the outcomes of patients with emergent large artery occlusion (LAO). Recent studies suggest that AIS in COVID-19 patients is more commonly associated with LAO [5], and that concomitant SARS-CoV2 infection increases mortality in patients with LAO [6]. At the same time, during the COVID-19 pandemic a decline in the global number of stroke hospitalisations and MT procedures has been observed [7].

Clinical rationale for the study

The literature on the outcomes of COVID-19-associated AIS patients treated with MT is scarce, and the studies show divergent results. These have been summarised in a recent systematic review [8]. The characteristics and treatment results of this group of patients still need to be evaluated.

Therefore, the aim of this study was to assess the clinical profiles and outcomes of patients with a confirmed COVID-19 infection and AIS treated with MT at the University Hospital in Krakow,Poland and to compare them to those of AIS patients treated with MT at the same time, but without a concomitant SARS-CoV2 infection.

Material and methods

In this retrospective study, we analysed the medical documentation of patients who had undergone MT for AIS in the Comprehensive Stroke Centre (CSC) of the University Hospital in Krakow, Poland during the COVID-19 pandemic between March 2020 and May 2021. Included were patients with a COVID-19 infection confirmed by a positive SARS-CoV2 PCR or antigen test from a nasopharyngeal swab obtained at admission or in the referring hospital, or before hospitalisation (if the patient did not match the criteria for recovery). The control group consisted of 167 AIS patients treated with MT in the CSC between March 2020 and February 2021, who tested negative for SARS-CoV2 at admission. Excluded were patients who were negative for COVID-19 at admission but who tested positive during hospitalisation, or those who were transferred to another centre and therefore lost to follow-up.

The procedures for acute stroke causative treatment in Małopolska Voivodship, where our centre is located, have been described elsewhere [9]. AIS patients with and without COVID-19 followed the same pathway of care. MT patients without SARS-CoV2 infection were admitted to the Stroke Unit, while those with a confirmed COVID-19 infection were transferred to a specialised Neurology Ward for COVID-19 (+) patients, where they were treated by neurologists from the same centre, with the same level of experience in acute stroke care. The guidelines for treatment of COVID-19 changed during the course of the pandemic, so the patients with SARS-CoV2 infection were treated according to the international recommendations pertaining at the time of their hospitalisation.

The patients who qualified for the study were followed according to the standard protocol of the Krakow Stroke Data Bank, as described in previous publications from our centre [10]. For the purposes of this study, we analysed the patients' age, sex, the presence and number of cardiovascular risk factors, time from stroke onset to the arrival at the CSC, time from arrival at the CSC to groin puncture, number of days of hospitalisation, treatment with intravenous thrombolysis, the immediate radiological effect of thrombectomy (measured using Thrombolysis in Cerebral Infarction scale, TICI), the neurological deficit (measured using National Institute of Health Stroke Scale, NIHSS) at admission and discharge from our centre, the functional outcome (measured using modified Rankin Scale, mRS) at discharge, and in-hospital mortality. Where available, the computed tomography perfusion imaging parameters at admission calculated using RAPID software (a post-processing tool used for qualification for MT in DAWN and DEFUSE-3 trials) [11, 12] were also analysed. We also analysed the available laboratory test results — fibrinogen, D-dimer, lactate dehydrogenase (LDH), lymphocyte count, and C-reactive protein (CRP).

The results were compared between groups of AIS patients with and without a COVID-19 infection. Statistical analysis was performed using a PS Imago Pro 6.0 program. We presented categorical data as counts and percentages, and continuous data as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical data was compared between groups using a Chi-square test. We tested continuous variables for normality with a Shapiro-Wilk test and compared them between groups using a t-Student test for normally distributed data and, in other cases, using a Mann-Whitney U test. We considered a two-sided p-value of less than 0.05 to be statistically significant.

In patients with COVID-19, we also noted the clinical and radiological symptoms of lung involvement. HRCT (high resolution computed tomography) images were analysed by the artificial intelligence technology software YITU Healthcare to automatically measure the relative (%) volume of inflammation in both lungs (the methodology was as described in a previous work from our centre) [13]. The chest X-ray images were assessed by a radiologist using a semiquantitative chest X-ray severity score [14].

The study was approved by the Bioethics Committee of the District Medical Council in Krakow (opinion number 143/KBL/OIL/2020) and conducted in accordance with the Declaration of Helsinki. As a part of the CRACoV-HHS project it was also approved by the Bioethics Committee of the Jagiellonian University in Cracow (opinion number 1072.6120.333.2020 dated December 7, 2020).

Results

We identified 16 patients with a COVID-19 infection and AIS who received treatment with MT in the CSC between March 2020 and May 2021. One patient was transferred after procedure to an Intensive Care Unit of another hospital, lost to follow-up, and not included in the final analysis. Four patients were diagnosed with COVID-19 before the onset of stroke, and two of them had already been hospitalised when the stroke occurred. The patients' individual characteristics, including their SARS-CoV2 infection clinical picture, are set out in Table 1.

The patients were aged 49 to 85 with a median age of 70 years (IQR = 17). Eight (53.3%) were female. The most common cardiovascular risk factor was arterial hypertension, found in 13 (86.7%) patients. There were no statistically significant differences between groups of patients with and without COVID-19 with respect to age, sex, the presence of individual cardiovascular risk factors, or the total amount of cardiovascular risk factors (Tab. 2).

CT perfusion with post-processing analysis with RAPID software was performed in 11 and 138 patients with, and without, COVID-19 infection respectively. There were no statistically significant differences in the volumes of total ischaemia, penumbra or necrosis between patients with and without COVID-19 infection (Tab. 2).

Patients with COVID-19 had a longer time from stroke onset to arrival at the Comprehensive Stroke Centre [307.3 (SD = 183.7) vs. 227.3 (SD = 115.7) minutes], but this difference was not statistically significant ($p = 0.062$). They also had a longer time from arrival at the CSC to groin puncture: this difference was small but statistically significant [104.27 (SD = 51.47) vs. 97.63 (SD = 156.94) minutes, $p = 0.044$] (Tab. 2). There were no statistically significant differences between the compared groups with respect to the severity of neurological deficit at admission and discharge (measured using the NIHSS scale), the functional outcome at discharge (measured using the mRS scale), the percentage of patients treated with intravenous thrombolysis, the percentage of successful reperfusions (defined as TICI 2b-3), or in-hospital mortality. There was a statistically significant difference between the groups concerning the number of days of hospitalisation: 23.7 (SD = 11.9) for COVID (+) patients versus 10.5 (SD = 6.9) for COVID (–) patients, $p < 0.001$.

The levels of CRP and LDH were significantly higher, and the lymphocyte count significantly lower, in COVID (+) patients compared to the control group (see Tab. 2). There was no statistically significant difference in D-dimer level, but this may be due to the fact that it is not routinely assessed in COVID (–) stroke patients in our centre, in fact only when thrombosis is suspected. It was impossible to compare fibrinogen levels due to the small data sample.

All our results are summarised in Table 2.

Discussion

To the best of our knowledge, this study is the first in Poland to present the characteristics of patients with COVID-19-associated AIS after MT. It is also the first study to compare stroke size in MT-treated patients with and without COVID-19 using CT-perfusion imaging with post-processing analysis with RAPID software.

LAO in COVID-19 patients seems to be associated with higher mortality than in patients without SARS-CoV2 infection [6]. However, previous studies on the outcomes of COVID-19 patients treated with MT produced mixed results, as presented in a recent systematic review [8]. Some of the research has shown poor outcomes in such patients. A study by Escalard et al. including 10 patients showed an in-hospital mortality rate of 60% [15]. A recent multicentre study by Cagnazzo et al. which included 93 COVID (+) patients showed a 30-day mortality of 29% [16]. A study by Pop et al. involving 13 COVID (+) patients reported mortality of 15.3% and a high incidence of in-hospital thrombotic complications in this group [17].

On the other hand, some studies have reported similar outcomes of COVID (+) and COVID (–) patients. A prospective international study by al Kasab et al. compared 13 COVID (+) MT-treated patients to a group of 445 COVID (–) MT-treated patients. This revealed that patients with a SARS-CoV2 infection had a higher NIHSS score at admission, but did not differ in respect to in-hospital mortality, number of days of hospitalisation, or functional outcome measured with mRS at discharge. At the same time, COVID (+) patients were significantly younger than COVID (–) ones, which may have influenced the results [18].

In our study, the MT-treated AIS patients with a SARS-CoV2 infection also presented with similar outcomes to patients without COVID-19 (including mortality 6.7% vs. 12.6%).

We speculate that this may be due to several reasons.

Firstly, there were no clinical differences at admission parameters between our COVID (+) and COVID (–) MT-treated AIS patients. There was a similar age distribution, gender ratio, and number of cardiovascular risk factors. Moreover, there were no significant differences in stroke volume (as counted by perfusion CT analysis with RAPID software). Secondly, there was no statistically significant difference between groups when it came to the time from stroke onset to arrival at the CSC. The difference between groups concerning time from arrival at the CSC to groin puncture was statistically significant, but

Table 1. Individual characteristics of COVID-19-associated MT patients treated with MT in CDC between March 2020 and May 2021

	Age, sex	Comorbidities	Time from stroke onset to arrival (mins)	NIHSS at admission to CSC	LAO localisation	Intravenous thrombolysis (0 = no, 1 = yes)	Perfusion CT parameters (as calculated by RAPID software)	TICI	COVID-19 clinical and radiological symptoms	Treatment of COVID-19	Days of hospitalisation	Complications	Outcome
1	66, M	Arterial hypertension Aortic aneurysm Atrial fibrillation Peripheral atherosclerosis	490	16	M1-LMCA	0	CBF < 30% = 62 mL Tmax > 6 s = 215 mL Mismatch volume = 153 mL	0	Sore throat Fever Cough Desaturation Lung involvement (HRCT) = 14.21%	Passive oxygen therapy dexamethasone LMWH	50	Haemorrhagic transformation Brain oedema Pneumonia Splenic haematoma	NIHSS = 17 mRS = 5
2	79, F	Metastatic breast cancer Arterial hypertension Atrial fibrillation Peripheral atherosclerosis Dyslipidemia	174	15	RICA	0	—	0	— Chest X-ray severity score = 15	LMWH	30	Deep vein thrombosis	NIHSS = 16 mRS = 5
3	56, F	Arterial hypertension Dyslipidemia Breast cancer	518	16	M1-RMCA	1	CBF < 30% = 20 mL Tmax > 6 s = 61 mL Mismatch volume = 41 mL	3	— Lung involvement (HRCT) = 9.24%	LMWH	10	—	NIHSS = 2 mRS = 1
4	49, M	Arterial hypertension Chronic kidney disease Kidney transplant in 2002 GERD Skin melanoma in the past	0	2	LICA	1	—	3	Cough Fever Chest X-ray severity score = 7	LMWH	15	Deep vein thrombosis	NIHSS = 2 mRS = 1
5	82, F	Arterial hypertension History of stroke Hypothyroidism Dementia	102	20	M1-RMCA	1	CBF < 30% = 34 mL Tmax > 6 s = 151 mL Mismatch volume = 117 mL	3	Cough desaturation Chest X-ray severity score = 8	Passive oxygen therapy	2	Haemorrhagic transformation Subarachnoid haemorrhage	Deceased
6	62, M	Arterial hypertension Peripheral atherosclerosis Diabetes mellitus Obesity History of smoking Alcohol abuse Gout	300	15	M1-RMCA	1	—	3	Desaturation Chest X-ray severity score = 4	Passive oxygen therapy Dexamethasone LMWH	28	RICA dissection Pneumonia	NIHSS = 6 mRS = 2
7	83, F	Arterial hypertension Atrial fibrillation Peripheral atherosclerosis Dyslipidemia Diabetes mellitus Obesity	250	21	LMCA + LACA	1	—	3	Desaturation Lung involvement (HRCT) = 1.82%	Passive oxygen therapy LMWH	18	Clostridium difficile infection	NIHSS = 16 mRS = 5
8	85, F	Arterial hypertension Atrial fibrillation Dyslipidemia Peripheral atherosclerosis Dementia	729	21	M1-LMCA	0	CBF < 30% = 7 mL Tmax > 6 s = 95 mL Mismatch volume = 88 mL	3	Desaturation Chest X-ray severity score = 10	Passive oxygen therapy Dexamethasone LMWH	21	Haemorrhagic transformation Pneumonia	NIHSS = 22 mRS = 5

Table 1 cont. Individual characteristics of COVID-19-associated MT patients treated with MT in CDC between March 2020 and May 2021

	Age, sex	Comorbidities	Time from stroke onset to arrival (mins)	NIHSS at admission to CSC	LAO localisation	Intravenous thrombolysis (0 = no, 1 = yes)	Perfusion CT parameters (as calculated by RAPID software)	TICI	COVID-19 clinical and radiological symptoms	Treatment of COVID-19	Days of hospitalisation	Complications	Outcome
9	72, F	Arterial hypertension Atrial fibrillation Dyslipidemia Hypothyroidism Thrombocytopenia	276	4	M2-LMCA	0	CBF < 30% = 0 mL Tmax > 6 s = 16 mL Mismatch volume = 16 mL	3	— Lung involvement (HRCT) = 2.08%	LMWH	18	Haemorrhagic transformation Pneumonia	NIHSS = 4 mRS = 2
	Age, sex	Comorbidities	Time from stroke onset to arrival (mins)	NIHSS at admission	LAO	Intravenous thrombolysis	Perfusion CT parameters	TICI	COVID-19 clinical and radiological symptoms	Treatment of COVID-19	Days of hospitalisation	Complications	Outcome
10	78, M	Arterial hypertension Chronic heart failure Atrial fibrillation Prostate hypertrophy Peripheral atherosclerosis	265	17	M2-LMCA	1	CBF < 30% = 0 mL Tmax > 6 s = 141 mL Mismatch volume = 141 mL	3	Desaturation Lung involvement (HRCT) = 44.12%	Passive oxygen therapy Dexamethasone LMWH	36	Haemorrhagic transformation Pneumonia	NIHSS = 1 mRS = 0
11	70, F	Arterial hypertension Atrial fibrillation Peripheral atherosclerosis Dyslipidemia Diabetes mellitus Double mastectomy (2010)	485	7	V1-RVA	0	CBF < 30% = 0 mL Tmax > 6 s = 8 mL Mismatch volume = 8 mL	3	Desaturation Lung involvement (HRCT) = 19.52%	Passive oxygen therapy Dexamethasone LMWH Remdesivir	21	Humerus fracture	NIHSS = 2 mRS = 2
12	70, M	Arterial hypertension Coronary artery disease Peripheral atherosclerosis History of TIA Dyslipidemia Diabetes mellitus	282	20	LICA	1	CBF < 30% = 22 mL Tmax > 6 s = 59 mL Mismatch volume = 37 mL	3	Desaturation Lung involvement (HRCT) = 49.79%	Passive oxygen therapy Dexamethasone LMWH	30	Pneumonia Clostridium difficile infection	NIHSS = 12 mRS = 5
13	68, M	Arterial hypertension Diabetes mellitus Coronary artery disease Peripheral atherosclerosis Biological heart valve	288	17	M1-LMCA	0	CBF < 30% = 0 mL Tmax > 6 s = 36 mL Mismatch volume = 36 mL	2b	Desaturation Lung involvement (HRCT) = 0.41%	Passive oxygen therapy Dexamethasone LMWH Remdesivir	32	UTI Urinary retention	NIHSS = 6 mRS = 1
14	55, M	Peripheral atherosclerosis History of smoking	296	8	LICA	0	CBF < 30% = 5 mL Tmax > 6s = 85 mL Mismatch volume = 80 mL	3	Dyspnoea Fever Lung involvement (HRCT) = 17.53%	Passive oxygen therapy Dexamethasone LMWH Remdesivir	32	Pneumonia	NIHSS = 2 mRS = 1
15	65, F	Peripheral atherosclerosis Bladder cancer Kidney cancer	154	5	RICA	0	CBF < 30% = 0 mL Tmax > 6 s = 32 mL Mismatch volume = 32 mL	0	— Lung involvement (HRCT) = 2.28%	LMWH	15	RICA dissection	NIHSS = 5 mRS = 2

Table 2. Comparison of COVID (+) and COVID (–) patients with AIS treated with MT

	COVID (+)	COVID (–)	P-value
Demographics	N = 15*	N = 167*	
Age (years)	70 (IQR = 17)	70 (IQR = 17)	p = 0.965
Female sex (%)	8 (53.3%)	83 (49.7%)	p = 1.000
Cardiovascular risk factors	N = 15*	N = 167*	
Arterial hypertension (%)	13 (86.7%)	115 (68.9%)	p = 0.237
Coronary artery disease (%)	2 (13.3%)	38 (22.8%)	p = 0.528
Artificial heart valve (%)	0 (0%)	4 (2.4%)	p = 1.000
Atrial fibrillation (%)	7 (46.7%)	69 (41.3%)	p = 0.787
Peripheral artery atherosclerosis (%)	11 (73.3%)	129 (77.2%)	p = 0.751
History of stroke/TIA (%)	2 (13.3%)	16 (9.6%)	p = 0.647
Dyslipidemia (%)	7 (46.7%)	56 (33.5%)	p = 0.396
Diabetes mellitus (%)	5 (33.3%)	34 (20.4%)	p = 0.320
Obesity (%)	2 (13.3%)	14 (8.4%)	p = 0.626
History of smoking (%)	2 (13.3%)	39 (23.4%)	p = 0.526
Chronic kidney disease (%)	1 (6.7%)	15 (9%)	p = 1.000
Total sum of risk factors	3.5 (SD = 1.6)	3.2 (SD = 1.5)	p = 0.575
CT perfusion parameters	N = 11	N = 138	
CBF < 30% [mL]	13.6 (SD = 19.8)	21.0 (SD = 32.9)	p = 0.560
Tmax > 6 s [mL]	81.7 (SD = 64.4)	121.1 (SD = 82.6)	p = 0.096
Mismatch volume [mL]	68.1 (SD = 50.8)	100.0 (SD = 71.5)	p = 0.117
Disease course	N = 15*	N = 167*	
Time from stroke onset to admission (min)	307.3 (SD = 183.7)	227.3 (SD = 115.7) N = 166	p = 0.062
Time from admission to groin puncture	104.27 (SD = 51.47)	97.63 (SD = 156.94)	p = 0.044
NIHSS score at admission	13.3 (SD = 6.6)	15.5 (SD = 8)	p = 0.505
Intravenous thrombolysis (%)	7 (46.7%)	105 (62.9%)	p = 0.270
Full reperfusion (TICI 2b-3) (%)	12 (80%)	148 (88.6%)	p = 0.398
NIHSS at discharge	8.1 (SD = 7.1) N = 14	8.8 (SD = 9.6) N = 145	p = 0.778
mRS at discharge	2.9 (SD = 2)	3.1 (SD = 2.1)	p = 0.817
In-hospital mortality (%)	1 (6.7%)	21 (12.6%)	p = 0.699
Days of hospitalisation	23.7 SD = 11.9)	10.5 (SD = 6.9)	p < 0.001
Laboratory tests results			
Fibrinogen [g/L]	4.07 (SD = 1.88) N = 2	2.87 (SD = 1.09) N = 146	Analysis impossible, sample too small
D-dimer [mg/L]	10.1 (SD = 12.36) N = 14	7.46 (SD = 9.56) N = 16	p = 0.580
Ldh [u/L]	330.92 (SD = 158.58) N = 12	224.62 (SD = 55.69) N = 13	p = 0.015
Lymphocyte count [1 x 10^3/uL]	1.09 (SD = 0.50) N = 14	1.60 (SD = 0.64) N = 60	p = 0.003
CRP [mg/L]	39.77 (SD=38.02) N = 15	17.80 (SD = 23.25) N = 162	p = 0.004

*unless specified otherwise

small. This is probably due to the standardised pathway of care that was implemented for both groups of patients during the pandemic, including a separate part of the Emergency Department and CT laboratory, as well as transport pathways for COVID (+) patients. Thirdly, after the procedure both groups of patients were treated in highly specialised wards (the Stroke Unit or the Neurology/COVID-19 ward) with specialists trained in stroke care present in both of them. What

is more, good outcomes of our patients may also be a result of their relatively mild COVID-19 course. None of our patients required intensive care or mechanical ventilation. In 2020 and 2021 (up to the time of writing), there were seven disqualifications of COVID (+) patients from mechanical thrombectomy in our centre, and none of the seven was due to severe general condition caused by COVID-19; they were all based on the neurological criteria. Four patients were disqualified due to recanalisation of the artery after intravenous thrombolysis, two patients due to predominance of irreversible ischaemic changes in neuroimaging, and one patient due to haemorrhagic transformation of the stroke.

Our study has some limitations. Firstly, it was a retrospective analysis and the study group was relatively small. Secondly, the patients had a mild-to-moderate COVID-19 course which might also have an important impact on their outcomes. Thirdly, the small group of patients with COVID-19 treated with MT did not allow for multivariable analysis.

Clinical implications / future directions

Our research suggests that in patients with MT-treated AIS associated with COVID-19 who do not require intensive care, the outcome may be similar to that in MT-treated AIS without concomitant SARS-CoV2 infection. Not only the patients' clinical profiles, but also efficient organisation and the implementation of standardised pathways of care, seem to play important roles in the final result of the treatment.

The outcomes of COVID-19-associated AIS patients treated with MT should be reported in larger, and preferably prospective and multicentre, studies.

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Does ASTRAL score at hospital admission predict symptomatic haemorrhagic transformation in acute ischaemic stroke after revascularisation? A pilot single-centre study

Milena Świtońska[1], Artur Słomka[2], Natalia Piekuś-Słomka[3], Ewa Żekanowska[2], Grzegorz Meder[4], Paweł Sokal[1], Simona Lattanzi[5]

[1]Department of Neurosurgery and Neurology, Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum, Faculty of Health Sciences, Bydgoszcz, Poland

[2]Department of Pathophysiology, Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum, Faculty of Pharmacy, Bydgoszcz, Poland

[3]Department of Inorganic and Analytical Chemistry, Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum, Faculty of Pharmacy, Bydgoszcz, Poland

[4]Department of Interventional Radiology, Jan Biziel University Hospital No. 2, Bydgoszcz, Poland

[5]Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy

ABSTRACT

Introduction. Accurately predicting outcomes after acute ischaemic stroke (AIS) is a major clinical goal. The aim of this pilot study was to evaluate the prognostic validity and accuracy of the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) score in predicting symptomatic haemorrhagic transformation (sHT) in patients with AIS who have undergone revascularisation.

Material and methods. Consecutive patients hospitalised for AIS who underwent treatment with intravenous thrombolysis (IVT) and/or mechanical thrombectomy (MT) were identified, and their ASTRAL scores at hospital admission were estimated. The study endpoint was sHT within 24 hours of stroke onset. The predictive performance of the ASTRAL score was investigated through logistic regression analysis and discrimination and calibration tests.

Results. Sixty-eight AIS patients, with a median age of 69 (58-79) years, were included. sHT occurred in 20 (29.4%) of the 68 patients. The ASTRAL score was significantly higher in patients who developed sHT compared to non-sHT patients [36 (34-38) versus 24 (17-32); $p<0.001$]. The ASTRAL score was an independent predictor of sHT, and showed good discriminative power (area under the curve 0.88; 95% confidence interval, 0.789-0.965).

Conclusions and clinical implications. ASTRAL score is an independent predictor of sHT and shows high predictive accuracy in patients with AIS. Future studies are warranted to confirm these results.

Key words: acute ischaemic stroke, revascularisation, haemorrhagic transformation, ASTRAL

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Introduction

Despite a global decline in mortality from stroke, the rates of death and hospitalisation remain very high [1]. Intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) are well-established treatments for acute ischaemic stroke (AIS). However, they are associated with an increased risk of bleeding, including symptomatic haemorrhagic transformation (sHT) [2, 3], so the early identification of patients at high risk of this complication is a major challenge in neurological care.

Address for correspondence: Artur Słomka, Department of Pathophysiology, Nicolaus Copernicus University in Torun, Ludwik Rydygier Collegium Medicum, M. Sklodowskiej-Curie 9 Str., 85–094 Bydgoszcz, Poland; e-mail: artur.slomka@cm.umk.pl

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The Acute Stroke Registry and Analysis of Lausanne (ASTRAL) scoring system was initially designed by Ntaios et al. [4] to predict unfavourable 3-month outcomes in patients with cerebral infarction, defined as a modified Rankin Scale (mRS) score > 2. The model includes the following six variables: age (A), severity of stroke assessed on admission by means of National Institutes of Health Stroke Scale (NIHSS) score (S), time from symptom onset to admission (T), visual field range (R), acute glucose level (A), and level of consciousness (L). Interestingly, the accuracy of this scoring system to predict sHT has not previously been evaluated. In this pilot study, we have examined the role of the ASTRAL score collected at hospital admission in predicting sHT in AIS patients undergoing revascularisation.

Material and methods

We included in this study consecutive patients with AIS admitted to the Interventional Stroke Treatment Centre of University Hospital No. 2 in Bydgoszcz, Poland from January 2017 to December 2019. We did not include patients treated in 2020 or 2021 due to the possible impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on the variables studied. All patients were admitted within 24 hours of symptom onset. Patients with haemorrhagic stroke, transient ischaemic attack (TIA), recent myocardial infarction (MI), active infection, liver or kidney failure, cancer, and steroid therapy were excluded. We also excluded patients with procedural intracranial haemorrhage, i.e. intracerebral haemorrhage clearly associated with the procedure itself as secondary to arterial dissection or vessel perforation and subarachnoid haemorrhage. The diagnosis of AIS was made in accordance with World Health Organisation (WHO) criteria. Any stroke was classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria and to the Oxfordshire Community Stroke Project (OCSP) [5, 6]. Stroke severity was quantified using the National Institutes of Health Stroke Scale (NIHSS). The extension of the ischaemic lesion was estimated based on the Alberta Stroke Programme Early CT Score (ASPECTS) on head CT performed in an emergency before causal treatment. Further details on study design and data collection have previously been published [7].

Patients with AIS received causal treatment (intravenous thrombolysis [IVT] and/or mechanical thrombectomy [MT]) following the recommendations of the American Heart Association/American Stroke Association [8]. Thrombectomy was performed by the same interventional radiologist (GM) in patients who had an occluded large cerebral artery, i.e. the middle cerebral artery (M1/M2) or basilar artery, using aspiration catheters alone, stent-retrievers alone, or both, depending on the occlusion type/location and the choice of the neuro-interventionist. The degree of recanalisation was assessed using the Thrombolysis in Cerebral Infarction (TICI) scale [9]. A follow-up CT scan was performed routinely within 24 hours from IVT and/or MT, and thereafter on an individual basis in the case of any clinical deterioration.

Symptomatic haemorrhagic transformation (sHT) was defined as parenchymal haematoma (PH) > 30% of the infarcted area with a significant space-occupying effect or clot remote from the infarcted area (PH2) according to the criteria of the European Cooperative Acute Stroke Study II (ECASS II) [10–12] associated with a worsening of the NIHSS score by 4 or more points within 24 hours of stroke onset [13].

The ASTRAL score has been estimated on the basis of age, stroke severity according to admission NIHSS score, time delay between symptom onset or last proof of good health (in cases of unknown onset of stroke) and admission, presence of deficits in visual field, blood glucose levels at admission, and level of consciousness [4]. The ASTRAL score was calculated for each AIS patient at hospital admission.

The normal distribution of each continuous variable was assessed using a Shapiro-Wilk test. Values were reported as medians (interquartile ranges) or the number of patients. The characteristics of patients with sHT and without sHT were compared using the Mann-Whitney U test and Pearson's $\chi 2$ tests. According to Receiver Operating Characteristics Curve (ROC) analysis, the optimal cut-off value was determined as the point maximising the Youden function, which is the difference between the true positive rate and the false-positive rate over all possible cut-off point values. Results were considered significant for p values < 0.05 (two-sided). STATISTICA software was used (version 13.3, TIBCO Software Inc., Palo Alto, CA, USA).

The study protocol was designed following local and international ethics criteria for human research. The Bioethical Commission at the Collegium Medicum of Nicolaus Copernicus University (Bydgoszcz, Poland) approved the study (KB 694/2016), and written informed consent was obtained from the patients or their family members. Anonymised data will be shared upon request from any qualified investigator.

Results

In the present study, 381 patients were initially screened and a total of 68 patients with AIS were selected and included according to our inclusion and exclusion criteria. The reasons for exclusion were: evidence of active infection before admission or any systemic infection that occurred during the first 48 hours after causal treatment (n = 227); cancer, chronic inflammation, autoimmune disease, or steroid therapy (n = 30); and the unavailability of medical records as discharge occurred on the same day as admission (n = 56). Recombinant tissue plasminogen activator (rtPA) was administered intravenously to 53 patients, 24 of whom also received MT. Fifteen patients underwent MT alone as they exceeded the time window (> 4.5 hours) for the IVT. Demographic and clinical characteristics of the study population are set out in Table 1, which also presents the factors associated with an unfavourable prognosis

Table 1. Demographic and clinical characteristics of study population

Parameter [unit]		AIS patients (n = 68)	Non-sHT (n = 48)	sHT (n = 20)	P-value
Age [years]		69 (58–79)	67 (55–78)	73 (64–81)	0.135
Male gender		34 (50%)	22 (46%)	12 (60%)	0.287
Body mass index (BMI), [kg/m2]		27 (24–31)	27 (24–32)	28 (25–31)	0.819
Medical history and ischaemic stroke risk factors [n,%]	Coronary artery disease (CAD)	18 (26%)	10 (21%)	8 (40%)	0.103
	Previous ischaemic stroke	10 (15%)	7 (15%)	3 (15%)	0.965
	Hypertension	50 (74%)	34 (71%)	16 (80%)	0.435
	Diabetes mellitus (DM)	22 (32%)	14 (29%)	8 (40%)	0.384
	Dyslipidemia	38 (56%)	29 (60%)	9 (45%)	0.243
	Atrial fibrillation (AF)	24 (35%)	12 (25%)	12 (60%)	0.006
	Current smokers	20 (29%)	13 (27%)	7 (35%)	0.514
Anticoagulant therapy [n,%]	Vitamin K antagonists	8 (12%)	5 (10%)	3 (15%)	0.593
	Acetylsalicylic acid (ASA)	21 (31%)	14 (29%)	7 (35%)	0.635
Systolic blood pressure (SBP), [mmHg]		140 (130–160)	130 (130–150)	155 (143–180)	0.001
Diastolic blood pressure (DBP), [mmHg]		80 (80–90)	80 (80–85)	90 (80–100)	0.001
Left ventricle ejection fraction (LVEF), [%]		60 (50–65)	60 (50–65)	59 (45–60)	0.084
Laboratory parameters	Aspartate transaminase (AST), [U/l]	21 (16–27)	20 (16–25)	22 (18-29)	0.156
	Alanine transaminase (ALT), [U/l]	17 (13–25)	17 (13–26)	17 (11-21)	0.436
	Serum creatinine [mg/dL]	0.89 (0.73–1.10)	0.85 (0.69–1.07)	1.04 (0.80-1.15)	0.030
	Low-density lipoprotein (LDL), [mg/dL]	86 (72–119)	91 (74–135)	76 (67-93)	0.071
	Glucose [mg/dL]	128 (107–160)	122 (106–151)	140 (108–198)	0.146
	International normalised ratio (INR)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.2 (1.1–1.4)	0.006
	Activated partial thromboplastin time (aPTT), [s]	26.5 (25.1–29.4)	26.2 (24.5–29.5)	27.5 (25.8–29.2)	0.279
Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification [n, %]	Large-artery atherosclerosis (LAA)	13 (19%)	8 (17%)	5 (25%)	0.003
	Small vessel occlusion (SVO)	5 (7%)	5 (10%)	0	
	Cardioembolism (CE)	27 (40%)	13 (27%)	14 (70%)	
	Stroke of other determined aetiology (SOA)	3 (4%)	3 (6%)	0	
	Stroke of undetermined aetiology (SUA)	20 (29%)	19 (40%)	1 (5%)	
Oxfordshire Community Stroke Project (OCSP) classification [n, %]	Lacunar infarct (LACI)	13 (19%)	13 (27%)	0	0.001
	Partial anterior circulation infarct (PACI)	29 (43%)	22 (46%)	7 (35%)	
	Total anterior circulation infarct (TACI)	17 (25%)	6 (13%)	11 (55%)	
	Posterior circulation infarct (POCI)	9 (13%)	7 (15%)	2 (10%)	
Type of therapy [n, %]	Thrombolysis (IVT)	29 (43%)	28 (58%)	1 (5%)	0.00004
	Thrombolysis (IVT) and mechanical thrombectomy (MT)	24 (35%)	15 (31%)	9 (45%)	
	Mechanical thrombectomy (MT)	15 (22%)	5 (10%)	10 (50%)	
Stroke scales	Acute Stroke Registry and Analysis of Lausanne (ASTRAL)	29 (22–35)	24 (17–32)	36 (34–38)	0.000001
	National Institutes of Health Stroke Scale (NIHSS)	13 (7–17)	10 (6–15)	17 (15–21)	0.0003
	Alberta Stroke Programme Early CT Score (ASPECTS)	9 (9–10)	10 (8–10)	9 (9–10)	0.938
Thrombolysis in Cerebral Infarction (TICI) scale [n, %]	TICI0	4 (11%)	3 (15%)	1 (5%)	0.364
	TICI2a	1 (3%)	0	1 (5%)	
	TICI2b	11 (28%)	7 (35%)	4 (21%)	
	TICI3	23 (59%)	10 (50%)	13 (68%)	

following IS [14]. The study population consisted of 34 males and 34 females, with a median age of 69 (58–79) years. A total of 20 out of 68 (29.4%) patients experienced sHT. Our cohort was then divided into two groups depending on the presence or absence of sHT (Table 1). The two groups did not significantly differ in most clinical and laboratory characteristics, except that the sHT group tended to have a higher NIHSS, more elevated serum creatinine levels, and a greater international normalised ratio (INR) than the non-sHT group. Additionally, patients from the sHT group were more likely to have AF and higher blood pressure, but not other risk factors. The two groups also differed in the TOAST and OCSP classification and the type of therapy.

The median ASTRAL score at admission was 29 (22–35). Symptomatic haemorrhagic transformation (sHT) within 24 hours of stroke onset was diagnosed in 20 (29.4%) patients, of whom one underwent IVT alone, nine underwent IVT plus MT, and 10 underwent MT alone. The ASTRAL score was significantly higher in patients who developed sHT compared to non-sHT patients [36 (34–38) vs. 24 (17–32); $p < 0.001$, Figure 1A]. In ROC analysis with respect to sHT, the area under the curve (AUC) was 0.877 (95% CI, 0.789–0.965; SE, 0.045; Figure 1B). The Youden's index identified 35 to be the best cut-off of the ASTRAL score to discriminate patients experiencing sHT, yielding a sensitivity of 75% and a specificity of 92%.

Discussion

This pilot study showed that the ASTRAL score can predict with good discriminative power sHT in AIS patients undergoing revascularisation. Patients who developed sHT after revascularisation had significantly higher ASTRAL values compared to patients with AIS and no sHT. Furthermore, a score of 35 on the ASTRAL scale was the optimal threshold to predict haemorrhagic transformation of a brain infarct.

Developed from the ASTRAL registry as an integer-based score to predict 3-month functional status in AIS [4], the ASTRAL score has been externally validated in AIS patients undergoing IVT [15], and in patients with embolic strokes of undetermined source [16]. This scoring system has also shown remarkable consistency in predicting long-term functional outcomes and mortality in unselected AIS patients, both in European and non-European populations [17–20]. Interestingly, the ASTRAL score has been demonstrated to predict outcomes of AIS patients with greater accuracy than physicians. In an online anonymous survey, 244 physicians interested in stroke from 32 different countries provided outcome estimates in randomly allocated structured scenarios of recent real-life stroke patients: 56.8% of the physicians' estimates about the percentage probability of 3-month mRS > 2 were accurate, compared to 86.5% of the ASTRAL score estimates [21].

Clinical grading systems can be useful tools to stratify patient risk and estimate prognosis, to help counsel patients and their families, and to standardise communication among healthcare providers. As practical tools to promote information, scoring models need to be easily computed and widely applicable in clinical practice. In this regard, the ASTRAL score contains readily accessible parameters, does not require imaging data or complex mathematical algorithms, and can be used early in an emergency setting. The availability of a scoring system that is easy to perform and interpret in everyday clinical practice, and is able to predict sHT, appears to be extremely important considering that IS patient management differs

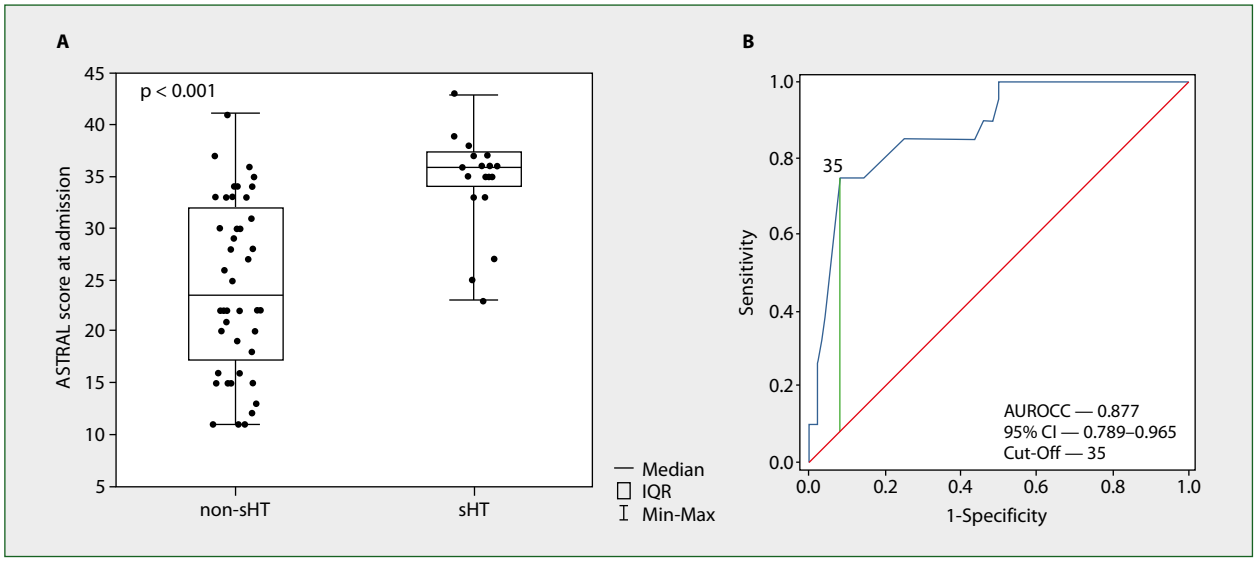

Figure 1. Comparison of Acute Stroke Registry and Analysis of Lausanne (ASTRAL) scores between symptomatic haemorrhagic transformation (sHT) patients and non-sHT patients (**A**). Receiver operating characteristics analysis for prediction of sHT in acute ischaemic stroke (AIS) patients undergoing revascularisation (**B**)

significantly depending on the region of Poland [22]. To the best of our knowledge, this is the first study to highlight the potential role of the ASTRAL score as a predictor of sHT in patients treated with IVT and/or MT. The previous study by Asuzu et al. [23] did not find any association between the ASTRAL score and sHT. Differences between the studies may help explain these discrepant findings. It is worth noting that in the earlier study, a different definition of sHT was adopted (i.e. National Institute of Neurological Diseases and Stroke (NINDS) vs. ECASS II) [23]. Also, although the demographic and clinical characteristics of patients included in the two studies were overall similar, differences existed in the treatment strategies, as patients included in the Asuzu et al. study underwent treatment with IVT only. Further studies are needed to fully explore how acute stroke treatment may influence the predictive role of the ASTRAL score. Other scales with potential use in sHT prediction include the DRAGON, Stroke-TPI (stroke-thrombolytic predictive instrument), and HAT (haemorrhage after thrombolysis) scores, among others [23]. Promising observations have also been made with the TURN (thrombolysis risk using mRS and NIHSS) score, which, due to its simplicity, may be an excellent tool in predicting sHT, but requires validation in IS patients after MT [24, 25]. Another indicator with a proven high predictive value of HT after IS is the HTI (haemorrhagic transformation index), regardless of the use of IV rt-PA [26]. However, the HTI is an indicator with a rather complex structure, being composed of ASPECTS, NIHSS, hyperdense middle cerebral artery (HMCA) sign, and the presence of AF on ECG at admission. This complexity limits its use in neurological practice.

An essential element of our study is the high rate of sTH observed in patients with AIS. Many factors can influence the onset of sHT [27], and well-known factors include, but are not limited to, stroke severity, reperfusion therapy, hypertension, hyperglycaemia, and age [28]. Factors that significantly increase the risk of sHT in patients undergoing revascularisation treatment are also poor collateral status and variables related to the MT procedure [29, 30].

The patients included in our study who developed sHT had a relatively severe course of AIS, frequent incidence of AF, and high blood pressure, all of which are associated with sHT [2, 27]. Moreover, 70% of patients in the sHT group were diagnosed with cardioembolic (CE) stroke, a crucial aetiological component of sHT [30]. All these factors may have contributed to the high incidence of sHT observed in our study, which undoubtedly requires further detailed analysis.

As a pilot research study, it may be considered reliable for the development of preliminary insights and for suggesting working hypotheses. Some shortcomings need to be considered in the interpretation of the findings, such as the small sample size and the inherent limits of any single-centre retrospective analysis, e.g. selection and collection biases resulting from residual confounding due to unmeasured or incompletely characterised covariates. Future studies, if possible prospective multicentre cohort studies, should also include in the statistical analysis other factors mentioned in the previous paragraph that may influence the occurrence of sHT.

In this study, due to the relatively small sample size, such results have not been presented. Our research also lacks data on the technical aspects of MT due to the pilot nature of this treatment programme in the clinic. These aspects should be considered in subsequent investigations, especially in the light of recent studies showing that the degree of recanalisation after MT depends on the time elapsed from stroke onset to groin puncture [31]. However, these procedural characteristics do not seem to affect the ASTRAL value itself, which is assessed at admission to the hospital, i.e. before any causal treatment of AIS has been performed. Our study's main strengths include the use of widely accessible variables and the cost-effectiveness of the ASTRAL score. Furthermore, low heterogeneity existed in baseline patient characteristics, because all patients had no pre-morbid neurological dysfunctions.

Previously, various clinical and laboratory parameters have been proposed to predict the haemorrhagic transformation of AIS. These parameters, including age and well-defined ischaemic stroke comorbidities, have been characterised by a relatively high variability and inconsistent sensitivity in determining the risk of HT [32, 33]. Furthermore, the predictive models are usually based on assessing several parameters simultaneously, which may hinder decision-making in rapid neurological diagnosis [34]. Specific laboratory parameters, such as the measurement of blood caveolin-1 and caveolin-2, are not routinely used, and the laboratory methods used to determine their levels have not been sufficiently validated [33, 35].

Therefore, our research suggests a high clinical utility of the ASTRAL score to predict sHT after the causative treatment of AIS subjects. Our study also provides an incentive for further studies assessing the possibility of combining ASTRAL and other parameters for sHT risk assessment.

Conclusions and clinical implications

In summary, the ASTRAL score can predict symptomatic haemorrhagic transformation in AIS patients undergoing reperfusion therapies. Its good discriminatory ability may widen the applicability and broaden the potentiality of this tool as a reliable instrument in clinical practice and stroke research. Further investigations are warranted to validate these encouraging findings in larger independent cohorts of patients treated with thrombectomy, or thrombolysis combined with thrombectomy.

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TECHNICAL NOTE

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Fronto-orbito-zygomatic (FOZ) approach for infratemporal fossa lesions extending to middle cranial fossa: our experience and review of literature

Fabrizio Mancini[1], Alessandra Marini[1], Riccardo Paracino[1], Giuseppe Consorti[2], Maurizio Iacoangeli[1], Mauro Dobran[1]

[1]Department of Neurosurgery, Università Politecnica delle Marche, Azienda Ospedali Riuniti, Ancona, Italy
[2]Department of Oral and Maxillo-facial Surgery, Università Politecnica delle Marche, Azienda Ospedali Riuniti, Ancona, Italy

ABSTRACT

Aim of the study. Tumours of the infratemporal fossa (ITF) are rare and include primary tumours, contiguity lesions and metastases. Surgical resection is the gold standard. The fronto-orbito-zygomatic (FOZ) approach is commonly used in order to obtain safe access to the lateral skull base and ITF to resect intra- and extra-cranial tumours. We here describe our series of ITF lesions extending to the middle cranial fossa and/or orbit, treated by single- or two piece FOZ.

Material and methods. All cases of single- or two-piece FOZ approach for an infratemporal fossa lesion extending to the middle cranial fossa operated at our Institution from January 2014 to January 2018 were retrospectively reviewed. The follow-up was for a minimum of four months and a maximum of 60 months. The inclusion criteria were lesions involving the ITF with an extension to the middle cranial fossa and/or orbit. Baseline characteristics of patients, tumour localisation, tumour extension, diffusion route, histology, extent of tumour resection, post-operative treatment, and post-operative complications were evaluated.

Results. Nine patients underwent a surgical procedure with a FOZ approach, two of them with a single-piece approach and the remainder with a two-piece one. All patients had an ITF localisation. Gross total removal (GTR) was achieved in 7/9 patients. Only one patient, with non-total removal (NTR), underwent radiotherapy.

Conclusions. For the treatment of ITF fossa tumours extending to the orbit and or middle cranial fossa, we believe that both FOZ techniques are effective and allow a good medial extension toward the cavernous sinus and parasellar region. But a two-piece craniotomy may ensure a more medial extension and a wider angle of work compared to a one-piece craniotomy.

Key words: fronto-orbito-zygomatic approach, infratemporal fossa tumours, middle cranial fossa tumours, FOZ

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Introduction

Tumours of the infratemporal fossa (ITF) are rare entities, with an incidence of less than 3% of all head and neck cancers. ITF include primary tumours, contiguity lesions and metastases [1]. Contiguity lesions arise from surrounding structures such as the paranasal sinus, oral cavity, nasopharynx parotid gland, external ear canal and middle-cranial fossa [2–4]. Primary intrinsic infratemporal fossa tumours include a limited number of primary lesions, and metastases have only rarely been described [5, 6]. Surgical resection is considered the gold standard for the treatment of this tumour, even if the complex anatomical structures of ITF and skull base represent a particular challenge for the surgeon, with a high rate of perioperative morbidity and tumour recurrence, due to the difficulty of obtaining a complete surgical resection [7].

Address for correspondence: Riccardo Paracino, Department of Neurosurgery, Università Politecnica delle Marche, Azienda Ospedali Riuniti, Via Conca 71, Ancona, Italy; e-mail: r.paracino@gmail.com

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Among these lesions, those extending intracranially to the middle cranial fossa and/or orbit are even more difficult to treat, especially when the medial extension involves the cavernous sinus. Several surgical approaches have been described, all aiming to achieve the maximal surgical exposure concomitantly with sparing the cranial nerve and vessels [8–11].

The fronto-orbito-zygomatic (FOZ) approach is commonly used in order to obtain safe access to the lateral skull base and ITF, considering that it provides a wide working space and a multidirectional surgical corridor to resect these complex intra- and extra-cranial tumours [12–16]. The wide bone resection of the FOZ approach provides a minimal brain retraction and several techniques have been described, including single-piece and two-piece craniotomy. While numerous descriptions of this technique are available for the treatment of pure intracranial or pure ITF fossa lesion, data regarding tumours of the ITF contemporary extending into the middle cranial fossa is lacking.

We here describe our series of ITF lesions extending to the middle cranial fossa and/or orbit, treated by a single- or two-piece FOZ, reporting surgical techniques, anatomy and indications for these two approach variants. An illustrative case of rare ITF metastases by lung adenocarcinoma treated with one-piece FOZ is also described.

Material and methods

From 2014 to 2018, all patients who underwent a surgical procedure with a single- or two-piece- FOZ approach for an infratemporal fossa lesion extending to the middle cranial fossa, were retrospectively reviewed, and all data was collected in the Ospedali Riuniti of Ancona Centre of the Politecnica delle Marche University. The follow-up was for a minimum of four months and a maximum of 60 months. Other than one patient who died after four months, consequent upon his primary tumour, all other patients had a follow-up of at least two years. Our study inclusion criteria were lesions involving the ITF with an extension to the middle cranial fossa and/or orbit; all the patients had complete pre- and post-operative radiological exams, and had a long-term follow-up performed by the same senior surgeons (neurosurgeon and maxillofacial surgeon). The approaches are described and compared in the technical note provided below.

Data regarding age, gender, pre-operative symptoms, tumour localisation, tumour extension (pterygopalatine fossa, lesser sphenoidal wing, orbit, cavernous sinus, paranasal sinus), diffusion route (through oval, spinous and rotundum foramina or the presence of temporal bone erosion), histology, extent of tumour resection (gross total, near total or subtotal surgical resection), post-operative treatment (radiotherapy and/or chemotherapy), post-operative Karnofsky Performance Status (KPS), recurrence requiring surgery, and complications were evaluated. The baseline characteristics of our series are set out in Table 1.

Results

From January 2014 to September 2018, nine patients underwent a surgical procedure with a FOZ approach, two of them with a single-piece approach and seven with a two-piece one. All patients had an ITF localisation (Fig. 1): the orbit was involved in four patients, the cavernous sinus and the lesser sphenoidal wing in six, the paranasal sinuses in three, and the pterygopalatine fossa (PPF) in five. The diffusion was through the oval foramen in one case, rotundum foramen in two cases, a temporal bone erosion was evidenced in two cases, and one patient had a spinous foramen route diffusion. Relative to the histology, one case was a metastasis from adenocarcinoma of the lung, and another was a schwannoma; the remaining cases were meningiomas (WHO grade I in four cases and grade II in three cases). Presenting symptoms and signs included visual deficit, diplopia, trigeminal neuralgia or numbness (V2 and V3), proptosis and palpable mass.

GTR was achieved in all cases except for two in which diffusion through the foramina complicated complete excision. Only one patient, with NTR resection for atypical meningioma, underwent radiotherapy. Another patient had a single dose of chemotherapy for lung metastasis, followed by rapid progression of lung disease and death. The KPS was higher than 80 in all the cases analysed, and notably was 100 in five patients. Three patients had a recurrence, but all of them had a grade II meningioma or NTR. Considering the nasal component as localisation of the recurrence in two patients, they underwent a second surgery by an endoscopic endonasal approach. We report below an illustrative case of a patient who underwent a single-piece FTOZ approach for rare ITF metastases of lung metastasis (Tab. 1).

Case presentation

A 63-year-old man with a four-week history of progressive and resistant to carbamazepine trigeminal neuralgia, involving V2 and V3 territory, presented to our Department with rapid visual deficit and mild proptosis involving the left eye. Neurological examination revealed, in addition to the previously reported neuralgia, left eye blindness and deficit in left eye abduction due to direct involvement of lateral rectus muscle. Brain MRI and CT scans showed a mass in the infratemporal fossa (ITF), extending into the pterygopalatine fossa (PPF), middle cranial fossa and orbit; only the epidural space without apparent invasion of meninges and brain parenchyma was observed (Fig. 2). Considering his long working history of exposure to dyes and dust, a primitive lesion from the parasinuses region was supposed. Anyway, the screening chest

Table 1. Baseline characteristics of patients and operative outcomes according to surgical intervention type

Patient	Sex, age	Location	Diffusion route	Approach	Histology	Extent of resection	Radiotherapy/ chemotherapy	Outcome (KPS)	Recurrence and follow-up
Case 1	M, 58	Orbit Cavernous sinus Sphenoidal sinus IFT LSW	Oval foramen	Two-piece FTOZ	Meningioma grade II	NTR	RT	80	Recurrence at 9 years, nasal component. Treated with EEA
Case 2	F, 48	IFT LSW Cavernous sinus	None	Two-piece FTOZ	Meningioma grade I	GTR	N	100	No recurrence, 3 years FU
Case 3	M, 64	IFT PPF	Temporal bone erosion	Two-piece FTOZ	Meningioma grade II	GTR	N	80	No recurrence, decided for cardiovascular failure, 1 year FU
Case 4	M, 59	Orbit Cavernous sinus IFT LSW PPF	None	Single-piece FTOZ	Adenocarcinoma of lung	GTR	N	80	4 months, progression of lung disease
Case 5	F, 47	Cavernous sinus IFT LSW	Temporal bone erosion	Single-piece FTOZ	Meningioma grade I	GTR	N	90	No recurrence, 4 years FU
Case 6	M, 62	IFT PPF Ethmoidal sinus	Rotundum foramen	Two-piece FTOZ	Meningioma grade II	GTR	N	100	Recurrence at 3 years, nasal component. Treated with EEA
Case 7	M, 64	IFT PPF	Spinous foramen	Two-piece FTOZ	Meningioma grade I	NTR	N	100	Recurrence at 7 years, NED
Case 8	F, 53	Orbit Cavernous sinus IFT LSW PPF	Rotundum foramen	Two-piece FTOZ	Meningioma grade I	GTR	N	100	No recurrence, 6 years FU
Case 9	M, 67	Orbit Cavernous sinus Sphenoidal sinus IFT LSW	None	Two-piece FTOZ	V cranial nerve Schwannoma	GTR	N	100	No recurrence at 2 years, NED

Ch — chemotherapy; EEA — endoscopic endonasal approach; FTOZ —fronto-temporal-orbitozygomatic approach; FU — follow up; IFT — infratemporal fossa; LSW — lesser sphenoidal wing; N — no; PPF — pterygopalatine fossa; RT — radiotherapy; Y — yes

X-ray, completed with total body CT scan, showed a right apical oval lung lesion of approximately 3.5 cm, without any other location of disease.

In this case we attempted surgery. The decision making was based on the progressive and excruciating neuralgia, the need for a histological diagnosis, as well as decompression. Despite the medial extension of the lesion toward the cavernous sinus, a single-piece FOZ approach was chosen having considered the good working angle in a patient with less risk of manipulation on the orbit. The details of the technical note are reported below. Interestingly, an intra-operative specimen deponed for a metastasis. In any case, a gross total removal was attempted due to the patient's symptoms.

Surgical technique

The patient was positioned supinely with head fixed on a head holder (Mayfield®) and turned to the right by around 35 degrees. A reverse question mark skin incision was planned, starting 4 cm below the zygomatic process just in front of the tragus and terminating behind the hairline at the ipsilateral pupillary line; the posterior "C" shape extended immediately behind the auricle (Fig. 3). The skin flap was elevated and reflected anteriorly with fish hooks, exposing the fronto-temporal bone, zygomatic arch and orbital rims. An anterior pericranial flap was elevated starting at the level of the

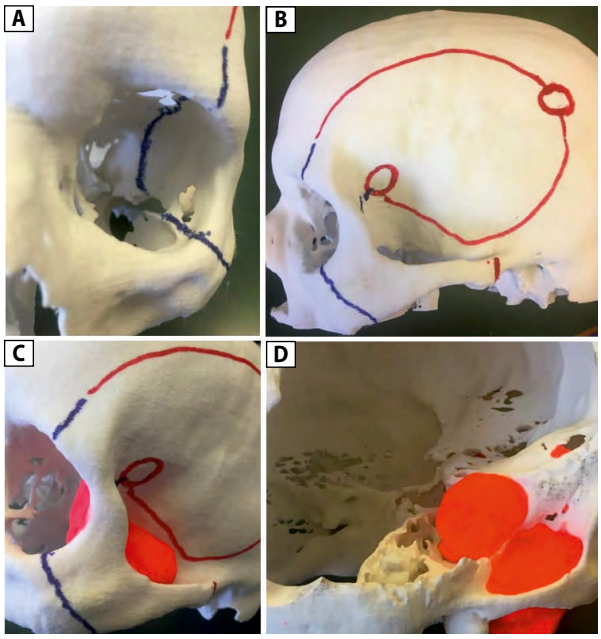

Figure 1. Representation of tumour localisation (ITF, PPF, orbit, middle cranial fossa) and craniotomy (fronto-orbito-zygomatic one--piece). **A.** Intraorbital craniotomy is made with piezoelectric osteotome (blue line) starting at supraorbital rim and going down along posterior wall of orbit and inferiorly to lateral portion of orbital fissure; **B.** 'One-piece' fronto-orbito-zygomatic craniotomy with key--hole and parietal burr-holes using both standard craniotome (red line) and piezoelectric osteotome (blue line); **C.** Tumour mass in ITF invading lateral orbital wall; **D.** Tumour mass involving both ITF and middle cranial fossa with medial extension toward cavernous sinus

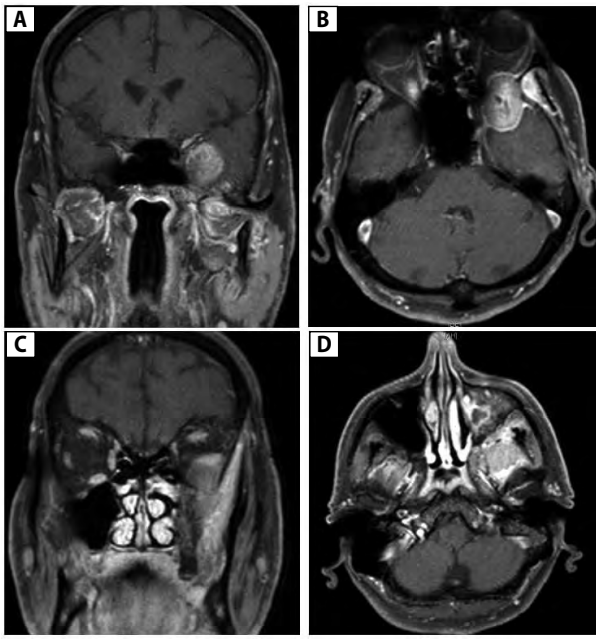

Figure 2. Lesion of left ITF with extension to extra-dural space of middle cranial fossa and lateral wall of orbit

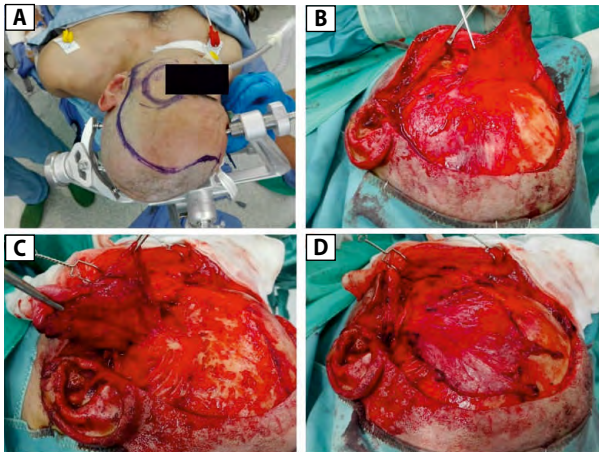

Figure 3. Patient positioning and surgical approach. **A.** Bi-coronal skin incision; **B.** Preparation of galeal flap, **C.** After posterior zygomatic arch osteotomy, temporal muscle is detached and mobilised; **D.** Reconstruction of temporal muscle

coronal suture and extending laterally until the superior temporal line; during anterior dissection toward the supraorbital rims, care must be taken to identify the supraorbital neuro-vascular bundle that is separated and reflected with the flap. Therefore, the peri-orbita was gently dissected from the orbital rim. The subfascial-subpericranial technique was used to protect the frontal branch of the facial nerve and to preserve the continuity between the frontal pericranial flap (medial to the superior temporal line) and the superficial and the deep layers of the temporal fascia (lateral to the superior temporal line). The temporal muscle was mobilised by subpericranial dissection and this was reflected inferiorly, moving his tendon as a pivot through a small osteotomy (about 5 mm) of the posterior root of the zygomatic arch. One burr hole was made just above the posterior root of the zygoma: the first cut started at the burr hole and extended superiorly and anteriorly ending about 10 mm behind the supraorbital rim and 4 mm lateral and 10 mm to the supraorbital notch; the second cut started at the burr hole and ran inferiorly and anteriorly along the squamous temporal bone until a point about 5 mm behind the frontozygomatic suture. The orbital and zygomatic part of craniotomy was then complete with piezoelectric osteotome. The peri-orbit was retracted and the cut was made across the supraorbital rim, lateral to the supraorbital notch, to the posterior and lateral wall of the orbit extending inferiorly to the lateral portion of the inferior orbital fissure and then laterally across the body of the zygoma, just above the zygomaticofacial foramen. The sphenoid bone was fractured with gentle hand movement and the entire

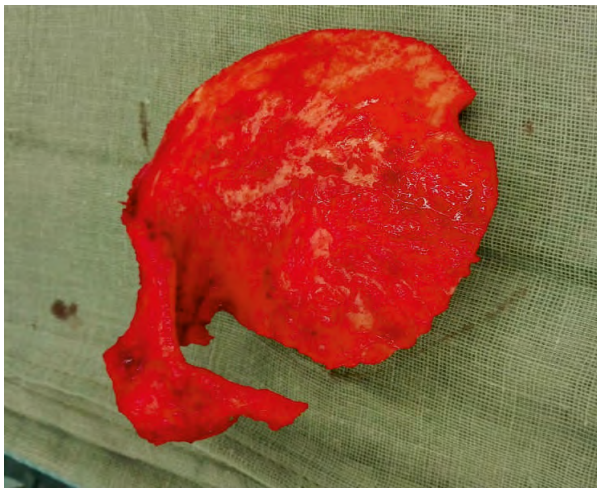

Figure 4. One-piece fronto-orbito-zygomatic bone flap

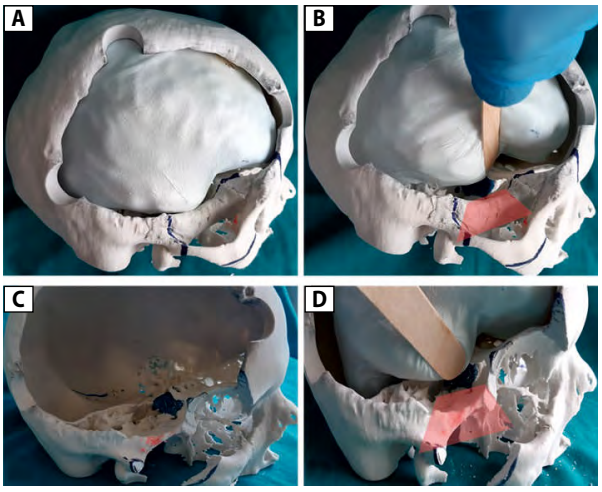

Figure 5. Representation of two-piece FOZ craniotomy. **A.** After pterional craniotomy, both temporal bone and sphenoid ridge are drilled; **B** and **C** — intraorbital and lateral orbit osteotomy are performed under direct vision; **D** — this allows more extensive orbital roof removal compared to one-piece FOZ variety and permits a wider angle of work with better visualisation of basal frontal and cavernous sinus

one-piece bone flap was removed (Fig. 4). A yellow-greyish lesion involving the infratemporal fossa, orbit and the anterior temporal skull-base was easily identified. The extracranial dissection of the tumour was performed in a superior-to-inferior direction until the pterygopalatine fossa, following the interface between a capsule and normal tissue. At the pterygopalatine fossa, the tumour was crossed by the internal maxillary artery that was ligated with a haemoclip and sectioned to achieve a complete tumour resection. With the use of a microscope, we then performed intracranial-epidural dissection of the tumour that was bleeding profusely and, at the temporal pole, the dura mater was infiltrated. Dura was opened and there was no brain invasion by the tumour. Near gross-tumour resection was obtained, with the more medial part of epidural mass toward the cavernous sinus and clinoid process left in place because of infiltration and adherence with the neuro-vascular structure. The bone flap was repositioned, fixed with plate and screw, and the temporal muscle was replaced and sutured to the temporal bone.

Discussion

We reviewed a case series of tumours of the ITF fossa with extension to the middle cranial fossa and/or orbit treated by a fronto-orbito-zygomatic (FOZ) approach.

Historically, this approach was first described in 1912 by McArthur [17] as a removal of the supraorbital ridge in a case of frontal craniotomy and in 1913 by Frazier [18] as a feasible option in a case of pituitary tumours. Afterwards, Jane et al. revised it, describing for the first time a one-piece FOZ craniotomy, including anterior orbital roof osteotomy in a single flap, for the treatment of vascular lesions located in the anterior skull base and orbit.

In the early 1980s, Hakuba [15] and Pellerin [19] revived the orbito-zygomatic-malar craniotomy to obtain access to anterior and middle skull base, upper third of clivus and posterior fossa. Since then, this approach has evolved into a number of technical adaptations by several authors, such as Al Mefty [20–23] and others, who have included a plethora of variations, extending the indication and improving the surgical outcomes. Nevertheless, tumours involving concomitantly extra-cranial (ITF, PPF) and intracranial compartments (middle cranial fossa and/or orbit) are infrequent [23, 24]. In consequence, the vast majority of early papers reported a FOZ approach merely for pure intracranial lesions, in order to increase the working angle of the classical frontal approach.

Tumours of the infratemporal fossa (ITF) comprise a wide range of histological types that include both malignant and benign lesions. Globally, the outcome is poor due to the complex anatomy of this region, which makes surgical excision very challenging concomitantly to the indolent growth of these lesions that leads to delayed diagnosis. Adenoid cystic carcinoma, squamous cell carcinoma, and adenocarcinoma are the most frequent malignant tumours, while among benign lesions, meningiomas, nasopharyngeal fibromas and schwannomas are most frequently encountered [25]. Metastases of the ITF are extremely rare. In a series of 27 patients, Conley [1] reported only two cases of metastases: one was an ovary cancer and one was a melanoma, while Shapshay [26] described two cases of squamous cell carcinomas with unknown primary location. Case reports include metastases from the uterine cervix, colorectal cancer and renal cell carcinoma [6].

Infratemporal fossa tumours were classically managed with a direct approach to this complex anatomical region. These approaches may be classified into two principal varieties: anterior and lateral approaches [27].

Anterior approaches include midfacial degloving, facial translocation and transmaxillary approaches. Compared to lateral approaches, the anterior ones allow a more direct and natural corridor, avoiding craniotomies, as well as remaining extradural, thus reducing the incidence of CSF leakage, decreasing the risk of facial nerve palsy, and preventing lesions to the temporo-mandibular joint (TMJ). Among lateral approaches, the classical lateral access the infratemporal fossa described by Fisch [28] provides a good exposure of concomitantly the middle and anterior skull base and the infratemporal fossa. The approach characteristics include facial nerve transposition, resection of the mandibular condyle, mobilisations of the zygoma and lateral orbital rim, in order to increase the working angle [9, 28]. Another lateral approach is the subtemporal-preauricular one, popularised by Sekhar [11], which is a substantial modification of the Fisch approach and offers some advantages: a decreased incidence of facial nerve damage, preservation of hearing conduction, minimal brain retraction, direct access to the ipsilateral petrous and upper cervical internal carotid artery, and reconstruction of extensive cranial base defects with the use of a muscle flap.

Even if the Fisch and Sekhar approaches are considered to be a milestone, both of them require a wide skin incision and bone destruction, with a full but demolitive access to the ITF. Considering our illustrative case, where the tumour involved the middle skull base and ITF extending to the pterygopalatine fossa (PPF) and orbit, the pre-operative concept was to use a more superior corridor, without the need to remove the mandible; as a consequence, we decided on a less invasive standard approach to the lateral skull base tumours, i.e. the fronto-orbito-zygomatic (FOZ) approach.

The FOZ approach may be considered an extensive modification of the classic pterional craniotomy. Since its original description, it has rapidly evolved and is now considered the gold standard access to lateral skull base lesions [16]. It provides a better exposure with a multidirectional surgical corridor, and a wide working space with minimal brain retraction. Pathologies that may be managed by FOZ craniotomy include spheno-petro-clival meningiomas, trigeminal meningiomas, P1 segment aneurysms, giant sellar and parasellar tumours, and spheno-orbital meningiomas; globally, it may be used for any lesion extending from the orbit to the petrous apex in an anterior-to-posterior direction, and from ITF to cavernous sinus in a lateral-to-medial direction. Cavernous sinus involvement is considered one of the main aspects that could preclude extensive surgical resection, even in cases of wide surgical view.

As previously mentioned, Hakuba [15] first systematically described this approach for the treatment of parasellar and interpeduncular fossa lesions, aiming for a better anatomical exposure of the anterior cranial base compared to the classic pterional and subtemporal approaches [9, 16, 28, 29]. However, some authors recommend a two-piece craniotomy [15, 23] while others prefer a single-piece craniotomy. In two cases of our series, we preferred a single-piece craniotomy that was fashioned with classic craniotomy for temporal, lateral sphenoid and frontal bone and with the piezoelectric osteotome for orbital and medial sphenoid tract; a one-piece craniotomy may ensure a safe and easy reconstruction, while minimising risks for dural tearing during the craniotomy. In addition, after removing the orbits-zygomatic bone, an anatomical study has demonstrated an increase of the working angle, of 75% in sub-frontal, 46% in pterional, and 86% in sub-temporal, approaches [12]. Compared to a one-piece craniotomy, the two-piece FOZ craniotomy ensures greater orbital wall removal, and permits access also to the anterior communicating artery complex and basal frontal. This was required in the two-piece cases of our series where a tumour component was extensively located in the basal frontal lobe [27, 29]. In two-piece FOZ craniotomy, after pterional craniotomy, both temporal bone and sphenoid ridge are drilled and dura is detached from the middle skull base. Thus, intraorbital and lateral orbit osteotomies are performed under direct vision and this allows a more extensive orbital roof removal compared to the one-piece FOZ variety (Fig. 5). When performing a one-piece craniotomy, the intraorbital osteotomy is the key to increasing the amount of orbital roof removal and widening the angle of work.

In our illustrative case of lung adenocarcinoma metastasis, the tumour has a wide medial-to-lateral extension, from the pterygoid muscle in ITF to cavernous sinus medially, and therefore a two-piece craniotomy could ensure a wide angle of work (Fig. 5). Nevertheless, considering the left eye blindness, we could have performed a single-piece FOZ with a mild and safe periorbital and ocular bulb retraction, achieving a more medial intraorbital osteotomy than a usual one-piece craniotomy. As a result, the medial extension of tumour near cavernous sinus was exposed and gross total resection obtained, maintaining the advantages of the one-piece variety, such as a short time for the craniotomy, superior reconstruction, as well as a good cosmetic outcome.

In the other case of WHO grade I meningioma where a single-piece FOZ had been used, the patient's left eye was not impaired but the medial extension of the lesion was limited and there was no cavernous sinuous involvement; in such a condition, the orbital osteotomy ensured by the one-piece FOZ is sufficient to expose the tumour, even with gentle eye retraction aimed at preserving visual function.

Despite progress in surgical techniques, tumours invading both the middle cranial fossa and ITF still remain difficult to manage. In a series of 33 patients, Bao et al. [24] obtained a gross total resection in 23 patients; in 29 patients, the clinical status improved significantly. In our series, gross total removal was achieved in seven patients (77.8%), and a near total in the remaining cases; this high rate of GTR may be related to

the benign nature of most lesions as well as a good selection of the cases eligible to FOZ. The same authors [24] reported complications in 7/33 patients (21.2%) with unremarkable morbidity. In our series, we observed one patient with post-operative enophtalmos.

Recurrence was observed in 3/9 patients (33.3%) and was mainly related to a parasinuses nasal component, successively treated with an endoscopic endonasal approach. Nonetheless, the relationship between recurrence and the presence of a diffusion route in the bone remains unclear. As a matter of fact, these communicating lesions characteristically show route of spread, such as foramina, skull base erosion and, rarely, bone sutures [25]. As a consequence, it is likely that this aspect could lead to an arduous excision and, subsequently, to a recurrence in that area. However, some authors have emphasised the histology as a fundamental factor for bone spread. In fact, bone erosion is generally associated with more aggressive tumours. We can partially confirm this statement: we observed two cases of erosion of temporal bone, one WHO grade II and one grade I meningioma. Moreover, an aggressive tumour such as metastases from lung adenocarcinoma showed no bone erosion while spreading through the oval foramen. Regarding trigeminal neurinomas (TN), we report a single case that spread though the oval foramen. In their series of 27 patents surgically treated for TN, Yoshida et al. found 30% of extra-cranial extension, including ITF, orbit or pterygopalatine fossa and foramen ovale, as the most common route of spread. These lesions are characteristically dumbbell-shaped, and foramina are enlarged at CT scan without bone erosion. Invasion of the orbit can occur in two ways: direct extension from the middle cranial fossa via the superior orbital fissure, and indirect extension firstly from the middle cranial fossa to the pterygopalatine fossa and then via the inferior orbital fissure into the orbit. Surgical techniques to treat these tumours include a combination of zygomatic and orbitozygomatic craniotomy and the zygomatic-infratemporal approach.

Extension into the lateral wall of the cavernous sinus is considered challenging for surgeons. Nevertheless, it is possible to obtain a gross total resection, with a wide anatomical exposure. In their original series of 18 mixed type tumours involving cavernous sinus, Al-Mefty et al. [20, 21] achieved a complete resection in 15 (83%) cases; no tumours with extra-cranial extension was present in their series. A review of surgical outcomes in tumours involving cavernous sinus is difficult because the definition of involvement in not itself clear. Tumours originating in the cavernous sinus are extremely rare, whereas nasopharyngeal carcinoma and metastasis are the most common of those invading the cavernous sinus space; meningiomas often compress, rather than invade, the lateral wall of the cavernous sinus that is composed of two layers. In tumours extending from ITF to the cavernous sinus, this lateral-to-medial extension is the main factor that can limit complete surgical excision.

A surgical approach such as FOZ, both the one- and the two-piece, is very useful in this situation because it ensures a wide angle of work. In our series, 6/9 patients (67%) showed MRI evidence of cavernous sinus involvement; nonetheless, intraoperative evidence of clear invasion of the lateral wall was evident only in one case of WHO grade II meningioma, which was treated by near total surgical resection and radiotherapy, and recurred after nine years of follow-up.

Our illustrative case is characteristic in terms both of the surgical approach and the rarity of the pathology. Lung cancer is the most common malignant cancer worldwide and every year it causes about 1.6 million deaths. Non-small cell lung cancer (NSCLC) represents about 85% of all lung cancers, and lung squamous cell carcinoma (LUSC) and adenocarcinoma (LUAD) are the most common subtypes [30]. At the time of diagnosis, most tumours are unresectable stage IV and globally the five-year survival rate for NSCL is 24%. Lung carcinomas can metastasise through lymphatic and blood vessels. The most frequent sites of metastases are the brain, bones and adrenal glands. A preferential metastatic site among different subtypes has been described: adenocarcinoma tends to metastasise to the brain, while SCLC spreads to both the brain and the liver; specific mutations can predispose to brain metastases [31, 32]. Generally, brain metastases from a hematogenous route, irrespective of histological types, are intra-axial lesions that tend to be located at the junction between grey and white matter, near major arteries and are surrounded by oedema with mass effect. In our case, the tumour invaded the middle cranial fossa by contiguity from infra-temporal fossa (possibly through the foramen) and it was localised only in the epidural space with only focal dural involvement and no brain invasion.

The management of this lesion is different from that of conventional brain metastases from lung adenocarcinoma, but due to the rarity of the pathology no specific indications are known. Chaudhuri et al. have described the case of a 46-year-old woman who presented with proptosis as the only sign of a mass in the infratemporal fossa invading her right orbita. Thoracic CT scan demonstrated a voluminous lung mass, and biopsy of both lung and ITF masses showed a poorly differentiated metastatic adenocarcinoma. Palliative chemotherapy with pemetrexed and carboplatin plus radiotherapy to the orbital mass was started, but a rapid progression of primary disease was observed and the patient died five weeks after the last cycle of chemotherapy.

In our case, surgical intervention was dictated by the need to decompress the neural structure, control intracranial extension and make a histological diagnosis. Despite gross total resection being obtained, even our patient's prognosis was extremely poor and he died only

four months after diagnosis due to the progression of his pulmonary disease.

These kinds of tumour are extremely rare, and, due to the poor prognosis, a complex surgical approach such as FOZ craniotomy should be carefully evaluated compared to a simple biopsy.

Conclusion

For the treatment of ITF fossa tumours extending to the orbit and/or middle cranial fossa, we believe that a two-piece FOZ craniotomy ensures a wider angle of work compared to a one-piece craniotomy and it allows safer and more direct surgical access to the cavernous sinus and paresellar region. A one-piece craniotomy ensures safer and better reconstruction while not requiring extra surgical time.

We believe that the main anatomical feature of the lesion that should dictate which of the two should be used is the medial-to-lateral extension of the tumour, in particular the invasion of the cavernous sinus: for a tumour with limited intracranial extension and not involving the cavernous sinus, we prefer the one-piece FOZ craniotomy, while for a tumour that extends from the pterygoid muscle to the cavernous sinus, a wider angle of work is required and here the two-piece FOZ craniotomy represents the better choice. In some cases, when visual function is irreversibly compromised and an aggressive manipulation of the orbital content should be carried out, a one-piece FOZ craniotomy may be extended medially with a more medial intraorbital cut, allowing resection also of a lesion involving the cavernous sinus.

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The ethical review process and approval by our ethics committee was not required for the present study because it is a retrospective study on patients who required a life-saving intervention. Furthermore, the research data analysis has no effect on the participants or their medical care.

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

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Primary progressive multiple sclerosis overlapping with anti-GAD and anti-Hu antibodies positive neurological syndromes

Pavel Štourač[1], Jana Bednářová[2], Zbyšek Pavelek[3], Martin Vališ[3]

[1]Department of Neurology, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic
[2]Department of Clinical Microbiology, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech Republic
[3]Department of Neurology, University Hospital Hradec Králové and Faculty of Medicine, Charles University, Hradec Králové, Czech Republic

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To the Editors

Although still rare, there have been reports describing autoimmune demyelinating disorders associated with specific antibodies which overlap with multiple sclerosis (MS) and other demyelinating syndromes in clinical, radiological and immunological features.

A relationship between anti-myelin-associated glycoprotein (MOG) syndrome, anti-aquaporin-4 (AQ-4) neuromyelitis optica spectrum disorders, and anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis has been described. The opportunity of discovering yet unknown associations is based on the presumption of the co-occurrence of immune mediated diseases [1]. The association of multiple sclerosis with glutamic acid decarboxylase (GAD) neurological syndromes has only been reported in one case [2, 3]. The associated neurological syndromes include stiff-person syndrome (SPS), cerebellar ataxia, epilepsy, and limbic encephalitis. Paraneoplastic origin is rare, and comorbidities include autoimmune thyreoiditis, pernicious anaemia and vitiligo [4].

More than 85% of patients with anti-Hu antibodies harbour small cell lung cancer (SCLC) or, less frequently, other tumours. Anti-Hu antibodies can be found in the sera of 2% of patients without a tumour after five years, but these antibodies are not detected in normal subjects or in other neurological disorders [5].

We present one case of non-paraneoplastic anti-Hu brainstem syndrome and one case of progressive GAD ataxia syndrome associated with primary progressive multiple sclerosis (PP-MS).

Case 1

A 57-year-old woman had been treated for autoimmune thyreoiditis with levothyroxinum natricum (Euthyrox tablets) since December 2018. No cardiovascular or rheumatoid diseases were present, including negative laboratory screeening. In 2014, she suffered from vertigo, and mild balance and coordination difficulties. In 2018, her condition worsened with additionally reported diplopia, dysarthria, unsteady walking with falls, fatigue and paraesthesias. Neurological examination discovered limb and gait ataxia, supranuclear vertical gaze palsy, diplopia, low reflexes and imperative micturion with EDSS grade 5.0. Tests for hereditary ataxias and anti-MOG and anti-AQ4 were negative. Anti-GAD antibodies were detected in serum. Paraneoplastic origin of anti-GAD antibodies was excluded by negative positron emission tomography (PET) of the whole body. MRI brain scan discovered multiple hyperintense lesions predominantly in juxtacortical and periventricular locations, fulfilling the 2017 McDonald criteria for multiple sclerosis. No lesions or atrophy were found in the cerebellum. Cerebrospinal fluid analysis (CSF) showed normal cell count and protein content, but positive oligoclonal IgG bands in CSF and serum (n-5/n-1). MRZ (measles, rubella, zoster) reaction was positive. The treatment included intravenous methylprednisolone, intravenous immunoglobulins, and plasmapheresis,

Address for correspondence: Pavel Stourac, University Hospital Brno, Jihlavska 20, 62500 Brno, Czech Republic; e-mail: Stourac.pavel@fnbrno.cz
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with temporary stabilisation mostly after the plasmapheresis. The patient's walking worsened, with the need of the support of a walking stick (EDSS 6.0) in 2020. MRI examinations in 2020, 2021 confirmed multiple white matter hyperintense lesions, some of them with T1-hypointense correlates and no lesions in the cerebellum. CSF analysis showed an increased number of oligoclonal IgG bands in CSF and serum (n-11/n-6). Increased kappa free light chain (κFLC) index value of 12.3 (normal range 0.8–5.9) was detected. Anti-GAD antibodies persisted in serum and cerebrospinal fluid. These CSF results are consistent with the so-called disease-related pattern for multiple sclerosis. Rituximab (600 mg intravenously) administered every six months led to clinical stabilisation. The patient fulfilled the diagnostic criteria for PP-MS (2017) by confirmed EDSS progression, hyperintense lesions in typical locations in MRI brain scan, and by the presence of oligoclonal IgG bands in CSF. PP-MS, GAD-associated cerebellar ataxia, and autoimmune thyreoiditis represent a unique trio of immune-mediated disorders with overlapping symptoms.

Case 2

A 69-year-old man without cardiovascular, rheumatoid or other significant comorbidities had developed brain stem syndrome with nystagmus, diplopia, vertigo, dysphagia, dysarthria, gait and limb ataxia in 1998. Initial MRI brain scan was normal. Anti-Hu antibodies were detected in serum and CSF, with otherwise normal CSF findings. Malignancy was excluded by repeated PET and bronchoscopy. MRI brain scan in 2006 revealed mild cerebellar atrophy but no lesions. The patient´s condition insidiously worsened and in 2012 he started to use a walking stick, and intermittently a wheelchair (EDSS 6.5). MRI brain scans during the period 2014-2020 showed new hyperintense lesions in juxtacortical, periventricular and brainstem locations, fulfilling MRI criteria for multiple sclerosis. Anti-Hu antibodies were constantly positive in serum and CSF. CSF analysis showed mild pleocytosis, intrathecal IgG synthesis confirmed by oligoclonal IgG bands in CSF and serum (n-8/n-3) in 2021.

The patient fulfills diagnostic criteria for PP-MS with severe progressive cerebellar syndrome, walking impairment reflected by EDSS, hyperintense lesions in typical locations in MRI brain scan, positive oligoclonal IgG bands in CSF in parallel with anti-Hu brainstem syndrome without tumour. Treatment with intravenous methylprednisolone and symptomatic treatment of fatigue and spasticity were partly effective.

This case has two unique aspects: firstly displaying clinically associated and overlapping PP-MS and anti-Hu brainstem syndrome; and secondly a very unusual long-term anti-Hu positivity of non-paraneoplastic origin.

There is evidence of a different immunological mechanism in both disorders. The pathological role of anti-GAD and anti-Hu antibodies is still a matter of debate. GAD-related neurological syndromes are uncommon and account for about

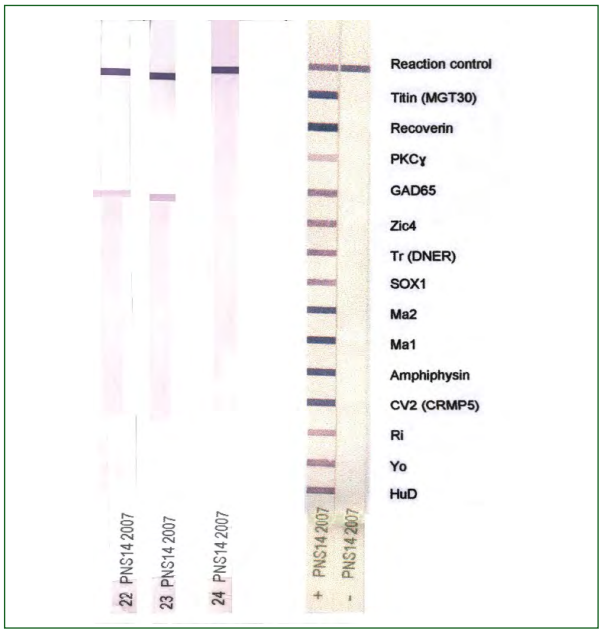

Figure 1. Immunoblot with positive anti-GAD65 antibodies in serum and cerebrospinal fluid (left to right) of patient with GAD cerebellar ataxia syndrome (Ravo, Germany)

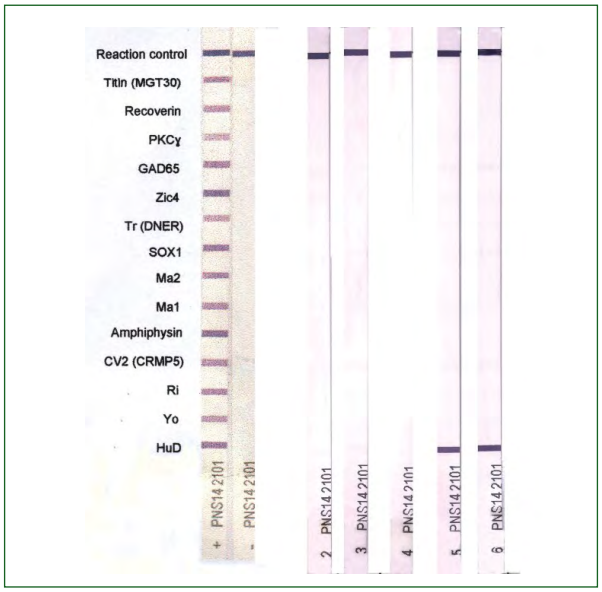

Figure 2. Immunoblot with positive onconeural anti-Hu antibodies in serum and cerebrospinal fluid (left to right) of patient with anti-Hu positive brainstem syndrome of non-paraneoplastic origin (Ravo,Germany)

2% of sporadic progressive cerebellar ataxia and for 12% of cerebellar ataxia of unknown origin [6, 7]. Anti-GAD antibodies occur in SPS syndrome, progressive encephalomyelitis with rigidity and myoclonus (PERM), cerebellar ataxia, limbic and extralimbic encephalitis, epilepsy and oculomotor dysfunction and nystagmus [8]. Increased titre of anti-GAD antibodies is

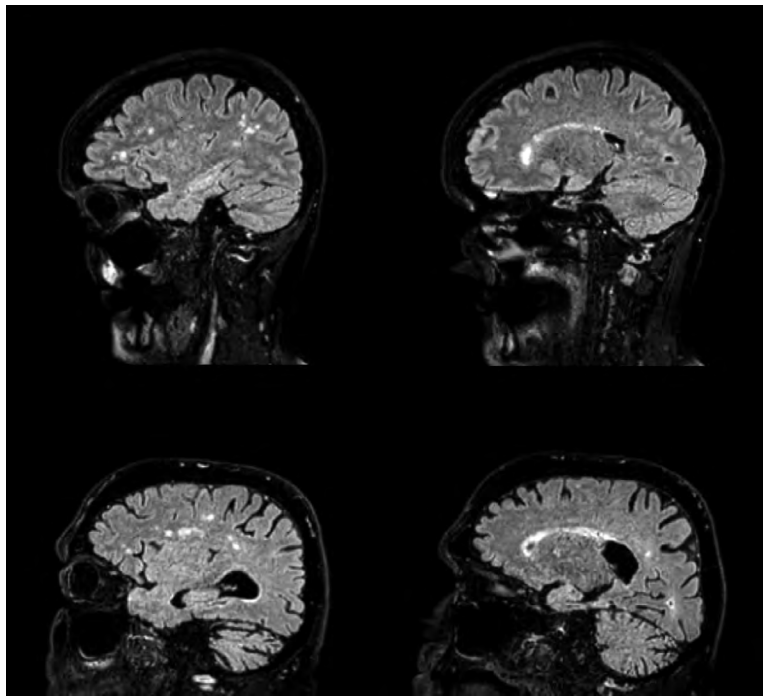

Figure 3. MRI of brain demonstrating typical finding of MS in 3D fluid-attenuated inversion recover (FLAIR) images of brain in sagittal plane. Scans a and b belong to Case 1; scans c and d belong to Case 2

neither a non-specific epiphenomenon of neuronal damage, nor a common feature of recognised neuroimmunological disorders. Anti-GAD antibodies may be a pathogenetic agent or a marker for an ongoing autoimmune process, or both [9]. This patient´s paraesthesias, fatigue, cognitive disorder and imperative micturion belong to a typical profile of PP-MS. The patient also has autoimmune thyreoiditis which is associated with SPS/cerebellar ataxia syndrome in c.50% of cases [10].

In GAD-associated cerebellar ataxia, MRI usually shows cerebellar atrophy with preservation of medulla oblongata [11]. The patient´s MRI brain scan showed multiple hyperintense lesions of typical locations up to 12 mm in size fulfilling MS diagnostic criteria. There is only one report of a patient developing epilepsy with extralimbic encephalitis with cortico-subcortical lesions in T2W/FLAIR MRI [12]. CSF analysis showed oligoclonal IgG bands in CSF and elevated kappa free light chains index with a high sensitivity (89-95%) and specificity (95-100%) for multiple sclerosis [13]. A positive MRZ reaction supported the MS diagnosis [14].

In the diffential diagnosis, we excluded compressive lesions, systemic autoimmune disorders, sarcoidosis, CNS infections including HTLV-1, syphilis, borreliosis and inherited disorders. The paraneoplastic syndromes with onconeural anti-Hu antibodies present disorders as sensory neuronopathy/encephalomyelitis, limbic encephalitis, brainstem encephalopathy, opsoclonus-myoclonus and myelopathy. Anti-Hu antibodies have 99% specificity and 82% sensitivity in detecting paraneoplastic neurological syndromes [15]. There is a reported prevalence of 32% for brainstem dysfunction and 25% for cerebellar dysfunction in anti-Hu positive patients.

The absence of a tumour and the permanent positivity of anti-Hu antibodies for 23 years, in spite of repeated oncological screeening including PET investigation, are unique features of this case. The continuous deterioration in walking paralled by an increasing number of hyperintense lesions in typical brain locations and positive CSF findings confirmed the diagnosis of PP-MS associated with anti-Hu brainstem syndrome. Compressive, autoimmune, infectious and inherited disorders were excluded in the differential diagnosis. There are no reports of long-term non-paraneoplastic anti-Hu syndromes, but there is a hypothesis that immune reaction could eliminate a tumour localised in situ at the beginning of oncogenesis, although this has not been proved experimentally yet [16].

Both these cases are important in terms of differential diagnoses in respect of different immune mechanisms, treatment and prognosis.

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LRRK2 R1441C mutation causing Parkinson's Disease in an Egyptian family

Shan Ali, Zbigniew K. Wszolek

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

Key words: Egyptian, leucine-rich repeat kinase 2 gene, Parkinson's Disease, R1441C mutation

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To the Editors

The most common cause of familial Parkinson's Disease (PD) involves mutations in the gene encoding leucine-rich repeat kinase 2 (LRRK2). The LRRK2 R1441C variant is the second most common, and has been implicated as a cause of PD [1]. A literature review revealed that this variant has been seen in kindreds originating from Europe and America, and more rarely from Asia and Africa [1]. It has never been reported in Egypt.

We here present the first Egyptian family with inherited PD due to R1441C mutation in LRRK2, as seen in Figure 1. Genetic testing confirmed that the proband was a carrier of the LRRK2 R1441C gene mutation. He was unaware of the medical history of his grandparents.

The proband was a 57-year-old male patient who came to our clinic for a second opinion regarding a diagnosis of PD. His symptomatic disease onset was at 49 years and he presented with left leg dragging, soon followed by a reduced mobility of his left hand. He was clinically diagnosed with PD at age 52. At age 57, he showed typical akinetic-rigid PD manifesting as bradykinesia and rigidity which were more pronounced on the left side. He exhibited hypomimia, hypophonia, a decreased rate of blinking, a reduced arm swing while walking, shuffling gait, and gait freezing. However, he had no resting tremor, extraocular impairment, dyskinesias, or cognitive deficits. On the pull test, he was able to recover on his own. The patient required minimal assistance in daily living activities and exhibited risky behaviour, excessive daytime sleepiness, nightmares and depression. He had an excellent response to carbidopa/levodopa therapy, and his depression was well controlled with escitalopram. Head magnetic resonance imaging studies done at ages 55 and 56 showed no brain abnormalities. Past medical history included gastric bypass surgery at age 54.

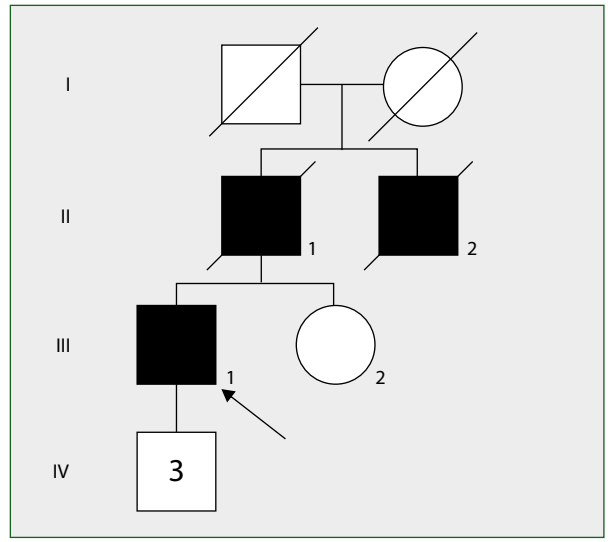

Figure 1. Pedigree of an Egyptian family with inherited *LRRK2* R1441C mutation causing Parkinson's Disease (PD). An arrow indicates the proband. Squares represent males and circles represent females. Black symbols represent individuals with PD. Diagonal lines through symbols represent decreased persons. A symbol with a number inside represents number of offspring

The clinical features of sporadic PD and inherited PD from LRRK2 R1441C mutation are similar, and this was the case with our patient as he showed typical akinetic rigid type parkinsonian motor symptoms and depression. The proband

Address for correspondence: Shan Ali, Department of Neurology, Mayo Clinic College of Medicine, 4500 San Pablo Rd, Jacksonville, FL 32224, USA; e-mail: ali.shan@mayo.edu

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did not have cognitive impairment; this is consistent with the hypothesis that LRRK2 mutation carriers show slower cognitive decline [2].

A 2017 literature review of PD patients with R1441C mutation in LRRK2 found the mutation present in American (including western Nebraska), Italian, Irish, Belgian, German, Russian, Spanish, Singaporean, and Chinese populations [1]. This mutation has not been reported in the Polish population [3]. LRRK2 G2019S mutations are common in Egypt and North Africa (including Mauritania, Morocco, Algeria, Tunisia and Libya) [4]. However, we here present the first family of Egyptian origin with inherited PD due to the LRRK2 R1441C mutation. It would be beneficial to study the Egyptian population for LRRK2 gene mutations, particularly for the R1141C mutation. Understanding the geographical landscape of LRRK2 mutation globally is important, since medication trials and gene therapies specifically designed to treat LRKK2 mutation carriers are under development [5].

Ethical compliance statement: *We conducted all genetic analyses under approval of the institutional review board (IRB) of Mayo Clinic Florida. Written informed consent was obtained. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.*

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Severity grading of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

James F. Meschia

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

To the Editors

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited small-vessel disease caused by various mutations in the *NOTCH3* gene, typically resulting in an unpaired cysteine [1]. Pathologically, patients develop granular osmiophilic deposits in small blood vessels. Patients often present with migraines, later developing lacunar strokes, vascular cognitive impairment, and dementia. The phenotypic expression of the disease is highly variable, and depends in part on the precise nature of the NOTCH3 gene mutation [2].

However, as with other inherited disorders [3], knowledge of the genetic mutation alone is insufficient to characterise CADASIL patients. The presence of vascular risk factors such as hypertension and tobacco smoking strongly influences phenotypic expression [4]. Current pharmacotherapy is limited to non-disease modifying drugs for treating migraine and cognitive symptoms.

As better understanding of the pathophysiology of the disease accrues and gene therapy technology evolves, consideration is being given to future disease-modifying trials [5]. However, one obstacle to developing therapies for CADASIL is its rarity. Powering randomised trials poses a challenge, even when the intervention has a major effect. This challenge is familiar to physicians studying new therapies for uncommon cancers. In oncological trials, it is commonplace to grade the severity of the disease and to restrict enrollment in such trials to individuals of a specific grade or grades. This results in a less heterogeneous patient population at trial entry, reducing imbalances in treatment groups in the trial itself. Progress in developing rational therapies for CADASIL might be accelerated by the adoption of a simple grading system, analogous to the Hoehn and Yahr scale for Parkinson's Disease [6].

The CADASIL grading system here being proposed is informed by more than two decades of clinical experience and previous CADASIL cohort studies describing the natural history of the disease (Table 1). In a cohort of 300 patients, the onset of migraines was found to occur at a median age of 28 years, and median age at onset of lacunar stroke was 48 [7]. In a separate cohort of 411 patients, median age at first stroke was 50.7 years in men and 52.5 in women; median age at time of onset of assistance with walking was 58.9 years in men and 62.1 in women; and median age at time of becoming bedridden was 62.1 years for men and 66.5 for women [8]. A consecutive series of 147 CADASIL patients demonstrated that the lacunar

Table 1. CADASIL Clinical Grading System

Grade	Description
0: Asymptomatic	Patient free of neurological symptoms referrable to CADASIL
1: Migraine only	Patient has suffered at least one migraine-like headache with or without aura
2: Stroke or MCI	Patient has had at least one stroke or transient ischaemic attack with brain imaging confirming the presence of a symptomatic infarct, and/or mild cognitive impairment with brain imaging showing signs of small vessel disease
3: Gait assistance or dementia	Patient requires assistance from another person or from devices like a cane or walker for walking due to neurological gait disorder and/or requires assistance in daily activities due to dementia but is not confined to bed
4: Bedbound	Patient is confined to bed for most of day

CADASIL — cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MCI — mild cognitive impairment

Address for correspondence: James Meschia MD, Mayo Clinic, Jacksonville, FL 32224, USA; e-mail: meschia.james@mayo.edu

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lesion burden is proportional to the severity of the cognitive impairment [9].

The proposed CADASIL Grading System would only apply to patients known to have a pathogenic *NOTCH3* mutation, a brain MRI showing characteristic ischaemic lesions, or a skin biopsy showing characteristic intravascular deposits. An asymptomatic relative of a patient with CADASIL would be considered to have Grade 0 disease only if there was evidence that the patient was an asymptomatic carrier of a pathogenic mutation. Grading a patient requires only a neurological assessment and clinically indicated brain imaging.

Patients are to be scored by the highest category for which they qualify. For example, a patient who presents with migraines and requires a walking stick because of a non-orthopaedic gait disorder would be considered to have Grade 3 disease. Not every patient will progress linearly through each grade, and so it would not be appropriate to refer to the grades as 'stages'. For example, some patients go on to have a stroke and ultimately become bedridden without ever having had a migraine. Nonetheless, the proposed grading system is intended to reflect progressively more severe small vessel disease.

The CADASIL Grading System is not intended to act as a substitute for standardised testing to characterise the cognitive burden of disease, or to take the place of standardised assessments of functional capacity. Other features of CADASIL such as encephalopathy, apathy, and mood disorders have not been included in the proposed Grading System because of suspected poor sensitivity and reliability of diagnosing these conditions in the absence of extensive testing dedicated to screening for them.

In conclusion, a simple grading system for CADASIL is proposed, with higher grades intended to reflect more severe small vessel disease. It is hoped that grading will allow for more homogeneous patient populations in future CADASIL clinical trials, and more consistent descriptions of patient populations in observational studies. Although this proposed system would appear to be valid, future studies will be needed to test its reliability in diverse patient populations.

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Hypertrophic pachymeningitis associated with Sjögren's syndrome: case report and literature review

Chihiro Kondo[1], Takayasu Mishima[1], Hidekazu Mera[1], Shinsuke Fujioka[1], Hironori Fukumoto[2], Tooru Inoue[2], Katsuhisa Miyake[3], Mikiko Aoki[4], Kazuki Nabeshima[4], Yoshio Tsuboi[1]

[1]Department of Neurology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan
[2]Department of Neurosurgery, Faculty of Medicine, Fukuoka University, Fukuoka Japan
[3]Division of Nephrology and Rheumatology, Department of Internal Medicine, Faculty of Medicine, Fukuoka University, Fukuoka Japan
[4]Department of Pathology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

To the Editors

A 60-year-old woman presented with fever and headache. Neurological examination was unremarkable. However, anti-SS-A (Sjögren's Syndrome-A) and anti-SS-B antibodies were detected in the serum without dry eye or dry mouth. Later, generalised tonic convulsions occurred and administration of levetiracetam was initiated. She was referred to our department due to the presence of dysesthesia on the left side of the body. Neurological examination confirmed dysesthesia in the left side of the body including the face. Deep tendon reflex was exaggerated in all extremities, with positive Hoffmann and Trömner's reflexes. Meningeal irritation signs were not observed. Serum immunological tests, including those for angiotensin converting enzyme (ACE), proteinase-3-anti-neutrophil cytoplasmic antibodies (PR3-ANCA), and myeloperoxidase-anti-neutrophil cytoplasmic antibodies (MPO-ANCA), were negative. Serum IgG4 level was within the normal range. Saxon and Schirmer's tests were positive, and the patient was diagnosed with Sjögren's syndrome (SS). Cerebrospinal fluid (CSF) examination showed a slight elevation of protein level with a normal glucose level and cell count. Brain magnetic resonance imaging (MRI) showed thickened dura mater in the right parietal region in a diffusion-weighted image (DWI) and in a fluid-attenuated inversion recovery image (FLAIR) (Fig. 1A and B). Hypertrophic pachymeningitis (HP) was suspected, and a dural biopsy was performed.

The pathological findings showed mild fibrosis and infiltration of inflammatory cells. No malignant lesion or presence of vasculitis was detected (Fig. 1C and D). Immunohistochemically, cerebral cortex on the surface staining revealed both CD3 and CD20 positive lymphocytes, and CD68-positive microglia, in the perivascular region. All of these glial cells were negative for IDH-1, and ATRX expression was well retained. Although dural pathology showed only mild inflammation, due to the exclusion of other diseases we diagnosed HP associated with SS. After the dural biopsy, the patient was treated with two courses of intravenous methylprednisolone (1 g/day) for three days. Soon after the treatment, the patient's headache and dysesthesia improved, and oral prednisolone (50 mg/day) was started, followed by gradual tapering. A brain MRI 94 days after the treatment showed an improvement of the thickened region (Fig. 1E and F). Currently, the patient's treatment comprises oral prednisolone at 10 mg/day without the recurrence of symptoms.

HP is a rare disease characterised by thickened dura mater. This disease often presents with headache, fever, visual loss, and double vision with accompanying cranial nerve pathology (frequently in cranial nerves II–VIII). Occasionally, HP occurs idiopathically. Infection, sarcoidosis, and certain autoimmune diseases have been reported as secondary causes of HP. In a nationwide survey of 159 HP patients conducted in Japan, the underlying disease was revealed to be idiopathic in 44%, ANCA-related in 30.2%, and IgG4/multifocal fibrosclerotic systemic disease-related in 8.8% of the cases [1]. In our review of the literature, nine cases of HP associated with SS have been reported worldwide (Table S1). Consistent with the presented case, frequent clinical features in these nine cases were fever and headache that developed following neurological symptoms such as increased deep tendon reflexes, sensory disorders, or muscle weakness. The site of dural thickening was variable: three cases of spinal thickening and seven cases in intracranial

Address for correspondence: Yoshio Tsuboi, Department of Neurology, Fukuoka University, 7-45-1, Nanakuma, Johnan-ku, Fukuoka 814-0180, Japan; tel: +81-92-801-1011 (ext. 3520), e-mail: tsuboi@cis.fukuoka-u.ac.jp

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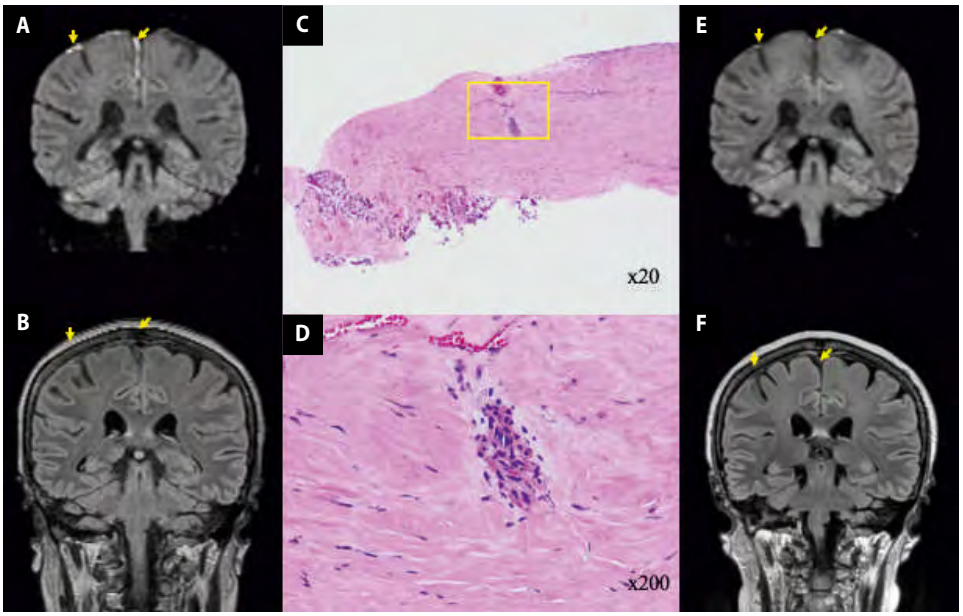

Figure 1. Magnetic resonance imaging (MRI) of brain with thickened dura mater at right parietal region in diffusion-weighted (DWI); **A.** Fluid-attenuated inversion recovery image (FLAIR); **B.** Follow-up MRI did not show dura mater thickening **(E, F)**. Photomicrographs of sections of dura mater tissue stained with hematoxylin and eosin showed thickened dura mater (magnification 20x); **C.** Mild fibrosis and infiltration of inflammatory cells (magnification 200x) **(D)**

dural thickening. Regarding pathological findings, a dural biopsy was also performed in 52 of the HP patients included in the Japanese survey. The findings primarily revealed fibrosis and infiltration of inflammatory cells, with some cases showing granuloma. IgG4-positive plasma cells were observed in 11 cases (seven cases of IgG4/multifocal fibrosclerotic systemic disease-related and four ANCA-related cases) [1]. In ANCA-related HP, the pathological findings mainly show fibrosis and infiltration of inflammatory cells, and sometimes IgG4 positive cells or granulomas [2–4]. In HP associated with SS, dural biopsy has been performed in five cases, including the present case, revealing nonspecifically fibrosis and infiltration of inflammatory cells, which may be the pathological characteristics of this condition.

Regarding treatment, idiopathic or autoimmunity-associated HP is usually treated with steroid therapy as the first-line treatment. In some cases of idiopathic HP, and those of ANCA- and IgG4-related HP, additional immunosuppressant treatment may be required. The present case was successfully treated with steroid therapy without recurrence. Other reported cases of SS-associated HP were also treated with steroid therapy alone, and eight of the nine cases showed no recurrence. Only one case was treated with an immunosuppressant. Nakano et al. reported that moderate-dose steroids may be sufficient for the treatment of HP in SS (Table S1). In addition to hypertrophic pachymeningitis, aseptic meningitis is another central nervous system disorder associated with Sjogren's syndrome. Contrast-enhanced MRI is necessary to distinguish between meningitis and HP, and a dural biopsy should be performed if possible.

In conclusion, our case report and review of the literature reveal that the pathological findings of HP associated with SS show nonspecific regions. In addition, we conclude that steroid therapy should be started immediately after the diagnosis of HP associated with SS because such therapy is confirmed to be effective.

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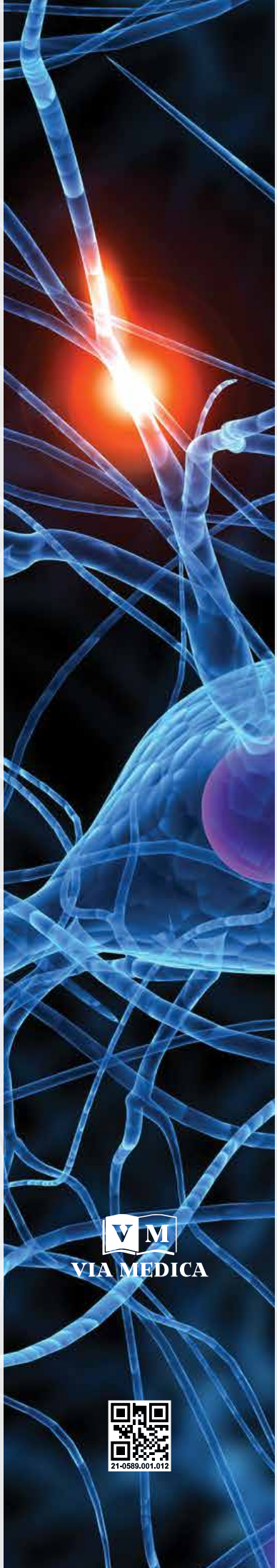

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