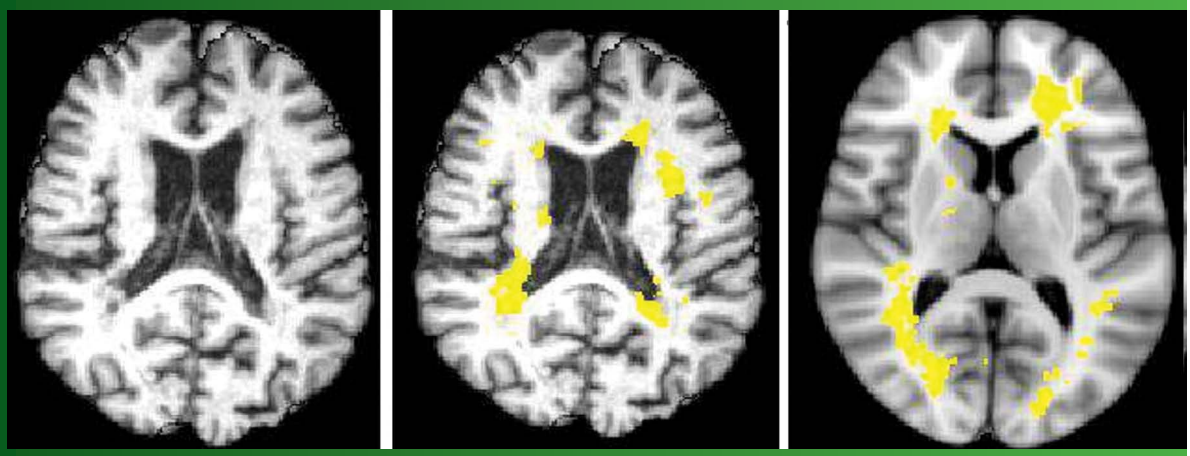
NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF NEUROLOGY AND NEUROSURGERY

The Official Journal of Polish Neurological Society

2019, vol. 53, no. 1



INVITED REVIEW ARTICLE

1 **A systematic review of Gamma-aminobutyric Acid Receptor Type B autoimmunity**
J.H McKay et al.

REVIEW ARTICLE

8 **Neurosurgical cadaveric and in vivo large animal training models for cranial and spinal approaches and techniques — a systematic review of the current literature**
C.O. Morosanu et al.

RESEARCH PAPERS

18 **Spatial distribution of white matter degenerative lesions and cognitive dysfunction in relapsing-remitting multiple sclerosis patients**
N. Nowaczyk et al.

26 **Electrophysiological and clinical assessment of dysautonomia in multiple system atrophy (MSA) and progressive supranuclear palsy (PSP): a comparative study**
M. Nojszewska et al.

34 **Trigone ventricular meningiomas — clinical characteristics, histopathology and results of surgical treatment**
K. Leśniewski et al.

43 **Familial occurrence of carpal tunnel syndrome**
P. Puchalski et al.

47 **How does early decompressive craniectomy influence the intracranial volume relationship in traumatic brain injury (TBI) patients?**
P. Jasielski et al.

55 **Outcomes of traumatic brain injury: the prognostic accuracy of various scores and models**
J.D. Charry et al.

Established: 1938

VIA MEDICA

ISSN 0028-3843

www.journals.viamedica.pl/neurologia_neurochirurgia_polska

NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF NEUROLOGY AND NEUROSURGERY

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

VIA MEDICA

NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF NEUROLOGY AND NEUROSURGERY

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

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

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

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

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

Current Impact Factor of Neurologia i Neurochirurgia Polska (2017) is 0.817

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

Cover photo: Natalia Nowaczyk et al., see figure legend on page 20.

18-0354.001.001

NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF
NEUROLOGY
AND NEUROSURGERY

The Official Journal of Polish Neurological Society

2019, vol. 53, no. 1

Table of Contents

Editorial note

Mariusz Siemiński, Jarosław Sławek, Zbigniew K. Wszolek

INVITED REVIEW ARTICLE

A systematic review of Gamma-aminobutyric Acid Receptor Type B autoimmunity 1

Jake H. McKay, Elliot L. Dimberg, Alfonso S. Lopez Chiriboga

REVIEW ARTICLE

Neurosurgical cadaveric and in vivo large animal training models for cranial and spinal approaches and techniques — a systematic review of the current literature 8

Cezar Octavian Morosanu, Liviu Nicolae, Remus Moldovan, Alexandru Stefan Farcasanu, Gabriela Adriana Filip, Ioan Stefan Florian

RESEARCH PAPERS

Spatial distribution of white matter degenerative lesions and cognitive dysfunction in relapsing-remitting multiple sclerosis patients 18

Natalia Nowaczyk, Alicja Kalinowska-Łyszczarz, Włodzimierz Paprzycki, Sławomir Michalak, Radosław Kaźmierski, Mikołaj A. Pawlak

Electrophysiological and clinical assessment of dysautonomia in multiple system atrophy (MSA) and progressive supranuclear palsy (PSP): a comparative study 26

Monika Nojszewska, Anna Potulska-Chromik, Zygmunt Jamrozik, Piotr Janik, Beata Zakrzewska-Pniewska

Trigone ventricular meningiomas — clinical characteristics, histopathology and results of surgical treatment **34**

Kamil Leśniewski, Przemysław Kunert, Ewa Matyja, Tomasz Czernicki, Katarzyna Wójtowicz, Jakub Wojciechowski, Andrzej Marchel

Familial occurrence of carpal tunnel syndrome **43**

Piotr Puchalski, Zbigniew Szlosser, Mir-Saeed Yekaninejad, Andrzej Zyluk

How does early decompressive craniectomy influence the intracranial volume relationship in traumatic brain injury (TBI) patients? **47**

Piotr Jasielski, Zbigniew Czernicki, Piotr Dąbrowski, Waldemar Koszewski, Rafał Rojkowski

Outcomes of traumatic brain injury: the prognostic accuracy of various scores and models **55**

Jose D. Charry, Sandra Navarro-Parra, Juan Solano, Luis Moscote-Salazar

Attitudes towards neurology among medical undergraduates **61**

Anna Pokryszko-Dragan, John Mottershead, Gill Aitken

No association between MRI changes in the lumbar spine and intensity of pain, quality of life, depressive and anxiety symptoms in patients with low back pain **74**

Anna Babińska, Wojciech Wawrzynek, Elżbieta Czech, Jarosław Skupiński, Jarosław Szczygieł, Beata Łabuz-Roszak

Stroke and TIA mimics in patients referred to a neurological emergency department by non-ambulance physicians, ambulance physicians and paramedics **83**

Dorota Kozera-Strzelińska, Michał Karliński, Grzegorz Rak, Magdalena Wojdacz, Halina Sienkiewicz-Jarosz, Iwona Kurkowska-Jastrzębska

Prevalence and extent of right-to-left shunt on contrast-enhanced transcranial Doppler in patients with chronic hyperventilation syndrome: results of a case-control study **90**

Jacek Staszewski, Kazimierz Tomczykiewicz, Anna Piusińska-Macoch, Adam Stępień

LETTERS TO THE EDITOR

Delayed onset of Takotsubo syndrome after epileptic seizure **95**

Claudia Stöllberger, Josef Finsterer

EDITORIAL NOTE

Neurologia i Neurochirurgia Polska
Polish Journal od Neurology and Neurosurgery
2019, Volume 53, no. 1

ISSN 0028–3843

New Publisher of the *Polish Journal of Neurology & Neurosurgery (Neurologia i Neurochirurgia Polska)*

Mariusz Siemiński[1], Jarosław Sławek[2], Zbigniew K. Wszolek[3]

[1] *Department of Emergency Medicine, Medical University of Gdansk, Gdańsk, Poland.*
[2] *Department of Neurological-Psychiatric Nursing, Medical University of Gdansk, Gdańsk, Poland*
[3] *Mayo Clinic Florida, Jacksonville, Florida, USA*

To Our Readership: With great pleasure we announce that the new publisher of the *Polish Journal of Neurology and Neurosurgery (Neurologia i Neurochirurgia Polska)* is the Polish publishing house, *Via Medica*. *Via Medica* is based in Gdansk and Warsaw, Poland. The Editors of the *Polish Journal of Neurology and Neurosurgery* are looking forward to our association with the new publishing team, particularly with Dr. Lukasz Stolarczyk, who serves as Director of Medical Informatics, and with Ms. Dorota Czarnocka who serves as a Technical Editor for our Journal. *Via Medica* is a long-term partner of the *Polish Neurological Society*. It also publishes the *Polski Przegląd Neurologiczny*, an educational journal of the *Polish Neurological Society* and the official internet portal of this Society.

We welcome you to our new website hosted by the new publisher: https://journals.viamedica.pl/neurologia_neurochirurgia_polska. All necessary information regarding the submission of the manuscripts can be found at this website. We again thank the Elsevier team for their support of the Journal for the last few years.[1]

We encourage you to submit your best articles to our Journal. We will work hard to further improve our publication speed. Last year we were able to improve the time from submission to final editorial outcome by nearly a third from 25.3 weeks in 2017 to 18.5 weeks in 2018. We hope that with our new publishing house we will be able to manage the manuscript processing effectively and provide innovative solutions to ever changing publishing requirements. We are looking forward to partnering with you, our international and Polish authors and readers to make the *Polish Journal of Neurology and Neurosurgery* even better publishing platform. We appreciate the dedication of our international and Polish reviewers. We thank the Polish Neurological Society and Polish Society of Neurosurgeons for their financial support.

References

1. Wszolek ZK, Slawek J, Sieminski M. Editorial announcement — the change of publisher of the Polish Journal of Neurology & Neurosurgery (Neurologia i Neurochirurgia Polska. Neur Neurol Pol 2018; 52: 637.

INVITED REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 1, pages: 1–7
DOI: 10.5603/PJNNS.a2018.0005

ISSN 0028–3843

A systematic review of Gamma-aminobutyric Acid Receptor Type B autoimmunity

Jake H. McKay[1], Elliot L. Dimberg[1], Alfonso S. Lopez Chiriboga[2]

[1]Mayo Clinic, Jacksonville, Florida, USA

[2]Mayo Clinic Minnesota, Rochester, Minnesota, USA

ABSTRACT

Objective. To review the available research to describe the clinical characteristics and neoplastic associations of patients with gamma-aminobutyric acid receptor type B (GABAB-R) autoantibodies.

Methods. Literature was reviewed on PubMed, Mendeley literature search, and the American Academy of Neurology database for articles published from June 2008 to October of 2018 using a variety of key words. These key words include: „gamma-aminobutyric acid seizures," „gamma-aminobutyric acid limbic encephalitis", „GABA(B) receptor antibodies," „autoimmune encephalitis," „autoimmune epilepsy," „GABA(B) encephalitis, „ and "GABA paraneoplastic." With the results, the papers were reviewed in a systematic manner.

Results. A total of 10 studies were reviewed. A summary of the demographic, clinical, and serological findings of the cases detailed in the literature are provided. An additional illustrative case is described. In total, 94 patients were reviewed.

Conclusions. GABAB-R autoimmune disease is characterized by refractory seizures or status epilepticus and frequent association with small cell lung cancer. Additionally, a substantial minority of patients have non-inflammatory CSF.

Key words: Gamma-aminobutyric acid seizures, gamma-aminobutyric acid receptor type B, GABA(B) receptor antibodies, autoimmune encephalitis, autoimmune epilepsy, GABA-B encephalitis, GABA limbic encephalitis, GABA paraneoplastic (*Neurol Neurochir Pol 2019; 53 (1): 1–7*)

Introduction

The field of autoimmune neurology has evolved rapidly in the years following the discovery of N-methyl-D-aspartate receptor (NMDA-R) encephalitis in 2007 [1]. As more neural autoantibodies have been discovered, cases of encephalitis previously presumed to be viral or idiopathic have been determined to be autoimmune in aetiology [2]. Gamma--aminobutyric acid receptor type B ($GABA_B$-R) antibody autoimmune encephalitis, first described in the literature in 2010 by Lancaster et al. [3], has been followed by several additional case series and retrospective studies [4, 5].

As more clinical cases have been reported, the profile of the clinical, radiological, and serological characteristics of $GABA_B$-R autoimmunity has continued to expand. While symptoms of limbic encephalitis (seizures, confusion, and memory loss) and frequent association with small cell lung cancer (SCLC) were characteristics originally proposed [3, 5]memory loss, and confusion, compatible with limbic encephalitis (LE, additional associated features have become apparent, including: status epilepticus, ataxia, epileptiform electroencephalogram (EEG) findings, and sometimes benign cerebrospinal fluid (CSF) studies [5–7]. Given the neoplastic associations of $GABA_B$-R antibody encephalitis, and its tendency to respond to immunosuppressive treatment [5] prompt recognition of the disorder is crucial as this can improve oncologic and neurologic outcomes.

$GABA_B$-R is a G-protein coupled receptor known to play a role in the suppression of neural or seizure activity [8] and is widely distributed in the hippocampus, thalamus and cerebellum [9]. GABA receptor is composed of $GABA_{B1}$ and $GABA_{B2}$ subunits. Binding of GABA to the $GABA_{B1}$ subunit results in conformational changes, causing inhibition of neuronal firing activity principally by inhibiting presynaptic calcium channels [8]. There is evidence that a lack of normal $GABA_B$-R structure and function can lead to spontaneous seizures [10]. Autoantibodies in the CSF of anti-GABA receptor encephalitis patients prevent activation of GABA receptors in

Address for correspondence: Jake H. McKay, Mayo Clinic, Jacksonville, Florida, United States, e-mail: mckay.jake@mayo.edu

vitro by blocking receptor function without altering receptor surface density [11].

In this study, we review the current literature relating to $GABA_B$-R autoimmunity, describing the clinical features, laboratory evaluation, oncologic associations, and treatment response of the disorder in a comprehensive manner. We will also provide an illustrative new clinical case of $GABA_B$-R antibody encephalitis on which the diagnosis was obtained post-mortem, as testing was unavailable at the time of presentation.

State of the art

We identified a total of 94 confirmed cases of $GABA_B$-R encephalitis, including case series from Lancaster et al. [3], Boronat et al. [4], Höftberger et al. [5], Guan et al. [6], Onugoren et al. [7], Kim et al. [12], and Chen et al. [13]. Additionally, several case reports, including one of our own, were included in the analysis [14–16]. All studies were retrospective. The average patient age was 59.6 years, with a range of 16 to 84 years. We only included patients of 16 years or older, given the frequently distinct paraneoplastic associations in paediatric patients [17]. However, we do recognise that, in the paediatric literature, $GABA_B$-R encephalitis has been rarely reported, including a patient as young as three years old [18]. The male to female ratio was 59:35, with males comprising 62.8% (59/94) of the total number of cases. While most studies focus on Caucasian patients, the studies by Guan, Kim, and Chen have described the disorder in an East Asian population (n = 34).

Patients most commonly presented with seizures, which were diagnosed in 84.0% (79/94) of cases on initial evaluation, with status epilepticus in 9.6% (9/94). Limbic symptoms characterised by confusion, disorientation, or behavioural change were seen in 67.1% (51/76) of patients at the time of presentation, whereas gait ataxia and gait instability were seen in 11.7% (11/94). The presenting symptoms are summarised in Table 1. Of all patients, 14.9% (14/94) ultimately developed coma or required an Intensive Care Unit (ICU) level of care for airway support or ventilator management. An atypical case with coexistent anti-Hu and anti-CV2 autoantibodies was described with vertigo, hiccups, and vomiting, and was ultimately found to have brainstem involvement [14]. A summary of the symptoms encountered throughout the course of illness is presented in Table 2. The mean follow-up for cases with clearly defined data was 10.4 months, with a range from hospital discharge to 90 months (n = 66).

CSF findings

Of the cases with available CSF data, 59.3% (51/86) had CSF pleocytosis, and 43.9% (29/66) had elevated protein in CSF. Testing for $GABA_B$-R autoantibodies was more sensitive in CSF than serum, with autoantibodies for $GABA_B$-R identified in 98.3% (71/72) of subject CSF and 88.1% (69/77) of serum samples.

Imaging findings

Magnetic resonance imaging (MRI) brain findings appeared to have a strong predilection for the temporal lobes, with 54.8% (51/94) of cases having either unilateral or bilateral temporal lobe hyperintensity on MRI brain T2. Of patients with temporal lobe hyperintensity on brain MR T2 imaging, bilateral temporal lobe hyperintensity occurred in 59.5% (25/42) of cases with available data.

Table 1. Summary of the most commonly encountered presenting symptoms

Study	Subjects	Seizures	Status Epilepticus	Ataxia	Confusion/Behavioural Change
Lancaster [3]	15	13	3	0	2
Boronat [4]	11	9	1	1	9
Höftberger [5]	20	18	0	1	17
Guan [6]	18	16	0	2	ND
Onugoren [7]	10	8	2	3	8
Kim [12]	5	3	0	0	5
Chen [13]	11	11	3	1	9
Alexopoulos [14]	1	0	0	0	0
Jarius [15]	1	0	0	1	0
Mimbrera [16]	1	0	0	1	0
Illustrative case	1	1	0	1	1
Total:	94	79	9	11	51 (n = 76)
Percentage:		84.0%	9.6%	11.7%	67.1%

ND — no data

Table 2. Summary of the symptoms encountered during illness

Study	Subjects	Seizure	GTC Seizure	Status Epilepticus	Memory Impairment	Confusion	Agitation/ Behavioural change	Coma/ ICU	Ataxia
Lancaster [3]	15	15	8	3	15	15	5	4	1
Boronat [4]	11	8	ND	1	6	4	4	ND	1
Höftberger [5]	20	20	ND	1	20	20	ND	1	2
Guan [6]	18	17	17	4	12	ND	11	4	3
Onugoren [7]	10	8	8	2	6	5	5	2	3
Kim [12]	5	3	3	0	2	5	5	0	0
Chen [13]	11	11	11	3	9	7	9	1	1
Alexopoulos [14]	1	0	0	0	0	0	0	0	0
Jarius [15]	1	0	0	0	0	0	1	0	1
Mimbrera [16]	1	0	0	0	1	1	1	1	1
Illustrative case	1	1	1	1	1	1	0	1	1
Total:	94	83		15	72	58 (n = 76)	41(n = 74)	14	14
Percentage:		88.30%		16.00%	76.80%	76.30%	55.40%	14.90%	14.90%

ND — no data

Electrophysiologic studies

EEG was documented for 66 patients, and 57.6% (38/66) had either temporal lobe seizures, interictal epileptiform abnormalities, or focal temporal slowing.

Oncologic association

Neoplasm was detected in 49.5% (46/93) of cases, with 91.3% (42/46) of the neoplastic cases being small cell lung cancer. There were three patients assumed to be SCLC based on a diagnosis of lung cancer and a clinical history that did not have a final pathologic confirmation [6]. Additional associated neoplasms reported include: one neuroendocrine tumour [3], one carcinoid of the thymus [4] one type B1 thymoma [14], and one melanoma [15]. The patient with type B1 thymoma had associated anti-Hu and anti-CV2 antibodies, and the patient with melanoma had associated Glutamic Acid Decarboxilase (GAD-65) antibodies, whereas the patients with associated neuroendocrine tumour and carcinoid of the thymus had no reported additional antibodies. The youngest patient with reported SCLC was a 42 year-old female [19]. The most commonly reported autoantibodies associated with $GABA_B$-R autoimmune disease were anti-Hu (10.8%, 9/83), anti-SOX1 (10.8%, 9/83), anti-GAD65 (8.5%, 8/94), and N-type voltage gated calcium antibodies (4.8%, 4/83). Isolated cases with associated voltage-gated potassium channel, BR serine/threonine-protein kinase 2, NMDA-R, and CV2 autoantibodies have also been described.

Treatment outcome

Outcomes demonstrate a robust response to either immunotherapy or a combination of immunotherapy and cancer treatment when appropriate, with 86.3% (63/73) of patients treated either demonstrating partial or complete recovery. Of those treated with immunosuppressive agents, 34.2% (25/73) of patients demonstrated a complete response, as defined by a return to a prior baseline or modified Rankin scale of 0–1, depending on the metric used.

The most common immunosuppressive agents utilised were corticosteroids, IVIg, plasmapheresis, and steroid sparing agents. Tables 3A and 3B summarise treatment types and responses. Outcomes in patients without immunotherapy and/or cancer treatment were poor, with 6 out of 9 (66.7%) dying. Interestingly, the two reported by Guan to have survived without immunotherapy and/or cancer treatment were treated with AEDs [6]. However, exact time to follow-up for these patients was not available, beyond that it was at least one month. Of the four patients treated with only AEDs, one demonstrated complete recovery, one demonstrated partial improvement, one remained stable without improvement, and the remaining one died. Due to the high mortality of SCLC, control of the underlying neoplasm was often the long-term limiting factor in patients with SCLC.

Illustrative case

In 2003, we encountered an 84 year-old gentleman with a history of heavy cigarette smoking, alcohol abuse, and atrial

Table 3 A. Treatment responses in patients treated with immunosuppression, AED, or no treatment. One unidentified patient was treated with chemotherapy

	Patients Treated	Full Recovery	Partial Recovery	No Response
Steroids	16	9 (56.2%)	7 (43.8%)	0
Ivlg	15	6 (40%)	6 (40%)	3 (20%)
Steroids + IVIG[1]	13	5 (33.5%)	7 (53.8%)	1 (7.7%)
Steroids + PLEX	5	1 (20%)	2 (40%)	2 (40%)
Steroids+IVIG+PLEX	2	0	2	0
Steroid Sparing Agent + Corticosteroid	3	1	1	1
Steroid Sparing Agent + IVIG or PLEX ± Steroids	5	0	4 (80%)	1 (20%)
AED Only	4	1	1	2
No Treatment	6	0	0	6
Total:	69	23	30	16
Percentage:		33.3%	43.5%	23.2%

Table 3 B. Treatment responses in patients treated with chemotherapy or combined chemotherapy and immunosuppression. All patients in this category had confirmed neoplasm. Some patients had additional radiotherapy

	Patients Treated	Full Recovery	Partial Recovery	No Response
Chemo only	6	0	4	2
Chemo + corticosteroids	1	1	0	0
Chemo + IVIG	2	1	1	0
Chemo + Steroids + IVIG	9	1	6	2
Corticosteroids + IVIG±PLEX+Chemo	1	0	1	0
Chemo + Steroid Sparing Agent + Steroids + Chemo	1	0	1	0
Total:	20	3	13	4
Percentage:		15%	65%	20%

fibrillation who presented due to an unwitnessed presumed first generalised seizure with associated cognitive decline and ataxia with subacute gait instability. His initial neurologic examination was notable for intact cognition, reduced left hemibody light touch, left greater than right heel to shin ataxia, left greater than right finger to nose dysmetria, and gait ataxia.

On day 12, repeat brain MRI was performed with and without demonstrated right mesial temporal lobe hyperintensity on T2 imaging with increased restricted diffusion of the right mesial temporal lobe, insula, and adjacent basal ganglia (Fig. 1). Lumbar puncture was performed, with CSF laboratory values of: < 1 WBC, 20 RBC, normal glucose, protein 70, NSE elevated 31.6, and two oligoclonal bands. CSF infectious studies were all negative, including: HSV PCR, fungal studies, AFB culture, viral culture, Cryptococcus Ag, EBV, and West Nile Ag.

The patient experienced rapidly progressive cognitive decline with a parallel worsening seizure course, with obtundation and non-convulsive status epilepticus NCSE within 21 days (Fig. 2), followed by death. Seizures arose from the right hemisphere and were refractory to phenytoin with partial EEG response to high dose fosphenytoin and valproate combination therapy. Fine needle aspirate of a pulmonary mass was positive for SCLC.

This patient's case was reviewed retrospectively in 2018, and it was proposed that $GABA_B$-R autoimmune encephalitis was the most likely cause of death based on the patient's clinical characteristics of ataxia with seizures progressing to status epilepticus [4] imaging profile consistent with limbic encephalitis, small-cell lung cancer association [5] and CSF without pleocytosis [4]. Laboratory testing of stored patient's serum and CSF by cell based assays were both positive for $GABA_B$-R antibodies, confirming the diagnosis 15 years later.

Clinical implications

The number of identified cases of $GABA_B$-R antibody autoimmunity available for review has expanded in the literature

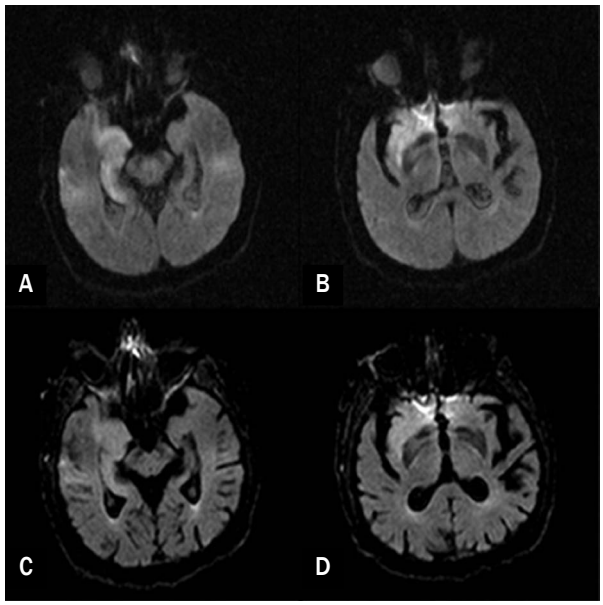


Figure 1. Brain MRI DWI sequence with restricted diffusion of the right mesial temporal lobe, insula, and basal ganglia (A,B) and corresponding brain MRI T2 hyperintensity (C,D)

since the original description in 2010. As a result, a distinctive clinical syndrome has become increasingly solidified, characterised by the cardinal features of refractory seizures or status epilepticus and frequent SCLC association. This review demonstrates that the disease is more common in males than in females, that bilateral temporal lobe hyperintensity is a very frequent radiographic finding, that a substantial minority have noninflammatory CSF, and that ataxia is more frequent in these patients than most physicians had previously appreciated. The included data from Asian countries reveals that $GABA_B$-R autoimmunity is probably not bound by race or ethnicity and most likely has a similar clinical syndrome worldwide, as the frequency of SCLC is high. The study also highlights that other associated neoplasms besides SCLC may be present in a small group of patients, suggesting that a comprehensive oncologic evaluation is warranted.

While features of $GABA_B$-R Ab mediated autoimmune disease can overlap with other common autoimmune diseases of the central nervous system (CNS), $GABA_B$-R autoimmunity should be suspected over NMDA-R encephalitis in individuals with older average age of onset, with the average of onset being 59 years versus 21 respectively [20]. $GABA_B$-R

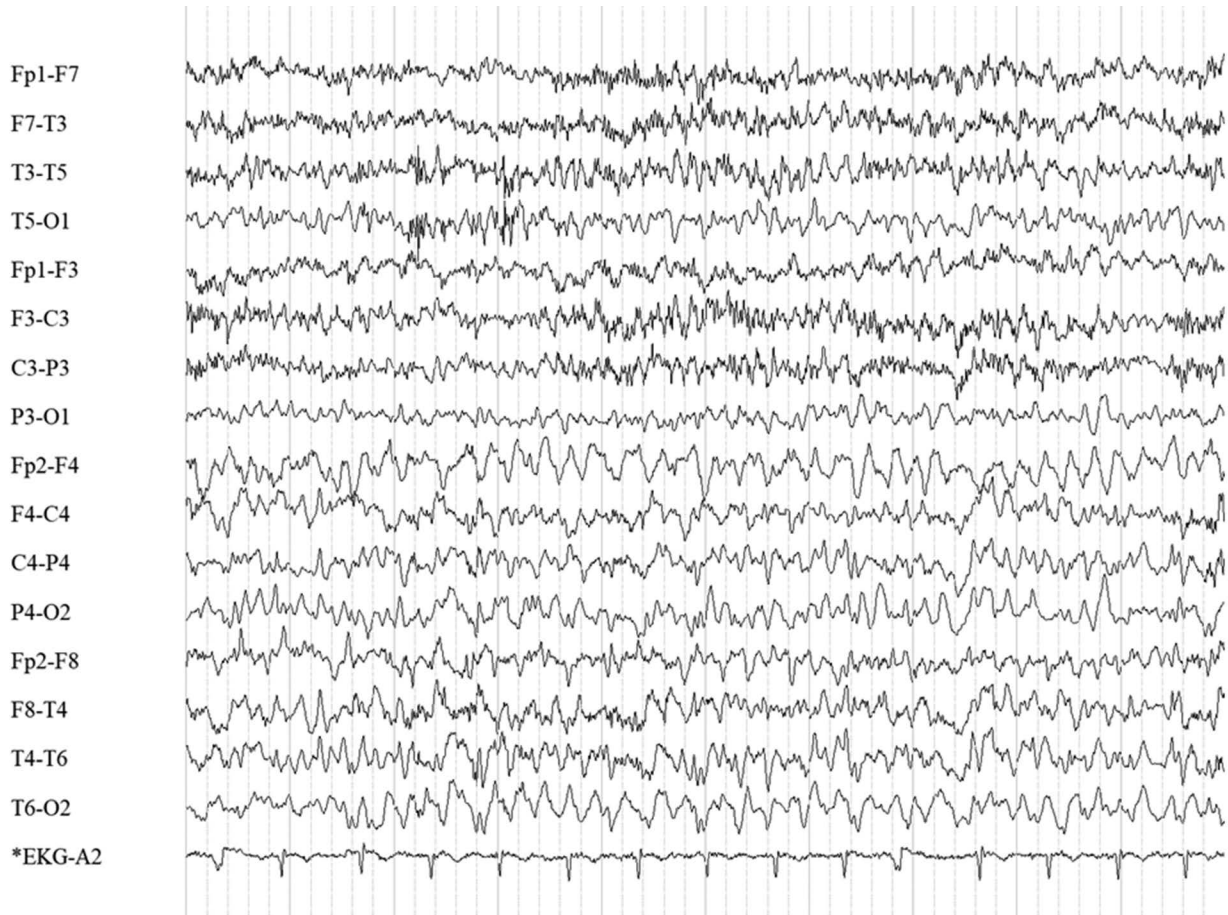


Figure 2. EEG demonstrating non-convulsive status epilepticus, with right hemisphere predominance

autoimmunity is also more common in males (2:1), whereas NMDA-R autoimmune encephalitis is female predominant (8:1). Additionally, $GABA_B$-R autoimmunity is more likely to present with seizures or associated ataxia and has different oncologic associations (SCLC versus ovarian teratoma) compared to NMDA-R autoimmune encephalitis [21]. While anti-Hu autoantibodies are commonly seen in association with SCLC, with a similar average age of onset (63 years) as $GABA_B$-R autoimmunity, it is much more likely to present with paraneoplastic peripheral neuropathy than seizure or limbic encephalitis [22]. In cases of isolated ataxia in association with SCLC, anti-Hu and anti-$GABA_B$-R antibodies should be strongly considered in the differential.

The recognition of $GABA_B$-R autoimmunity has important clinical implications for patient outcomes, as untreated patients are more likely to die or progress to coma. The recognition that CSF can be non-inflammatory is important, as CSF pleocytosis is often used as a clinical justification for empiric treatment of suspected autoimmune neurological disorders while waiting for autoantibody testing results. Additionally, it has been recently reported that patients with antibodies targeting cell surface proteins can often have a non-inflammatory CSF [23]. The retrospective diagnosis in our patient deceased 15 years earlier was made possible by the subsequent discovery and characterisation of the clinical, imaging, and laboratory findings of $GABA_B$-R autoimmune encephalitis.

Aggressive treatment with immunosuppression is warranted in the event of suspected $GABA_B$-R autoimmune encephalitis, given the high potential for improvement, and the deleterious outcomes in patients who are not treated. None of the untreated patients in the literature have recovered spontaneously. The available data on treatment and response is likely influenced by the tendency to treat more responsive cases with corticosteroid agents alone, and then subsequently add further treatments to the regimen for refractory cases. Patients treated with corticosteroids alone versus IVIg alone did show a more robust treatment response on average (56.2% *vs* 40% complete recovery). However, given the small number of patients, the lack of randomisation, and the retrospective data collection, no definitive conclusions as to the superiority of different immunosuppressive agents can be drawn. Treatment with a combination of chemotherapy and immunosuppression probably implied a poorer oncologic picture, so it is not surprising that response rates were not as favourable in this group. The five-year survival rate of SCLC is less than 10% [24] which ultimately will limit the life expectancy in patients found to have associated SCLC, but immunosuppressive therapies can still often lead to improvement in symptoms attributable to $GABA_B$-R autoimmune encephalitis.

Clinicians should consider a diagnosis of $GABA_B$-R autoimmune encephalitis in patients with new onset refractory seizures with associated SCLC with or without ataxia, even in the absence of CSF pleocytosis. It would be best to assess both serum and CSF samples, but CSF has the higher yield of detection based on available data. In adult patients with suspected or confirmed $GABA_B$-R autoimmune encephalitis, an initial chest CT to screen for SCLC is appropriate [25]. However, if chest CT is negative with positive serum or CSF $GABA_B$-R antibodies, whole body PET-scan is indicated, as this has been demonstrated to be superior to CT alone when screening for occult neoplasm in the setting of paraneoplastic antibodies [25, 26]. While the youngest patient on record with associated SCLC was 42 years of age, it is reasonable to screen younger adults found to have $GABA_B$-R antibodies, given the high oncologic association, close to 50%. If a neoplasm is discovered, oncology consultation should be sought so that appropriate oncological therapies can be administered [22, 27]. In the event that a neoplasm is not identified on initial screening, we recommend following the screening guidelines drawn up by the European Federation of Neurological Societies [25].

Future directions

An area for potential future study could be assessing the effectiveness of different types of AEDs in cases of $GABA_B$-R associated epilepsy, particularly those cases with status epilepticus. Further long-term cognitive outcome follow-up data is also needed. Additionally, as more cases are reported, the understanding of the epidemiology and clinical characteristics of $GABA_B$-R autoimmunity will continue to increase.

Ethical approval was not necessary for preparation of this article.

This publication was prepared without any external sources of funding.

References:

1. Dalmau J, Tüzün E, Wu Hy, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007; 61(1): 25–36, doi: 10.1002/ana.21050, indexed in Pubmed: 17262855.
2. Gable MS, Sheriff H, Dalmau J, et al. The frequency of autoimmune N-methyl-D-aspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis. 2012; 54(7): 899–904, doi: 10.1093/cid/cir1038, indexed in Pubmed: 22281844.
3. Lancaster E, Lai M, Peng X, et al. Antibodies to the GABAB receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. The Lancet Neurology. 2010; 9(1): 67–76, doi: 10.1016/s1474-4422(09)70324-2.
4. Boronat A, Sabater L, Saiz A, et al. GABA(B) receptor antibodies in limbic encephalitis and anti-GAD-associated neurologic disorders. Neurology. 2011; 76(9): 795–800, doi: 10.1212/WNL.0b013e31820e7b8d, indexed in Pubmed: 21357831.
5. Höftberger R, Titulaer MJ, Sabater L, et al. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. Neurology. 2013; 81(17): 1500–1506, doi: 10.1212/WNL.0b013e3182a9585f, indexed in Pubmed: 24068784.
6. Guan HZ, Ren HT, Yang XZ, et al. Limbic Encephalitis Associated with Anti-γ-aminobutyric Acid B Receptor Antibodies: A Case Series

from China. Chin Med J (Engl). 2015; 128(22): 3023–3028, doi: 10.4103/0366-6999.168989, indexed in Pubmed: 26608981.
7. Onugoren MD, Deuretzbacher D, Haensch CA, et al. Limbic encephalitis due to GABABand AMPA receptor antibodies: a case series. Journal of Neurology, Neurosurgery & Psychiatry. 2014; 86(9): 965–972, doi: 10.1136/jnnp-2014-308814.
8. Benarroch EE. GABAB receptors: structure, functions, and clinical implications. Neurology. 2012; 78(8): 578–584, doi: 10.1212/WNL.0b013e318247cd03, indexed in Pubmed: 22351795.
9. Fritschy JM, Meskenaite V, Weinmann O, et al. GABAB-receptor splice variants GB1a and GB1b in rat brain: developmental regulation, cellular distribution and extrasynaptic localization. Eur J Neurosci. 1999; 11(3): 761–768, indexed in Pubmed: 10103070.
10. Schuler V, Lüscher C, Blanchet C, et al. Epilepsy, hyperalgesia, impaired memory, and loss of pre- and postsynaptic GABA(B) responses in mice lacking GABA(B(1)). Neuron. 2001; 31(1): 47–58, indexed in Pubmed: 11498050.
11. Dalmau J, Geis C, Graus F. Autoantibodies to Synaptic Receptors and Neuronal Cell Surface Proteins in Autoimmune Diseases of the Central Nervous System. Physiological Reviews. 2017; 97(2): 839–887, doi: 10.1152/physrev.00010.2016.
12. Kim TJ, Lee ST, Shin JW, et al. Clinical manifestations and outcomes of the treatment of patients with GABAB encephalitis. J Neuroimmunol. 2014; 270(1-2): 45–50, doi: 10.1016/j.jneuroim.2014.02.011, indexed in Pubmed: 24662003.
13. Chen X, Liu F, Li JM, et al. Encephalitis with antibodies against the GABAB receptor: seizures as the most common presentation at admission. Neurological Research. 2017; 39(11): 973–980, doi: 10.1080/01616412.2017.1351062.
14. Alexopoulos H, Dagklis IE, Akrivou S, et al. Autoimmune encephalitis with GABAB antibodies, thymoma, and GABAB receptor thymic expression. Neurol Neuroimmunol Neuroinflamm. 2014; 1(4): e39, doi: 10.1212/NXI.0000000000000039, indexed in Pubmed: 25364773.
15. Jarius S, Steinmeyer F, Knobel A, et al. GABAB receptor antibodies in paraneoplastic cerebellar ataxia. J Neuroimmunol. 2013; 256(1-2): 94–96, doi: 10.1016/j.jneuroim.2012.12.006, indexed in Pubmed: 23332614.
16. DeFelipe-Mimbrera A, Masjuan J, Corral Í, et al. Opsoclonus-myoclonus syndrome and limbic encephalitis associated with GABAB receptor antibodies in CSF. J Neuroimmunol. 2014; 272(1-2): 91–93, doi: 10.1016/j.jneuroim.2014.04.009, indexed in Pubmed: 24814391.
17. Wells EM, Dalmau J. Paraneoplastic neurologic disorders in children. Curr Neurol Neurosci Rep. 2011; 11(2): 187–194, doi: 10.1007/s11910-010-0169-4, indexed in Pubmed: 21161703.
18. Kruer MC, Hoeftberger R, Lim KY, et al. Aggressive course in encephalitis with opsoclonus, ataxia, chorea, and seizures: the first pediatric case of γ-aminobutyric acid type B receptor autoimmunity. JAMA Neurol. 2014; 71(5): 620–623, doi: 10.1001/jamaneurol.2013.4786, indexed in Pubmed: 24590315.
19. Chen X, Liu F, Li JM, et al. Encephalitis with antibodies against the GABA receptor: seizures as the most common presentation at admission. Neurol Res. 2017; 39(11): 973–980, doi: 10.1080/01616412.2017.1351062, indexed in Pubmed: 28974152.
20. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013; 12(2): 157–165, doi: 10.1016/S1474-4422(12)70310-1, indexed in Pubmed: 23290630.
21. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 2008; 7(12): 1091–1098, doi: 10.1016/S1474-4422(08)70224-2, indexed in Pubmed: 18851928.
22. Graus F. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain. 2001; 124(6): 1138–1148, doi: 10.1093/brain/124.6.1138.
23. Escudero D, Guasp M, Ariño H, et al. Antibody-associated CNS syndromes without signs of inflammation in the elderly. Neurology. 2017; 89(14): 1471–1475, doi: 10.1212/WNL.0000000000004541, indexed in Pubmed: 28878050.
24. Kalemkerian GP. Small Cell Lung Cancer. Semin Respir Crit Care Med. 2016; 37(5): 783–796, doi: 10.1055/s-0036-1592116, indexed in Pubmed: 27732999.
25. Titulaer MJ, Soffietti R, Dalmau J, et al. European Federation of Neurological Societies. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. Eur J Neurol. 2011; 18(1): 19–e3, doi: 10.1111/j.1468-1331.2010.03220.x, indexed in Pubmed: 20880069.
26. McKeon A, Apiwattanakul M, Lachance DH, et al. Positron emission tomography-computed tomography in paraneoplastic neurologic disorders: systematic analysis and review. Arch Neurol. 2010; 67(3): 322–329, doi: 10.1001/archneurol.2009.336, indexed in Pubmed: 20065123.
27. Mundiyanapurath S, Jarius S, Probst C, et al. GABA-B-receptor antibodies in paraneoplastic brainstem encephalitis. J Neuroimmunol. 2013; 259(1-2): 88–91, doi: 10.1016/j.jneuroim.2013.04.004, indexed in Pubmed: 23628208.

REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 1, pages: 8–17
DOI: 10.5603/PJNNS.a2019.0001

ISSN 0028–3843

Neurosurgical cadaveric and in vivo large animal training models for cranial and spinal approaches and techniques — a systematic review of the current literature

Cezar Octavian Morosanu[1], Liviu Nicolae[1], Remus Moldovan[2], Alexandru Stefan Farcasanu[3], Gabriela Adriana Filip[2], Ioan Stefan Florian[4]

[1]Department of Neurosurgery, Southmead Hospital, North Bristol NHS Trust, Bristol, UK
[2]Department of Physiology, Iuliu Hatieganu University of Medicine and Pharmacy, Romania
[3]Faculty of Physics, Babes-Bolyai University, Cluj-Napoca, Romania
[4]Department of Neurosurgery, Iuliu Hatieganu University of Medicine and Pharmacy, Romania

ABSTRACT

Introduction. Due to its high complexity, neurosurgery consists of a demanding learning curve that requires intense training and a deep knowledge of neuroanatomy. Microsurgical skill development can be achieved through various models of simulation, but as human cadaveric models are not always accessible, cadaveric animal models can provide a reliable environment in which to enhance the acquisition of surgical dexterity. The aim of this review was to analyse the current role of animal brains in laboratory training and to assess their correspondence to the procedures performed in humans.

Material and methods. A Pubmed literature search was performed to identify all the articles concerning training cranial and spinal techniques on large animal heads. The search terms were 'training model', and 'neurosurgery' in association with 'animal', 'sheep', 'cow', and 'swine'. The exclusion criteria were articles that were on human brains, experimental fundamental research, or on virtual simulators.

Results. The search retrieved 119 articles, of which 25 were relevant to the purpose of this review. Owing to their similar neuroanatomy, bovine, porcine and ovine models prove to be reliable structures in simulating neurosurgical procedures. On bovine skulls, an interhemispheric transcalosal and retrosigmoid approach along with different approaches to the Circle of Willis can be recreated. Ovine model procedures have varied from lumbar discectomies on sheep spines to craniosynostosis surgery, whereas in ex vivo swine models, cadaveric dissections of lateral sulcus, median and posterior fossa have been achieved.

Conclusions. Laboratory training models enhance surgical advancements by familiarising trainee surgeons with certain neuroanatomical structures and promoting greater surgical dexterity. The accessibility of animal brains allows trainee surgeons to exercise techniques outside the operating theatre, thus optimising outcomes in human surgical procedures.

Key words: cadaveric, training, neurosurgical model, large animals
(*Neurol Neurochir Pol 2019; 53 (1): 8–17*)

Introduction

Neurosurgery, through its various approaches and techniques, requires a refinement of surgical skills that can only be achieved through continuous practice. Consequently, the necessity for training structures is essential in the understanding of the anatomical background on which surgical steps are constituted. Cadaveric human heads have the disadvantage of

Address for correspondence: Cezar Octavian Morosanu, Deparment of Neurosurgery Southmead Hospital, Bristol, e-mail: cezaroctavian.morosanu@yahoo.com

being inaccessible to every institution due to ethical considerations. However, animal models are characterised by a high feasibility in cost-efficient reproducibility. Consistent practice pays large dividends in the operating theatre.

Education in medical training in the past decade has undergone various metamorphoses, reaching a point where virtual reality can be accessed to train surgical gestures. But the value of biologic material is irreplaceable since it is the only one which provides genuine hands-on training on a texture that is similar to human tissue. Ruminant and porcine models have been successfully used to recreate operations of high fidelity in the neurosurgical field. In a comparative study, Sidhu et al. [1] revealed that training on biological tissues was more efficient for gaining fine motor skills than on synthetic devices. Furthermore, certain studies have acknowledged the deficit in educating surgical skills in certain areas. For instance, Boszczyk et al. looked into the competence of European neurosurgical trainees in spine surgery, and drew attention to confidence issues in the management of spinal trauma and various approaches. In any domain requiring dexterity, it is vital for novices to practice basic techniques in order to train their striatum/cerebellar based functions [2].

The rationale behind our review was to answer the question as to whether cadaveric animal models play a role in the cerebral and spinal surgical learning curve. In order to understand the current knowledge about training models, the aim was to gather all the information available in the literature to establish the current status of neurosurgical simulation in cadaveric animal brains. The hypothesis was that animal models have a high impact on trainee activity and development and are an adequate replacement for human cadavers. This would give them a potential role in the curricula of trainees.

Material and methods

Our review was structured with the PRIMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology [3] and comprises an analysis of the past 15 years on articles referring to training techniques on cadaveric animal cephalic extremities or spines. The search terms were a combination of 'training model' and 'neurosurgery' with 'animal' OR 'sheep' OR 'cow' OR 'swine'.

Eligibility criteria

Only manuscripts that were articles in English were taken into consideration. Inclusion criteria were the description of cranial and spinal procedures that were simulated on ex vivo and in vivo material that had been obtained from veterinary-controlled facilities. All studies that evaluated live surgery in fundamental research, biomechanical experiments on nonliving tissues, case reports, veterinary studies or any other article that described procedures with any purpose other than surgical training were excluded. Furthermore, anatomical research was not relevant to the purpose of this review.

Literature search

Comprehensive literature searches were performed on Pubmed and Google Scholar, using a timeframe from 2003 to 2018 and the results were imported to EndNote X5.

Study selection

The criteria for study selection focused on the set of techniques. Abstracts and in extenso papers were verified for information regarding any method of training with the primary target of improving surgical procedures.

There were certain exclusion criteria taken into consideration such as the publication of abstracts only, letters, comments, reviews, or meta-analyses; animal studies; languages other than English; duplicate studies; veterinary purposes; aspects related to comparative anatomy, artificial material or virtual reality or human cadaveric training models. Furthermore, any other training model in a non-neurosurgical field such as otology or rhinology was excluded. After removing excluded abstracts, full articles were obtained and studies were screened once again more thoroughly, using the same exclusion criteria (Fig. 1).

Data collection process and data items

The analysis was undertaken by two reviewers independently (COM and LN) and any discrepancy was solved through a consensus. Data regarding the year of the study, the name of the first author, the type of animal model used, and the procedure used for training were collected.

The literature search revealed 119 articles of interest, of which 25 were deemed suitable for inclusion (Tab. 1).

Results

The search retrieved 119 articles, 25 of which were in accordance with our criteria. There appears to be an increased interest in ovine heads generating accurate models, both for spinal and cranial procedures. Bovine heads, both injected with silicone and fresh from butchery, carry the advantage of having large anatomical elements that have greater visibility under the microscope. The only in vivo model was a porcine head used to assess competency in bone drilling, dissecting the brain and preserving cerebral vessels under microscopic magnification.

Ovine models

Due to their particular anatomy and size, sheep (*Ovis aries*) have been used as experimental large animal models in a multitude of specialities in biomedical research varying from orthopedics for biomaterial implants [4] to cardiovascular surgery [5]. In terms of neuroanatomical similarities, sheep exhibits many resemblances to the human regarding electroencephalographic elements [6], neuroradiological features [7] (Fig. 2, Fig. 3), functional imaging [8], neurovascular structure [9] as well as sleep homeostasis [10], making it an

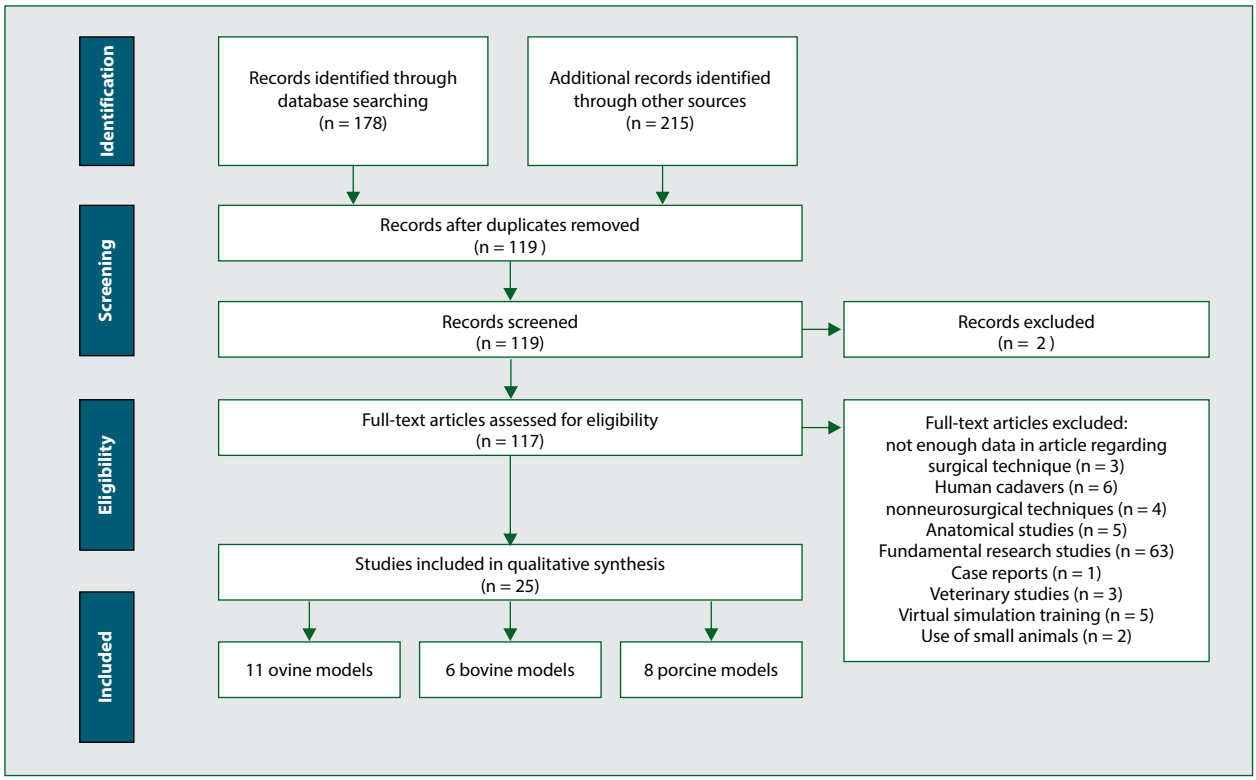


Figure 1. PRISMA 2009 Flow Diagram. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

excellent specimen in translational neuroscience. Cadaveric sheep brains (Fig. 4) provide very accurate teaching material for mammalian cerebral anatomy and are highly accessible to everyone to learn the homologous neural structures through careful dissection [11]. Several neurosurgical techniques have been attempted to enhance knowledge and familiarity with certain cranial approaches. Hamamcioglu et al. (2008) described a four-step laboratory dissection under the operating microscope of cranial nerves in the posterior fossa. Positioned in the lateral side, a 3x3 cm craniectomy was performed in the ovine skull in the right paramedian suboccipital bone. Access to the cerebellomedulary cistern and cerebellopontine angle was done through the retraction of the right cerebellar lobe medially. This permits the dissection of the right cranial nerves and nerves VII to IV. This step was followed by the opening of the right lateral cerebellomedullary cistern with an arachnoid knife and a pair of microscissors and dissection of the lower cranial nerves IX to XII using appropriate instruments such as bipolar forceps and suction tube. Identification of the right cerebellopontine angle and cranial nerves V, VII and VIII. The last step has the potential of training in the field of trigeminal decompression identifying the necessary elements and placing a small piece of plastic sheet between the trigeminal nerve and the vessel [12].

Another ovine cranial approach is the one focusing on orbital surgery simulation proposed by Altunrende et al. [13] that could prove an effective manner of training both for neurosurgeons as well as for ophthalmologists. The superior orbitotomy approach and the frontal intracranial approach have been described and divided into different surgical steps. The orbitotomy starts with a subperiostal periorbital dissection aiming to remove the superior orbital margin and roof, which allows access to the retroocular structures, with a rongeur. The second procedure permits the visualisation of the optic nerve and the optic canal through a 3x3 cm craniectomy in the frontal bone. After opening the dura in a semicircular manner, the dissection of the sylvian fissure, carotid and basal cisterns and the optic nerve in the anterior skull base can be performed. The optic canal was unroofed using a rongeur, and the optic nerve was exposed. Although the topographic anatomy and the size of the ovine orbit are different in certain aspects, the model can be easily used to aid training in orbital surgery.

In the field of paediatric neurosurgery, training in the area of craniosynostosis can be very useful in familiarizing the surgical trainee in the operative steps, the thickness of the calvarial and facial bone being similar to that found in paediatric patients. The craniofacial procedure was designed in three steps and can be used to understand the surgical options in cases of anterior plagiocephaly, trigonocephaly, and brachycephaly. After performing the subperiosteal and subperiorbital dissection, the bifrontal craniotomy is commenced. The

Table 1. Literature focused on specified animal anatomical regions

Year	Author	Cadaveric model	Organ	Procedure
2003	Borucki et al.	Pig	Brain	Endoscopy in the cerebellopontine angle
2005	Kalayci et al.	Sheep	Spine	Lumbar discectomy
2006	Hicdonmez et al.	Cow	Brain	Approach to the Circle of Willis
2006	Hicdonmez et al.	Sheep	Brain	Craniosynostosis surgery
2006	Hamamcioglu et al.	Cow	Brain	Interhemispheric-transcallosal approach
2008	Hamamcioglu et al.	Sheep	Brain	Posterior fossa and cranial nerves dissection
2009	Walker et al.	Deer	Spine/Skull	Minimally invasive spinal surgery/Calvarium drilling
2011	Olabe et al.	Pig	Brain	Aneurysm surgery
2011	Anderson et al.	Calf	Spine	Dural repair
2012	Suslu et al.	Sheep	Spine	Pedicle screw fixation
2012	Suslu et al.	Sheep	Spine	Transforaminal epidural injection
2013	Suslu et al.	Cow	Brain	Retrosigmoid approach
2014	Suslu et al.	Sheep	Spine	Lumbar microdiscectomy
2014	Aurich et al.	Pig	Brain	Various cortical dissections
2014	Altunrende et al.	Sheep	Brain	Orbital and optic nerve dissection
2014	Silva et al.	Pig	Brain	Skull base endoscopy and microsurgery
2014	Vavruska	Sheep	Brain	Intraoperative brain ultrasound
2015	Kamp et al.	Sheep	Brain	Tumour dissection
2015	Smith et al.	Sheep	Spine	Perfused spine dissections
2015	Regelsberger et al.	Pig	Brain	In vivo sulcal, transcortical dissection
2016	Gragnaniello et al.	Sheep	Spine	Spinal mass
2017	Cuellar et al.	Pig	Spine	Endoscopic interlaminar discectomy
2018	Gokyar et al.	Cow	Brain	Bilateral sylvian cisterns, interhemispheric fissure, and hemispheric sulcus dissection
2018	Hanrahan et al.	Pig	Brain	Dura mater suturing
2018	Hanrahan et al.	Pig	Brain	Intracranial bolt insertion

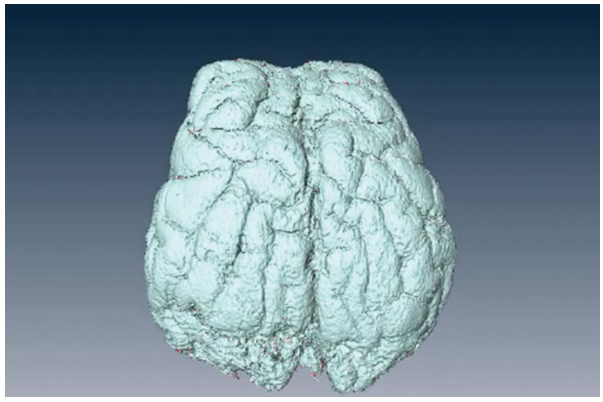


Figure 2. MRI 3D reconstruction of a sheep brain – superior view

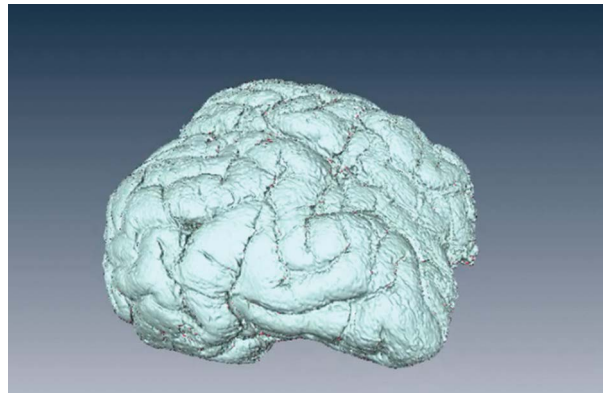


Figure 3. MRI 3D reconstruction of a sheep brain – lateral view

supraorbital bar is separated from the dura and osteotomies aid in its separation from the orbital roof and nasal midline. The last step implies the reconstruction of the forehead. This is done with appropriate fixation from plates and screws and involves advancing the supraorbital bar and positioning it in the proper anatomy [14]. Compared to virtual simulators [15], the model is cheaper, easy to manouevre, and does not require any complex technological instrumentation. It should be noted that despite the fact that human cadaveric models are much more suitable for training, there has not yet been described

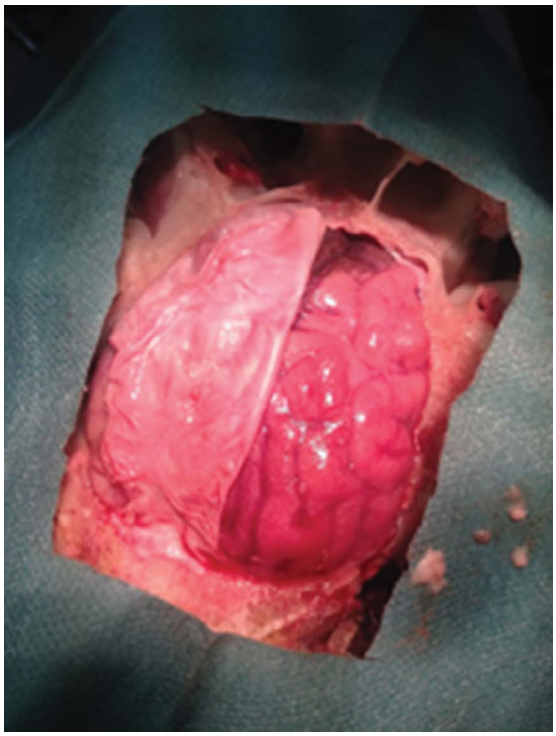


Figure 4. Dissection of cadaveric sheep head

a model in the literature that can achieve the development of surgical skills on a paediatric skull.

There have also been attempts to determine a model suitable for neuro-oncological training, to enhance surgical dexterity in handling cerebral tissue and distinguishing it from abnormal anatomy. Thus, Kamp et al. (2015) recreated cerebral masses in cadaveric sheep brains using an agar-agar and ink solution that was injected subcortically through an 18 gauge needle. With proper instrumentation such as a surgical microscope, an ultrasound device and a CUSA (ultrasonic tissue ablation system), a corticotomy and gyrus dissection were performed in order to reach the targeted tumour. Although it is an in vitro design, it can assist us greatly in our understanding of the preservation of eloquent areas in oncological surgery. The model was assessed by two senior neurosurgeons, five phycians and ten medical students, receiving good and very good overall feedback [16]. A collection of procedures that could prove to be highly useful in the laboratory was also designed by Sabel M. [17]. These include basic principles of planning a procedure, craniotomy skills using a coconut, familiarisation with the microscopic field where sutures can be enhanced on chicken wings, subpial resection and tumour resection on a synthetic model. To aid certain approaches to such a pathology, intraoperative ultrasound is frequently used to assess the position of the tumour. Training in this regard has been explored by Vavruska et al. [18], who evaluated the sheep brain with a transducer and identified similar structures to the human brain.

In terms of spinal surgery, lumbar discectomy was experimented by Kalayci et al. [19] and a model of lumbar microdiscectomy was proposed by Suslu et al. (2014) on ovine spines under fluoroscopic guidance. Sheep lumbar intervertebral discs have proven to have similar levels of water content, collagen percentage and fibre orientation to those in human, collagen percentage and fibre orientation angles to their human counterparts [20]. In Suslu's study, exposure of the lumbar spine was carried out through an incision in the median fascia and dissection of the paravertebral muscles from the lamina in a subperiosteal plane. Using the operating microscope, the microdiscectomy was carried out through a partial hemilaminectomy, preserving the epidural fat and the ligamentum flavum. The ligament was dissected away from the dura and eventually removed laterally to visualise the nerve root and the pedicle. The posterior longitudinal ligament was afterwards incised after retracting the thecal sac with the nerve roots and the disc was removed [21].

In addition, the same author performed two other spinal procedures on sheep spines, namely a percutaneous lumbar transforaminal epidural injection [22], and a laboratory pedicular screw fixation [23]. The epidural injection is a procedure through which a steroid is injected into the intervertebral foramen, and it is used for lumbar disc pathology with intense pain. It requires a good understanding of the anatomy of the region, and a cadaveric model can provide the resources to identify them. Suslu et al. (2012) described a four-step technique in which a 22 gauge needle is inserted percutaneously in the ovine spine through the neural foramen with the help of anteroposterior and oblique fluoroscopic images. After checking that the needle is in the proper position, lateral to the 6 o'clock site under the lumbar pedicle, 2 mL of non-ionic contrast material is injected to assess the contrast spread along the epidural space.

The other method innovated by Suslu et al. (2011) was the laboratory pedicular screw fixation. This technique first requires the identification of the main pedicle landmarks. Under C-arm fluoroscopy, a Kerrison rongeur is used to decorticate the bone followed by the manual insertion of a handled awl in the vertebral body through the centre of the pedicle. After taking appropriate precautions, a 4.5 mm diameter and 35 mm length screw is positioned in the tunnel formed in the vertebral structures. This relatively straightforward method can be easily learned, and, in improving the experience of spinal surgery trainees, will ultimately lead to fewer neurologic injuries due to screw misplacements and better surgical outcomes.

There has also been a perfused spine model described by Smith et al. (2015) in a rural setting. The main vessels were ligated, catheterised and connected to a pump and the subdural space was filled with SALF water, thus simulating the qualities of a living tissue. The training techniques utilized here consist of watertight dural suturing and leak repair [24]. In terms of more complex spine surgery, the mass effect related pathology, such as the one seen in tumours, has been documented by

Gragnaniello et al. [25] who in 2016 described a fluoroscopic injection with Stratathane resin ST-504 into an ovine spine, thus creating a similar spinal lesion.

Bovine models

The anatomy of the central nervous system of domestic cattle has been less studied in comparison with other species [26]. Ruminant brains in general have a similar organisation, with differences involving the architecture of the insula, of the diencephalon, the arrangement of the gyri in the cortex as well as the position of the visual and olfactory systems [27]. The neuromorphology of bovines is very similar to that of sheep, and the imagistic particularities can be used in translational research due to their structure [28]. Given their weight and structure, their brains can be successfully used in neurodegenerative disease investigations [29]. The angioanatomy has certain particularities. The vascular structure supply of the arterial circle of the brain, for example, in the Bos genus, is done mainly by the maxillary artery through a particular anatomical element identified as the *paired* rostral epidural rete mirabile. The *unpaired* caudal epidural rete mirabile contributes to the circle of the brain from vertebral and occipital arteries, thus making it a characteristic trait in these animals [30].

One of the procedures that can be performed on bovine heads is the interhemispheric-transcallosal approach to the lateral ventricle, which simulates in a very accurate manner the surgical steps performed in humans. This consists of four steps, each corresponding to a part of the human intervention allowing the visualisation of the callosomarginal and pericallosal arteries, as well as the cingulate gyrus. The first step is a paramedian craniectomy and the retraction of the frontoparietal lobe. This develops an access point to enhance the dissection of the callosomarginal arteries and the corpus callosum. Opening the corpus callosum and eventually entering the ventricle can reveal further neuroanatomical elements, such as the choroid plexus or the foramen of Monro, and also vascular structures such as the septal and thalamostriate veins [31].

Another bovine microneurosurgical model that has been successfully assessed by Hicdonmez et al. (2006) is a procedure that aimed to coordinate surgical steps in order to perform an adapted pterional approach towards the circle of Willis. Hicdonmez, too, utilized a four step approach, in four stages as well, starting with access to the carotid and chiasmatic cisterns by retraction of the right frontal lobe. The optic nerve, the rostral/anterior cerebral artery and the medial cerebral artery can also be viewed in this point. The nomenclature used for the anterior cerebral artery in bovine vascular anatomy is 'rostral cerebral artery'; the term 'posterior cerebral artery' is replaced by 'caudal cerebral artery' and the frontal lobe is known as the 'rostral lobe'. Other elements that can be observed after opening the chiasmatic cistern are the optic chiasm, the anterior communicating artery complex, the internal ethmoidal artery and the corresponding A1 of the anterior cerebral artery in the human brain. The dissection of the internal carotid artery is carried out in order to identify the trajectory of various vessels and located medially to it is the pituitary stalk. The authors simulated a clipping of the exit segment of the caudal communicating artery from the internal carotid artery, and this proved highly significant in mimicking the conditions in which aneurysm surgery is performed [32].

The retrosigmoid approach was also achieved on a silicone injected cow brain by Suslu et al. (2013) who accessed the cerebellopontine angle (CPA) and exemplified the anatomical elements that can be encountered in such a procedure. The experimental design allowed an enhanced understanding of neurostructures through the red and blue silicone injected in the major vessels. Visualisation of the right cerebellar lobe was made possible through a right paramedian suboccipital craniectomy. The lobe was retracted medially and the cistern was opened through gentle dissection. The right CPA and cranial nerves VII and VIII were identified. This was followed by the opening of the lateral cerebellomedullary cistern which revealed the IX, X, XI and XII cranial nerves from the brainstem [33].

In a more recent study, cerebral dissection on cow brains was also achieved by Gokyar et al. [34] who dissected bilaterally the sylvian cisterns, as well as the interhemispheric fissure and hemispheric sulcus.

Bovine models have been found to be of use in spinal procedures, as well. A calf spinehas has proven useful in recreating dural repairs [35], while a deer model has been tested in a nontransparent Plexiglass frame for minimally invasive spinal surgery and assessed by surgical trainees who noticed encouraging results [36].

Porcine models

Swine models have been a useful tool in general digestive laparoscopic surgery [37], urology [38], maxillofacial surgery [39], paediatric surgery [40] and oculoplastics [41] for a long time. There have also been comparative studies that aimed to evaluate the effectiveness of both human cadaveric and pig models. These identified higher relevance in swines for tissue handling and the ability to dissect anatomical planes [42]. Their use in neurosurgery has been increasing because there are numerous similarities to the human cerebrum [43]. Magnetic resonance imaging in pigs has revealed impressive equivalences [44, 45], permitting various introspections in the field of deep brain stimulation [46] as well as in neurovascular research [47].

Various cranial procedures have been investigated both in vivo and ex vivo. In the nonliving head, the interhemispheric fissure can be dissected, allowing the inspection of the cingulate gyrus, callosomarginal and pericallosal arteries. This also accesses the corpus callosum through which the lateral ventricle and the foramen of Monro could be visualised in the context of a transcallosal approach. Middle fossa dissection enabled the identification of the middle meningeal arteries and the V2, V3 branches of the trigeminal nerve. The optic nerve

and the carotid artery were observed through an approach in the lateral sulcus. The cerebellopontine angle was evaluated through instrumentations to the cerebellum, and the brainstem was carefully dissected to expose the fourth ventricle and cranial nerves [48].

Furthermore, Silva et al. [49] achieved microsurgical and endoscopic procedures on a nonliving swine head, managing to perform a transnasal approach and a middle and posterior fossa dissection, thus demonstrating the similarities between human and pig anatomical areas.

In pig models, suturing the dura mater was a skill that was trained under the microscope in a more recent study performed by Hanrahan et al. [50]. In this swine model, the authors investigated the effect that anxiety has on hand tremor, assessing dexterity through the Johnson O'Connor Tweezer Test and anxiety through the Westside Test Anxiety Scale. Their conclusion was that tremor does not interfere with the ability to suture the dura and that confidence plays a major role in our task performance.

Another technique that was investigated by the same author on swine models was the insertion of an intracranial pressure monitor in an ex vivo pig head. This was done with the aim of developing an interest among medical students in neurosurgery. A Codman hand drill, an intracranial pressure monitor and a transducer were the instruments used on the cadaveric specimen, and the training was accompanied by lectures related to the pathophysiology of raised pressure in the cranium [51].

Although not cadaveric models, it is relevant to discuss in vivo models that have been successful in developing surgical skills for the sole purpose of exemplifying the usefulness of animals in training young neurosurgeons. Compared to other models, pigs seem to have unique qualities that render them excellent in in vivo practice. Regelsberger et al. (2015) used living pigs to perform neurosurgical procedures, to establish microsurgical principles in order to work under the surgical microscope, to manoeuvre neurosurgical instruments in a living brain, and to control bleeding during tissue handling. Certain aspects were trained such as the proper use of surgical equipment in a craniotomy, the basics of cerebral sulcal, transcortical, parenchymal and subpial tissue dissection, the management of sinusoidal, subarachnoid or intracerebral bleeding through various techniques, and dural repair. Due to its realistic laboratory set up, the course was widely appreciated by the participants, and the management of complications that occurred on a living brain was an important key learning point for neurosurgical physicians, an element that has an immense advantage over cadaveric models [52].

Aneurysm surgery was also experimented in swine by inducing this vascular pathology on 1-2 months old domestic pigs. A bifurcation aneurysm was created by two arteries and one vein, and then sulfuric acid was applied to contribute to the fragility of the vessel. The experiment created 22 aneurysms in different locations simulating situations such as thrombosis or rupture. Clipping techniques were trained as well as vascular reconstruction in emergency circumstances [53].

Another living animal model was used by Borucki et al. (2003) in performing a neuroendoscopic procedure in pigs. The aim was to expose the cerebellopontine angle through the retrosigmoid approach, training surgical steps that are valuable in acoustic neuroma surgery [54].

Experimental spinal surgery on pigs was only attempted by Cuellar et al. [55], who successfully managed to operate an endoscopic interlaminar discectomy.

Discussion

The role of laboratory cadaveric and non-cadaveric animal dissection is quintessential in developing surgical skills to be able to practice microneurosurgical interventions on patients. The purpose of this review was to elaborate on collection of all the known methods of animal model training and assess their effectiveness in harnessing important abilities in the management of surgical patients. Apart from temporal bone dissection, all current animal neurosurgical procedures were reviewed. Techniques such as temporal bone drilling, although valuable to the neurosurgeon, are mostly used in ENT training courses and vary from training on chicken eggs [56] to 3D printed models [57]. Swine models are frequent examples in this kind of technique [58], and sheep temporal bones have also been used [59], but there is a multitude of experimental designs that have proven their utility. A very insightful review on this topic was published by Bergin et al. [60] which identified 11 animal models that can be used for middle ear surgery, as well as Wiet et al. [61] who researched otologic training models.

Human cadavers are the most accurate training models. Working on cadavers has the advantages of enhancing the visualisation of the anatomy that the neurosurgeon will have to face during any surgical intervention. The limitations are clearly the costs of keeping, and the difficulties in obtaining, human cadavers, as well as the ethical quandaries that are particular to the legislation of each country. Despite all of these obstacles, the educational benefit is indisputable. There have also been attempts to perfuse cadavers to bring about a more realistic approach in human brains such as endoscopic skull base procedures [62] or aneurysm surgery [63].

Live animals compared to nonliving animals have clear advantages. However, in familiarizing the neurosurgical trainee to the anatomical background, cadaveric models prove equally as important. Identifying anatomical elements of the ovine, bovine or porcine brain and spine helps better understanding of human anatomy. Maneoeuvring different components with microinstruments familiarises the trainee with surgical conditions, and allows the development of their dexterity in working with fragile neurostructures.

Surgical workshops on live animals must have local approvals and meet adequate requirements both from an ethical

and veterinary point of view. Local laws and animal research codes of practice have to be followed. There needs to be a clear justification for the use of animals and a careful assessment if the education goals can be met by other means (e.g. cadaveric, simulation workshops). The participants require an appropriate postgraduate level of training to maximize their benefit. During these workshops, adequate veterinary supervision is mandatory to ensure monitoring and maintaining anaesthesia to minimise any animal suffering.

In the context of ethics, there are some limitations on the use of bovine anatomical elements in training in countries such as India, or the use of porcine models in the Middle East due to cultural issues, meaning that there is a need to consider other animal options.

The disadvantage of cadaveric brains is that there is no indicator of haemorrhage, whereas managing haemostasis is an important aspect of any operation. In this context, pigs are the only animals cited in the literature to have had neurosurgical training procedures done in in vivo conditions.

Another risk that is related to sheep and cow central nervous tissue is that of contracting ovine or bovine spongiform encephalopathy. However, although this issue is present, it is highly unlikely that such a pathology will be encountered if the head specimens are sourced from a unit that is under veterinary supervision.

Training in nonliving brains has an important impact on surgical experience. A survey done on 100 neurosurgery programmes in the USA evaluated the prevalence, particularities and extent of laboratory dissection in different departments across the country. The courses varied from one to six sessions annually, with an active participation of trainee surgeons from years 2 to 6, covering topics such as cranial, spinal and neuroendoscopy approaches to cadavers or virtual reality simulators. These courses are regarded as very important, and the results of the questionnaire revealed that 89.2% of doctors would support a national dissection curriculum and manual [64].

So, rather than being occasional courses carried out by national or international societies, animal cadaver courses could be implemented as important hands-on workshops on a regular basis in the training of surgeons.

Conclusions

Animal models provide highly valuable experience for those training to be neurosurgeons. Although there are various obstacles to overcome such as anatomical differences, enhancing surgical skills on animal brains can improve performance on the operating table. Ovine, bovine as well as porcine cerebrums and spines are usually easily obtained. This subsequently makes them ideal material for mimicking surgical procedures. Furthermore, frequent workshops and operative courses on these models should be popularised during surgical training to help trainees develop a better comprehension of neuroanatomy and better neurosurgical outcomes.

Declaration of interest

There are no conflicts of interest. We do not have a financial relationship to the work, neither have we received any other form of financial support, nor any government or company grants or research support.

Acknowledgements

The authors wish to thank the significant contribution of Mr. Dan Priscu and Dr. Adelina Priscu in proofreading the article.

References

1. Sidhu RS, Park J, Brydges R, et al. Laboratory-based vascular anastomosis training: a randomized controlled trial evaluating the effects of bench model fidelity and level of training on skill acquisition. J Vasc Surg. 2007; 45(2): 343–349, doi: 10.1016/j.jvs.2006.09.040, indexed in Pubmed: 17264015.
2. Haase J, Boisen E. Neurosurgical training: more hours needed or a new learning culture? Surg Neurol. 2009; 72(1): 89–95; discussion 95, doi: 10.1016/j.surneu.2009.02.005, indexed in Pubmed: 19559933.
3. Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Medicine. 2009; 6(7): e1000097, doi: 10.1371/journal.pmed.1000097.
4. Sartoretto SC, Uzeda MJ, Miguel FB, et al. SHEEP AS AN EXPERIMENTAL MODEL FOR BIOMATERIAL IMPLANT EVALUATION. Acta Ortop Bras. 2016; 24(5): 262–266, doi: 10.1590/1413-785220162405161949, indexed in Pubmed: 28149193.
5. DiVincenti L, Westcott R, Lee C. Sheep (Ovis aries) as a model for cardiovascular surgery and management before, during, and after cardiopulmonary bypass. J Am Assoc Lab Anim Sci. 2014; 53(5): 439–448.
6. Opdam HI, Federico P, Jackson GD, et al. A sheep model for the study of focal epilepsy with concurrent intracranial EEG and functional MRI. Epilepsia. 2002; 43(8): 779–787, indexed in Pubmed: 12180994.
7. Boltze J, Förschler A, Nitzsche B, et al. Permanent middle cerebral artery occlusion in sheep: a novel large animal model of focal cerebral ischemia. J Cereb Blood Flow Metab. 2008; 28(12): 1951–1964, doi: 10.1038/jcbfm.2008.89, indexed in Pubmed: 18698332.
8. Lee W, Lee SD, Park MY, et al. Functional and diffusion tensor magnetic resonance imaging of the sheep brain. BMC Vet Res. 2015; 11: 262, doi: 10.1186/s12917-015-0581-8, indexed in Pubmed: 26467856.
9. Hoffmann A, Stoffel MH, Nitzsche B, et al. The ovine cerebral venous system: comparative anatomy, visualization, and implications for translational research. PLoS One. 2014; 9(4): e92990, doi: 10.1371/journal.pone.0092990, indexed in Pubmed: 24736654.
10. Perentos N, Martins AQ, Cumming RJM, et al. An EEG Investigation of Sleep Homeostasis in Healthy and CLN5 Batten Disease Affected Sheep. J Neurosci. 2016; 36(31): 8238–8249, doi: 10.1523/JNEUROSCI.4295-15.2016, indexed in Pubmed: 27488642.
11. Grisham W. Resources for teaching Mammalian neuroanatomy using sheep brains: a review. J Undergrad Neurosci Educ. 2006; 5(1): R1–R6, indexed in Pubmed: 23495310.

12. Hamamcioglu MK, Hicdonmez T, Tiryaki M, et al. A laboratory training model in fresh cadaveric sheep brain for microneurosurgical dissection of cranial nerves in posterior fossa. Br J Neurosurg. 2008; 22(6): 769–771, doi: 10.1080/02688690802477573, indexed in Pubmed: 19085361.
13. Altunrende ME, Hamamcioglu MK, Hıcdonmez T, et al. Microsurgical training model for residents to approach to the orbit and the optic nerve in fresh cadaveric sheep cranium. J Neurosci Rural Pract. 2014; 5(2): 151–154, doi: 10.4103/0976-3147.131660, indexed in Pubmed: 24966554.
14. Hicdonmez T, Parsak T, Cobanoglu S. Simulation of surgery for craniosynostosis: a training model in a fresh cadaveric sheep cranium. Technical note. J Neurosurg. 2006; 105(2 Suppl): 150–152, doi: 10.3171/ped.2006.105.2.150, indexed in Pubmed: 16922078.
15. Coelho G, Warf B, Lyra M, et al. Anatomical pediatric model for craniosynostosis surgical training. Childs Nerv Syst. 2014; 30(12): 2009–2014, doi: 10.1007/s00381-014-2537-x, indexed in Pubmed: 25183390.
16. Kamp MA, Knipps J, Steiger HJ, et al. Training for brain tumour resection: a realistic model with easy accessibility. Acta Neurochir (Wien). 2015; 157(11): 1975–81; discussion 1981, doi: 10.1007/s00701-015-2590-6, indexed in Pubmed: 26407857.
17. Sabel M. Getting Ready for Brain Tumor Surgery Paperback. Thieme 2016: Thieme.
18. Vavruska J, Buhl R, Petridis AK, et al. Evaluation of an intraoperative ultrasound training model based on a cadaveric sheep brain. Surg Neurol Int. 2014; 5: 46, doi: 10.4103/2152-7806.130314, indexed in Pubmed: 24818053.
19. Kalayci M, Cagavi F, Gül S, et al. A training model for lumbar discectomy. J Clin Neurosci. 2005; 12(6): 673–675, doi: 10.1016/j.jocn.2004.12.004, indexed in Pubmed: 16054364.
20. Reid JE, Meakin JR, Robins SP, et al. Sheep lumbar intervertebral discs as models for human discs. Clin Biomech (Bristol, Avon). 2002; 17(4): 312–314, indexed in Pubmed: 12034126.
21. Suslu HT, Tatarli N, Karaaslan A, et al. A practical laboratory study simulating the lumbar microdiscectomy: training model in fresh cadaveric sheep spine. J Neurol Surg A Cent Eur Neurosurg. 2014; 75(3): 167–169, doi: 10.1055/s-0032-1330114, indexed in Pubmed: 23397126.
22. Suslu H. A practical laboratory study simulating the percutaneous lumbar transforaminal epidural injection: training model in fresh cadaveric sheep spine. Turk Neurosurg. 2012; 22(6): 701–705, doi: 10.5137/1019-5149.JTN.5899-12.2, indexed in Pubmed: 23208900.
23. Turan Suslu H, Tatarli N, Hicdonmez T, et al. A laboratory training model using fresh sheep spines for pedicular screw fixation. Br J Neurosurg. 2012; 26(2): 252–254, doi: 10.3109/02688697.2011.619598, indexed in Pubmed: 22087885.
24. Smith A, Gagliardi F, Pelzer NR, et al. Rural neurosurgical and spinal laboratory setup. J Spine Surg. 2015; 1(1): 57–64, doi: 10.3978/j.issn.2414-469X.2015.09.02, indexed in Pubmed: 27683680.
25. Gragnaniello C, Abou-Hamden A, Mortini P, et al. Complex Spine Pathology Simulator: An Innovative Tool for Advanced Spine Surgery Training. J Neurol Surg A Cent Eur Neurosurg. 2016; 77(6): 515–522, doi: 10.1055/s-0036-1583940, indexed in Pubmed: 27367357.
26. Zimmerl U. Il sistema nervoso. In: Bossi V, Caradonna GB, Spampani G. ed. Trattato di Anatomia veterinaria, Vol 3. Vallardi, Milano 1909: 4–294.
27. Schmidt MJ, Langen N, Klumpp S, et al. A study of the comparative anatomy of the brain of domestic ruminants using magnetic resonance imaging. Vet J. 2012; 191(1): 85–93, doi: 10.1016/j.tvjl.2010.12.026, indexed in Pubmed: 21277239.
28. Schmidt MJ, Pilatus U, Wigger A, et al. Neuroanatomy of the calf brain as revealed by high-resolution magnetic resonance imaging. J Morphol. 2009; 270(6): 745–758, doi: 10.1002/jmor.10717, indexed in Pubmed: 19123244.
29. Ballarin C, Povinelli M, Granato A, et al. The Brain of the Domestic Bos taurus: Weight, Encephalization and Cerebellar Quotients, and Comparison with Other Domestic and Wild Cetartiodactyla. PLoS One. 2016; 11(4): e0154580, doi: 10.1371/journal.pone.0154580, indexed in Pubmed: 27128674.
30. Zdun M, Frąckowiak H, Kiełtyka-Kurc A, et al. The arteries of brain base in species of Bovini tribe. Anat Rec (Hoboken). 2013; 296(11): 1677–1682, doi: 10.1002/ar.22784, indexed in Pubmed: 24106047.
31. Hicdonmez T, Hamamcioglu MK, Parsak T, et al. A laboratory training model for interhemispheric-transcallosal approach to the lateral ventricle. Neurosurg Rev. 2006; 29(2): 159–162, doi: 10.1007/s10143-005-0014-4, indexed in Pubmed: 16374648.
32. Hicdonmez T, Hamamcioglu MK, Tiryaki M, et al. Microneurosurgical training model in fresh cadaveric cow brain: a laboratory study simulating the approach to the circle of Willis. Surg Neurol. 2006; 66(1): 100–4; discussion 104, doi: 10.1016/j.surneu.2005.09.027, indexed in Pubmed: 16793460.
33. Turan Suslu H, Ceylan D, Tatarlı N, et al. Laboratory training in the retrosigmoid approach using cadaveric silicone injected cow brain. Br J Neurosurg. 2013; 27(6): 812–814, doi: 10.3109/02688697.2013.772095, indexed in Pubmed: 23458576.
34. Gökyar A, Cokluk C. Using of Fresh Cadaveric Cow Brain in the Microsurgical Training Model for Sulcal-Cisternal and Fissural Dissection. J Neurosci Rural Pract. 2018; 9(1): 26–29, doi: 10.4103/jnrp.jnrp_390_17, indexed in Pubmed: 29456341.
35. Anderson PA. Surgical simulation: Dural repair. http://www.cns.org/publications/cnsq/pdf/CNSQ_11summer.pdf (2014 Sep 08).
36. Walker JB, Perkins E, Harkey HL. A novel simulation model for minimally invasive spine surgery. Neurosurgery. 2009; 65(6 Suppl): 188–195, doi: 10.1227/01.NEU.0000341534.82210.1B.
37. La Torre M, Caruso C. The animal model in advanced laparoscopy resident training. Surg Laparosc Endosc Percutan Tech. 2013; 23(3): 271–275, doi: 10.1097/SLE.0b013e31828b895b, indexed in Pubmed: 23751991.
38. He B, Musk GC, Mou L. Laparoscopic surgery for orthotopic kidney transplant in the pig model. J Surg Res. 2013; 184(2): 1096–1101, doi: 10.1016/j.jss.2013.03.015.
39. Mardas N, Dereka X, Donos N, et al. Experimental model for bone regeneration in oral and cranio-maxillo-facial surgery. J Invest Surg. 2014; 27(1): 32–49, doi: 10.3109/08941939.2013.817628, indexed in Pubmed: 23957784.
40. Esposito C, Escolino M, Draghici I, et al. Training Models in Pediatric Minimally Invasive Surgery: Rabbit Model Versus Porcine Model: A Comparative Study. J Laparoendosc Adv Surg Tech A. 2016; 26(1): 79–84, doi: 10.1089/lap.2015.0229, indexed in Pubmed: 26619331.
41. Zou C, Wang JQ, Guo X, et al. Pig eyelid as a teaching model for severe ptosis repair. Ophthalmic Plast Reconstr Surg. 2012; 28(6): 472–474, doi: 10.1097/IOP.0b013e31826a5146, indexed in Pubmed: 23138217.
42. Stefanidis D, Yonce TC, Green JM, et al. Cadavers versus pigs: which are better for procedural training of surgery residents outside the OR?

Surgery. 2013; 154(1): 34–37, doi: 10.1016/j.surg.2013.05.001, indexed in Pubmed: 23809483.
43. Sauleau P, Lapouble E, Val-Laillet D, et al. The pig model in brain imaging and neurosurgery. Animal. 2009; 3(8): 1138–1151, doi: 10.1017/S1751731109004649, indexed in Pubmed: 22444844.
44. Conrad MS, Dilger RN, Johnson RW. Brain growth of the domestic pig (Sus scrofa) from 2 to 24 weeks of age: a longitudinal MRI study. Dev Neurosci. 2012; 34(4): 291–298, doi: 10.1159/000339311, indexed in Pubmed: 22777003.
45. Conrad MS, Sutton BP, Dilger RN, et al. An in vivo three-dimensional magnetic resonance imaging-based averaged brain collection of the neonatal piglet (Sus scrofa). PLoS One. 2014; 9(9): e107650, doi: 10.1371/journal.pone.0107650, indexed in Pubmed: 25254955.
46. Gorny KR, Presti MF, Goerss SJ, et al. Measurements of RF heating during 3.0-T MRI of a pig implanted with deep brain stimulator. Magn Reson Imaging. 2013; 31(5): 783–788, doi: 10.1016/j.mri.2012.11.005, indexed in Pubmed: 23228310.
47. Habib CA, Utriainen D, Peduzzi-Nelson J, et al. MR imaging of the yucatan pig head and neck vasculature. J Magn Reson Imaging. 2013; 38(3): 641–649, doi: 10.1002/jmri.24003, indexed in Pubmed: 23348984.
48. Aurich LA, Silva Junior LF, Monteiro FM, et al. Microsurgical training model with nonliving swine head. Alternative for neurosurgical education. Acta Cir Bras. 2014; 29(6): 405–409, indexed in Pubmed: 24919051.
49. Silva L, Aurich L, Monteiro F, et al. Microsurgical and Endoscopic Training Model with Nonliving Swine Head: New Alternative for Skull Base Education. Journal of Neurological Surgery Part B: Skull Base. 2014; 75(S 01), doi: 10.1055/s-0034-1370596.
50. Hanrahan J, Sideris M, Pasha T, et al. Hands train the brain-what is the role of hand tremor and anxiety in undergraduate microsurgical skills? Acta Neurochir (Wien). 2018; 160(9): 1673–1679, doi: 10.1007/s00701-018-3609-6, indexed in Pubmed: 29968093.
51. Hanrahan J, Sideris M, Tsitsopoulos P, et al. Increasing motivation and engagement in neurosurgery for medical students through practical simulation-based learning. Annals of Medicine and Surgery. 2018; 34: 75–79, doi: 10.1016/j.amsu.2018.08.002.
52. Regelsberger J, Eicker S, Siasios I, et al. In vivo porcine training model for cranial neurosurgery. Neurosurg Rev. 2015; 38(1): 157–63; discussion 163, doi: 10.1007/s10143-014-0572-4, indexed in Pubmed: 25240530.
53. Olabe J, Olabe J, Roda J. Microsurgical cerebral aneurysm training porcine model. Neurol India. 2011; 59(1): 78–81, doi: 10.4103/0028-3886.76872, indexed in Pubmed: 21339668.
54. Borucki Ł, Szyfter W. [Evaluation of an animal model in endoscopic surgery of the cerebello-pontine angle]. Otolaryngol Pol. 2003; 57(3): 385–388, indexed in Pubmed: 14524182.
55. Cuéllar G, Rugeles J. ENDOSCOPIC INTERLAMINAR DISCECTOMY. USE OF SWINE CADAVERS AS A TRAINING MODEL. Coluna/Columna. 2017; 16(2): 116–120, doi: 10.1590/s1808-185120171602147361.
56. Meléndez García JM, Araujo Da Costa AS, Rivera Schmitz T, et al. Temporal bone dissection practice using a chicken egg. Otol Neurotol. 2014; 35(6): 941–943, doi: 10.1097/MAO.0000000000000390, indexed in Pubmed: 24841916.
57. Mowry SE, Jammal H, Myer C, et al. A Novel Temporal Bone Simulation Model Using 3D Printing Techniques. Otol Neurotol. 2015; 36(9): 1562–1565, doi: 10.1097/MAO.0000000000000848, indexed in Pubmed: 26375979.
58. Garcia L, Andrade J, Testa J. Anatomical study of the pigs temporal bone by microdissection. Acta Cirurgica Brasileira. 2014; 29(suppl 3): 77–80, doi: 10.1590/s0102-86502014001700014.
59. Gurr A, Stark T, Probst G, et al. [The temporal bone of lamb and pig as an alternative in ENT-education]. Laryngorhinootologie. 2010; 89(1): 17–24, doi: 10.1055/s-0029-1224158, indexed in Pubmed: 19691010.
60. Bergin M. Systematic review of animal models of middle ear surgery. World Journal of Otorhinolaryngology. 2013; 3(3): 71, doi: 10.5319/wjo.v3.i3.71.
61. Wiet GJ, Sørensen MS, Andersen SA. Otologic Skills Training. Otolaryngol Clin North Am. 2017; 50(5): 933–945, doi: 10.1016/j.otc.2017.05.005, indexed in Pubmed: 28822580.
62. Pham M, Kale A, Marquez Y, et al. A Perfusion-based Human Cadaveric Model for Management of Carotid Artery Injury during Endoscopic Endonasal Skull Base Surgery. J Neurol Surg B Skull Base. 2014; 75(5): 309–313, doi: 10.1055/s-0034-1372470, indexed in Pubmed: 25301092.
63. Aboud E, Aboud G, Al-Mefty O, et al. "Live cadavers" for training in the management of intraoperative aneurysmal rupture. Journal of Neurosurgery. 2015; 123(5): 1339–1346, doi: 10.3171/2014.12.jns141551.
64. Kshettry VR, Mullin JP, Schlenk R, et al. The role of laboratory dissection training in neurosurgical residency: results of a national survey. World Neurosurg. 2014; 82(5): 554–559, doi: 10.1016/j.wneu.2014.05.028, indexed in Pubmed: 24875190.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 1, pages: 18–25
DOI: 10.5603/PJNNS.a2018.0001

ISSN 0028–3843

Spatial distribution of white matter degenerative lesions and cognitive dysfunction in relapsing-remitting multiple sclerosis patients

Natalia Nowaczyk[1], Alicja Kalinowska-Łyszczarz[2], Włodzimierz Paprzycki[3], Sławomir Michalak[2], Radosław Kaźmierski[4], Mikołaj A. Pawlak[4]

[1] Department of Health Psychology and Clinical Psychology, Institute of Psychology, Adam Mickiewicz University in Poznan, Poland
[2] Division of Neurochemistry and Neuropathology, Department of Neurology, Poznan University of Medical Sciences (PUMS), 49 Przybyszewskiego Street, Poznan, Poland
[3] Department of Neuroradiology, Poznan University of Medical Sciences, Poland
[4] Department of Neurology and Cerebrovascular Disorders, Poznan University of Medical Sciences, L. Bierkowski Hospital, Poznan, Poland

ABSTRACT

Aim. The aim of this study was to assess degenerative lesion localisation in the course of relapsing-remitting multiple sclerosis (RRMS) and to identify the association between localisation and the frequency of T1-hypointense lesions (black holes) with cognitive dysfunction. We also searched for neuroradiological predictors of cognitive dysfunction in patients. The clinical rationale for the study was previous research, and our own findings suggest that lesion localisation plays an important role in cognitive performance and neurological disability of MS patients.

Material and methods. Forty-two patients were included in the study. All subjects underwent neuropsychological examination using Raven's Coloured Progressive Matrices, a naming task from the Brief Repeatable Battery of Neuropsychological Tests, and attention to detail tests. Magnetic resonance imaging (MRI) was acquired on 1.5 Tesla scanner and black holes were manually segmented on T1-weighted volumetric images using the FMRIB Software Library. Linear regression was applied to establish a relationship between black hole volume per lobe and cognitive parameters. Bonferroni correction of voxelwise analysis was used to correct for multiple comparisons.

Results. The following associations between black hole volume and cognition were identified: frontal lobes black hole volume was associated with phonemic verbal fluency ($t = -4.013$, $p < 0.001$), parietal black hole volume was associated with attention ($t = -3.776$, $p < 0.001$), and parietal and temporal black hole volumes were associated with nonverbal intelligence ($p < 0.001$). The volume of parietal black holes was the best predictor of cognitive dysfunction.

Conclusions. Our approach, including measurement of focal axonal loss based on T1-volumetric MRI sequence and brief neuropsychological assessment, might improve personalised diagnostic and therapeutic decisions in clinical practice.

Key words: relapsing-remitting multiple sclerosis (RRMS), T1-hypointense lesions, black holes, magnetic resonance imaging (MRI), cognitive dysfunction

(*Neurol Neurochir Pol 2019; 53 (1): 18–25*)

Address for correspondence: Natalia Nowaczyk, Department of Health Psychology and Clinical Psychology, Institute of Psychology, Adam Mickiewicz University in Poznan, Szamarzewskiego 89, 60-568 Poznan, Poland, e-mail: natalia.nowaczyk@amu.edu.pl

Introduction

Multiple sclerosis (MS) is the most common autoimmune disease of the central nervous system (CNS) in young adults. It is defined as a chronic neuroinflammatory and neurodegenerative disease, which in its most typical course leads to relapses and remissions of various neurological symptoms, resulting from focal demyelinating lesions of the CNS [1]. Magnetic resonance imaging (MRI) is a key tool in MS diagnosis, monitoring, measuring treatment response and predicting disability. While disease activity is usually related to T2 or FLAIR hyperintense white matter lesions, or gadolinium enhancing T1 lesions, the neurodegenerative aspect of MS is represented by T1 hypointense lesions with high water content. These are called black holes [2]. Depending on the degree of neuronal damage, black holes can be classified as persistent, transitional or slowly evolving lesions [3–4]. Some of the focal degenerative changes may be transformed into persistent black holes [2, 5–6]. Early evolution of severe neurodegenerative lesions indicates more aggressive and rapidly disabling disease [7].

Currently, treatment guidelines do not address the occurrence of new black holes as an indication to escalate therapy, despite the fact that those lesions are irreversible and over time are followed by brain atrophy. Black holes represent complete demyelination with irreversible axonal damage on the focal level. As such, they are likely to contribute to disease progression, which has been shown in several studies [8–9]. Also, their clinical relevance may be reflected by their associations with other MRI parameters (lower supratentorial and infratentorial brain volume) [10], clinical data (disease duration, score of EDSS) [10–11] and cognitive impairment [12].

In the course of multiple sclerosis, 40–70% of patients develop cognitive dysfunction [13]. The most commonly observed deficits related to MS include executive dysfunction, low verbal fluency, and difficulties in visuospatial performance, short-term memory, abstract reasoning and attention [14–15]. These may be accompanied or related to depression or general fatigue. Several MRI parameters have been correlated with cognitive dysfunction in MS patients. While total white matter T2 lesion volume load is a modest correlate for MS- related cognitive impairment [16], measures of neurodegeneration, including brain atrophy, are stronger predictors of cognitive dysfunction [17–18]. These measures include black holes, but also other MRI parameters that correlate with cognitive dysfunction and clinical markers of disability, such as fractional anisotropy (FA) or mean diffusivity (MD) coefficient, derived from diffusion tensor imaging (DTI) methods [19]. Similar results have been obtained by using functional MRI or magnetisation transfer (MT) imaging [20]. These techniques, although potentially superior, require additional scanning time and advanced post-processing, which makes black holes assessment a more feasible yet reliable method.

The purpose of the present study was to assess the spatial distribution of MS-related white matter neurodegenerative lesions and its association with cognitive impairment, focusing on the following domains: nonverbal intelligence, attention, and phonemic verbal fluency. We hypothesised there is an association between localisation and the frequency of black holes and examined cognitive functions, and that black holes in the brain lobes are predictors of cognitive functioning.

Clinical rationale for the study

Early detection of neurodegenerative changes in multiple sclerosis should prompt a change in patient therapy. However, current treatment guidelines do not indicate any specific actions based on detection of new black holes. We evaluated the relationship between black holes in selected cortical regions of the brain and the severity of cognitive deficits.

The complete extent of brain damage cannot be estimated without a precise neurocognitive assessment. Neglecting the cognitive component of patient dysfunction might result in missing an important insight into disease progression, and the main reason behind the decline of quality of life in young individuals with MS.

Materials and methods

Cohort characteristics

Forty-two patients (25 women, 17 men) with relapsing-remitting multiple sclerosis fulfilling the 2010 McDonald criteria [21] at the time of diagnosis were recruited for the study. The mean disease duration was 5.6 years (range 0–24). Four patients were diagnosed at the time of inclusion into the study, while the longest time since diagnosis was 24 years in one patient. Age and EDSS measures are presented in Table 1. Thirty six percent of patients had obtained higher education. Significant comorbidities were found in three subjects: bronchial asthma (n = 2) and ulcerative colitis (n = 1). Beck Depression Inventory (BDI) scores ranged from 0 to 39 (median = 7, interquartile range, IQR = 1-12). Exclusion criteria included: current relapse stage or relapse within the last eight weeks, immunomodulatory therapy in the last year, age older than 65 years, concomitant psychiatric disease, current use of neuroleptics or antiepileptic drugs, alcohol or drug abuse, diagnosis of another autoimmune or neoplastic pathology, relevant motor deficit in the dominant hand, upper limb ataxia or loss of visual acuity, and dementia. The neurological, MRI and neuropsychological examinations were all performed within a one month period. Patients treated with intravenous steroids within the previous three months, or immunomodulation at any point before baseline assessment, were not included in the study.

Procedure

All subjects underwent a neurological examination, psychometric assessment and MRI examination. Psychometric tests used for the assessment of cognition included:

— Raven's Coloured Progressive Matrices (RCPM; non-verbal intelligence) [22]

- Attention to detail test (attention) [23]
- Spontaneous word list generation test, which is a modified version of phonemic naming task from Brief Repeatable Battery of Neuropsychological Tests (phonemic verbal fluency).

Structural MRI was performed on 1.5 Tesla MRI scanner (Siemens Avanto, Erlangen, Germany), with the use of Magnetisation Prepared Rapid Acquisition Gradient Echo (MPRAGE, TR = 2400 ms, TE = 3.61 ms, IR = 1000 ms, slice thickness 1.2 mm, pixel band width 180 Hz, FOV 240 × 240 mm, voxel size 1.25 × 1.25 × 1.20 mm) and FLAIR space sequence (TR = 6000ms, TE = 359 ms, IR = 2200ms, slice thickness 1.5 mm, pixel band width 930 Hz, FOV 227 × 260 mm, voxel size 1.01×1.01×1.50mm).

Structural analysis of T1-weighted sequences was performed with the use of FSL (FMRIB Software Library, https://fsl.fmrib.ox.ac.uk/fsl; version 5.0.6) [24] installed on Linux (Ubuntu 16.04 LTS). The analysis included: manually segmenting black holes by a reader blinded to clinical status, reproduction of manual segmentation after four weeks, and Bland-Altman assessment of intra-rater reproducibility. Probabilistic brain MNI152 atlas included in the FSL package was registered to each patient using *flirt* and black hole volume from each lobe was extracted using the *fslstats* tool.

Manual segmentation allowed the creation of masks of the black holes (dark area in T1-weighted sequences). Detailed detection of images was possible with the use of the *fslview* tool. Before the brain extraction procedure, the masks of degenerative changes in white matter were created by using the *fslview* and *fslmerge* (to concatenate the images) technique.

Secondly, brain and structure extraction were performed by the *fslroi* command and Brain Extraction Tool (BET) of FSL. *Fslroi* command allows extraction of a selected region of the brain based on the determination of the size values of individual axes. BET methods were needed to delete non-brain tissue from images of the whole head. We also estimated the inner and outer skull surfaces, and outer scalp surfaces, for good quality T1 input images. Two parameters were used: the force threshold (f = 0.44) and the gradient threshold (g = 0). The level of the force threshold was optimised. The duration of the brain extraction process was up to one minute.

A registration process was necessary to fit extracted scans and masks to the MN152 atlas of the FSL program. Before masks registration, the binarisation procedure (masks value = 1, other brain structure = 0, default value of threshold) was conducted using the *fslmaths* technique. In our linear registration, the parameters were set on 12 degrees of freedom (three rotations, three translations, three scales, and three warps), the cost function (such as mutual information), and three-linear interpolation. The result of this affine transformation process was a linear transformation matrix needed to receive standard images nearing to the atlas template. After the registration, the masks and scans were matched using the *ApplyXFM* option.

Brain lobes were selected based on the structural atlas MN152 of brain template images. Automated image registration algorithms were used to align brain MRI images with the target image [25]. By using the MN152 brain atlas (the volumetric coordinate system created by averaging MRI scans of 152 people) it was possible to analyse nine anatomical structures: frontal, parietal, occipital and temporal lobes, thalamus, insula, caudate, putamen and cerebellum. For the result of linear registration for each scan, see Figure 1.

Statistical analysis

Non-parametric mapping software (NPM) was used to analyse all scans with fitted plaques' masks in the MNI152 atlas. In cases of binarised masks, we used a Voxel Based Morphometry (VBM) technique in MRICRON ver. 2012 software. We calculated statistical maps for each cognitive dysfunction and black hole spatial distribution. Each variable was evaluated using a Shapiro-Wilk normality test. Normally distributed variables

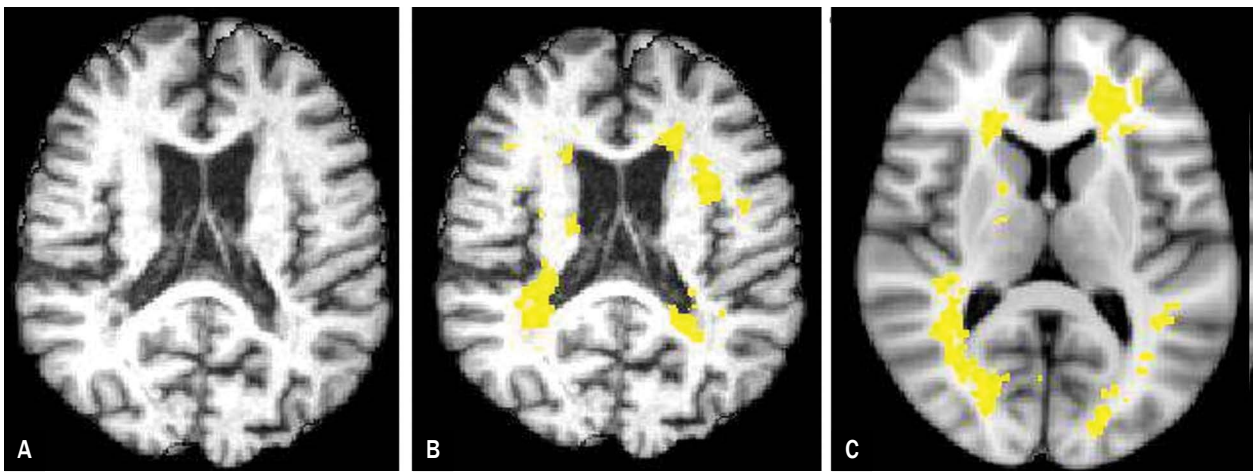


Figure 1. A linear registration of multiple sclerosis plaques and scans of axial brain section in magnetic resonance imaging (MRI): (**A**) extracted brain, (**B**) extracted brain after linear registration with prepared masks, (**C**) previous image fitted to the MNI152 atlas

were summarised using mean and standard deviation. For non-normally distributed continuous variables, median and interquartile range (IQR) were calculated. Finally, linear regression analysis and stepwise regression analysis were conducted to identify associations between black hole volume per lobe and cognitive dysfunctions. BPF was calculated according to the formula: grey and white matter volume / total intracranial volume derived from FSL FAST. We applied Bonferroni correction for multiple comparisons. We also calculated Spearman's correlation coefficients for BPF and global black hole volume. Statistical analyses were performed using the RCRAN statistical environment (www.r-project.org) and the RStudio 1.1.453 graphical interface.

Results

Descriptive statistics for variables in the study

The descriptive statistics for all the measured variables are presented in Table 1.

Table 1. Descriptive statistics for clinical data of the examined group

Variable	Median(IQR) or *Mean(SD)	Range
Age	*39.55 (11.3)	18–63
EDSS	1.00 (0–2.0)	0–6
Cognitive functions		
Phonemic verbal fluency	*20.05 (4.38)	12–31
Nonverbal intelligence	33 (30–35)	20–36
Attention	7 (5–8)	1–8
Volumetric measurements		
BPF	*0.77 (0.03)	0.70–0.85
Spatial distribution of black hole load per lobe [cm^3]		
Frontal lobes	0.62 (0.18–2.39)	0.00–15.23
Parietal lobes	1.10 (0.09–3.45)	0.00–15.63
Temporal lobes	0.06 (0.00–0.63)	0.00–17.21
Occipital lobes	0.26 (0.00–1.71)	0.00–10.00
All MS plaques	7.02 (1.82–16.48)	0.21–87.05

Spatial distribution of degenerative lesions

Lesion distribution maps for nonverbal intelligence, phonemic verbal fluency and attention are represented in Figure 2.

Lobar black hole lesion load

Spatial heterogeneity of black hole location limits the clinical interpretation of the VBM results. Therefore, we calculated black hole lesion load for each lobe and conducted stepwise regression to identify the lobe where the lesion load was the best predictor of cognitive dysfunction.

Stepwise linear regression performed using black hole lesion load identified parietal lobe damage as the main predictor of cognitive dysfunction for each domain. Parietal lesion load predicted 2 to 29% of variance in the cognitive functioning. Detailed results are presented in Table 2. BPF did not correlate with total black hole lesion load (*rho* = -0.161, $p = 0.348$), but there was a correlation with the temporal black hole load (*rho* = -0.344, $p = 0.040$). No significant differences ($p > 0.05$) of the volumetric parameters were found for gender or level of education in the studied MS cohort.

Discussion

We found that in RRMS cohort parietal lobe black hole lesion load was predicting cognitive dysfunction for each evaluated domain: attention, phonemic verbal fluency, and nonverbal intelligence. The role of the parietal lobe is focused on multimodal information integration, which is crucial for intelligence and attention control. Both these functions are frequently impaired in multiple sclerosis patients [26]. We observed the highest lesion load in parietal lobes, and the lowest in occipital lobes. The results of voxel-wise analysis identified lesions associated with dysfunction in other structures as well. Specifically, attention deficit was associated with caudate lesions, and nonverbal intelligence and phonemic verbal fluency deficits were associated with frontal lobe lesions.

In previous studies, the incidence of black holes explained disharmonious cognitive and emotional processing in MS [27]. The location of degenerative white matter lesions can be associated with subsequent development of atrophy in distant brain regions [28–31].

Most of the published studies have focused on the relationship between black holes and neurological disability measured with the EDSS scale [32]. However, black holes are also associated with cognitive dysfunction [33]. This aspect has been underestimated and only a few studies have provided detailed analysis of this association [16]. In one study, T1 hypointense lesions were shown to correlate with Stroop test performance [34]. In another study, which analysed cognitive event-related potentials (ERPs), white matter degenerative lesion volume was associated with semantic and phonemic verbal fluency [14]. Both the Stroop test and the verbal fluency test require high performance in executive functions. This suggests that spatial distribution of degenerative white matter lesions could influence executive functions and other cognitive domains, including attention or auditory processing [35]. Similar results were found by Hojjat et al. [12]. According to their study, there were regional perfusion associations with cognitive dysfunction.

As for the choice of the psychometric tests, we used easily accessible tools that could be applied in everyday clinical practice. Following the literature, we decided to assess cognitive functions that had already been described as being affected in the course of MS [36], namely attention, which we measured with the use of an attention to detail test [23], and non-verbal intelligence (involving the visuo-spatial processes), which we assessed with Raven's Coloured Progressive Matrices [22]. To assess the

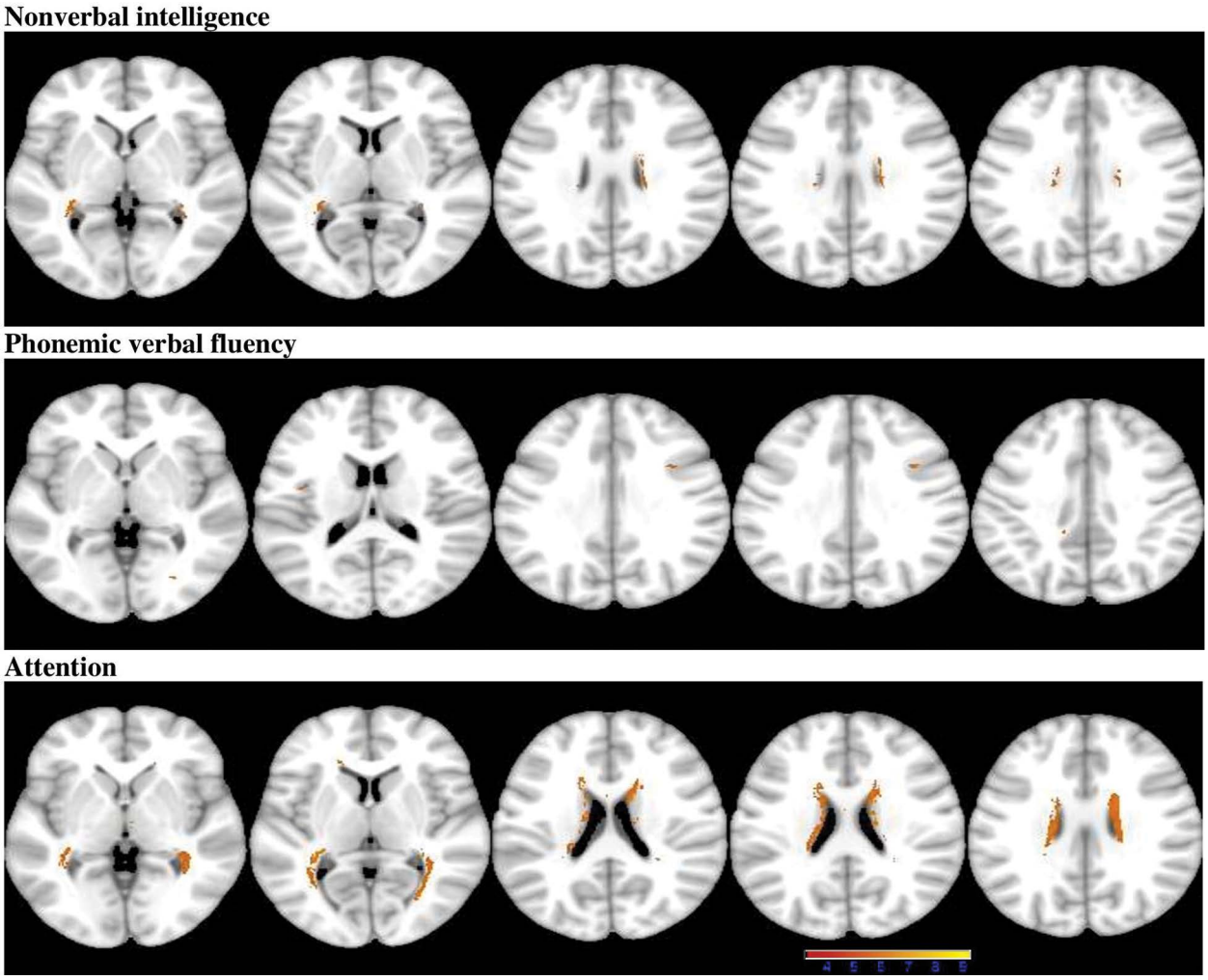


Figure 2. Statistical maps of black hole distribution for each cognitive function computed using Voxel Based Morphometry (VBM) analysis (Brunner-Munzel z statistics). Lesions are overlaid on the Montreal Neurological Institute (MNI) brain in axial slices. Colored voxels were -log of the p value ($p < 0.05$). The equivalent of Bonferroni-corrected threshold was 5.112 and the equivalent of BM threshold was 3.1734.

phonemic verbal fluency we used a modified version of the Word List Generation (WLG), which is a phonemic naming task in the original BRB-N [37]. WLG is a semantic verbal fluency test. In our study, we decided to measure one type of verbal fluency. Phonemic verbal fluency, which consists in generating words for a given letter in a minute, requires higher efficiency of executive functions than semantic fluency [38–40].

Individual lesions in multiple sclerosis always run the chance of damaging critical infrastructure and causing widespread dysfunction of structures distant to the lesion. This is often hard to prove because of low lesion burden per studied group. To solve that problem, grouping lesions based on atlas information might confer meaningful and easy-to-obtain information for every clinician. Modern image processing software is perfectly capable of producing a black hole lesion report per lobe, which in turn conveys the risk of cognitive dysfunction.

As for our methodological approach, the advantage of conducting linear registration using FMRIB's Linear Image Registration Tools (FLIRT) is that it may be fully automated, although it is significant to analyse the default values of the parameters. Also, according to Tam et al. [41] the assessment of the association between black holes volume and clinical parameters will be more precise if unpaired segmentation and paired registration methods are used. Literature data confirm that both fully-automated [42] and semi-automated [43] segmentation methods are justified. Manual lesion segmentation, such as we applied in the current study, is time consuming, and so in clinical practice its usefulness may be limited. Automated methods of black holes analysis are more likely to be used in everyday practice.

In the current study we chose to investigate white matter black holes. While it would be interesting to relate cognitive dysfunction also to cortical lesions in our cohort, this was not possible due to the sequence protocol and magnet field that we

Table 2. Linear regression analysis of T1- weighted black holes in multiple sclerosis patients

Volumes of black holes in brain structures	R^2 adjusted	F	β	t	p
Phonemic verbal fluency					
Frontal lobes	0.269	16.108	-0.536	-4.013	.000
Parietal lobes	0.233	13.476	-0.502	-3.671	.001
Temporal lobes	0.132	7.221	-0.391	-2.687	.010
Occipital lobes	0.039	2.679	-0.251	-1.637	.109
Attention					
Frontal lobes	0.100	5.542	-0.349	-2.354	.024
Parietal lobes	0.244	14.257	-0.513	-3.776	.001
Temporal lobes	0.107	5.895	-0.358	-2.428	.020
Occipital lobes	0.088	4.940	-0.332	-2.223	.032
Nonverbal intelligence					
Frontal lobes	0.195	10.954	-0.464	-3.310	.002
Parietal lobes	0.290	17.732	-0.554	-4.211	.000
Temporal lobes	0.283	17.157	-0.548	-4.142	.000
Occipital lobes	0.098	5.456	-0.346	-2.336	.025

used. Cortical pathology is difficult to visualise in a conventional MRI protocol. Although the value of grey matter pathology has been increasing, as shown by the inclusion of cortical localisation in the latest version of MS criteria [44], it is still largely underestimated due to technical difficulties in their visualisation. Neither T2*-weighted gradient echo nor Double Inversion Recovery (DIR) sequences are routinely available. Also, high-field magnets, which are also more sensitive to cortical pathology, are not at a routine disposal. Nevertheless, cortical lesions have in fact been shown to be associated with cognition and disability in MS patients [45].

Our study is limited by its small, relatively heterogeneous sample size and relatively long and differential disease duration. The sample size was limited by the exclusion criteria, including immunomodulation therapy, which is currently widely available for RRMS and thus the sample size is limited. However, we wanted to avoid the possible influence of immunomodulatory drugs on brain volumetry results. Also, we focused solely on degenerative white matter lesions without taking into account FLAIR lesions and atrophy accumulated over time. This reductionist approach stemmed from the context of this work, which was primarily a masters' thesis of the first author. Another limitation is the choice of basic psychometric tests to assess cognitive dysfunction. However, this could also be a potential advantage, as they can be used without charge or time consumption in an everyday clinical practice setting.

Clinical implications and future directions

The pathophysiological substrate of cognitive dysfunction in MS is not fully understood. Several MRI markers have been suggested as predictors of cognitive impairment. Over recent years, attention has shifted to more and more sophisticated parameters derived from advanced image analysis. In this paper, we are revisiting the aspect of traditional and relatively easily identified T1 hypointense lesions detected on volumetric T1-weighted images as predictors of poor cognitive performance. We suggest that modern image processing software should be used to obtain a black hole lesion mapping report. Such a report could aid in assessing the individual risk of cognitive dysfunction in MS patients, and in selecting the patients for detailed neuropsychological assessment. Also, linking cognitive dysfunction to degenerative white matter lesions could be an important predictor of MS patients' quality of life. It may aid in selecting patients in need of neuropsychological rehabilitation [46].

Studies on a larger sample size and using standardised batteries of neuropsychological tests are needed to enable the use of black hole spatial distribution analysis in everyday clinical practice.

Conflict of interest: *NN and WP: No conflict of interest declared. AKŁ received personal compensation for speaking services and/or travel cost compensation and/or research grants from Biogen, Bayer, Merck Serono, Novartis, Teva Pharmaceuticals, CSL Behring, Shire, Sanofi-Genzyme, Roche. SM received personal compensation for speaking services and/or travel cost compensation and/or research grants from Bayer, TEVA, Novartis, Lundbeck, Biogen Idec and EUROIMMUN. RK received speaking honoraria and/or consultancy fees and/or travel expenses from Actavis, Biogen Idec, Chiesi, Gilead, Novartis, Vertex and Zambon. MAP received speaking honoraria and/or travel engagements and/or research grants from Novartis, Roche, Biogen, Merck, Teva Pharmaceuticals.*

Acknowledgement and financial support: *Alicja Kalinowska-Lyszczarz was supported by National Science Centre grants 2012/05/D/NZ6/00989 and 2012/07/B/NZ6/03529. Mikolaj A. Pawlak was supported by National Science Centre grant 2011/01/D/NZ4/05801. We would like to thank our patients who participated in the study.*

Ethics: *This study was approved by the Internal Review Board at the Poznan University of Medical Sciences. Written informed consent was obtained from all the study participants.*

References

1. Rovira A, Montalban X. MR brain iron mapping in MS: a potential neurodegenerative marker or just another technique? Neurology. 2011; 77(18): 1660–1661, doi: 10.1212/WNL.0b013e318236f120, indexed in Pubmed: 21975201.
2. Sahraian MA, Radue EW, Haller S, et al. Black holes in multiple sclerosis: definition, evolution, and clinical correlations. Acta Neurol Scand. 2010; 122(1): 1–8, doi: 10.1111/j.1600-0404.2009.01221.x, indexed in Pubmed: 20003089.
3. Zhang Y, Traboulsee A, Zhao Y, et al. Texture analysis differentiates persistent and transient T1 black holes at acute onset in multiple sclerosis: a preliminary study. Mult Scler. 2011; 17(5): 532–540, doi: 10.1177/1352458510395981, indexed in Pubmed: 21270058.
4. Elliott C, Wolinsky JS, Hauser SL. Detection and characterisation of slowly evolving lesions in multiple sclerosis using conventional brain MRI. Multiple Sclerosis Journal. 2017; 23: 52–53.
5. Papadopoulou A, von Felten S, Traud S, et al. Evolution of MS lesions to black holes under DNA vaccine treatment. J Neurol. 2012; 259(7): 1375–1382, doi: 10.1007/s00415-011-6361-x, indexed in Pubmed: 22222856.
6. van Walderveen MA, Kamphorst W, Scheltens P, et al. Histopathologic correlate of hypointense lesions on T1-weighted spin-echo MRI in multiple sclerosis. Neurology. 1998; 50(5): 1282–1288, indexed in Pubmed: 9595975.
7. Mitjana R, Tintoré M, Rocca MA, et al. Diagnostic value of brain chronic black holes on T1-weighted MR images in clinically isolated syndromes. Mult Scler. 2014; 20(11): 1471–1477, doi: 10.1177/1352458514526083, indexed in Pubmed: 24576831.
8. Truyen L, Waesberghe Jv, Walderveen Mv, et al. Accumulation of hypointense lesions ("black holes") on T1 spin-echo MRI correlates with disease progression in multiple sclerosis. Neurology. 1996; 47(6): 1469–1476, doi: 10.1212/wnl.47.6.1469.
9. Paolillo A, Coles AJ, Molyneux PD, et al. Quantitative MRI in patients with secondary progressive MS treated with monoclonal antibody Campath 1H. Neurology. 1999; 53(4): 751–757, indexed in Pubmed: 10489036.
10. Paolillo A, Pozzilli C, Gasperini C, et al. Brain atrophy in relapsing-remitting multiple sclerosis: relationship with 'black holes', disease duration and clinical disability. J Neurol Sci. 2000; 174(2): 85–91, indexed in Pubmed: 10727693.
11. Rossi F, Giorgio A, Battaglini M, et al. Relevance of brain lesion location to cognition in relapsing multiple sclerosis. PLoS One. 2012; 7(11): e44826, doi: 10.1371/journal.pone.0044826, indexed in Pubmed: 23144775.
12. Hojjat SP, Cantrell CG, Carroll TJ, et al. Perfusion reduction in the absence of structural differences in cognitively impaired versus unimpaired RRMS patients. Mult Scler. 2016; 22(13): 1685–1694, doi: 10.1177/1352458516628656, indexed in Pubmed: 26846987.
13. Rogers JM, Panegyres PK. Cognitive impairment in multiple sclerosis: evidence-based analysis and recommendations. J Clin Neurosci. 2007; 14(10): 919–927, doi: 10.1016/j.jocn.2007.02.006, indexed in Pubmed: 17659875.
14. Kimiskidis VK, Papaliagkas V, Sotirakoglou K, et al. Cognitive event-related potentials in multiple sclerosis: Correlation with MRI and neuropsychological findings. Mult Scler Relat Disord. 2016; 10: 192–197, doi: 10.1016/j.msard.2016.10.006, indexed in Pubmed: 27919489.
15. Rao SM, Leo GJ, Bernardin L, et al. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology. 1991; 41(5): 685–691, indexed in Pubmed: 2027484.
16. Rossi F, Giorgio A, Battaglini M, et al. Relevance of brain lesion location to cognition in relapsing multiple sclerosis. PLoS One. 2012; 7(11): e44826, doi: 10.1371/journal.pone.0044826, indexed in Pubmed: 23144775.
17. Zivadinov R, Jakimovski D, Gandhi S, et al. Clinical relevance of brain atrophy assessment in multiple sclerosis. Implications for its use in a clinical routine. Expert Rev Neurother. 2016; 16(7): 777–793, doi: 10.1080/14737175.2016.1181543, indexed in Pubmed: 27105209.
18. Kalinowska-Łyszczarz A, Pawlak MA, Pietrzak A, et al. Subcortical gray matter atrophy is associated with cognitive deficit in multiple sclerosis but not in systemic lupus erythematosus patients. Lupus. 2018; 27(4): 610–620, doi: 10.1177/0961203317735186, indexed in Pubmed: 28992796.
19. Tovar-Moll F, Evangelou IE, Chiu AW, et al. Diffuse and focal corticospinal tract disease and its impact on patient disability in multiple sclerosis. J Neuroimaging. 2015; 25(2): 200–206, doi: 10.1111/jon.12171, indexed in Pubmed: 25318661.
20. van Munster CEP, Uitdehaag BMJ. Outcome Measures in Clinical Trials for Multiple Sclerosis. CNS Drugs. 2017; 31(3): 217–236, doi: 10.1007/s40263-017-0412-5, indexed in Pubmed: 28185158.
21. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011; 69(2): 292–302, doi: 10.1002/ana.22366, indexed in Pubmed: 21387374.
22. Carter P. The complete book of intelligence tests. John Wiley and Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, England 2005.
23. Spreen O, Strauss EA. A compendium of neuropsychological tests. 2nd ed. Oxford University Press, New York, Oxford 1998.
24. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004; 23 Suppl 1: S208–S219, doi: 10.1016/j.neuroimage.2004.07.051, indexed in Pubmed: 15501092.
25. Mandal PK, Mahajan R, Dinov ID. Structural brain atlases: design, rationale, and applications in normal and pathological cohorts. J Alzheimers Dis. 2012; 31 Suppl 3: S169–S188, doi: 10.3233/JAD-2012-120412, indexed in Pubmed: 22647262.
26. Chiaravalloti ND, Stojanovic-Radic J, DeLuca J. The role of speed versus working memory in predicting learning new information in multiple sclerosis. J Clin Exp Neuropsychol. 2013; 35(2): 180–191, doi: 10.1080/13803395.2012.760537, indexed in Pubmed: 23350959.
27. Thaler C, Faizy T, Sedlacik J, et al. T1- Thresholds in Black Holes Increase Clinical-Radiological Correlation in Multiple Sclerosis Patients. PLoS One. 2015; 10(12): e0144693, doi: 10.1371/journal.pone.0144693, indexed in Pubmed: 26659852.

28. Rocca MA, Comi G, Filippi M. The Role of T1-Weighted Derived Measures of Neurodegeneration for Assessing Disability Progression in Multiple Sclerosis. Front Neurol. 2017; 8: 433, doi: 10.3389/fneur.2017.00433, indexed in Pubmed: 28928705.
29. Wartenburger I, Kühn E, Sassenberg U, et al. On the relationship between fluid intelligence, gesture production, and brain structure. Intelligence. 2010; 38(1): 193–201, doi: 10.1016/j.intell.2009.11.001.
30. Koziol JA, Wagner S, Sobel DF, et al. Asymmetries in the spatial distributions of enhancing lesions and black holes in relapsing-remitting MS. J Clin Neurosci. 2005; 12(8): 895–901, doi: 10.1016/j.jocn.2004.11.010, indexed in Pubmed: 16249086.
31. Batista S, Zivadinov R, Hoogs M, et al. Basal ganglia, thalamus and neocortical atrophy predicting slowed cognitive processing in multiple sclerosis. J Neurol. 2012; 259(1): 139–146, doi: 10.1007/s00415-011-6147-1, indexed in Pubmed: 21720932.
32. Correale J, Peirano I, Romano L. Benign multiple sclerosis: a new definition of this entity is needed. Mult Scler. 2012; 18(2): 210–218, doi: 10.1177/1352458511419702, indexed in Pubmed: 21865415.
33. Thaler C, Faizy TD, Sedlacik J, et al. T1 Recovery Is Predominantly Found in Black Holes and Is Associated with Clinical Improvement in Patients with Multiple Sclerosis. AJNR Am J Neuroradiol. 2017; 38(2): 264–269, doi: 10.3174/ajnr.A5004, indexed in Pubmed: 28059711.
34. Ruggieri S, Fanelli F, Castelli L, et al. Lesion symptom map of cognitive-postural interference in multiple sclerosis. Mult Scler. 2018; 24(5): 653–662, doi: 10.1177/1352458517701313, indexed in Pubmed: 28337941.
35. Adusumilli G, Trinkaus K, Sun P, et al. Intensity ratio to improve black hole assessment in multiple sclerosis. Mult Scler Relat Disord. 2018; 19: 140–147, doi: 10.1016/j.msard.2017.11.020, indexed in Pubmed: 29223871.
36. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. The Lancet Neurology. 2008; 7(12): 1139–1151, doi: 10.1016/S1474-4422(08)70259-X.
37. Huijbregts SCJ, Kalkers NF, de Sonneville LMJ, et al. Differences in cognitive impairment of relapsing remitting, secondary, and primary progressive MS. Neurology. 2004; 63(2): 335–339, indexed in Pubmed: 15277630.
38. Henry JD, Crawford JR. A meta-analytic review of verbal fluency performance following focal cortical lesions. Neuropsychology. 2004; 18(2): 284–295, doi: 10.1037/0894-4105.18.2.284, indexed in Pubmed: 15099151.
39. Piskunowicz M, Bieliński M, Zgliński A, et al. Testy fluencji słownej– zastosowanie w diagnostyce neuropsychologicznej. Psychiatria Polska. 2013; 47(3): 475–485.
40. Troyer AK, Moscovitch M, Winocur G, et al. Clustering and switching on verbal fluency: the effects of focal frontal- and temporal-lobe lesions. Neuropsychologia. 1998; 36(6): 499–504, indexed in Pubmed: 9705059.
41. Tam RC, Traboulsee A, Riddehough A, et al. Improving the clinical correlation of multiple sclerosis black hole volume change by paired-scan analysis. Neuroimage Clin. 2012; 1(1): 29–36, doi: 10.1016/j.nicl.2012.08.004, indexed in Pubmed: 24179734.
42. Tam RC, Traboulsee A, Riddehough A, et al. The impact of intensity variations in T1-hypointense lesions on clinical correlations in multiple sclerosis. Mult Scler. 2011; 17(8): 949–957, doi: 10.1177/1352458511402113, indexed in Pubmed: 21502309.
43. Thaler C, Faizy TD, Sedlacik J, et al. The use of multiparametric quantitative magnetic resonance imaging for evaluating visually assigned lesion groups in patients with multiple sclerosis. J Neurol. 2018; 265(1): 127–133, doi: 10.1007/s00415-017-8683-9, indexed in Pubmed: 29159467.
44. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018; 17(2): 162–173, doi: 10.1016/S1474-4422(17)30470-2, indexed in Pubmed: 29275977.
45. Harrison D, Roy S, Oh J, et al. Association of Cortical Lesion Burden on 7-T Magnetic Resonance Imaging With Cognition and Disability in Multiple Sclerosis. JAMA Neurology. 2015; 72(9): 1004–1012, doi: 10.1001/jamaneurol.2015.1241.
46. Bakirtzis C, Ioannidis P, Messinis L, et al. The Rationale for Monitoring Cognitive Function in Multiple Sclerosis: Practical Issues for Clinicians. Open Neurol J. 2018; 12: 31–40, doi: 10.2174/1874205X01812010031, indexed in Pubmed: 30008964.

RESEARCH PAPERS

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 1, pages: 26–33
DOI: 10.5603/PJNNS.a2019.0005

ISSN 0028–3843

Electrophysiological and clinical assessment of dysautonomia in multiple system atrophy (MSA) and progressive supranuclear palsy (PSP): a comparative study

Monika Nojszewska, Anna Potulska-Chromik, Zygmunt Jamrozik, Piotr Janik, Beata Zakrzewska-Pniewska

Department of Neurology, Medical University of Warsaw, Poland

ABSTRACT

Clinical rationale for the study. Autonomic nervous system (ANS) involvement in different parkinsonian syndromes has been frequently discussed. It is well established in multiple system atrophy (MSA), whereas it is less evident in progressive supranuclear palsy (PSP).

Aims of the study. The aims were to assess the presence and pattern of ANS involvement in MSA and PSP using noninvasive tests i.e. the sympathetic skin response (SSR) test and the R-R interval variation (RRIV) test; to analyse the relationship between clinical and electrophysiological abnormalities in both disorders; and to assess whether an autonomic profile might help to differentiate them.

Materials and methods. Clinical and electrophysiological assessments of dysautonomia were performed in 59 patients with MSA (24 cases of MSA-C and 35 cases of MSA-P), these 59 cases including 31 females, mean disease duration 4.2 ± 2.7 years, mean age 60.3 ± 8.4 years, and in 37 patients with PSP (12 females, mean disease duration 4.6 ± 3.6 years, mean age 67.5 ± 6.1 years) and the results were compared to the results obtained from 23 healthy controls matched for age and sex.

Results. Clinical dysautonomia assessed by an Autonomic Symptoms Questionnaire was observed in 97% of the MSA patients and in 84% of the PSP patients. SSR was abnormal in 64% and RRIV was abnormal in 73% of MSA cases. In PSP cases, these figures were 78% and 81% respectively. Dysautonomia was clinically more pronounced in MSA compared to PSP ($p < 0.05$), whereas electrophysiological testing revealed frequently subclinical ANS damage in PSP patients.

Conclusions and clinical implications. Our results point to the complementary role of electrophysiological tests in the diagnostic work-up of dysautonomia in parkinsonian syndromes.

Key words: MSA, PSP, autonomic nervous system, dysautonomia, SSR, RRIV
(*Neurol Neurochir Pol 2019; 53 (1): 26–33*)

Introduction

Although generally believed to be uncommon, in fact autonomic disorders are ubiquitous in neurological disease, including movement disorders [1].

Sympathetic skin response (SSR) is a relatively simple electrophysiological test used in clinical practice to assess the reflex activity of sympathetic sudomotor pathways [2–5], and is employed to evaluate pre- and postganglionic sympathetic activity [2, 3]. SSR has been used to assess ANS function in various peripheral and central neurological disorders [2, 4, 6]. On the other hand, R-R interval variability (RRIV) reflects the state of parasympathetic innervation of the heart [6], and gives an insight into sympathovagal tone [7]. Cyclic

Address for correspondence: Anna Potulska-Chromik, Department of Neurology, Medical University of Warsaw, Poland, e-mail: apotulska@wum.edu.pl

deep breathing is the best validated stimulus; both afferent and efferent pathways are vagally mediated and inhibited by anticholinergic agents [1].

MSA is a rare and fatal neurodegenerative disorder that is characterised by a variable combination of parkinsonism, cerebellar impairment, and autonomic dysfunction [8]. PSP is also a neurodegenerative disorder with early postural instability and falls, vertical supranuclear gaze palsy, akinetic--rigid predominant and typically symmetric parkinsonism with poor response to levodopa, pseudobulbar palsy, and frontal release signs [9–12]. Nowadays, PSP can be divided into PSP-parkinsonism (PSP-P), PSP-Richardson's syndrome (PSP-RS) and into several other clinical subtypes [13], while MSA can be classified as either MSA-cerebellar (MSA-C), or MSA-parkinsonism (MSA-P) [14]. Diagnostic criteria have been proposed for the clinical diagnosis of PSP and MSA [10, 14, 15]. However, pathological brain examination post mortem remains the gold standard for diagnostic classification. The mean survival rate in patients with PSP has been estimated to be 6–7 years [9, 16]; in patients with MSA it is 6–10 years [17–19]. According to recent research in MSA, severe dysautonomia and the early development of combined autonomic and motor features are unfavourable predictors of survival [20]. In PSP, early dysphagia, cognitive symptoms, PSP-RS phenotype and urinary incontinence have been found to be highly predictive of shorter survival in some studies [10, 11, 16, 20, 21], whereas sleep disturbances and possible hallucinations have been suggested in another study [22].

It is well established that pronounced autonomic failure appears early in MSA, whereas it is less evident in PSP [23–26]. The objectives of our study were: to evaluate the presence and pattern of ANS involvement in MSA and PSP using two noninvasive electrophysiological tests (SSR and RRIV); to analyse the relationship between clinical and electrophysiological abnormalities in both disorders; and to assess whether an autonomic profile might help to differentiate them.

Materials and methods

Patients

Clinical and electrophysiological assessments of dysautonomia were performed in 59 patients with MSA: 24 with a diagnosis of MSA-C [15 men (62.5%)] and 35 with a diagnosis of MSA-P [22 women (62.9%)], and in 37 patients with PSP (with classical Richardson's syndrome phenotype). The MSA and PSP diagnosis was probable in 48 (81.4%) and 31 patients (83.8%) respectively. In the rest of the patients, the diagnosis was possible. The mean age in the MSA group was 60.3 ± 8.4 years (range 40–79), and in the PSP group it was 67.5 ± 6.1 years (range 58–80). The mean disease duration was 4.2 ± 2.7 years (range 1–14) in the MSA group, and 4.6 ± 3.6 years (range 1–20) in the PSP group. In the MSA group, 31 patients (52.5%) were treated with L-dopa (mean dose 861 ± 391 mg daily; range 200–1,800 mg) while in the PSP group 28 patients (75.7%) received this treatment with a mean dose of 804 ± 304 mg (range: 300–1,600). The mean age in the MSA-C group was 59.0 ± 7.8 years (range 49–79), and in the MSA-P group it was 61.3 ± 8.8 years (range 40–78). Patients with the presence of focal cerebral lesions in CT or MRI scans and other neurological or previously diagnosed severe systemic disorders (such as arterial hypertension or diabetes mellitus) or who were taking anticholinergic drugs, neuroleptics or drugs known to markedly influence autonomic functions (high doses of beta-blockers etc.), or with a history of alcohol or drug abuse were excluded from the study [27]. The control group consisted of 23 volunteers [16 women (69.6%)] with a mean age of 56.6 ± 14.0 years (range 42–91).

All patients were diagnosed and treated at the Department of Neurology, Medical University of Warsaw. The diagnosis of MSA was made according to the criteria established by Gilman et al. [14] and PSP according to the National Institute for Neurological Diseases and Stroke and The Society for PSP (NINDS-SPSP) [10] by movement disorders specialists (APCh, PJ, ZJ) based on a detailed history and a neurological examination. Antiparkinsonian treatment (mostly L-dopa medication) was not interrupted before examination, but the last dose was taken at least 24 hours before the examination took place.

Methods

Electrophysiological studies and clinical evaluations were performed at the Evoked Potential and Autonomic System Laboratory of the Department of Neurology, Medical University of Warsaw, between 2008 and 2015. All patients and controls gave informed consent to the protocol (for electrophysiological tests and clinical evaluation). The study protocol was reviewed and approved by the Bioethical Committee at the Medical University of Warsaw (No AKBE 13/2006). All the procedures were in accord with the standards of the Committee on Human Experimentation of the Medical University of Warsaw, and with the Helsinki Declaration of 1975.

Clinical evaluation

The clinical evaluation of dysautonomia was performed by two independent physicians (MN and BZP) on the same day as RRIV and SSR tests. We assessed the incidence and distribution of symptoms of dysautonomia as well as their intensity. We modified the Autonomic Symptoms Questionnaire proposed by Low [28] to evaluate the intensity of dysautonomia semiquantitatively using an arbitrarily defined score system (0 points — no symptoms; 1 point — symptoms present. Orthostatic hypotension was defined as a blood pressure decrease of 30 mmHg systolic or 15 mmHg diastolic within three minutes after standing up from a recumbent position according to MSA criteria [8]: 0 points — no symptoms; 1 point — mild → symptoms present only when there were

facilitating conditions; 2 points — severe → symptoms present at all times, disabling).

Electrophysiological tests

SSR and RRIV tests were recorded in subjects lying in a semi-darkened room, with a temperature of 22—26°C, after having relaxed for several minutes. Tests were recorded at the same time of day (between 10.00 and 13.00), within a few hours after a light meal using the Viking IV, Nicolet Biomedical Inc. (Multi-Mode Program Plus, version 4.0). Both tests were performed according to a protocol recommended by IFCN and described earlier [27]. The frequency of breaths during deep breathing was six per minute. The normal values were not corrected for age.

SSR

The latency and amplitude (peak to peak) of the highest response were measured (five evoked responses were registered, but only the one of the shortest latency was analysed). The SSR was considered abnormal if the latency was longer by more than two standard deviations (SDs) than that of the control group, or if a response was absent (i.e. not elicited by three consecutive stimulations). Additionally, we evaluated the degree of SSR abnormality using a five-level scale created in our Laboratory: 0 points — normal response; 1 point — increased latency in one limb; 2 points — increased latency in both limbs or the absence of a response from one limb; 3 points — increased latency in one limb and the absence of a response from the other limb; 4 points — absence of response from both limbs.

RRIV

The RRIV result was considered abnormal if we registered decreased RRIV at rest or during deep breathing, or if no increase of the RRIV during deep breathing could be observed. Additionally, we evaluated the degree of RRIV abnormality using a three-level scale created in our Laboratory: 0 points — normal RRIV test at rest AND during deep breathing AND an increase of the RRIV during deep breathing; 1 point — abnormal (decreased) RRIV test at rest OR during deep breathing OR no increase of the RRIV during deep breathing; 2 points — abnormal (decreased) RRIV test at rest AND during deep breathing AND no increase of the RRIV during deep breathing.

Combined electrophysiological score

A combined electrophysiological score, with values ranging from 0 to 6, was created by combining the results from our SSR and RRIV scores.

Statistical analysis

Prior to analysis, the normality of distribution of the functional variables was tested by Shapiro-Wilk test. Where non-normal distribution was found, correlations analysis between different parameters was performed using Spearman's correlation coefficients test. For group comparison, Wilcoxon rank-sum, Chi-square and Fisher exact tests were used. Statistical significance was defined as $p < 0.05$. Values are presented as mean ± SD. As an additional analysis, logistic regression was used to calculate the significance level because of the presence of confounding factors such as age and gender (in some group comparisons).

Results

The demographic profile of the two studied groups differed significantly: patients in the PSP group were older than patients in the MSA group ($p < 0.001$), and the majority of them were male (67.6% in the PSP group *vs* 47.5% in the MSA group; NS). This difference was more clearly seen when the PSP group was compared to the MSA-P group which contained only 13 men (31.1%, $p < 0.05$). The control group was matched for age and sex to the MSA group, but there were statistically significant differences between the control group and the PSP group. Volunteers were younger ($p = 0.001$), and the majority of them were female ($p = 0.005$).

Clinical evaluation

Clinical symptoms of dysautonomia were found in 96.6% (57/59) of our MSA patients and in 83.8% (31/37) of PSP patients. The distribution of symptoms differed significantly between these groups, especially when orthostatic hypotension, dizziness and urinary incontinence were evaluated (Tab. 1).

When the MSA group was divided into MSA-P and MSA-C subgroups, orthostatic hypotension, urinary incontinence and constipation were significantly more often reported in the former. We did not find significant differences between MSA-C and PSP, although comparing PSP to MSA-P we found statistically significant differences in the frequency of all symptoms, except for urinary retention and constipation.

In semiquantitative evaluation of the intensity of dysautonomia, the mean score was higher in the MSA group as a whole (3.4 ± 1.8 points) than in the PSP group (2.7 ± 1.8 points), but this tendency did not reach statistical significance ($p = 0.054$). When compared to PSP only, the MSA-P subgroup (mean 3.9 ± 1.7 points) results differed significantly. The intensity of clinical symptoms of dysautonomia was also more severe in the MSA-P subgroup than in the MSA-C (mean 2.7 ± 1.7 points) subgroup ($p < 0.05$).

Electrophysiological tests

SSR

The mean values of SSR from upper and lower limbs in controls, MSA and PSP patients are presented in Table 2. Technical reasons meant that we could not evaluate SSR results in three patients from each patient group.

The mean values of SSR latency in MSA and PSP patients were significantly higher than in controls for both the upper and lower limbs.

Table 1. Frequency of symptoms of dysautonomia in MSA (n = 59) and PSP (n = 37) groups in Autonomic Symptoms Questionnaire for semiquantitative evaluation of dysautonomia. Modified from Low, 1997

Symptom of dysautonomia	MSA group No of patients (%)	PSP group No of patients (%)	P value*
Orthostatic hypotension	41 (69.5)	19 (51.4)	P < 0.05
mild	16 (39)	12 (63.2)	
severe	25 (61)	7 (36.8)	
Urinary incontinence	40 (67.8)	17 (45.9)	P < 0.05
Urinary retention	18 (30.5)	15 (40.5)	NS
Impotence (in men)	15 (53.6)	12 (48)	NS
Dizziness	22 (37.3)	5 (13.5)	P < 0.05
Syncope	20 (33.9)	8 (21.6)	NS
Constipation	19 (32.2)	15 (40.5)	NS

*P < 0.05 Chi square test; NS — not statistically significant

Table 2. Latency of SSR test (in upper and lower limbs) and RRIV test results (at rest and during deep breathing) in MSA (n = 59) and PSP (n = 37) patients and control group (n = 23)

	SSR latency (sec) mean ± SD (range)		RRIV test results (%) mean ± SD (range)	
	upper limb	lower limb	R mean	R–DB
MSA	1.58 ± 0.3*	2.11 ± 0.3*	7.26 ± 4.42**	14.41 ± 7.88**
	(1.04–2.42)	(1.45–2.92)	(2.31–27.0)	(2.75–36.85)
PSP	1.63 ± 0.24*	2.12 ± 0.3*	5.78 ± 2.23**	12.19 ± 6.84**
	(1.24–2.34)	(1.68–2.97)	(1.93–10.98)	(2.26–29.40)
Control group	1.37 ± 0.12	1.89 ± 0.23	11.96 ± 5.36	29.86 ± 16.53
	(1.12–1.60)	(1.49–2.29)	(4.96–24.07)	(8.40–61.40)

MSA — multiple system atrophy; PSP — progressive supranuclear palsy; R mean — mean HRV at rest; R-DB — HRV during deep breathing; RRIV — R-R interval variation test; sec — seconds; SD — standard deviation; SSR — sympathetic skin response; *statistically significant changes compared to control group (p < 0.05, using t-Test); **statistically significant changes compared to control group (p < 0.05, using Wilcoxon test)

In only 21 (35.6%) patients with MSA and in eight (21.6%) patients with PSP, the SSR results were within normal limits. In 11 (18.6%) patients in the MSA group, a response was not registered in the upper limbs, and in 20 (33.9%) patients a response was not registered in the lower limbs. These changes in the upper limbs were more pronounced in the MSA-P subgroup than in the MSA-C subgroup (22.9% *vs* 12.5% respectively). In the PSP group, SSR was not registered in the upper limbs in 13 (35.4%) patients and in the lower limbs in 21 (56.8%) patients. The differences between the MSA and PSP groups were statistically significant (for both the upper and lower limbs).

The distribution of SSR abnormalities (in scores) in MSA and PSP patients is shown in Figure 1a.

RRIV

The mean values of RRIV response at rest and during deep breathing in controls, MSA and PSP patients are presented in Table 2. Technical reasons meant we could not evaluate RRIV results in five patients from each patient group.

All mean values of RRIV parameters in MSA and PSP patients were significantly lower than in controls.

Most of the patients reached the highest score of 2 points on our scale of RRIV changes intensity, with the highest rate in the MSA-P subgroup (51.4%). Only in 16 (27.1%) patients with MSA and in seven (18.9%) patients with PSP were the results of RRIV normal (Fig. 1b).

Combined electrophysiological score

A combined electrophysiological score could be obtained in 51 MSA and 30 PSP patients. Only in eight (15.7%) patients with MSA [three (15.0%) with MSA-C and five (16.1%) with MSA-P] and in two (6.7%) patients with PSP were the results of both tests (SSR and RRIV) within normal limits. In the MSA patients, the intensity of change most frequently seen (29.4%) was 'mild' (a score of 2). On the other hand, in the PSP group 'severe' changes (a score of 6) were found most often (30.0%) but only in 9.8% of patients in the MSA group, although this tendency did not reach statistical significance (p = 0.057) (Fig. 1c). Within the MSA group there was a tendency to

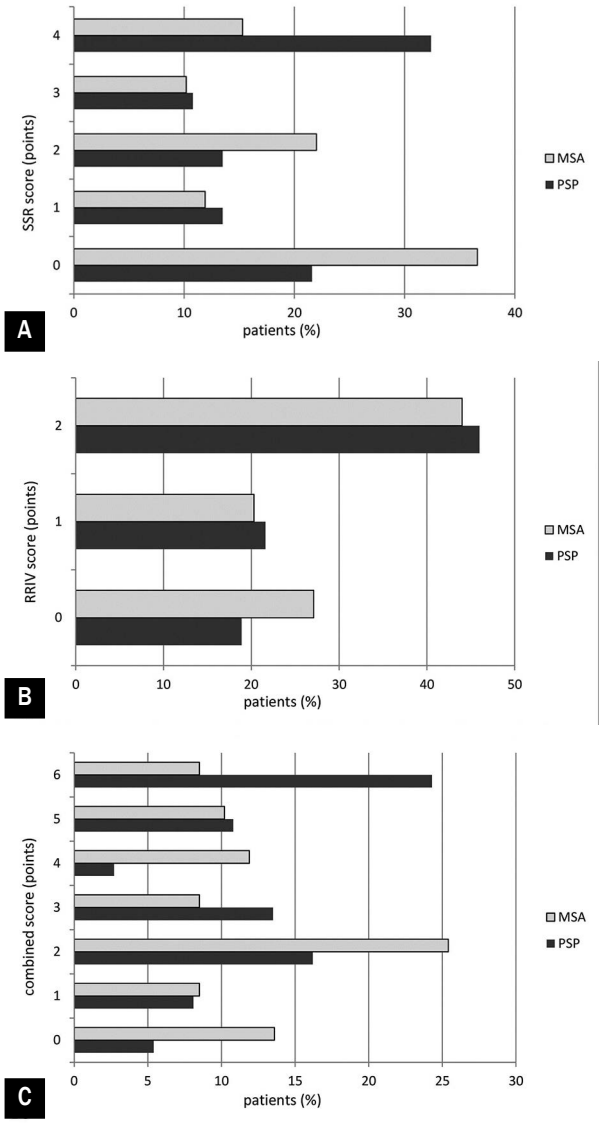


Figure 1. Distribution of intensity of SSR (1a) and RRIV (1b) abnormalities (in scores) and results in combined electrophysiological score (1c) in MSA (n = 59) and PSP patients (n = 37). MSA — multiple system atrophy; PSP — progressive supranuclear palsy; RRIV — R-R interval variation test; sec — seconds; SD — standard deviation; SSR — sympathetic skin response

more severe changes (scores 5 and 6) in the MSA-P subgroup compared to MSA-C patients.

We found a mild, but significant, correlation between the results of SSR and RRIV tests in the PSP group ($r = 0.38$; $p < 0.05$). In the MSA group as a whole, as well as after division into subgroups, we found no such correlation.

Correlation between clinical and electrophysiological assessments of dysautonomia

The relationship between the presence and degree of electrophysiological changes (SSR and RRIV scores evaluated together and separately) and the intensity of clinical symptoms in the groups of patients with MSA and PSP were also analysed. In the MSA group, we found statistically significant correlations between clinical symptom score and SSR score as well as with the combined electrophysiological score (both $r = 0.44$; $p < 0.001$). An even stronger correlation was found in the MSA-P subgroup ($r = 0.57$ and $r = 0.56$ respectively; $p < 0.001$). In PSP and MSA-C patients, no such correlation was found. No relationship between age, duration of disease and the values of the parameters analysed in the SSR and RRIV tests was revealed by a Spearman correlation test.

Discussion

Dysautonomia is common in parkinsonian syndromes affecting a wide spectrum of domains. It is well established that pronounced autonomic failure appears early in MSA, whereas it is less evident in PSP [23–26, 29].

In our study nearly 97% patients with MSA and 84% with PSP presented clinical signs of dysautonomia and they could be seen most frequently in the MSA-P subgroup. Our results are consistent with previous studies of MSA, where early and severe autonomic failure with predominant involvement of urinary and cardiovascular domains has been described as a key feature of the disease [19, 30–33]. The ANS involvement in PSP is not so clearly established.

In our study the intensity of symptoms in PSP in most cases was mild. In some reviews, constipation and urinary incontinence have been described as the most prevalent non-motor features of PSP, especially in the late stages of the disease [22]. Other studies have noted orthostatic hypotension, dizziness, lack of sweating and sexual dysfunction [16, 21, 23, 24, 34, 35]. Some authors have emphasised that comorbidities such as benign prostatic hypertrophy or medication use could explain some of these symptoms, because in many PSP patients objective evidence of autonomic dysfunction could not be found in diagnostic tests [22, 34, 36, 37]. There have also been reports that there are no prominent autonomic abnormalities in PSP [13, 25, 26, 29, 38], and the presence of cardiovascular symptoms has even been proposed as an exclusion criterion for PSP [25].

We found abnormal SSR results in 59% of MSA patients and in 70% of patients with PSP. The pattern of involvement was distinct in both disorders, and those differences were statistically significant. The degree of SSR abnormalities was greater in the PSP than in the MSA group, and greater in the MSA-P than in the MSA-C subgroup.

Many studies have reported abnormalities in SSR results in 69%, and even up to 100%, of MSA patients [7, 35, 40–44]. Bordet et al. calculated the sensitivity of SSR examination in MSA diagnosis as 0.69 and the specificity as 0.92 [7]. On the other hand, Reimann et al. did not find differences in SSR results between MSA, PSP and PD groups [43], but they evoked SSR using acoustic stimulation. They also included in their study patients with significant comorbidities known to affect

ANS function such as diabetes mellitus. The differences with our results could be caused by the SSR protocol applied. We used electrical stimulus to evoke SSR, because some of our patients with parkinsonism poorly cooperated during examination. This type of stimulus is easier to standardise in patients with central nervous system disorders [7, 39, 40] and has been found to provide the most reproducible responses [5].

SSR involves both the pre- and postganglionic sympathetic systems [2, 3, 6].The preganglionic efferent pathway is mainly the output of the intermediolateral column (ILC) of the spinal cord, which is frequently involved in the pathological process in MSA [19]. Such a central lesion might be the main determinant of abnormal SSR, as opposed to postganglionic dysfunction which can be seen for example in PD [7, 45].

Reports assessing SSR in patients with PSP and PD have shown that sudomotor function was markedly more involved in the former [46]. Pressor responses induced by emotional or physical stimuli or mental stress have also been reported to be diminished in PSP [25, 35]. This type of sweating on the palms and soles is independent of the ambient temperature (so-called 'emotional sweating') and is regulated by the limbic system, motor system and reticular formation [35]. Many of these structures are known to be frequently affected by the neurodegenerative process in PSP [7, 12, 22, 48]. Hence, similarly to MSA, sympathetic dysfunction in PSP may also be classified as of central, preganglionic origin.

There is also the possibility that the lack of SSR could be attributed to age. Drory and Korczyn reported that SSR could not been evoked in the hand in 27% of normal subjects above 60 years of age [39]. On the other hand however, Hay et al. reported the presence of responses in all elderly subjects [47]. Although there was a significant age difference between PSP patients and the control group in our study, a logistic model of analysis additionally proved that the differences in SSR results between both groups were independent of age.

We found abnormal RRIV results in 64% of patients with MSA and in nearly 68% of PSP patients, and in most cases the intensity of changes was severe.

Previous reports have described a lower mean value of heart rate variation (HRV) especially after deep breathing in over 60% of patients with MSA [7, 29, 40]. Pathological results have been found at all ages and within a short disease duration. However, other results did not confirm these findings [49].

Besides ILC, many ANS structures are affected by neurodegenerative changes in MSA, including dorsal vagal motor nucleus [19], which seems to be responsible for RRIV changes in MSA [7]. Because RRIV reflects the sympathovagal balance, so impairment in the sympathetic part of ANS reflected by SSR abnormalities might also contribute to RRIV changes [7].

Contrary to our results, previous reports have shown no remarkable changes in HRV in PSP [23, 25]. In the study conducted by Kikkawa et al. the mean HRV value at rest was lower in PSP than in the control group [35]. Holmberg et al. found only in four out of 14 patients with PSP decreased HRV during controlled deep breathing and limited hypotensive response during orthostatic provocation. In most cases (64%), the results of both tests did not differ from controls [29].

Tau pathology in PSP is widely distributed in the brain, resulting in damage to various pathways [12, 13]. It has been hypothesised that different PSP disease phenotypes might emerge from the preferential spread of tau through different brain networks that are functionally and neuroanatomically connected [13]. Therefore, we cannot exclude that in some patients neuropathological changes can spread and involve directly the parasympathetic structures responsible for RRIV changes in PSP. On the other hand, the involvement of sites important for the sympathovagal balance might also contribute to the RRIV changes seen in our patients with PSP.

Only in 16% of MSA patients and in 7% of PSP patients were the results of both electrophysiological tests within normal limits. The changes in laboratory tests were more pronounced in the PSP patients than in the MSA patients, but their distribution was not significantly different. We found a statistically significant correlation between the intensity of clinical symptoms of dysautonomia and the combined electrophysiological score in MSA patients, especially in the MSA-P subgroup. Other studies have found no such correlation in MSA [40].

Clinical implications and future directions

In parkinsonian syndromes, especially in MSA, a different degree of autonomic failure occurs that might significantly impair a patient's quality of life [12, 19, 20, 22, 31, 50]. Therefore a systematic investigation of dysautonomia has been proposed as a relevant diagnostic assessment in parkinsonian syndromes [7, 33, 35, 40–42].

According to our results, sympathetic and parasympathetic involvement occurs in both MSA and PSP, but the intensity of changes varies between these two disorders and can be assessed by non-invasive electrophysiological tests. In MSA, a significant correlation between the intensity of clinical symptoms of dysautonomia and electrophysiological tests results can be found, whereas abnormal results of electrophysiological tests without clinical evidence of dysautonomia is more suggestive of PSP.

References

1. Weimer LH. Autonomic testing: common techniques and clinical applications. Neurologist. 2010; 16(4): 215–222, doi: 10.1097/NRL.0b013e3181cf86ab, indexed in Pubmed: 20592565.
2. Fagius J, Wallin BG. Sympathetic reflex latencies and conduction velocities in normal man. J Neurol Sci. 1980; 47(3): 433–448, indexed in Pubmed: 7420119.
3. Fagius J, Wallin BG. Sympathetic reflex latencies and conduction velocities in patients with polyneuropathy. J Neurol Sci. 1980; 47(3): 449–461, indexed in Pubmed: 7420120.

4. Shahani BT, Halperin JJ, Boulu P, et al. Sympathetic skin response–a method of assessing unmyelinated axon dysfunction in peripheral neuropathies. J Neurol Neurosurg Psychiatry. 1984; 47(5): 536–542, indexed in Pubmed: 6330307.
5. Elie B, Guiheneuc P. Sympathetic skin response: normal results in different experimental conditions. Electroencephalogr Clin Neurophysiol. 1990; 76(3): 258–267, indexed in Pubmed: 1697257.
6. Shahani BT, Day TJ, Cros D, et al. RR interval variation and the sympathetic skin response in the assessment of autonomic function in peripheral neuropathy. Arch Neurol. 1990; 47(6): 659–664, indexed in Pubmed: 2161208.
7. Bordet R, Benhadjali J, Destee A, et al. Sympathetic skin response and R-R interval variability in multiple system atrophy and idiopathic Parkinson's disease. Mov Disord. 1996; 11(3): 268–272, doi: 10.1002/mds.870110309, indexed in Pubmed: 8723143.
8. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology. 2008; 71(9): 670–676, doi: 10.1212/01.wnl.0000324625.00404.15, indexed in Pubmed: 18725592.
9. Davis PH, Golbe LI, Duvoisin RC, et al. Prevalence and natural history of progressive supranuclear palsy. Neurology. 1988; 38(7): 1031–1034, indexed in Pubmed: 3386818.
10. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology. 1996; 47(1): 1–9, indexed in Pubmed: 8710059.
11. Santacruz P, Uttl B, Litvan I, et al. Progressive supranuclear palsy: a survey of the disease course. Neurology. 1998; 50(6): 1637–1647, indexed in Pubmed: 9633705.
12. Golbe LI. Progressive supranuclear palsy. Semin Neurol. 2014; 34(2): 151–159, doi: 10.1055/s-0034-1381736, indexed in Pubmed: 24963674.
13. Boxer AL, Yu JT, Golbe LI, et al. Advances in progressive supranuclear palsy: new diagnostic criteria, biomarkers, and therapeutic approaches. Lancet Neurol. 2017; 16(7): 552–563, doi: 10.1016/S1474-4422(17)30157-6, indexed in Pubmed: 28653647.
14. Gilman S, Low PA, Quinn N, et al. Consensus statement on the diagnosis of multiple system atrophy. J Neurol Sci. 1999; 163(1): 94–98, indexed in Pubmed: 10223419.
15. Payan CAM, Viallet F, Landwehrmeyer BG, et al. NNIPPS Study Group. Disease severity and progression in progressive supranuclear palsy and multiple system atrophy: validation of the NNIPPS–Parkinson Plus Scale. PLoS One. 2011; 6(8): e22293, doi: 10.1371/journal.pone.0022293, indexed in Pubmed: 21829612.
16. O'Sullivan SS, Massey LA, Williams DR, et al. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. Brain. 2008; 131(Pt 5): 1362–1372, doi: 10.1093/brain/awn065, indexed in Pubmed: 18385183.
17. Ben-Shlomo Y, Wenning GK, Tison F, et al. Survival of patients with pathologically proven multiple system atrophy: a meta-analysis. Neurology. 1997; 48(2): 384–393, indexed in Pubmed: 9040727.
18. Wenning GK, Geser F, Krismer F, et al. European Multiple System Atrophy Study Group. The natural history of multiple system atrophy: a prospective European cohort study. Lancet Neurol. 2013; 12(3): 264–274, doi: 10.1016/S1474-4422(12)70327-7, indexed in Pubmed: 23391524.
19. Fanciulli A, Wenning GK. Multiple-system atrophy. N Engl J Med. 2015; 372(3): 249–263, doi: 10.1056/NEJMra1311488, indexed in Pubmed: 25587949.
20. Glasmacher SA, Leigh PN, Saha RA. Predictors of survival in progressive supranuclear palsy and multiple system atrophy: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2017; 88(5): 402–411, doi: 10.1136/jnnp-2016-314956, indexed in Pubmed: 28250027.
21. dell'Aquila C, Zoccolella S, Cardinali V, et al. Predictors of survival in a series of clinically diagnosed progressive supranuclear palsy patients. Parkinsonism Relat Disord. 2013; 19(11): 980–985, doi: 10.1016/j.parkreldis.2013.06.014, indexed in Pubmed: 23968651.
22. Arena JE, Weigand SD, Whitwell JL, et al. Progressive supranuclear palsy: progression and survival. J Neurol. 2016; 263(2): 380–389, doi: 10.1007/s00415-015-7990-2, indexed in Pubmed: 26705121.
23. Gutrecht JA. Autonomic cardiovascular reflexes in progressive supranuclear palsy. J Auton Nerv Syst. 1992; 39(1): 29–35, indexed in Pubmed: 1629523.
24. van Dijk JG, Haan J, Koenderink M, et al. Autonomic nervous function in progressive supranuclear palsy. Arch Neurol. 1991; 48(10): 1083–1084, indexed in Pubmed: 1929903.
25. Kimber J, Mathias CJ, Lees AJ, et al. Physiological, pharmacological and neurohormonal assessment of autonomic function in progressive supranuclear palsy. Brain. 2000; 123 (Pt 7): 1422–1430, indexed in Pubmed: 10869054.
26. Brefel-Courbon C, Thalamas C, Rascol O, et al. Lack of autonomic nervous dysfunction in progressive supranuclear palsy, a study of blood pressure variability. Clin Auton Res. 2000; 10(5): 309–312, indexed in Pubmed: 11198487.
27. Zakrzewska-Pniewska B, Gawel M, Szmidt-Salkowska E, et al. Clinical and functional assessment of dysautonomia and its correlation in Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2012; 27(8): 592–599, doi: 10.1177/1533317512459792, indexed in Pubmed: 23007287.
28. Low PA. Clinical Autonomic Disorders: Classification and Clinical Evaluation. In: ed. Clinical Autonomic Disorders. Evaluation and Management. 2nd ed. Lippincott–Raven, New York. 1997: 3–13.
29. Holmberg B, Kallio M, Johnels B, et al. Cardiovascular reflex testing contributes to clinical evaluation and differential diagnosis of Parkinsonian syndromes. Mov Disord. 2001; 16(2): 217–225, indexed in Pubmed: 11295773.
30. Sakakibara R, Hattori T, Uchiyama T, et al. Urinary dysfunction and orthostatic hypotension in multiple system atrophy: which is the more common and earlier manifestation? J Neurol Neurosurg Psychiatry. 2000; 68(1): 65–69, indexed in Pubmed: 10601404.
31. Laurens B, Vergnet S, Lopez MC, et al. Multiple System Atrophy - State of the Art. Curr Neurol Neurosci Rep. 2017; 17(5): 41, doi: 10.1007/s11910-017-0751-0, indexed in Pubmed: 28378233.
32. Iodice V, Lipp A, Ahlskog JE, et al. Autopsy confirmed multiple system atrophy cases: Mayo experience and role of autonomic function tests. J Neurol Neurosurg Psychiatry. 2012; 83(4): 453–459, doi: 10.1136/jnnp-2011-301068, indexed in Pubmed: 22228725.
33. Kimpinski K, Iodice V, Burton DD, et al. The role of autonomic testing in the differentiation of Parkinson's disease from multiple system atrophy. J Neurol Sci. 2012; 317(1-2): 92–96, doi: 10.1016/j.jns.2012.02.023, indexed in Pubmed: 22421352.
34. Wenning GK, Scherfler C, Granata R, et al. Time course of symptomatic orthostatic hypotension and urinary incontinence in patients with postmortem confirmed parkinsonian syndromes: a clinicopathological study. J Neurol Neurosurg Psychiatry. 1999; 67(5): 620–623, indexed in Pubmed: 10519868.

35. Kikkawa Y, Asahina M, Suzuki A, et al. Cutaneous sympathetic function and cardiovascular function in patients with progressive supranuclear palsy and Parkinson's disease. Parkinsonism Relat Disord. 2003; 10(2): 101–106, indexed in Pubmed: 14644000.
36. Sakakibara R, Hattori T, Tojo M, et al. Micturitional disturbance in progressive supranuclear palsy. J Auton Nerv Syst. 1993; 45(2): 101–106, indexed in Pubmed: 8282945.
37. Valldeoriola F, Valls-Solé J, Tolosa ES, et al. Striated anal sphincter denervation in patients with progressive supranuclear palsy. Mov Disord. 1995; 10(5): 550–555, doi: 10.1002/mds.870100504, indexed in Pubmed: 8552104.
38. Asahina M, Vichayanrat E, Low DA, et al. Autonomic dysfunction in parkinsonian disorders: assessment and pathophysiology. J Neurol Neurosurg Psychiatry. 2013; 84(6): 674–680, doi: 10.1136/jnnp-2012-303135, indexed in Pubmed: 22942216.
39. Drory VE, Korczyn AD. Sympathetic skin response: age effect. Neurology. 1993; 43(9): 1818–1820, indexed in Pubmed: 8414038.
40. De Marinis M, Stocchi F, Gregori B, et al. Sympathetic skin response and cardiovascular autonomic function tests in Parkinson's disease and multiple system atrophy with autonomic failure. Mov Disord. 2000; 15(6): 1215–1220, indexed in Pubmed: 11104208.
41. Asahina M, Kikkawa Y, Suzuki A, et al. Cutaneous sympathetic function in patients with multiple system atrophy. Clin Auton Res. 2003; 13(2): 91–95, doi: 10.1007/s10286-003-0072-z, indexed in Pubmed: 12720092.
42. Asahina M, Akaogi Y, Yamanaka Y, et al. Differences in skin sympathetic involvements between two chronic autonomic disorders: multiple system atrophy and pure autonomic failure. Parkinsonism Relat Disord. 2009; 15(5): 347–350, doi: 10.1016/j.parkreldis.2008.08.001, indexed in Pubmed: 18805037.
43. Reimann M, Schmidt C, Herting B, et al. Comprehensive autonomic assessment does not differentiate between Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. J Neural Transm (Vienna). 2010; 117(1): 69–76, doi: 10.1007/s00702-009-0313-y, indexed in Pubmed: 19763772.
44. Yokota T, Hayashi M, Tanabe H, et al. Sympathetic skin response in patients with cerebellar degeneration. Arch Neurol. 1993; 50(4): 422–427, indexed in Pubmed: 8460965.
45. Wang SJ, Fuh JL, Shan DE, et al. Sympathetic skin response and R-R interval variation in Parkinson's disease. Mov Disord. 1993; 8(2): 151–157, doi: 10.1002/mds.870080206, indexed in Pubmed: 8474481.
46. Sasaki I, Takeuchi H, Deguchi K, et al. [Autonomic nervous function in progressive supranuclear palsy–comparison with Parkinson's disease and healthy controls]. Rinsho Shinkeigaku. 1994; 34(10): 975–979, indexed in Pubmed: 7834957.
47. Hay JE, Taylor PK, Nukada H. Auditory and inspiratory gasp-evoked sympathetic skin response: age effects. J Neurol Sci. 1997; 148(1): 19–23, indexed in Pubmed: 9125386.
48. Homma S, Nakajima Y, Toma S, et al. Intracerebral source localization of mental process-related potentials elicited prior to mental sweating response in humans. Neurosci Lett. 1998; 247(1): 25–28, indexed in Pubmed: 9637401.
49. Gurevich TYu, Groozman GB, Giladi N, et al. R-R interval variation in Parkinson's disease and multiple system atrophy. Acta Neurol Scand. 2004; 109(4): 276–279, indexed in Pubmed: 15016010.
50. Brisinda D, Sorbo AR, Di Giacopo R, et al. Cardiovascular autonomic nervous system evaluation in Parkinson disease and multiple system atrophy. J Neurol Sci. 2014; 336(1-2): 197–202, doi: 10.1016/j.jns.2013.10.039, indexed in Pubmed: 24267739.

RESEARCH PAPERS

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 1, pages: 34–42
DOI: 10.5603/PJNNSPJNNS.a2019.0007

ISSN 0028–3843

Trigone ventricular meningiomas — clinical characteristics, histopathology and results of surgical treatment

Kamil Leśniewski[1], Przemysław Kunert[1], Ewa Matyja[2], Tomasz Czernicki[1], Katarzyna Wójtowicz[1], Jakub Wojciechowski[1], Andrzej Marchel[1]

[1]Department of Neurosurgery, Medical University of Warsaw, Poland
[2]Department of Experimental and Clinical Neuropathology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland

ABSTRACT

Aim of the study. Intraventricular meningiomas (IVMs) are rare tumours accounting for 0.5–3.0% of all meningiomas. IVMs require different surgical approaches and preparation in deep brain areas. The aim of our study was to present the clinico-histopathological characteristics and treatment outcomes of trigone IVMs in a series of 15 patients.

Materials and methods. Eight women and seven men (mean age 52) with 15 trigone IVMs were retrospectively analysed. Patients presented with headache (47%), psychoorganic syndrome (40%), hemianopsia (33%) or paresis (20%), including three (20%) patients with Karnofsky Performance Scale (KPS) < 80. Mean tumour size was 55.2 mm (range: 30–100 mm).

Results. Gross total tumour resection was performed in 14 (93%) cases, and subtotal in one (7%). A new deficit appeared in 83% (5/6) following a transparietal approach, in 14% (1/7) following a transtemporal approach, and in none of two patients following a transoccipital approach. Postoperative complications occurred in six (40%) patients; no patient died, but in two (13%) the new deficit was permanent. Tumour re-growth was found in two (13%) patients after 14 and 31 months. Meningiomas of WHO grade I occurred in 12, grade II in three, and grade III in one tumour recurrence. In long-term follow-up (mean: 60.8 months), including the results of revision operations, KPS: 80–100 was in 13 (87%) patients, KPS: 50 in one (severe hemiparesis after revision) and one patient was lost to follow-up (KPS: 100 on discharge).

Conclusions. 20% of IVMs in our series were atypical. The results of surgery for IVMs, although satisfactory in general, require further improvement by reducing the rate of focal deficits resulting from a surgical approach.

Key words: Intraventricular meningioma, surgical approach, morbidity, tumour recurrence
(*Neurol Neurochir Pol 2019; 53 (1): 34–42*)

Introduction

Intraventricular meningiomas (IVMs) are rare tumours accounting for 0.5–3.0% of all meningiomas. Their distinguishing feature is the lack of a dural attachment. IVMs require different surgical approaches and preparation in the vicinity of the central area of the brain. The first description of an intraventricular tumour with the morphology of a meningioma was presented by Shaw in 1854 [1] and MacDowell was the first to treat it surgically in 1881 [2]. In 1938, Cushing and Eisenhardt described three cases of intraventricular tumours in a group of 313 patients operated on for meningiomas, including the first case of a third ventricular meningioma [3]. Recently, Pereira et al. systematically reviewed 682 IVMs from 98 papers [4].

The aim of this study was to present the clinical and histopathological characteristics of trigone IVMs based on our series of 15 patients. The results of surgical treatment together with an analysis of postoperative complications are also presented. The study rationale is the rarity of IVMs and the need to accumulate published data about their clinical course and treatment.

Address for correspondence: Przemysław Kunert, Department of Neurosurgery, Medical University of Warsaw, Banacha 1a, 02-097 Warsaw, Poland, e-mail: przemyslaw.kunert@wum.edu.pl

Material and methods

A series of 15 consecutive patients operated on for trigone IVM from 1988 to 2016 were subjected to retrospective analysis. The information was obtained from patient hospital files, outpatient cards, radiological archives and histopathological archives. The 15 patients comprised eight (53%) women and seven (47%) men aged from 22 to 78 years (mean age 52). Only a CT scan with contrast was performed on the first three (20%) patients of the analysed period, and twophase MR imaging was employed in the remaining 12 cases. In two cases, cerebral digital subtraction angiography was also performed.

Surgical treatment

A transgyral approach was used in all cases, including a posterior temporal lobe approach in seven cases, a superior parietal lobule approach in six cases, and an occipital approach via the lateral ventricle posterior horn in two cases. The occipital approach was employed only in patients with already existing contralateral hemianopsia.

For tumours located in the dominant hemisphere, approaches through the superior parietal lobule (four cases), inferior temporal gyrus (two cases), or through the occipital lobe (one case) were used. Tumours in the non-dominant hemisphere were approached via the posterior middle temporal gyrus (five cases), via the upper parietal lobule (two cases) or through the occipital lobe (one case). Intraoperative neurophysiological monitoring and neuronavigation were not used. Gross total tumour resection was performed in 14 (93%) cases, and subtotal resection in one (7%) case.

Postoperative management

After the procedure, the patients were awakened and monitored over the first hours in the postoperative ward. Rehabilitation commenced on the first postoperative day and the patient was encouraged to attempt an upright position and ambulate on the second postoperative day. Two-phase CT scans were routinely performed to exclude clinically significant tumour residues and other adverse effects of the operation.

Postoperative evaluation

A postoperative course with complications was defined as the occurrence of at least one adverse event, including (1) the occurrence of, or an increase in, neurological deficit, (2) abnormal results of postoperative CT scan (pneumo-, hydrocephalus, intracranial bleeding, oedema or stroke) resulting in the need for separate management, (3) liquorrhea, (4) poor wound healing, and (5) systemic complications. The short-term outcome was assessed on the day of discharge using the Glasgow Outcome Scale [5] and the Karnofsky Performance Scale (KPS) [6]. The KPS was used to evaluate the long-term outcome. Data from the last outpatient visit was used for long-term evaluation. The risk of tumour recurrence was assessed based on the last follow-up MR imaging. Follow-up data was obtained in 14 (93%) patients, with a mean follow-up period of 5.1 years.

Histopathology

For the purposes of this study, due to the long analysed period (28 years), tumour specimens were subjected to histopathological verification to unify the nomenclature and grading according to the 2007 WHO central nervous system tumour classification.

Results

Signs and symptoms

The duration of symptoms ranged from 0.5 to 47 months (mean 7 months). Headaches were the most common reason for neuroimaging (47%). Psychoorganic syndrome was presented by 40% of the patients, and hemianopsia was found in 33% (Tab. 1 and Tab. 6). In one case, an asymptomatic tumour with a diameter of 66 mm was diagnosed incidentally after a head injury. Three (20%) patients presented with a KPS of less than 80 on admission (Tab. 2).

Dilatation of the ventricular system or the trapped ventricle in pre-operative imaging was found in 11 (73%) patients, including 5/7 with a history of headaches and 6/8 without a history of headaches.

Tumour characteristics

In seven (47%) of the 15 cases, the trigone lateral ventricular tumours were located on the left side, and in the other eight (53%) on the right side. Tumour size ranged from 30 to 100 mm (mean 55.2). Calcifications in the tumour mass in the CT images were found in six (46%) cases out of 13 patients for whom such a study was performed. Thirteen (87%) tumours demonstrated homogenous enhancement after contrast

Table 1. Signs and symptoms

Signs and symptoms	Number (%)
Headaches	7 (47%)
Mental disturbances	6 (40%)
Hemianopsia	5 (33%)
Papilledema	3 (20%)
Hemiparesis	3 (20%)
Gait disturbances	1 (7%)
Hemiaesthesia	2 (13%)
Aphasia	2 (13%)
Epilepsy	1 (7%)
Accidental diagnostics (asymptomatic tumour)	1 (7%)

Table 2. Condition of patients before surgery, at discharge, at 6-month follow-up, and the final accessible outcome according to the Karnofsky Performance Scale (KPS)

Before surgery		At discharge		6-mth follow-up		The final outcome*	
KPS	No (%)	KPS	No (%)	KPS	No (%)	KPS	No (%)
100	3 (20%)	100	8 (53%)	100	12 (86%)	100	12 (80%) **
90	7 (47%)	90	3 (20%)	90	1 (7%)	90	2 (13%)
80	2 (13%)	80	2 (13%)	80	1 (7%)	80	0
70	2 (13%)	70	2 (13%)	70	0	70	0
60	1 (7%)	60	0	60	0	60	0
50	0	50	0	50	0	50	1 (7%)***

*Including results of revision operations and the last accessible data; **One patient lost to follow-up following surgery; the short-term outcome is included here; ***This patient was lost to further follow-up following revision surgery; the short-term outcome following the second operation is included here

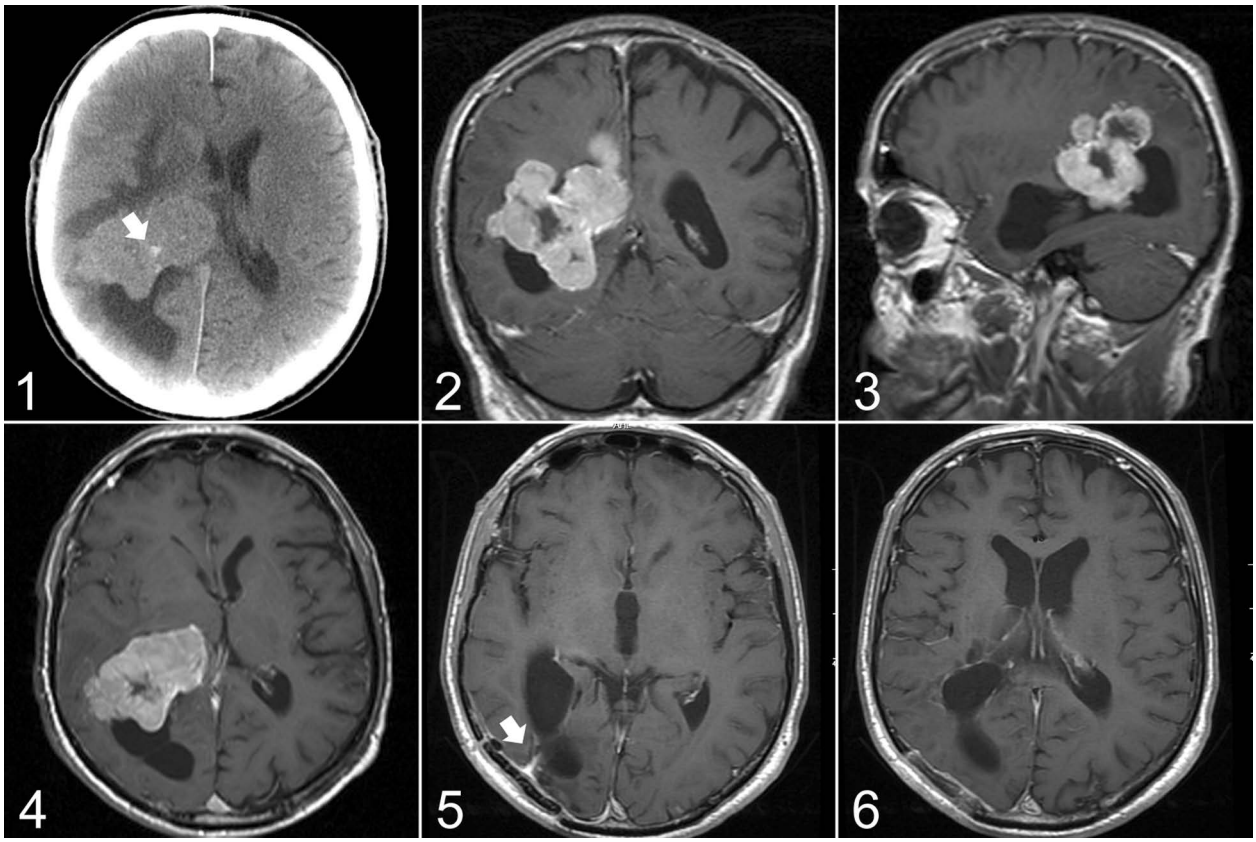


Figure 1.1. Preoperative, non-contrast CT showing a large isodense pathological mass with calcifications (arrow) in the right ventricular trigone with brain oedema surrounding; **Figure 1.2–1.4.** Preoperative, T1-weighted MR images demonstrating well-circumscribed polycyclic tumour, with non-homogeneous post-contrast enhancement; **Figure 1.5–1.6.** Follow-up MRI, obtained one year post-surgery, revealed no tumour re-growth. A corridor after transoccipital approach is visible (arrow)

administration (Fig. 1). There were no cases of intra-tumour cysts or haemorrhage into or out of the tumour. Cerebral angiography was performed in two patients with lateral ventricular tumours; in both cases, the vascular supply came from the anterior and posterior choroidal arteries.

Short-term outcomes

On the day of discharge, according to the GOS, a good recovery was achieved in 12 (80%) patients and mild disability in three (20%) patients. Thirteen (87%) patients were discharged from the hospital as being independent and able to lead

Table 3. Histopathology of intraventricular meningiomas

Histopathology subtype	No (%)
Transitional m. (WHO G I)	6 (40%)
Fibroblastic m. (WHO G I)	5 (33%)
Angiomatous m. (WHO G I)	1 (7%)
Atypical m. (WHO G II)	3 (20%)*

G — grade; m. — meningioma; *One of the atypical meningiomas re-grew and transformed to anaplastic form (WHO G III)

a normal life (KPS 80-100). Two patients had mild hemiparesis but were able to walk (KPS 70) (Tab. 2).

Histopathology

Meningiomas WHO grade I occurred in 13 patients and WHO grade II in three patients. One tumour re-grew as a WHO grade III (Tab. 3). The WHO grade I meningiomas included six transitional subtypes (Fig. 2.1), five fibroblastic subtypes (Fig. 2.2) and one angiomatous subtype. Among the transitional meningiomas, some tumours exhibited a heterogenous pattern combined with angiomatous (one patient) and metaplastic/xanthomatous (one patient) areas. One fibroblastic meningioma presented a combined pattern with a transitional component. Three tumours with sheeting architecture, hypercellularity neoplastic cells with prominent nucleoli and mitotic figures were recognised as atypical meningiomas WHO grade II. They contained numerous small foci of spontaneous necrosis with peripheral pseudopalisading (Fig. 2.3) and foci of foamy (xanthomatous) cells (Fig. 2.4). Moreover, one recurrence of atypical meningioma appeared to be anaplastic WHO grade III (Fig. 2.5). This exhibited large areas of necrosis, marked cellular pleomorphism, and increased mitotic count that exceeded 20 mitoses per 10 HPFs (high-power fields). The neoplasm extensively invaded the brain parenchyma and was accompanied by a severe reaction of astroglial cells (Fig. 2.6).

Postoperative complications

No patient died in the perioperative period. However, the postoperative course was complicated in six (40%) patients (Tab. 4). Three patients (43%) after a left-sided approach, and three (38%) after a right-sided approach, demonstrated neurological sequelae of the surgery. A new or worsening of a pre-existing neurological deficit was most often found following a superior parietal lobule approach, i.e. in 5/6 (83%) cases (Tab. 5 and Tab. 6). In addition, in one case in this group, the procedure was complicated by a haematoma requiring reoperation, followed by liquorrhea treated with external CSF drainage. 1/7 (14%) patients, following a transtemporal approach, demonstrated transient confusion with confabulations associated with a local brain oedema. There was neither clinically significant hydrocephalus nor pneumocephalus in our series. Deep vein thrombosis in the lower extremities occurred in one (7%) patient.

Tumour recurrence

Tumour re-growth was found in two (13%) patients at 14 and 31 months after the first operation (average of 23 months). In both patients, the tumour was removed completely during the first surgery via the parietal lobule approach and the lower temporal gyrus approach. Both patients underwent revision surgery and, using the same surgical approaches as before, the tumours were completely removed. In the first patient, atypical meningioma was diagnosed (WHO grade II) after the first operation (patient N°5 in Tab. 6). Then the patient underwent supplementary fractioned radiotherapy with a dose of 5,600 cGy. After revision surgery, the patient was discharged from hospital with severe hemiparesis and hypoaesthesia (GOS = SD, KPS 50). A histopathological examination revealed an anaplastic meningioma (WHO grade III). In the second patient, a transitional meningioma (WHO grade I) was diagnosed following both the first and the revision surgery (patient N°6 in Tab. 6). After reoperation, the patient was discharged home with a satisfactory outcome (KPS 90, GOS = MD), and with a minor cognitive impairment.

No tumour progression was observed during the follow-up period of 12 years in the only patient following subtotal tumour resection. A tumour remnant of approximately 5 mm on the choroid vein was left in this case. No supplementary treatment was applied. A histopathological examination showed a transitional meningioma of WHO grade I.

Long-term outcomes

Follow-up data was available from 0.5 to 20.3 years (mean 5.1 years) after surgery in 14 patients. The only patient who was lost to follow-up was discharged home in good condition, with no neurological deficits (KPS 100). At six months follow-up, all remaining 14 patients could lead a normal life (KPS 80–100) (Tab. 2). Neurological deficit persisted in two patients (13%), including slight hemiparesis and hemianopsia (KPS 80) in one patient and partial alexia (KPS 90) in the other patient. The preoperative hemianopsia significantly subsided in both patients operated on via the occipital lobe. In the long-term assessment, including the results of revision operations, normal life activity (KPS 90–100) could be conducted by 13/14 (93%) patients. One patient was discharged from hospital after re-operation with severe hemiparesis (GOS = SD, KPS 50) and was lost to further follow-up.

Discussion

Intraventricular meningiomas account for 0.5–3.0% of intracranial meningiomas [3, 7–9] with a relatively higher appearance rate in children [8, 10, 11]. It is commonly considered that their origin is arachnoid cells in the mesenchymal stroma of the choroid plexus or the tela choroidea. IVMs occur more frequently in women, with an occurrence rate of 25–82% in published series [12–15]. In our series, no significant female

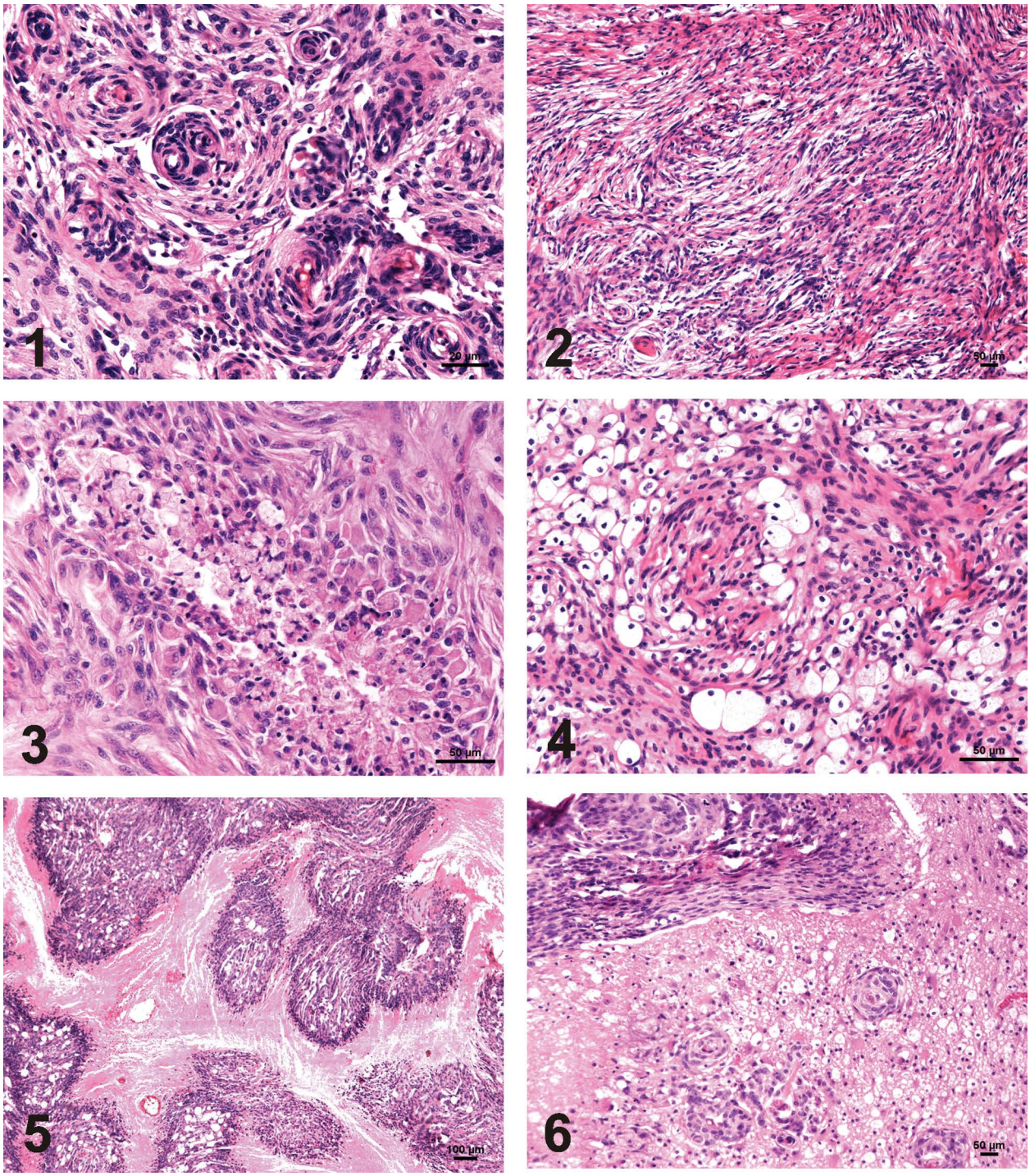


Figure 2.1. Transitional meningioma composed of whorls and cords of neoplastic cells; **Figure 2.2.** Fibroblastic meningioma consisting of spindle-shaped cells and pericellular collagen; **Figure 2.3.** Atypical meningioma exhibiting small foci of necrosis with peripheral pseudopalisading; **Figure 2.4.** Foci of foamy (xanthomatous) cells in atypical meningioma; **Figure 2.5.** Anaplastic meningioma with large areas of necrosis; **Figure 2.6.** Neoplastic invasion of the brain parenchyma associated with advanced astroglial reaction

predominance was observed (53% *vs* 47%). The mean age reported in the literature varies from 35 to 47 years [9, 16]; in our study, the mean age was 52 years.

Symptomatology

The most frequent IVM presentations are headaches, nausea, vomiting and visual disturbances, which are reported in

Table 4. Postoperative complications

	Postoperative complications	Number (%)
Neurological deficit		6 (40%)*
	including:	
	– deepening of preexisting deficit	3 (20%)
	– new	5 (33%)
	– transient deficit	4 (27%)
	– permanent deficit	2 (13%)
	– aphasia	1 (7%)
	– contralateral paresis	2 (13%)
	– homonymous hemianopsia	3 (20%)
	– confusion, confabulations	2 (13%)
Findings in postoperative unscheduled CT imaging	– brain oedema	1 (7%)
	– parenchymal haemorrhage	1 (7%)
	– hydrocephalus	0
	– stroke	0
	– symptomatic pneumocephalus	0
CSF leak		1 (7%)
Healing problems		1 (7%)
General complications	– deep vein thrombosis	1 (7%)

*The number of patients with complicated postoperative course (the number of adverse events is higher)

Table 5. New postoperative or deepening of preexisting neurological deficit depending on surgical approach

Surgical approach (No)	Postoperative neurological deficit No (%)
Transparietal (superior lobule) (No6)	5 (83%) including: 1. new homonymous hemianopsia — transient 2. new contralateral paresis — permanent 3. deepening of aphasia, new; confusion — transient 4. new contralateral paresis — transient 5. deepening of homonymous hemianopsia and new mild contralateral paresis — permanent
Transtemporal (No 7)	1 (14%) 1. confusion, confabulations — transient
Transoccipital (No 2)	0

40–80% of cases. Less common symptoms are mental disturbances, motor deficits, gait and balance disturbances, epilepsy and sensory deficits. In our series, headaches (47%) was the most common symptom, but only in one case was it the reason for investigation. Frequencies of mental disturbances (40%), hemianopsia (33%), papilledema (20%), hemiparesis (20%), gait disturbances (7%) and epileptic seizures (7%) (Tab. 1) were similar to other reported series [9, 13–15, 17, 18]. Due to their slow growth and specific localisation, intraventricular meningiomas can reach a considerable size, while headaches can occur for up to 15 years before a proper diagnosis is made [19]. The large mean tumour size (55 mm in our series) seems to confirm that these tumours can remain asymptomatic for a long time. This increases the probability of their incidental detection in the current era of widespread neuroimaging diagnostics. In our series, one tumour with a diameter of 66 mm was detected incidentally following a head injury. On the other hand, headaches without enlargement of the ventricular system (2/7 cases in our group) suggest that, in some cases, unrelated headaches may lead to a diagnosis of an asymptomatic tumour. In the Zanini series, as many as 3/5 tumours were diagnosed incidentally or due to non-specific symptoms [16]. In another series, a large number of IVMs were also detected incidentally [17]. Cerebrospinal fluid flow disorders, and direct pressure on neighbouring structures, have been mentioned as being the cause of the growing symptoms. The rich vascularisation of these tumours can sometimes lead to intralesional or intraventricular haemorrhages with rapid onset of symptoms [20, 21].

Characteristics of intraventricular meningiomas

The most common location of IVMs is the lateral ventricle, followed by the third and fourth ventricle [4]. Nakamura et al. analysed 532 cases of IVMs in publications up to 2003 and found that the frequencies were 77.8%, 15.6% and 6.6%, respectively [15]. In cases of lateral ventricle IVMs, left-side involvement is reported more frequently [7, 14, 22]. In our series, seven meningiomas were located on the left and eight on the right side.

Tumour calcifications in neuroimaging studies in our series were found in 46% of the patients. In the series of Ma et al., tumour calcifications were visible in 33% of the CT imaging studies [17]. Calcifications inside the tumour may indicate long-term tumour growth. This could be an argument for the observation of asymptomatic tumours. Interestingly, this option for IVMs has been mentioned [4], although we were unable to identify any reports of IVM observation in the Pubmed database. In the series of Nakamura et al., only 15% of intraventricular tumours were meningiomas [15].

Therefore, the rarity of intraventricular tumour location, and uncertainty as to its benign nature, favour oncological indications for surgical treatment.

Surgical technique

The choice of surgical approach to IVMs depends on the tumour size and location. This also includes the direction of the long axis of the tumour and the direction of tumour growth, taking into account the shortest distance to the surface of the brain. The choice of approach is also influenced by existing neurological deficits, by the distance from the tumour to the eloquent structures, and by a desire to minimise brain retraction around the operating corridor. For trigonal IVMs, we

Table 6. Clinical features and results of surgery in 15 cases of trigone ventricular meningiomas

No	Sex, age	Tumour size (mm), side	Signs and symptoms	Approach	Postoperative neurological sequelae	Tumour type and WHO grade	Karnofsky Performance Scale			Re-growth	Follow-up period [years]
							On admission	At discharge	Most recent		
1	M, 72	66, R	accidental	middle temporal	-	Transitional, WHO G I	100	100	100	No	0.5
2	M, 37	65, R	headaches	middle temporal	-	Transitional, WHO G I	100	100	100	No	3.9
3	F, 22	45, L	headaches, papilledema	superior parietal	permanent hemiparesis	Fibroblastic, WHO G I	90	90	90	No	1.6
4	M, 46	30, R	headaches, mental disturbances,	middle temporal	-	Transitional, WHO G I	90	100	100	No	8.2
5	M, 63	56, R	hemiaesthesia, hemianopsia	superior parietal	permanent hemiparesis, hemianopsia	Atypical, WHO G II > Anaplastic, G III*	90	70	80 > 50*	Yes	1.2
6	F, 58	58, L	mental disturbances	inferior temporal	-	Transitional, WHO G I	100	100	100 > 100*	Yes	20.3
7	M, 47	100, L	hemianopsia, aphasia	superior parietal	transient deepening of aphasia, confusion	Atypical, WHO G II	80	90	90	No	0.5
8	F, 65	53, L	headache, mental disturbances, hemiparesis, aphasia	superior parietal	-	Transitional, WHO G I	70	80	100	No	11.7
9	F, 72	44, R	hemiparesis	superior parietal	transient hemianopsia	Fibroblastic, WHO G I	70	70	100	No	6.2
10	F, 30	60, L	headache, hemianopsia	superior parietal	transient mild hemiparesis	Atypical, WHO G II	90	100	100	N/A	N/A
11	M, 43	35, L	epilepsy, hemianopsia	occipital	-	Fibroblastic, WHO G I	90	100	100	No	12,1
12	F, 64	64, R	headache, papilledema	middle temporal	transient confabulations	Angiomatous, WHO G I	90	100	100	No	0.8
13	F, 30	44, R	headache, mental disturbances, gait disturbances	middle temporal	-	Transitional, WHO G I	80	100	100	No	0.5
14	F, 52	45, L	mental disturbances, papilledema, hemiaesthesia	inferior temporal	-	Fibroblastic, WHO G I	60	80	100	No	1.8
15	M, 78	63, R	mental disturbances, hemiparesis, hemianopsia	occipital	-	Fibroblastic, WHO G I	90	90	100	No	1.8

*after revision surgery; F — female; G — grade; L — left; M — male; N/A — not available; R — right

used transcortical approaches through the posterior temporal lobe, the parietal lobe or the occipital lobe. However, other options, including transsulcal approaches, have also been employed [17, 23]. The routes through the posterior temporal and occipital lobes increase the risk of quadrantanopsia and hemianopsia. Nevertheless, these routes are often the shortest paths to the tumour and they make possible earlier control of the feeding vessels. The approach through the temporal lobe is also linked to a risk of damage to the vein of Labbe, and — if the tumour is located in the dominant hemisphere — aphasia. In two of our patients, the tumour was reached through the posterior part of the lower temporal gyrus. The transoccipital route was employed in two patients presenting with hemianopsia and with tumours progressing towards the occipital horn. Interestingly, a significant withdrawal of visual field narrowing was observed in both patients in long-term follow-up. This may indicate that, in the case of posterior horn tumours, the visual path may be significantly displaced. Incision within the upper parietal lobule gives a good insight into the medial and lateral part of the ventricular triangle. The access path to the ventricle runs medially from the fibres of the optic radiation, theoretically reducing the risk of optic pathway damage. However, the risk of apraxia and Gerstmann's syndrome remains [17]. In addition, our experience indicates that even permanent hemianopsia can occur with this approach. On the other hand, the interparietal, intraparietal or parieto-occipital approaches appear to be the most popular to trigonal IVMs [9, 12, 14–16, 18].

Histopathology

Based on the literature, about 90% of IVMs are benign tumours, 7–8% are atypical, and 3% are anaplastic tumours [4, 17]. Histopathologically, all subtypes of meningiomas are diagnosed, and fibromatous, fibroblastic, meningothelial and psammomatous are the most common. Pereira et al. in a recent systematic review emphasised that the fibrous subtype constitutes as much as 40% of all IVMs [4]. In our series, 12 (80%) meningiomas were WHO grade I and three (20%) meningiomas were atypical, including one with malignant transformation to WHO grade III. In the series of Ødegaard et al., 90% of IVMs were WHO grade I and, similarly, one of two WHO grade II meningiomas recurred rapidly following surgery as an anaplastic meningioma [9].

Treatment results

Ma et al. obtained satisfying long-term outcomes (KPS 80–100) in all 42 patients with available catamnesis [17]. Our results are very similar to other series published after 2000 [9, 26]. Most preoperative and postoperative deficits resolved over time (Tab. 2, 4, 5). In long-term evaluation, including the results of revision surgeries, 13/14 patients with available follow-up data were able to lead a normal life (KPS 90–100).

Complications and tumour recurrence

Perioperative mortality according to the available literature ranges from 0% to 42%. However, historically it reached as much as 75% for the 'en bloc' tumour removal technique [7, 15]. The mortality rate based on a systematic review is 4% [4]. In the series published since 2003, IVMs have been removed entirely in 95% of cases, with a total mortality rate of 1.6%, which is close to the results of surgery for convexity meningiomas [9, 12, 14, 15, 17–19]. In our group, no patient died in the perioperative period. The incidence of other complications varies between 0% and 60% [16, 17, 24], while in our series it was 40%. Most often, this was an increase in, or the occurrence of a new, neurological deficit associated with the operative approach. In our series, a permanent deficit occurred in only two (13%) patients (Tab. 4 and Tab. 5). The most common complication reported in the literature was hemianopsia in 11% of patients [9]. The risk of tumour recurrence in larger published series ranges from 0% to 20% [9, 12, 14–19]. Our tumour recurrence rate was 13%.

The results of surgery for IVMs, although satisfactory in general, require further improvement by reducing the rate of focal deficits resulting from a surgical approach. Currently, the planning of operative corridors based on functional MR with diffusion tensor imaging is a promising tool to avoid subcortical tract damage [25]. Also, the growing popularity of minimally invasive techniques, such as transsulcal approaches using tubular retractors to deep-seated lesions, gives hope for a further decrease in approach-related morbidity [26].

Conclusion

Intraventricular meningiomas usually attain large size before diagnosis. 20% of IVMs in our series was atypical. In our experience, neurological complications were most frequent if a transparietal approach was applied. The results of surgery for trigone IVMs, although satisfactory in general, require further improvement. Modern functional brain mapping should be employed more widely to allow more appropriate approach selection.

Conflict of interest: *The authors declare no conflict of interest.*
Ethical Statement: *No approval is required by the ethics committee of our institutions for retrospective analyses of patient records and imaging data.*

References

1. Shaw A. Fibrous tumor in the lateral ventricle of the brain, bony deposits in the arachnoid membrane of the right hemisphere. Transactions of the Pathological Society of London 1853. ; 5: 18–21.
2. M'Dowall TW. Large Calcareous Tumour, Involving Chiefly the Inner and Middle Portions of the Left Temporo-Sphenoidal Lobe, and Pressing upon the Left Crus and Optic Thalamus. Edinb Med J. 1881; 26(12): 1088–1093, indexed in Pubmed: 29647272.

3. Meningiomas: Their Classification, Regional Behavior, Life History, and Surgical End Results. Archives of Neurology And Psychiatry. 1939; 41(3): 657, doi: 10.1001/archneurpsyc.1939.02270150231022.
4. Pereira BJ, de Almeida AN, Paiva WS, et al. Natural history of intraventricular meningiomas: systematic review. Neurosurg Rev. 2018 [Epub ahead of print], doi: 10.1007/s10143-018-1019-0, indexed in Pubmed: 30112665.
5. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975; 1(7905): 480–484, indexed in Pubmed: 46957.
6. Karnofsky D, Burchenal J. The Clinical Evaluation of Chemotherapeutic Agents in Cancer. in: MacLeod C.M. Evaluation of Chemotherapeutic Agents. New York: Columbia University Press. ; 1949: 196–196.
7. Fornari M, Savoiardo M, Morello G, et al. Meningiomas of the lateral ventricles. Neuroradiological and surgical considerations in 18 cases. J Neurosurg. 1981; 54(1): 64–74, doi: 10.3171/jns.1981.54.1.0064, indexed in Pubmed: 7463122.
8. Kloc W, Imieliński BL, Wasilewski W, et al. Meningiomas of the lateral ventricles of the brain in children. Childs Nerv Syst. 1998; 14(8): 350–353, doi: 10.1007/s003810050242, indexed in Pubmed: 9753398.
9. Ødegaard KM, Helseth E, Meling TR. Intraventricular meningiomas: a consecutive series of 22 patients and literature review. Neurosurg Rev. 2013; 36(1): 57–64; discussion 64, doi: 10.1007/s10143-012-0410-5, indexed in Pubmed: 22847766.
10. Byard RW, Bourne AJ, Clark B, et al. Clinicopathological and radiological features of two cases of intraventricular meningioma in childhood. Pediatr Neurosci. 1989; 15(5): 260–264, indexed in Pubmed: 2488954.
11. Mircevski M, Mircevska D, Bojadziev I, et al. Surgical treatment of intraventricular meningiomas in childhood. Acta Neurochir Suppl (Wien). 1985; 35: 89–91, indexed in Pubmed: 3867264.
12. Bhatoe HS, Singh P, Dutta V. Intraventricular meningiomas: a clinicopathological study and review. Neurosurg Focus. 2006; 20(3): E9, indexed in Pubmed: 16599425.
13. Criscuolo GR, Symon L. Intraventricular meningioma. A review of 10 cases of the National Hospital, Queen Square (1974-1985) with reference to the literature. Acta Neurochir (Wien). 1986; 83(3-4): 83–91, indexed in Pubmed: 3492867.
14. Liu M, Wei Y, Liu Y, et al. Intraventricular meninigiomas: a report of 25 cases. Neurosurg Rev. 2006; 29(1): 36–40, doi: 10.1007/s10143-005-0418-1, indexed in Pubmed: 16220350.
15. Nakamura M, Roser F, Bundschuh O, et al. Intraventricular meningiomas: a review of 16 cases with reference to the literature. Surg Neurol. 2003; 59(6): 491–503; discussion 503, indexed in Pubmed: 12826353.
16. Zanini MA, Faleiros AT, Almeida CR, et al. Trigone ventricular meningiomas: surgical approaches. Arq Neuropsiquiatr. 2011; 69(4): 670–675, indexed in Pubmed: 21877039.
17. Ma J, Cheng L, Wang G, et al. Surgical management of meningioma of the trigone area of the lateral ventricle. World Neurosurg. 2014; 82(5): 757–769, doi: 10.1016/j.wneu.2014.05.026, indexed in Pubmed: 24878623.
18. Bertalanffy A, Roessler K, Koperek O, et al. Intraventricular meningiomas: a report of 16 cases. Neurosurg Rev. 2006; 29(1): 30–35, doi: 10.1007/s10143-005-0414-5, indexed in Pubmed: 16184406.
19. Lyngdoh BT, Giri PJ, Behari S, et al. Intraventricular meningiomas: a surgical challenge. J Clin Neurosci. 2007; 14(5): 442–448, doi: 10.1016/j.jocn.2006.01.005, indexed in Pubmed: 17350844.
20. Fu Z, Xu K, Xu B, et al. Lateral ventricular meningioma presenting with intraventricular hemorrhage: a case report and literature review. Int J Med Sci. 2011; 8(8): 711–716, indexed in Pubmed: 22135618.
21. Romeike BFM, Joellenbeck B, Skalej M, et al. Intraventricular meningioma with fatal haemorrhage: clinical and autopsy findings. Clin Neurol Neurosurg. 2007; 109(10): 884–887, doi: 10.1016/j.clineuro.2007.07.016, indexed in Pubmed: 17764829.
22. Guidetti B, Delfini R, Gagliardi FM, et al. Meningiomas of the lateral ventricles. Clinical, neuroradiologic, and surgical considerations in 19 cases. Surg Neurol. 1985; 24(4): 364–370, indexed in Pubmed: 3875905.
23. Kawashima M, Li X, Rhoton AL, et al. Surgical approaches to the atrium of the lateral ventricle: microsurgical anatomy. Surg Neurol. 2006; 65(5): 436–445, doi: 10.1016/j.surneu.2005.09.033, indexed in Pubmed: 16630901.
24. Menon G, Nair S, Sudhir J, et al. Meningiomas of the lateral ventricle — a report of 15 cases. Br J Neurosurg. 2009; 23(3): 297–303, doi: 10.1080/02688690902721862, indexed in Pubmed: 19533463.
25. Frati A, Pesce A, D'Andrea G, et al. A purely functional Imaging based approach for transcortical resection of lesion involving the dominant atrium: Towards safer, imaging-guided, tailored cortico-leucotomies. J Clin Neurosci. 2018; 50: 252–261, doi: 10.1016/j.jocn.2018.01.045, indexed in Pubmed: 29429789.
26. Eliyas JK, Glynn R, Kulwin CG, et al. Minimally Invasive Transsulcal Resection of Intraventricular and Periventricular Lesions Through a Tubular Retractor System: Multicentric Experience and Results. World Neurosurg. 2016; 90: 556–564, doi: 10.1016/j.wneu.2015.12.100, indexed in Pubmed: 26805678.

RESEARCH PAPERS

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 1, pages: 43–46
DOI: 10.5603/PJNNS.a2019.0004

ISSN 0028–3843

Familial occurrence of carpal tunnel syndrome

Piotr Puchalski, Zbigniew Szlosser, Andrzej Żyluk

Department of General and Hand Surgery, Pomeranian Medical University in Szczecin, Poland

ABSTRACT

The objective of this study was to investigate the incidence of familial carpal tunnel syndrome in patients admitted to the authors' institution for carpal tunnel release. Questionnaires completed by 120 patients: 92 women (77%) and 28 men (23%) at a mean age of 56 years at their baseline clinical examination were reviewed. Familial occurrence of the disease was noted in 21 patients (17%): 16 women and five men. Three family members were affected in three patients, two relatives in eight patients, and one relative in 10 patients, giving a total of 35 affected relatives. The patients' sisters (n = 16) were the most commonly involved, followed by mothers (n = 12), daughters (n = 2), brothers (n = 2), grandmothers (n = 2) and an aunt (n = 1). Bilateral manifestation of the disease was noted in 19 patients (90%) and in 31 (88%) of their affected relatives. The results suggest that carpal tunnel syndrome shows a moderate tendency to familial occurrence and, if so, it usually manifests bilaterally.

Key words: carpal tunnel syndrome, inheritable traits, familial predispositions, bilateral presentation
(*Neurol Neurochir Pol 2019; 53 (1): 43–46*)

Introduction

Controversy has been considerable regarding the incidence of familial occurrence of carpal tunnel syndrome (CTS). Individual families have been reported where most of the members have been affected, and the results of some population-based studies have shown a higher incidence of the condition among relatives of some patients. The first report of the occurrence of CTS among members of the same family was made in 1959 [1]. A decade later, Phalen noticed that a proportion of his CTS patients had declared occurrence of the same symptoms in their family members, suggesting familial predisposition to the syndrome [2]. These findings were confirmed by Radecki, who showed that 165 of 421 patients (39%) operated on for CTS had relatives suffering from the same symptoms in their hands [3]. The author suggests that inheritable carpal tunnel syndrome may be caused by biochemical, developmental or anatomical changes of the carpal tunnel. In contrast, on the basis of literature reviews, other authors have found that true inheritable carpal tunnel syndrome occurs very rarely [4].

The objective of this study was to investigate the incidence of familial carpal tunnel syndrome in patients admitted to the authors' institution for carpal tunnel release.

Materials and methods

Questionnaires completed at baseline clinical examination by 120 patients with CTS admitted to the authors' institution between December 2017 and March 2018 (a period of four months) were reviewed. The approval of the Bioethical Council of the local Medical University was obtained for funding the Carpal Tunnel Syndrome Register and for performance of further analyses. Informed consent was obtained from all subjects before enrolment. There were 92 women (77%) and 28 men (23%) with a mean age of 56 years (range 33–84).

The diagnosis of CTS was made on the basis of clinical and electrophysiological grounds. In all of these patients, nerve conduction studies were positive, confirming the diagnosis. The following grading scale of the severity of electrophysiological abnormalities was used in our study:

Grade I (mild). Decreased sensory nerve conduction (< 40 m/s) and SNAP recordable with normal (≥ 10 μV) or decreased (1–9 μV) amplitude. DML normal or slightly prolonged (3.5–4.0 ms). CMAP normal (≥ 4 mV). Normal EMG recording from APB.

Grade II (moderate). SNAP non-recordable. DML prolonged > 4 ms. CMAP normal or decreased (2–4 mV). Normal or moderately neurogenic EMG recording from APB.

Address for correspondence: Piotr Puchalski, Department of General and Hand Surgery, Pomeranian Medical University in Szczecin, Poland, e-mail: piotrpuch@onet.poczta.pl

Table 1. Demographic and clinical data obtained from patients with familial carpal tunnel syndrome

ID	Sex	Age	Duration of CTS	Affected relatives	Time of onset of CTS in relatives	Hand involved	Comorbidities	Treatment
1	F	67	20 y	2 sisters	10 and 20 years ago	Bilateral	No	Not operated
2	F	78	1 y	2 daughters	2 and 4 years ago	Bilateral	No	1 operated
3	M	55	2 y	Mother	15 years ago	Bilateral	Diabetes	Not operated
4	F	69	10 y	2 sisters	19 years ago	Bilateral	No	1 operated
5	M	56	10 y	Sister	5 years ago	Left	Thyroidectomy	Not operated
6	F	35	1 y	Mother and aunt	18 and 7 years ago	Bilateral	No	Not operated
7	F	51	5 y	Sister	7 years ago	Bilateral	No	Operated
8	F	55	5 y	Mother	10 years ago	Bilateral	No	Operated
9	F	49	10 y	Sister	9 years ago	Bilateral	No	Operated
10	F	45	8 y	Mother	15 years ago	Right	No	Not operated
11	M	65	2 y	2 brothers and sister	4 years ago	Bilateral	No	Not operated
12	M	51	7 y	Mother, sister	15 and 10 years ago	Bilateral	No	Operated
13	F	59	1 y	Sister	3 years ago	Right	No	Not operated
14	F	57	2 y	Mother, sister	3 and 2 years ago	Bilateral	No	Not operated
15	F	51	2 y	Grandmother	30 years ago	Bilateral	No	Operated
16	F	33	1 y	Grandmother, mother, sister	3-30 years ago	Bilateral	No	1 operated
17	M	51	7 y	Mother, sister	15 and 10 years ago	Bilateral	No	Operated
18	F	59	1 y	Sister	3 years ago	Right	No	Not operated
19	F	57	2 y	Mother, sister	3 and 2 years ago	Bilateral	Diabetes	Not operated
20	F	51	2 y	Mother	30 years ago	Bilateral	No	Operated
21	F	33	1 y	Grandmother, mother, sister	5-30 years ago	Bilateral	No	1 operated

Grade III (severe). SNAP non-recordable. DML prolonged > 4 ms. CMAP decreased < 2 mV) or non-recordable. EMG showing massive or complete muscle denervation.

Basic demographic and clinical information was recorded in the questionnaire (Tab. 1). All participants were then asked whether they knew of any family members with carpal tunnel syndrome. In the event of a positive answer, patients were asked to indicate which of their relatives was affected, when the disease was diagnosed, which hand was involved, and how they were treated. All information was self-reported. If a given patient knew about a family member who suffered from CTS, but was unable to provide the required details (did not recall), this case was not considered as 'familial CTS'. The presence of comorbidities potentially predisposed to CTS was also recorded [6].

Results

Familial occurrence of the disease was noted in 21 patients (17%): 16 women and five men. Three family members were affected in three patients, two relatives in eight patients, and one relative in 10 patients, giving a total of 35 affected relatives. Patients' sisters (n = 16) were the most commonly affected, followed by mothers (n = 12), daughters (n = 2), brothers (n = 2), grandmothers (n = 2) and an aunt (n = 1). Bilateral manifestation of the disease was noted in 19 of 21 patients (90%) and in 31 of 35 (88%) of their affected relatives. The disease in patients' family members was diagnosed 2-30 years earlier than in the patients themselves. Thirteen of 35 relatives (37%) were operated on. Three patients (14%) had comorbidities potentially predisposed to CTS: two had diabetes and one underwent thyroidectomy. No systemic disease, neuropathy, history of wrist trauma, or drug use was noted in other patients.

Discussion

The results of this study show a fairly common (17%) incidence of CTS among relatives of patients. This is significantly higher than in the general population (1%) and in women > 40 years old (5%) [5]. This result does not automatically confirm the hypothesis of inheritability of the syndrome in some families. There are many factors predisposing to CTS, such as constitutional traits (short height, thicksetness and obesity), diseases (diabetes, hypothyroidism, rheumatoid arthritis) or developmental and anatomical changes of the carpal tunnel

(4–8). Only some of them can be suspected of inheritability, but none were identified in our patients. Nevertheless, the occurrence of the syndrome in several members of one family may suggest that the risk of hereditary factors being present is higher than in the general population.

Several hereditary biochemical disorders have been identified predisposing to carpal tunnel syndrome, such as inheritable myopathies, familial hypercholesterolemia, familial amyloidosis, or hereditary neuropathy with liability to pressure palsies [9–11]. The incidence of CTS in families affected by these diseases is much higher than in the general population, and onset of the syndrome occurs early, usually in the second or third decade of life. Inheritable structural variations in the size of the tunnel or the volume of its contents have also been reported as predisposing to familial occurrence of the syndrome [12–14]. The results of our study also showed a significantly higher incidence of bilateral disease in patients with familial CTS: it occurred in 18 of 21 patients and in 31 of 35 their relatives. This finding was similar to that reported in a study by Alford et al.: 45% of patients with bilateral syndrome declared occurrence of the same symptoms in their family members, compared to 27% of patients with unilateral CTS declaring the same. The authors suggested the presence of inheritability of variations in the size of the carpal tunnel or its contents, which would manifest themselves bilaterally and may cause a predisposition for developing the syndrome [7].

The direct causes of idiopathic carpal tunnel syndrome remain obscure. Three different mechanisms are suspected to be involved in genetic predisposition to carpal tunnel syndrome: collagen synthesis, collagen degradation, and protection against oxidative stress effect in connective tissue. Several gene groups are involved in the regulation and modulation of these mechanisms, and results from the presented studies have shown their possible effect on the development of carpal tunnel syndrome. Variants within the COL1A1, COL5A1 and COL11A1 genes encoding synthesis of minor collagen subtypes may be potentially involved, as they alter the mechanical properties of tendons and other connective tissue structures within the carpal tunnel [15]. The collagen within connective tissue structures is also remodelled by matrix metalloproteinases (MMPs) and variants of these genes have also been investigated for their possible role in the risk of CTS development [16]. Next, the variants of genes encoding glutathione S-transferase synthesis were found to be involved in CTS aetiology [17]. These mechanisms may play a potential role as genetic risk factors in carpal tunnel syndrome and in its familial occurrence.

Self-reporting of the data placed unavoidable limitations on the accuracy of our data because we relied on patients' awareness of their family members' conditions. One may suspect that some of them, particularly in older age, might simply forget the presence of the disease in their relatives. In some families, their members live far away from each other and contact each other infrequently. We were not able to assess the degree to which our patients were underreporting family members with carpal tunnel syndrome of whom they were unaware. For this reason, the incidence of familial CTS in our material could be underestimated, in which case it emphasises still more the existence of the problem.

Clinical implications and future directions

The results of our study show that carpal tunnel syndrome has a moderate tendency to familial occurrence and that most familial cases occur in patients with bilateral disease. These findings seem not to have a direct translation into clinical practice, but may indicate the need for further investigations of this field. We believe that a question about family history should be added to the routine examination of each patient diagnosed with carpal tunnel syndrome.

References

1. TANZER RC. The carpal-tunnel syndrome; a clinical and anatomical study. J Bone Joint Surg Am. 1959; 41-A(4): 626–634, indexed in Pubmed: 13664702.
2. Phalen GS. Reflections on 21 years' experience with the carpal-tunnel syndrome. JAMA. 1970; 212(8): 1365–1367, indexed in Pubmed: 5467525.
3. Radecki P. The familial occurrence of carpal tunnel syndrome. Muscle Nerve. 1994; 17(3): 325–330, doi: 10.1002/mus.880170311, indexed in Pubmed: 8107710.
4. Gossett JG, Chance PF. Is there a familial carpal tunnel syndrome? An evaluation and literature review. Muscle Nerve. 1998; 21(11): 1533–1536, indexed in Pubmed: 9771681.
5. Atroshi I, Gummesson C, Ornstein E, et al. Prevalence of carpal tunnel syndrome in a general population. JAMA. 1999; 282(2): 153–158, indexed in Pubmed: 10411196.
6. Padua L, Coraci D, Erra C, et al. Carpal tunnel syndrome: clinical features, diagnosis, and management. Lancet Neurol. 2016; 15(12): 1273–1284, doi: 10.1016/S1474-4422(16)30231-9, indexed in Pubmed: 27751557.
7. Alford JW, Weiss APC, Akelman E. The familial incidence of carpal tunnel syndrome in patients with unilateral and bilateral disease. Am J Orthop (Belle Mead NJ). 2004; 33(8): 397–400, indexed in Pubmed: 15379235.
8. Żyluk A, Dąbal L, Szlosser Z. Constitutional factors and predisposition to carpal tunnel syndrome. Pol Orthop Traumatol. 2011; 76: 127–132.
9. Leifer D, Cros D, Halperin JJ, et al. Familial bilateral carpal tunnel syndrome: report of two families. Arch Phys Med Rehabil. 1992; 73(4): 393–397, indexed in Pubmed: 1554316.
10. Murakami T, Tachibana S, Endo Y, et al. Familial carpal tunnel syndrome due to amyloidogenic transthyretin His 114 variant. Neurology. 1994; 44(2): 315–318, indexed in Pubmed: 8309582.
11. Ihara Y, Nobukuni K, Namba R, et al. A family of familial hypercholesterolemia with cerebral infarction and without coronary heart disease. An unusual case with corneal opacity, polyneuropathy and carpal tunnel syndrome in the family: therapy with probucol and tocopherol nicotinate. J Neurol Sci. 1991; 106(1): 10–18, indexed in Pubmed: 1779233.

12. Michaud LJ, Hays RM, Dudgeon BJ, et al. Congenital carpal tunnel syndrome: case report of autosomal dominant inheritance and review of the literature. Arch Phys Med Rehabil. 1990; 71(6): 430–432, indexed in Pubmed: 2185719.
13. Iannicelli E, Chianta GA, Salvini V, et al. Evaluation of bifid median nerve with sonography and MR imaging. J Ultrasound Med. 2000; 19(7): 481–485, indexed in Pubmed: 10898302.
14. Mahjneh I, Saarinen A, Siivola J. Familial carpal tunnel syndrome: a report of a Finnish family. Acta Neurol Scand. 2001; 104(6): 377–379, indexed in Pubmed: 11903093.
15. Dada S, Burger MC, Massij F, et al. Carpal tunnel syndrome: The role of collagen gene variants. Gene. 2016; 587(1): 53–58, doi: 10.1016/j.gene.2016.04.030, indexed in Pubmed: 27090000.
16. Burger MC, De Wet H, Collins M. Matrix metalloproteinase genes on chromosome 11q22 and risk of carpal tunnel syndrome. Rheumatol Int. 2016; 36(3): 413–419, doi: 10.1007/s00296-015-3385-z, indexed in Pubmed: 26521080.
17. Kim JK, Koh YDo, Kim JS, et al. Oxidative stress in subsynovial connective tissue of idiopathic carpal tunnel syndrome. J Orthop Res. 2010; 28(11): 1463–1468, doi: 10.1002/jor.21163, indexed in Pubmed: 20872582.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal od Neurology and Neurosurgery
2019, Volume 53, no. 1, pages: 47–54
DOI: 10.5603/PJNNS.a2018.0002

ISSN 0028–3843

How does early decompressive craniectomy influence the intracranial volume relationship in traumatic brain injury (TBI) patients?

Piotr Jasielski[1], Zbigniew Czernicki[2], Piotr Dąbrowski[3], Waldemar Koszewski[2], Rafał Rojkowski[4]

[1]Department of Neurosurgery, Bielanski Hospital, Warsaw, Poland
[2]Department of Neurosurgery, II Faculty of Medicine, Medical University of Warsaw, Poland
[3]Department of Neurosurgery, Western Hospital in Grodzisk Mazowiecki, Grodzisk Mazowiecki, Poland
[4]Department of Radiology, Czerniakowski Hospital, Warsaw, Poland

ABSTRACT

Background. Decompressive craniectomy (DC) is a common neurosurgical procedure involving the removal of part of the skull vault combined with subsequent duroplasty. The goal of DC is to produce extra space for the swollen brain and/or to reduce intracranial pressure. In the present study, DC was performed in order to create space for the swollen brain.

Aim of the study:

1. to compare the volume alteration of selected intracranial fluid spaces before and after DC,
2. to evaluate the volume of post-decompressive brain displacement (PDBD) and the largest dimension of oval craniectomy (LDOC), and
3. to assess the early clinical effects of DC.

Material and methods. The study group consisted of 45 patients with traumatic brain injury (four females and 41 males, mean age 54.5 years) who underwent DC (not later than five hours after admission to hospital) due to subdural haematomas and/or haemorrhagic brain contusions localised supratentorially and diagnosed by computed tomography (CT). The mortality rate in the study group was 40%. Study calculations were performed using Praezis Plus software by Med Tatra, Zeppelin and Pax Station by Compart Medical Systems. For statistical analysis, IBM SPSS Statistics software was used.

Results. The DC-related additional space was responsible for a statistically significant increase in the volume of preoperatively compressed intracranial fluid spaces. The mean volume of extra space filled by the swollen brain was 42.2 ml ± 40.7. The best early treatment results were achieved in patients under the age of 55.

Conclusions. DC has limited effectiveness in patients aged over 70 years. In every patient with clamped basal cisterns, a skin incision enabling appropriate LDOC should be planned before surgery. DC should be as large as possible, and the limits of its dimensions should be the limits of anatomical safety.

Key words: traumatic brain injury, decompressive craniectomy, basal cistern volume, brain bulging
(*Neurol Neurochir Pol 2019; 53 (1): 47–54*)

Introduction

Traumatic brain injury (TBI) is one of the main unresolved health problems around the world. The long-term effects of TBI are a very important challenge for patients because of their suffering and disability. TBI is also a challenge for healthcare systems and involves a huge financial burden both for the families of the sick and for the general population [1].

The number of cases of TBI is high in poorly-developed and moderately-developed countries. The most common

Address for correspondence: Piotr Jasielski Department of Neurosurgery, Bielanski Hospital, Warsaw, Poland, e-mail: drjasielski@gmail.com

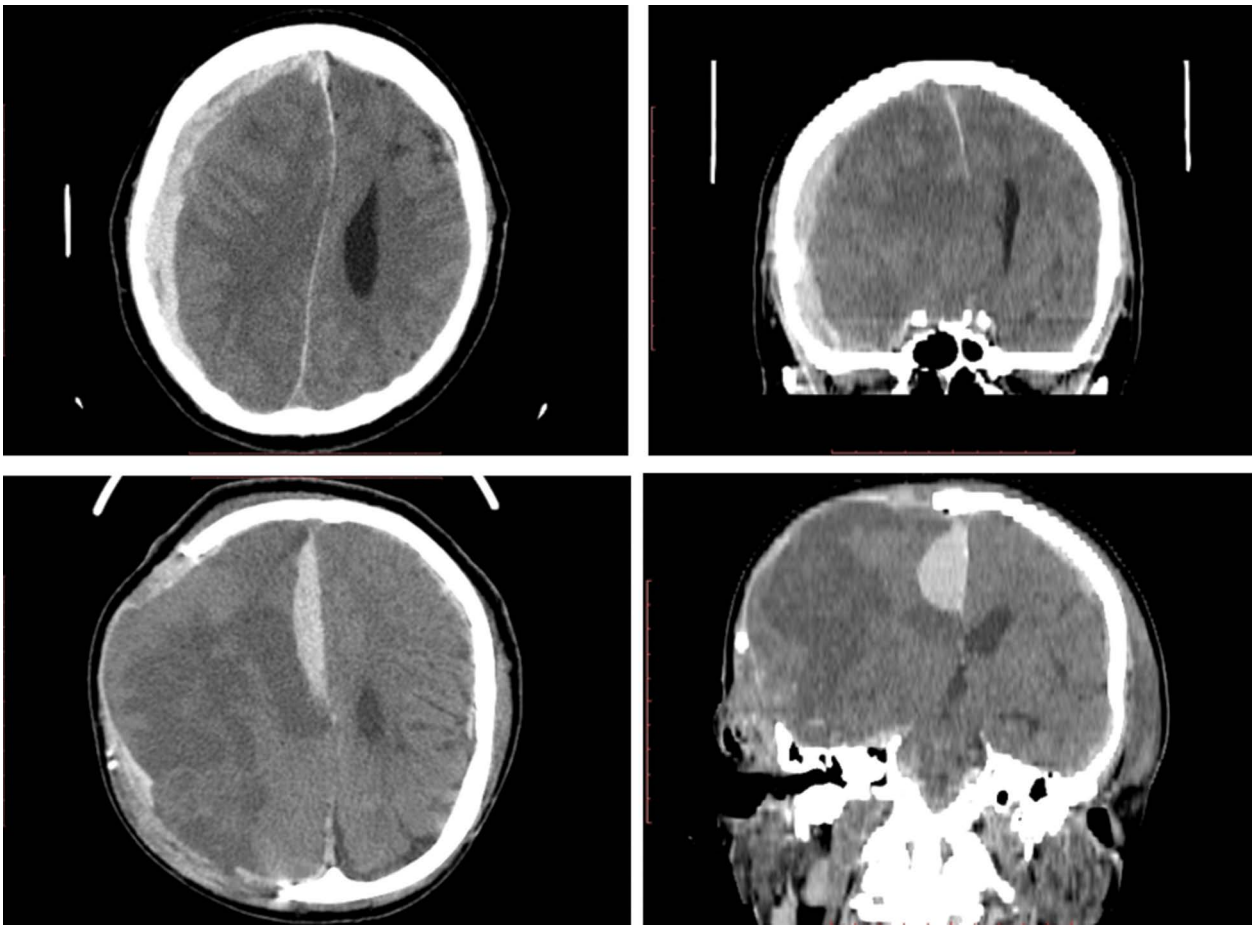


Figure 1. Post-decompressive brain displacement — computed tomography

causes here are traffic accidents and injuries experienced during physical exertion [2]. In well-developed countries, where the populations are older, the most common cause of TBI is falls [3]. Heavy TBIs are quite common in soldiers involved in warfare and in civilians who have been victims of terrorist attacks [4, 5]. The quality of life of people who suffer from severe TBI is quite low. The remaining life expectancy of these people is two to three times shorter than for the rest of the population [6].

Additional intracranial volumes resulting from injury (haematoma, cerebral oedema) lead to raised intracranial pressure (ICP), increased ischaemia, and hypoxia of the brain. One treatment option in this group of patients is to create additional space surgically by decompressive craniectomy (DC) (Fig. 1). Performing DC can also be necessitated by the intraoperative situation when the brain tissue bulges over the dura surface. Some neurosurgeons also perform DC when brain tissue initially does not enter the intraoperative lumen, but the occurrence of such a situation in the short term after surgery is anticipated.

Extensive knowledge of the pathophysiology of TBI, unfortunately, has not translated into significantly better outcomes for patients.

Aim of the study

- To evaluate clinical outcomes after performing DC with regard to the age of patients.
- To assess the alteration in volume of both the ambient and quadrigeminal cisterns before and after DC of different sizes, with regard to the age of patients.
- To evaluate the volume of post-decompressive brain displacement (PDBD) and the largest dimension of oval craniectomy (LDOC).

Material and methods

Out of 500 consecutive patients with TBI treated surgically in the Neurosurgery Department, 45 patients were enrolled in the study (four females, 41 males, mean age 54.5 years). DC was performed on patients with a post-traumatic haematoma and/or a haemorrhagic brain contusion, both localised supratentorially and diagnosed by computed tomography (CT). After removal of a haematoma, DC was performed as a result of increased intraoperative brain volume or as a result of the high probability of postoperative raised ICP. Craniectomies with LDOC below 11 cm were performed for haematoma

removal, and were not enlarged because no brain bulging was observed intraoperatively. The area of dura incision was tightly sealed using the autogenous periosteum of the skull. Plastic surgery of the dura was performed firstly to create additional space for the bulging brain tissue, secondly to provide a suitable barrier to isolate the brain, and finally to prevent postoperative CSF leakage.

In the study group, decompressive craniectomy was not a method of treating previously confirmed high ICP. The mean score according to the Glasgow Coma Scale (GCS) to qualify for surgery was 7, with a standard deviation of 3.8. The mean time between admission to the emergency unit (EU) and the start of anaesthesia for surgery was 127 minutes, and the shortest time was 20 minutes.

Criteria for exclusion of patients from the study group were: penetrating brain injury, brain stem injury, no intracranial haematoma, extradural haematoma and posterior fossa haematoma.

Cases were analysed taking into account a division into groups depending on age and state of consciousness before performing DC. Depending on age, four groups were identified. The first group consisted of 10 patients aged 40 years or below, the second of 15 patients aged 41–55, the third of 12 patients aged 56–70, and the fourth of eight patients aged 71 or above. For these four groups, the mean GCS score before DC was respectively: 9.0, 7.0, 6.5, and 6.5 and the mortality rates were 30.0%, 26.7%, 41.2%, and 75.0%. Acute subdural haematoma was found in five (out of 10) patients of Group 1, 11 (out of 15) patients in Group 2, eight (out of 12) patients in Group 3, and in all eight patients in Group 4. Haemorrhagic brain contusion was diagnosed in three, three, two, and one patient respectively, and acute subdural haematoma coexisting with haemorrhagic brain contusion in two, one, two, and two patients respectively.

The DC complications were analysed in the study group. Subcutaneous haematoma following DC was found in 8.9% (4/45) and parafalcine haematoma in 2.2% (1/45). Three of these five (60%) patients required reoperation due to mass effect or neurological deterioration. The rate of superficial wound healing complications was 4.4% (2/45).

The control group, which was used to compare the normal volume of selected intracranial CSF cisterns with the volume of the cisterns in the study group, consisted of 50 randomised patients who had reported to EU with severe headache of unknown origin without a prior history of TBI. In these patients, computed tomography of the head and neurological examination showed no abnormalities.

Upon admission to EU, computed tomography of the head was performed to visualise intracranial traumatic changes. Clinical status was assessed using a standard neurological examination. The GCS was used to evaluate patient reactivity. Patients were subjected to standard dehydration, analgesic and anticonvulsant therapy, and perioperative antibiotic prophylaxis was initiated. Patients were operated immediately after the indications for surgery were established. On average, on the second day after DC, a control computed tomography of the head was performed. On the 14th postoperative day, patients were assessed by neurological examination and the Extended Glasgow Outcome Scale (GOSE). The results of the digital version of computed tomography of the head were used for calculations. The volume of the intracranial structures and LDOC calculations were performed using the computer programs Praezis Plus by Tatra Med, Zeppelin and Pax Station by Compart Medical Systems.

Praezis Plus was used to evaluate the PDBD volume and LDOC. For unification, the volume measurements were made in each case by means of scans from convexity of the skull to the level of foramen magnum.

Pax Station was used to evaluate the volume of the cerebrospinal fluid (CSF) in selected structures. The area corresponding to the CSF on a computed tomography image of the head was assumed to be grayscale pixels in the range of 0-18 Hounsfield units. Fluid volume calculations were performed on three head CT scans of a total thickness of 7.5 mm. For the purpose of standardising measurements, in each case they were made 2.5–10.0 mm below the pineal gland. Using this method, the CSF volume in both the ambient and quadrigeminal cisterns before and after DC was calculated. The collected research material was analysed using the IBM SPSS Statistics software package.

Results

In the study group, 45 unilateral DCs were performed. The mortality rate in the study group was 40%.

The relationship between the LDOC of unilateral DC and the PDBD volume consumed by the swollen brain (Fig. 2).

The smallest value of LDOC, i.e. 8.4 cm, was associated with the formation of 25.6 ml of PDBD. Larger craniectomies, in the LDOC range of 8–10 cm, 10–12 cm and 12–14 cm,

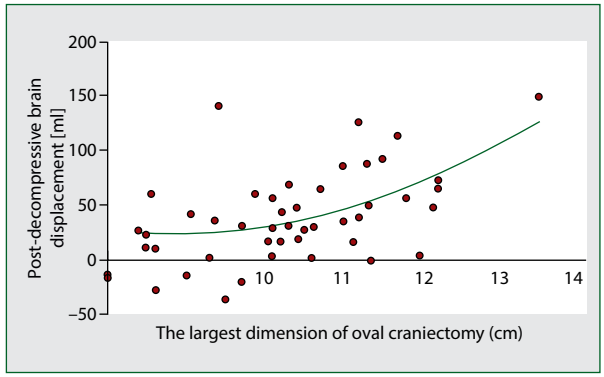


Figure 2. Post-decompressive brain displacement (r = 0.48, n = 45)

provided mean volumes of 25.9 ml, 41.7 ml and 90.6 ml of PDBD respectively; the largest DC with an LDOC of 13.5 cm had a volume of 148.9 ml of PDBD. Pearson's correlation coefficient for the examined features was r = 0.48. The correlation was statistically significant ($p < 0.05$). It is notable that, in some patients, the decompression area remained depressed after surgery; therefore PDBD values on the graph are negative.

Analysis of alteration in CSF volume of the selected basal cisterns — the ambient and quadrigeminal cistern, before and after DC

The results are shown in Table 1 and compared with the control group.

Prior to operation, the cisterns were most often clamped and their volume was about 0.5 ml, and this was three times smaller than in the control group. After surgery, the volume of the cisterns nearly doubled, reaching a mean volume of about 1 ml (Fig. 3). This change of volume was statistically significant ($p < 0.001$). The selected basal cistern volume (SBCV) after DC was also statistically significantly different from the control group ($p < 0.001$). In order to compare SBCV in the study group *vs* the control group, statistical calculations using the t-test (Student's *t*-test) for independent groups were performed. The t-test for dependent (paired) groups was used to compare the SBCV in the study group before and after the DC.

Table 1. SBCV in the test group before and after surgery and in the control group (mean, SD, p, median)

	SBCV before DC (n = 45)	SBCV after DC (n = 45)	SBCV in the control group (n = 50)
Mean (ml) ± SD	0.50 ± 0.56	0.98 ± 0.66	1.54 ± 0.58
p		< 0.001	
Median	0.33	0.81	1.48

Analysis of changes in the mean volume of CSF within selected basal cisterns before and after surgery in different age groups (Groups 1–4)

The t-test for dependent (paired) groups was used for statistical calculations. In Group 1, the selected basal cisterns were preoperatively clamped to the greatest extent and their mean volume was 0.32 ml. After surgery, the decompressed cisterns filled up with CSF and reached a volume of 0.84 ml, which was statistically significant ($p < 0.01$) relative to the baseline values. In Groups 2, 3 and 4, there was also a significant postoperative increase in SBCV ($p < 0.001$, $p < 0.001$, and $p < 0.01$, respectively). All results are shown in Table 2.

An age-specific analysis of the early effects of the applied treatment and an assessment of the neurological condition of patients 14 days after surgery (Groups 1–4)

The best outcomes evaluated on the 14th day after surgery were those in Group 1. Very good or good condition of the patients was found in 70% (GOSE = 7 or GOSE = 8), while death was reported in 30% of the patients (GOSE = 1). In Group 2, the results of the evaluation were respectively GOSE = 7 or GOSE = 8 in 53% of the patients and GOSE = 1 in 27% of the patients. In Group 3, GOSE = 7 or GOSE = 8 in 33% of

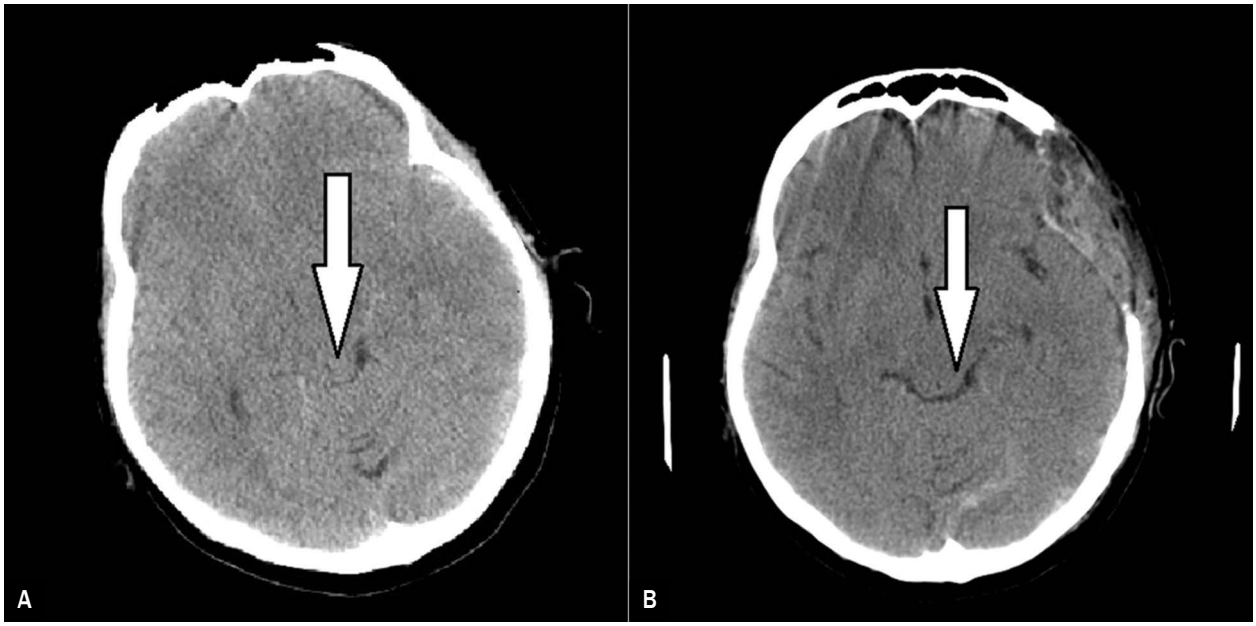


Figure 3. Selected basal cistern volume before and after decompressive craniectomy — computed tomography

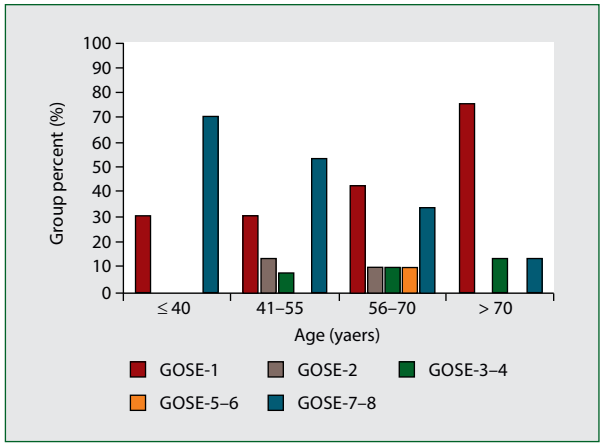


Figure 4. Clinical state of patients on the 14th day after DC in different age groups according to the GOSE scale (n = 45, ρ45 = −0.407)

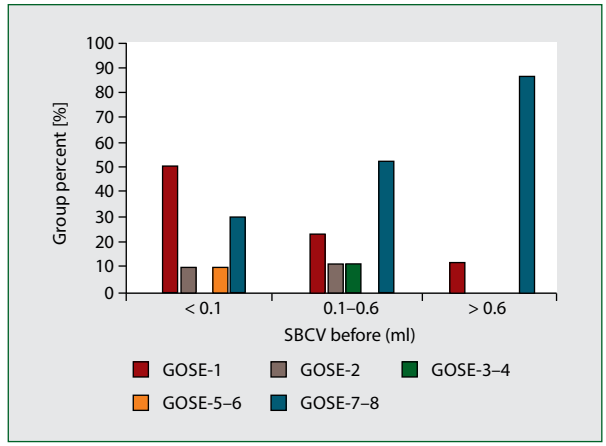


Figure 5. SBCV before DC and the clinical state of patients on the 14th postoperative day according to the GOSE scale (n = 45, ρ45 = 0.224, p = 0.122)

the patients and GOSE = 1 in 42% of the patients. In Group 4, very good or good condition of the patients (GOSE = 7 or GOSE=8) was found only in 12.5% of the patients while 75% of the patients died (GOSE = 1). The results of the above analysis are shown in Figure 4.

The Spearman rho correlation coefficient (ρ Spearman) showed a statistically significant negative correlation between age and the clinical state of patients evaluated with the GOSE scale 14 days after surgery (with increase in age, GOSE score decreased, ρ45 = −0.407, $p < 0.01$).

The correlations between pre- and postoperative SBCV and the volume of the PDBD and neurological condition of patients on the 14th day after surgery were estimated. There was no statistically significant correlation between SBCV and the neurological status of patients on the 14th postoperative day or between PDBD and the status of patients evaluated on the GOSE scale (Fig. 5). The only statistically significant correlation was found for the relationship between postoperative SBCV and the status of patients evaluated according to the GOSE scale on the 14th day after surgery in the age group up to 40 years ($r = 0.623$, $p < 0.05$). Pearson's correlation coefficient was used for calculations.

Discussion

This study presents volume changes of selected intracranial fluid spaces prior to and after DC, and the usefulness of PDBD space in patients after TBI. These parameters have been linked to the clinical state of patients 14 days after surgery, also taking into consideration their preoperative neurological condition and age. There have only been a few published studies concerning changes in the volume of the brain, herniating above the skull surface in TBI patients after DC. Single publications have reported that PDBD may be a good prognostic factor and that the decompression effect can be evaluated by measuring PDBD volume [7, 8]. However, this was not definitely confirmed in our current study. Severe traumatic brain injury has a poor prognosis regardless of the treatment method used. Evaluation of the volume change of the CSF cisterns before and after DC has also been rarely presented in the literature. No publication has been found on this subject concerning patients operated due to intracranial haematoma. The only text evaluating the volume of the basal CSF cisterns in patients after head injury is the study by Głowacki et al. [9]. The authors found that selected basal cisterns significantly reduce their volume after TBI, which was also confirmed in our current study. Based on the results of many publications, it is known that DC immediately, and in the long term, decreases ICP in a statistically significant way. It should also be noted that a reduction of the ICP is associated with an enlargement of the CSF space, but this does not mean an improvement of the neurological condition in every patient. The coefficient of correlation between preoperative cistern volume and the condition of patients on the 14th day after surgery was rather low for the whole study group. However, in our study we found that the volume of intracranial CSF cisterns increased significantly after DC in each age group. Therefore, this may be a good indicator of intracranial tightness.

The use of DC for the treatment of head injuries has a long history, but it remains controversial. Previous research has shown that DC results in lower ICP and increases cerebral perfusion pressure (CPP) [10–14]. However, there are many conflicting findings in the literature concerning treatment results. Some authors have reported good outcomes in less than 20% of patients [15], while others have reported good outcomes in more than 70% [16]. Further research should define the optimum criteria for decompressive craniectomy. However, it should be noted that too small a bone window, with LDOC less than 12 cm, has been confirmed to increase

Table 2. SBCV before and after DC in relation to age (mean, SD, p)

Group	1 (n = 10)		2 (n = 15)		3 (n = 12)		4 (n = 8)	
Age (in years)	up to 40		41–55		56–70		71+	
SBCV (mean (ml)±SD)	before DC	after DC	before DC	after DC	before DC	after DC	before DC	after DC
	0.32 ± 0.24	0.84 ± 0.63	0.55 ± 0.73	0.90 ± 0.75	0.32 ± 0.24	0.84 ± 0.63	0.55 ± 0.73	0.90 ± 0.75
p	< 0.01		< 0.001		< 0.001		< 0.01	

the chance of brain injury and poor outcome [17]. As yet, there are no clear guidelines for treating TBI. In everyday clinical practice, the benefits of DC must be thoroughly weighed against the risks. The long-term outcome of DC in TBI patients is not fully understood and it is difficult to interpret due to a variety of factors that may influence the condition of patients. Identification of these factors can improve treatment methods and life quality of head injury patients [10, 18–23]. Severe TBI is usually associated with a poor prognosis [14, 24–27]. Outcomes of DC have been described by some authors [28, 29], but the available studies were not randomised and were mostly based on small patient groups limited to individual centres. In this context, of particular interest are the results of RESCUE-ASDH – a multi-centre, pragmatic, parallel group randomised trial conducted by A. G. Kolias from the University of Cambridge's Department of Clinical Neurosciences. RESCUE-ASDH aimed to compare the clinical and cost-effectiveness of decompressive craniectomy versus craniotomy for the management of adult patients with head injuries undergoing evacuation of an acute subdural haematoma (ASDH).

While the DC procedure is technically straightforward, according to the literature it exposes a patient to risk complications which can negatively impact outcome. Such complications can be divided into three groups: a) haemorrhagic (postoperative haematoma, recurrent ipsilateral haematoma, contralateral haematoma, haemorrhagic transformation of brain contusion or ischaemic area), b) infectious/inflammatory (wound healing complications, meningitis and ventriculitis, abscess formation and epidural/subdural empyema), and c) CSF compartment disorders (hydrocephalus, subdural hygroma or CSF leak/fistula formation). Other complications of DC are syndrome of the trephined, paradoxical herniation, and falls on an unprotected cranium [30].

It should be remembered that in DC patients further cranioplasty is required in the future which may also be associated with complications similar to those found in DC, although some complications are characteristic for cranioplasty e.g. bone flap resorption/depression and cosmetic defects [30].

In our study, however, we did not find that DC complications were frequent and the procedure was not very risky, although it does not protect against all common risk of injury. It should be remembered that some of the above-mentioned situations (haemorrhagic transformation of brain contusion or ischaemic area, hydrocephalus, meningitis and ventriculitis, abscess formation and epidural/subdural empyema, especially in the case of penetrating injuries) can be a natural consequence of TBI, and can occur without surgery.

To summarise, despite the method limitations, decompressive craniectomy is a valuable treatment option for traumatic brain injury (TBI) management. That it helps to reduce post-traumatic intracranial volume disorders was confirmed in this study and this is in agreement with the results of other studies. However, the study group was heterogeneous and some factors could have influenced the final study results (e.g. patient age diversity, different initial neurological status, additional physician load). Moreover, even promptly performed DC remains an ineffective procedure in patients with very severe brain damage, which itself leads to a poor prognosis, regardless of the method of treatment.

DC is considered to be an effective method in selected post-traumatic cases in combination with conservative pharmacological treatment. Qualifications for operations should be determined on a case-by-case basis.

Conclusions

A statistically significant increase in the volume of preoperatively clamped intracranial CSF cisterns was observed in each age group after DC.

DC increases the volume reserve for the enlarged post-traumatic brain depending on the size of the removed skull vault.

The best early results of TBI management using DC were obtained in patients under the age of 55. It has limited effectiveness in the over 70 years old group.

If herniation of the brain tissues follows haematoma removal, the LDOC should be enlarged to a diameter of more than 12 cm. DC should be as large as possible, and the limits of its dimensions should be the limits of anatomical safety.

In every patient with clamped basal cisterns, a skin incision enabling appropriate LDOC should be planned before surgery.

Conflict of Interest: *The authors declare that they have no conflict of interest.*

Ethical approval: *The local bioethics committee approved the research project upon which this study was based.*

References

1. Fearnside MR, Simpson DA. Epidemiology. In: Reilly P, Bullock R (ed) Head Injury. Pathophysiology and management of severe closed injury. Chapman and Hall Medical, London. 1997: 3–24.
2. Maas AIR, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol. 2008; 7(8): 728–741, doi: 10.1016/S1474-4422(08)70164-9, indexed in Pubmed: 18635021.
3. Faul M, Wald M, Wu L, et al. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths, 2002-2006. 2010, doi: 10.15620/cdc.5571.
4. Ling G, Bandak F, Armonda R, et al. Explosive blast neurotrauma. J Neurotrauma. 2009; 26(6): 815–825, doi: 10.1089/neu.2007.0484, indexed in Pubmed: 19397423.
5. Roberts SAG, Toman E, Belli A, et al. Decompressive craniectomy and cranioplasty: experience and outcomes in deployed UK military personnel. Br J Neurosurg. 2016; 30(5): 529–535, doi: 10.1080/02688697.2016.1208807, indexed in Pubmed: 27437912.
6. Baguley IJ, Nott MT, Howle AA, et al. Late mortality after severe traumatic brain injury in New South Wales: a multicentre study. Med J Aust. 2012; 196(1): 40–45, indexed in Pubmed: 22256933.
7. Xiao F, Chiang IJ, Hsieh TMH, et al. Estimating postoperative skull defect volume from CT images using the ABC method. Clin Neurol Neurosurg. 2012; 114(3): 205–210, doi: 10.1016/j.clineuro.2011.10.003, indexed in Pubmed: 22035646.
8. Wirtz CR, Steiner T, Aschoff A, et al. Hemicraniectomy with dural augmentation in medically uncontrollable hemispheric infarction. Neurosurg Focus. 1997; 2(5): E3; discussion 1 p following E3, indexed in Pubmed: 15096004.
9. Glowacki M, Budohoski K, Marszalek P, et al. A non-invasive assessment of intracranial volume reserve by measuring cerebrospinal fluid volume with the aid of CT imaging. Acta Neurochir Suppl. 2010; 106: 199–202, doi: 10.1007/978-3-211-98811-4_37, indexed in Pubmed: 19812949.
10. Bohman LE, Schuster JM. Decompressive craniectomy for management of traumatic brain injury: an update. Curr Neurol Neurosci Rep. 2013; 13(11): 392, doi: 10.1007/s11910-013-0392-x, indexed in Pubmed: 24101348.
11. Cooper DJ, Rosenfeld JV, Wolfe R, et al. DECRA Trial Investigators, Australian and New Zealand Intensive Care Society Clinical Trials Group. Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med. 2011; 364(16): 1493–1502, doi: 10.1056/NEJMoa1102077, indexed in Pubmed: 21434843.
12. Chesnut R, Temkin N, Carney N, et al. A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury. New England Journal of Medicine. 2012; 367(26): 2471–2481, doi: 10.1056/nejmoa1207363.
13. Kolias AG, Adams H, Timofeev I, et al. Decompressive craniectomy following traumatic brain injury: developing the evidence base. Br J Neurosurg. 2016; 30(2): 246–250, doi: 10.3109/02688697.2016.1159655, indexed in Pubmed: 26972805.
14. Hutchinson PJ, Kolias AG, Timofeev IS, et al. RESCUEicp Trial Collaborators. Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. N Engl J Med. 2016; 375(12): 1119–1130, doi: 10.1056/NEJMoa1605215, indexed in Pubmed: 27602507.
15. Albanèse J, Leone M, Alliez JR, et al. Decompressive craniectomy for severe traumatic brain injury: Evaluation of the effects at one year. Crit Care Med. 2003; 31(10): 2535–2538, doi: 10.1097/01.CCM.0000089927.67396.F3, indexed in Pubmed: 14530763.
16. Olivecrona M, Rodling-Wahlström M, Naredi S, et al. Effective ICP reduction by decompressive craniectomy in patients with severe traumatic brain injury treated by an ICP-targeted therapy. J Neurotrauma. 2007; 24(6): 927–935, doi: 10.1089/neu.2005.356E, indexed in Pubmed: 17600510.
17. Wagner S, Schnippering H, Aschoff A, et al. Suboptimum hemicraniectomy as a cause of additional cerebral lesions in patients with malignant infarction of the middle cerebral artery. J Neurosurg. 2001; 94(5): 693–696, doi: 10.3171/jns.2001.94.5.0693, indexed in Pubmed: 11354398.
18. Kolias AG, Kirkpatrick PJ, Hutchinson PJ. Decompressive craniectomy: past, present and future. Nat Rev Neurol. 2013; 9(7): 405–415, doi: 10.1038/nrneurol.2013.106, indexed in Pubmed: 23752906.
19. Perel P, Arango M, Clayton T, et al. MRC CRASH Trial Collaborators. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. BMJ. 2008; 336(7641): 425–429, doi: 10.1136/bmj.39461.643438.25, indexed in Pubmed: 18270239.
20. Duhaime AC, Gean AD, Haacke EM, et al. Common Data Elements Neuroimaging Working Group Members, Pediatric Working Group Members. Common data elements in radiologic imaging of traumatic brain injury. J Magn Reson Imaging. 2010; 32(3): 516–543, doi: 10.1002/jmri.22259, indexed in Pubmed: 20815050.
21. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS Med. 2008; 5(8): e165; discussion e165, doi: 10.1371/journal.pmed.0050165, indexed in Pubmed: 18684008.
22. Mushkudiani NA, Engel DC, Steyerberg EW, et al. Prognostic value of demographic characteristics in traumatic brain injury: results from the IMPACT study. J Neurotrauma. 2007; 24(2): 259–269, doi: 10.1089/neu.2006.0028, indexed in Pubmed: 17375990.
23. Marshall LF, Marshall SB, Klauber MR, et al. The diagnosis of head injury requires a classification based on computed axial tomography. J Neurotrauma. 1992; 9(5): 287–92.
24. Honeybul S, Ho KM, Lind CRP, et al. Decompressive craniectomy for diffuse cerebral swelling after trauma: long-term outcome and ethical considerations. J Trauma. 2011; 71(1): 128–132, doi: 10.1097/TA.0b013e3182117b6c, indexed in Pubmed: 21460742.
25. Thomsen IV. Late psychosocial outcome in severe traumatic brain injury. Preliminary results of a third follow-up study after 20 years. Scand J Rehabil Med Suppl. 1992; 26: 142–152, indexed in Pubmed: 1488637.
26. Grauwmeijer E, Heijenbrok-Kal MH, Haitsma IK, et al. Employment Outcome Ten Years after Moderate to Severe Traumatic Brain Injury: A Prospective Cohort Study. J Neurotrauma. 2017; 34(17): 2575–2581, doi: 10.1089/neu.2016.4846, indexed in Pubmed: 28447873.
27. Turgeon AF, Lauzier F, Zarychanski R, et al. TBI-Prognosis Study Team and the Canadian Critical Care Trials Group. Prognostication in critically ill patients with severe traumatic brain injury: the TBI-Prognosis multicentre feasibility study. BMJ Open. 2017; 7(4): e013779, doi: 10.1136/bmjopen-2016-013779, indexed in Pubmed: 28416497.
28. Park JH, Park JE, Kim SH, et al. Outcomes of Ultra-Early Decompressive Craniectomy after Severe Traumatic Brain Injury - Treatment Outco-

mes after Severe TBI. Korean J Neurotrauma. 2014; 10(2): 112–118, doi: 10.13004/kjnt.2014.10.2.112, indexed in Pubmed: 27169044.
29. Rubiano AM, Villarreal W, Hakim EJ, et al. Early decompressive craniectomy for neurotrauma: an institutional experience. Ulus Travma Acil Cerrahi Derg. 2009; 15(1): 28–38, indexed in Pubmed: 19130336.
30. Kurland DB, Khaladj-Ghom A, Stokum JA, et al. Complications Associated with Decompressive Craniectomy: A Systematic Review. Neurocrit Care. 2015; 23(2): 292–304, doi: 10.1007/s12028-015-0144-7, indexed in Pubmed: 26032808.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 1, pages: 55–60
DOI: 10.5603/PJNNS.a2018.0003

ISSN 0028–3843

Outcomes of traumatic brain injury: the prognostic accuracy of various scores and models

Jose D. Charry, Sandra Navarro-Parra, Juan Solano, Luis Moscote-Salazar

Fundación Universitaria Navarra – UNINAVARRA, Neiva, Colombia

ABSTRACT

Introduction. Traumatic Brain Injury (TBI) is a worldwide health problem, and is a pathology that causes significant mortality and disability in Latin America. Different scores and prognostic models have been developed in order to predict the neurological outcomes of patients. We aimed to test the prognostic accuracy of the Marshall CT classification system, the Rotterdam CT scoring system, and the IMPACT and CRASH models, in predicting 6-month mortality and 6-month unfavourable outcomes in a cohort of trauma patients with TBI in a university hospital in Colombia.

Methods. We analysed 309 patients with significant TBI who were treated in a regional trauma centre in Colombia over a two year period. Bivariate and multivariate analyses were undertaken. The discriminatory power of each model, as well as its accuracy and precision, were assessed by logistic regression and AUC. Shapiro Wilks, chi2 and Wilcoxon test were used to compare the actual outcomes in the cohort against the predicted outcomes.

Results. The median age was 32 years, and 77.67% were male. All four prognostic models showed good accuracy in predicting outcomes. The IMPACT model had the greatest accuracy in predicting an unfavourable outcome (AUC 0.864; 95% CI 0.819 - 0.909) and in predicting mortality (AUC 0.902; 95% CI 0.862 - 0.943) in patients with TBI.

Conclusion. All four prognostic models are applicable to eligible TBI patients in Colombia. The IMPACT model was shown to be more accurate than the other prognostic models, and had a higher sensitivity in predicting 6-month mortality and 6-month unfavourable outcomes in patients with TBI in a university hospital in Colombia.

Key words: traumatic brain injury, prognosis models, neurological outcome
(*Neurol Neurochir Pol 2019; 53 (1): 55–60*)

Introduction

Traumatic brain injury (TBI) has a significant impact worldwide. Its incidence has been reported to be nearly 200 cases per 100,000 people worldwide [1]. According to the Global Burden of Disease Study published in 2010 by the World Health Organisation, trauma remains a public health problem and represents an important burden of disease for healthcare systems in Latin American countries [2–3]. In Colombia, the burden of such injuries particularly affects the male, economically active population aged between 12 and 45 years. In 2013, 26,000 deaths were due to trauma, and most of these were associated with interpersonal violence. Of these injuries, a large percentage was associated with closed TBI and penetrating TBI [4].

TBI remains the main cause of death and disability in young adults worldwide [5–6]. It is a heterogeneous disease in relation to cause, pathology, severity, and prognosis. This results in considerable uncertainty regarding the expected outcome of individual patients. Several outcome prediction models have been developed for the prognosis of TBI patients to address this uncertainty [7]. These prognostic models can be used to combine different characteristics of individual patients to predict their clinical outcome. Prognostic models may also be useful as tools to compare outcomes across institutions, healthcare systems, and countries, and may be

Address for correspondence: Jose D. Charry, Fundación Universitaria Navarra - Uninavarra, Calle 10 No. 6-41, Neiva – Colombia, e-mail: danielcharry06@gmail.com, phone: (+57) 3158019678

an essential part of the planning of new studies in the field of brain injury.

The Glasgow Outcome Scale (GOS) is widely used in TBI management and surgery outcome studies [8]. Two prognostic models (the International Mission for Prognosis and Analysis of Clinical Trials in TBI [IMPACT] model, and the Corticosteroid Randomisation After Significant Head Injury [CRASH] model), both based on large TBI clinical trial datasets, have recently been cross-validated and externally validated. [9–12].

IMPACT applies to adult patients (age ≥ 14 years) with a Glasgow Coma Scale (GCS) score of ≤ 12 to predict the probabilities of 6-month favourable outcome and 6-month mortality.

CRASH applies to adult patients (age ≥ 16 years) with a GCS score of ≤ 14 to predict the probabilities of 14-day mortality and 6-month unfavourable outcome.

The calculator models predict outcomes based on specific variables including country of incident, patient age, and clinical and imaging findings in the emergency room [13–14].

Another diagnostic technique for assessing TBI is brain imaging by computed tomography (CT) and magnetic resonance imaging (MRI). Brain imaging significantly aids early diagnosis and effective treatment of life-threatening conditions in patients with TBI [15]. However, brain CT is the gold standard for assessing patients with acute TBI. Currently, there are two CT-based systems for evaluating CT findings, the Marshall Classification System (MCS) and the Rotterdam Scoring System (RSS) [16–17].

The MCS, developed by Marshall et al. in 1991, was the first CT-based system for determining the prognosis of TBI. The MCS classifies CT findings into four grades: Grade 1, no pathologic findings; Grade 2, basal cisterns are present and midline shift is less than 5 mm; Grade 3, basal cisterns are compressed; and Grade 4, midline shift is greater than 5 mm. [16]. This system was developed primarily for predicting patient outcomes and the risk for increased intracranial pressure in patients with severe TBI.

In 2005 Maas et al. introduced the RSS. This system provides a better estimation of disease prognosis by using certain criteria such as basal cistern condition, midline shift, traumatic subarachnoid or intraventricular haemorrhage, and epidural haematoma. Rotterdam scores predict post trauma 6-month mortality rate as follows: score 1, 5%; score 2, 7%; score 3, 16%; score 4, 26%; score 5, 53%; and score 6, 61%.

In this study, we aimed to test the prognostic accuracy of the Marshall CT score and the Rotterdam CT score, as well as the accuracy of the International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT) and Corticosteroid Randomisation after Significant Head Injury (CRASH) models, in predicting 14-day mortality, 6-month mortality, and 6-month unfavourable outcomes in a cohort of trauma patients with TBI in a university hospital in Colombia.

Materials and methods

Patient population

This retrospective, observational cohort study was performed at Neiva University Hospital (NUH) in southern Colombia. Included in the study were patients with TBI who were admitted to NUH between January 2014 and December 2015. Approval was obtained from the NUH quality improvement office and the Ethical Committee of Neiva University Hospital prior to conducting this study.

NUH is a 504-bed, level I trauma centre and tertiary referral hospital in southern Colombia that admits approximately 2,000 adult trauma patients per year and has 30 adult ICU beds. This hospital is the primary trauma centre for 3.2 million inhabitants living in a region extending over 60,000 square miles. In order to be included in this study, patients had to be 18 years or older and suffering from TBI (loss of consciousness or change in consciousness level with a head and neck Abbreviated Injury Severity score ≥ 2). The Glasgow Coma Scale (GCS) was used to classify the trauma level: minor (GCS 15–13), moderate (GCS 9–12), or severe (GCS 3–8).

Clinical outcome

The variables and results were evaluated according to the Glasgow Outcome Scale (GOS) at 6 months post injury, creating a dichotomous variable with a favourable outcome (GOS 4 or 5), and an unfavourable outcome (GOS 1–3) [11, 12]. In addition, we evaluated the prediction of mortality that was given by the Marshall CT score, Rotterdam CT score, and the IMPACT and CRASH models versus those obtained in the study patients.

Prediction of outcome

We used the web-based prognosis calculator published by the CRASH collaborators and applied it to the patient group described above. The variables which were found by the CRASH study group to have the largest influence on the outcome, and were thus used in the CRASH prognostic calculator, were: country, age, Glasgow Coma Scale (GCS) score, pupil reactivity, and the presence of any other major trauma (defined as an injury which would have rendered the patient in need of in-hospital care in and of itself). If a CT scan of the brain was performed within eight hours of trauma, the following features on the scan were used in the calculation of prognosis: presence of petechial haematoma, obliteration of basal cisterns or the third ventricle, subarachnoid haemorrhage, midline shift, and non-evacuated haematoma. For the individual patient, the CRASH prognosis calculator predicts risk of mortality at 14 days after the injury and the risk of an unfavourable outcome (GOS 1–3) at 6 months after trauma with percentages at 95% [10].

The Marshall Classification System (MCS) was the first CT classification system to determine the prognosis of TBI.

The MCS classifies CT findings into four grades: Grade 1, no pathologic findings; Grade 2, basal cisterns are present and midline shift is less than 5 mm or presence of high density lesions or mixed of no more than 25 cc; Grade 3, basal cisterns are compressed with deviation of midline of no more than 5 mm; and Grade 4, midline shift is greater than 5 mm; mass evacuated and not evacuated mass. This system was developed primarily for predicting patient outcomes and the risk for increased intracranial pressure in patients with severe TBI [15].

The IMPACT model is an analysis that has been used for the development of prognosis models for mortality and unfavourable outcomes at six months in patients with moderate or severe TBI. In our study, we only included patients with severe TBI (Glasgow Coma Scale ≤ 8) on admission. Using IMPACT, the following criteria were evaluated: age, motor score, pupil reactivity, presentation of states of hypoxia, hypotension, Marshall CT classification, subarachnoid bleeding on CT, epidural mass on CT and laboratory tests such as glucose levels and haemoglobin [9–11].

The Rotterdam Scoring System (RSS) provides a better estimation of disease prognosis by using certain criteria such as basal cistern condition, midline shift, traumatic subarachnoid or intraventricular haemorrhage, and epidural haematoma. Rotterdam scores predict post trauma 6-month mortality rate as follows: score 1, 5%; score 2, 7%; score 3, 16%; score 4, 26%; score 5, 53%; and score 6, 61% [16].

Statistics

Values are reported as mean ± standard deviation. Discrete variables are reported as median and range. Logistic fit and receiver operating characteristic (ROC) statistics were used as indicated. The statistical software used was SPSS Statistics (Version 21, IBM Corporation) and the R software environment (Version 2.15.2, The R Foundation for Statistical Computing, Vienna, Austria). A p value < 0.05 was regarded as significant. The discriminatory power of the model, its accuracy and precision, were assessed by logistic regression and as the area under the receiver operating characteristic curve (AUC). Shapiro Wilks, chi2 and the Wilcoxon test were used to compare real outcomes in the cohort against predicted outcomes. We made a multivariate logistic regression and analysis. We excluded variables that were not significant at a 5% level. We quantified each variable's predictive contribution by its z score (the model coefficient divided by its standard error). We explored linearity and interactions between the variables and all predictors were evaluated by p value and the IC.

Results

309 patients were admitted with a diagnosis of TBI over a period of two years to Neiva University Hospital. Median age in the validation cohort was 32 years and 77.67% were male. 95.47% of the patients had experienced blunt trauma, the median of injury severity score was 4, imaging findings showed 23.3% had midline shift, and subdural haematoma was present in 28.8%. The characteristics of the 309 patients included in this study are set out in Table 1.

Six-month mortality was 12.62%. Six-month unfavourable outcome was 17.15%. The IMPACT model had the best rate of accuracy in predicting 6-month unfavourable outcome was 20% p < 0.001 (AUC 0.864; 95% CI 0.819 - 0.909) and 6-month mortality was 12% p < 0.001 (AUC 0.902; 95% CI 0.862 - 0.943) in patients with TBI. Mortality prediction by Marshall CT score was 13.5% p < 0.001 (AUC 0.819; 95% IC 0.769-0.869). The 6-month mortality prediction by CRASH prognosis calculator was 5.3% p < 0.001 (AUC 0.877; 95% IC 0.825-0.930). The six-month unfavourable outcome prediction by CRASH was 20% p < 0.001 (AUC 0.832; 95% IC 0.785-0.881). The 6-month mortality prediction by Rotterdam

Table 1. Characteristics of 309 patients with TBI

Variable	Value
Median age in years (IQR)	32 (23-47)
Number of males (%)	240 (77.67)
Median initial GCS score (IQR)	9 (6-15)
Median ISS score (IQR)	4 (4-16)
Motor vehicle accidents (%)	276 (89.32)
Pupils (%)	
Both nonreactive	49 (15.85)
One reactive	10 (3.23)
Both reactive	250 (80.91)
CT brain appearances (%)	
Effaced basal cistern	226 (73.14)
Midline shift	72 (23.30)
Subarachnoid blood	62 (20.06)
Epidural haematoma	38 (12.30)
Subdural haematoma	89 (28.80)
Surgical management, no. (%)	126 (40.78)
Drainage of epidural haematoma	23 (18.25)
Drainage of subdural haematoma	68 (53.96)
Decompressive craniectomy	9 (7.14)
ICP monitoring	26 (20.63)
Unfavourable outcomes (%)	53 (17.15)
Favourable outcomes (%)	256 (82.84)
Median length of ICU stay, days (IQR)	12 (6-14)
Median length of acute hospital ward stay, days (IQR)	26 (14-49)
Mortalities (%)	39 (12.62)

ICU — intensive care unit; IQR — interquartile range; GCS — Glasgow Coma Scale; ISS — Injury Severity Score

Table 2. Correlation between mortality and predictive models

Model	Six-month predicted mortality	Six-month mortality	Spearman's rho	p
Rotterdam CT score	7%		0.,031	0.000
Marshall CT score	13.5%		0.025	0.000
IMPACT	12%	12.62%	0.020	0.000
CRASH	5.3%		0.026	0.000
Model	Six-month predicted unfavourable outcome	Six-month unfavourable outcome	Spearman's rho	p
IMPACT	20%	17.15%	0.023	0.001
CRASH	20%		0.024	0.001

CT score was 7% p < 0.001 (AUC 0.875; 95% IC 0.814-0.936). These results are set out in Table 2.

Comparing the prediction of mortality and a six-month unfavourable outcome with the observed long-term are in Figure 1.

Discussion

TBI is a medical and surgical disease of major importance globally. [8] The World Health Organisation predicts that traffic accidents will be the third-leading cause of illness and injuries worldwide by 2020, and this is one of the most common causes of TBI. Prognostication is important when considering outcomes, especially when it's considered to be potentially life-saving. Traditionally, neurosurgeons have relied on individual clinical parameters such as age, initial GCS score, and pupillary responses, combined with a radiological assessment, to guide clinical decisions and when counselling family members and surrogate decision makers regarding prognosis [18].

Different models have been described for predicting mortality and adverse neurological outcomes in TBI patients, the best known of which are the Marshall CT score, the Rotterdam CT score, and the IMPACT and CRASH models. In our cohort study, we had patients who were victims of head trauma and in applying the four models we evaluated the observed versus the predicted outcomes 6 months after the trauma. We found good performance from all four models in predicting mortality. However, the IMPACT model had the best performance in our study. Different studies have been conducted into the validation of these models. In these studies, patients with severe and moderate traumatic brain injury have been evaluated, and use of the different models and scores has shown that their performance and sensitivity is high [19–23].

Studies related to TBI in populations of adolescents, adults and the elderly have revealed the presence of physical and cognitive consequences and inadequate emotional, behavioural, and inappropriate regulation [24]; some have even suggested that they may present a global functional disability [25] and long-term psychosocial disability [26]. Among the

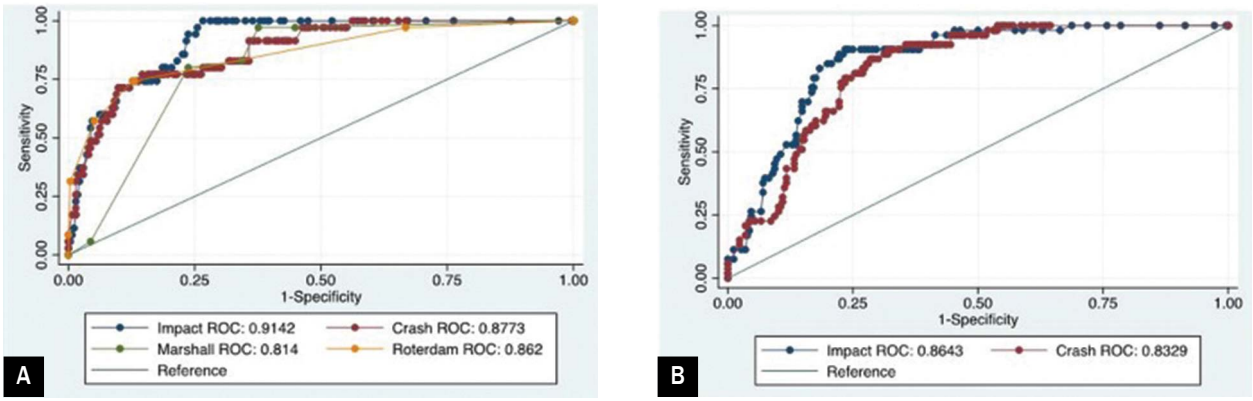


Figure 1. A. AUC of the models for six-month mortality, **B**. AUC of the models for six-month unfavourable outcome

survivors of trauma, a considerable proportion are left with important consequences that prevent their return to previous activities, or render impossible academic, professional or social progress [27]. This is why it is essential to implement neurocognitive rehabilitation programmes that favour the processes of adaptation and improvement of the quality of life of both patients and their families. The intervention that has been shown to be the most effective in addressing this type of health event is the non-pharmacological one, framed within a holistic model and a neurobehavioural paradigm that takes into account the results of the neuropsychological assessment and the individual's environment, in addition to adjusting to the needs of the patient and family members. Rehabilitation processes include the more complex processes involved in returning to work [28] and vocational aspects have been shown to be more effective when adapted to the conditions of each individual patient [29].

Conclusions

The Marshall CT score, Rotterdam CT score, IMPACT and CRASH models were useful in predicting mortality and unfavourable outcomes in TBI patients in a university hospital in Colombia. The IMPACT model was shown to be more accurate than the other prognostic models, and had a higher sensitivity in predicting 6-month mortality and 6-month unfavourable outcomes in patients with TBI.

Conflicts of interest/disclosures. *The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.*

References

1. Byass P, de Courten M, Graham WJ, et al. Reflections on the global burden of disease 2010 estimates. PLoS Med. 2013; 10(7): e1001477, doi: 10.1371/journal.pmed.1001477, indexed in Pubmed: 23843748.
2. Horton R. GBD 2010: understanding disease, injury, and risk. Lancet. 2012; 380(9859): 2053–2054, doi: 10.1016/S0140-6736(12)62133-3, indexed in Pubmed: 23245595.
3. Norton R, Kobusingye O. Injuries. New England Journal of Medicine. 2013; 368(18): 1723–1730, doi: 10.1056/nejmra1109343.
4. De la. Comportamiento del homicidio en Colombia, 2013. Forensis. ; 2013: 79–125.
5. Maas AIR, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. Lancet Neurol. 2008; 7(8): 728–741, doi: 10.1016/S1474-4422(08)70164-9, indexed in Pubmed: 18635021.
6. Ghajar J. Traumatic brain injury. The Lancet. 2000; 356(9233): 923–929, doi: 10.1016/s0140-6736(00)02689-1.
7. Perel P, Edwards P, Wentz R, et al. Systematic review of prognostic models in traumatic brain injury. BMC Med Inform Decis Mak. 2006; 6: 38, doi: 10.1186/1472-6947-6-38, indexed in Pubmed: 17105661.
8. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975; 1(7905): 480–484, indexed in Pubmed: 46957.
9. Murray G, Butcher I, McHugh G, et al. Multivariable Prognostic Analysis in Traumatic Brain Injury: Results from The IMPACT Study. Journal of Neurotrauma. 2007; 24(2): 329–337, doi: 10.1089/neu.2006.0035.
10. Perel P, Arango M, Clayton T, et al. MRC CRASH Trial Collaborators. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. BMJ. 2008; 336(7641): 425–429, doi: 10.1136/bmj.39461.643438.25, indexed in Pubmed: 18270239.
11. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS Med. 2008; 5(8): e165; discussion e165, doi: 10.1371/journal.pmed.0050165, indexed in Pubmed: 18684008.
12. Roozenbeek B, Lingsma HF, Lecky FE, et al. International Mission on Prognosis Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT) Study Group, Corticosteroid Randomisation After Significant Head Injury (CRASH) Trial Collaborators, Trauma Audit and Research Network (TARN). Prediction of outcome after moderate and severe traumatic brain injury: external validation of the International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) and Corticoid Randomisation After Significant Head injury (CRASH) prognostic models. Crit Care Med. 2012; 40(5): 1609–1617, doi: 10.1097/CCM.0b013e31824519ce, indexed in Pubmed: 22511138.
13. Honeybul S, Ho KM, Lind CRP, et al. The retrospective application of a prediction model to patients who have had a decompressive craniectomy for trauma. J Neurotrauma. 2009; 26(12): 2179–2183, doi: 10.1089/neu.2009.0989, indexed in Pubmed: 19645531.
14. Honeybul S, Ho KM, Lind CRP, et al. Observed versus predicted outcome for decompressive craniectomy: a population-based study. J Neurotrauma. 2010; 27(7): 1225–1232, doi: 10.1089/neu.2010.1316, indexed in Pubmed: 20412014.
15. Marshall LF, Marshall SB, Klauber MR, et al. The diagnosis of head injury requires a classification based on computed axial tomography. J Neurotrauma. 1992; 9 Suppl 1: S287–S292, indexed in Pubmed: 1588618.
16. Maas AIR, Hukkelhoven CW, Marshall LF, et al. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: a comparison between the computed tomographic classification and combinations of computed tomographic predictors. Neurosurgery. 2005; 57(6): 1173–82; discussion 1173, indexed in Pubmed: 16331165.
17. Huang YH, Deng YH, Lee TC, et al. Rotterdam computed tomography score as a prognosticator in head-injured patients undergoing decompressive craniectomy. Neurosurgery. 2012; 71(1): 80–85, doi: 10.1227/NEU.0b013e3182517aa1, indexed in Pubmed: 22382208.
18. Honeybul S, Ho KM, Lind CRP, et al. Validation of the CRASH model in the prediction of 18-month mortality and unfavorable outcome in severe traumatic brain injury requiring decompressive craniectomy. J Neurosurg. 2014; 120(5): 1131–1137, doi: 10.3171/2014.1.JNS131559, indexed in Pubmed: 24605836.
19. Wong GK, Teoh J, Yeung J, et al. Outcomes of traumatic brain injury in Hong Kong: validation with the TRISS, CRASH, and IMPACT models. J Clin Neurosci. 2013; 20(12): 1693–1696, doi: 10.1016/j.jocn.2012.12.032, indexed in Pubmed: 23993210.
20. Egea-Guerrero JJ, Rodríguez-Rodríguez A, Gordillo-Escobar E, et al. IMPACT Score for Traumatic Brain Injury: Validation of the Prognostic Tool in a Spanish Cohort. J Head Trauma Rehabil. 2018; 33(1): 46–52, doi: 10.1097/HTR.0000000000000292, indexed in Pubmed: 28195955.

21. Panczykowski DM, Puccio AM, Scruggs BJ, et al. Prospective independent validation of IMPACT modeling as a prognostic tool in severe traumatic brain injury. J Neurotrauma. 2012; 29(1): 47–52, doi: 10.1089/neu.2010.1482, indexed in Pubmed: 21933014.
22. Hukkelhoven CW, Steyerberg EW, Habbema JD, et al. Predicting outcome after traumatic brain injury: development and validation of a prognostic score based on admission characteristics. J Neurotrauma. 2005; 22(10): 1025–1039, doi: 10.1089/neu.2005.22.1025, indexed in Pubmed: 16238481.
23. Honeybul S, Ho KM. Predicting long-term neurological outcomes after severe traumatic brain injury requiring decompressive craniectomy: A comparison of the CRASH and IMPACT prognostic models. Injury. 2016; 47(9): 1886–1892, doi: 10.1016/j.injury.2016.04.017, indexed in Pubmed: 27157985.
24. Fraga H, Dourado I, Fernandes R, et al. Factores asociados a la incapacidad funcional global luego de transcurrido un año después del traumatismo craneoencefálico. Salud Colectiva. 2013; 9(3): 335, doi: 10.18294/sc.2013.190.
25. Andelic N, Sigurdardottir S, Arango-Lasprilla JC, et al. Long-Term Functional and Psychosocial Consequences and Health Care Provision after Traumatic Brain Injury. Behav Neurol. 2016; 2016: 2678081, doi: 10.1155/2016/2678081, indexed in Pubmed: 27034584.
26. Junqué C. Secuelas neuropsicológicas de los traumatismos craneoencefálicos. Revista de neurología. 1999; 28: 423–9.
27. The effectiveness of psychological interventions for aggressive behavior following acquired brain injury: A meta-analysis and systematic review.
28. Effective return-to-work interventions after acquired brain injury: A systematic review.
29. A manual-based vocational rehabilitation program for patients with an acquired brain injury: study protocol of a pragmatic randomized controlled trial (RCT).

RESEARCH PAPERS

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 1, pages: 61–73
DOI: 10.5603/PJNNS.a2018.0004

ISSN 0028–3843

Attitudes towards neurology among medical undergraduates

Anna Pokryszko-Dragan[1], John Mottershead[2], Gill Aitken[3]

[1]Department of Neurology, Wroclaw Medical University, Wroclaw, Poland
[2]Department of Neurology, Dunedin Public Hospital, Dunedin, New Zealand
[3]Clinical Education Programme, University of Edinburgh, United Kingdom

ABSTRACT

Diseases of the nervous system are an important contributor to clinical and social problems. Therefore there is a need to provide undergraduates and postgraduates of medical faculties with adequate training in neurology. However, many shortcomings have been observed in this field, often associated with students' negative perception of neurology. The aim of this study was to explore attitudes towards neurology amongst undergraduates of the medical faculty at Wroclaw Medical University, and the reasons for these attitudes. As a qualitative component of the study, a focus group discussion was conducted with six fifth year undergraduates. The findings of the focus group and a literature search informed the content of a questionnaire distributed among fifth year students of the medical faculty, including non-Poles attending English Division. The responses to the closed questions were analysed quantitatively and subjected to statistical analysis while the free text comments were analysed qualitatively. Triangulation of the findings from the focus group and the survey was performed. 134 Polish students and 75 English-speaking ones responded to the survey. The majority of participants perceived neurology to be interesting and important for medical education, and it was highly ranked as a potential future speciality. The majority of the survey respondents regarded neurology as difficult and mentioned specific drawbacks. In spite of similar general perceptions of neurology, Polish and English-speaking students differed in their perceptions of particular aspects, conditioned by diversity in cultural backgrounds and earlier experiences associated with neurology. The course in neurology affected attitudes towards the subject more than preceding experiences, mostly in a positive manner. The fifth year medical undergraduates expressed mostly positive attitudes towards neurology. Cultural background and the course in neurology were the main factors contributing to attitudes in these students.

Key words: neurology, undergraduates, attitudes, neurophobia
(*Neurol Neurochir Pol 2019; 53 (1): 61–73*)

Introduction

Diseases of the nervous system affect 30% of the population, with increasing morbidity associated with the ageing of societies, and these diseases constitute a significant clinical and social problem [1]. Therefore there is a clear need to educate competent neurologists and other specialists with appropriate knowledge in this field [1]. In the 1990s, the phenomenon of a fear of neurology was identified among medical students and named 'neurophobia' [2]. Despite progress in neurology and in methods of teaching, there is evidence from medical faculties [3–5] that 'neurophobia' remains a phenomenon. This may be associated with the diversity of healthcare settings, teaching resources and professionals involved in teaching neurology [6].

In the Polish literature there is limited evidence for this problem [7–8]. Undergraduate training in neurology in Poland is obligatory, follows official guidelines, and is provided by specialists. In recent years, no shortage of trained neurologists has been documented in Poland [9]. However, in informal discussions, teachers often complain about their students' reluctance to learn neurology, and neurologists complain about other specialists' poor competence in the basics of neurology. Therefore, undergraduate attitudes towards neurology seemed worthy of investigation in Poland.

Address for correspondence: Anna Pokryszko-Dragan, Department of Neurology, Wroclaw Medical University, Wroclaw, Poland, e-mail: annapd@interia.pl

In recent years, a growing diversity of medical students has been noted: English Divisions (the same curriculum taught in English) have developed at the majority of Polish medical faculties and the number of their non-Polish attendees is constantly increasing. A smaller group of non-Polish students also temporarily attends courses at medical faculties within the international exchange programme (the European Community Action Scheme for the Mobility of University Students - ERASMUS). These undergraduates may hold diverse attitudes towards particular specialities, including neurology, conditioned by the prevailing opinions in their countries of origin.

The aim of this study was to explore attitudes towards neurology among medical undergraduates and the background to these attitudes, including the impact of the course in neurology.

Material and methods

The participants in this study were fifth year students of the medical faculty at Wroclaw Medical University, who had completed the basic part of the neurology course (during their first semester) and were currently attending its second part (towards the end of the second semester). Fifth year students were selected because they shared the same status and experience and were available as respondents due to their obligatory participation in the neurology course.

Mixed qualitative and quantitative methods were used, mainly in a sequential manner. Qualitative methods were used to explore problems and quantitative methods were used to quantify and analyse data in a larger sample of participants. We integrated these two methods in a further stage of the study, with triangulation of findings from both components. Initially, a thorough literature review was conducted to formulate topics for discussion in the focus group and for an initial version of the questionnaire. The focus group was set up to allow students the opportunity to discuss their experiences and to support the formulation of the final version of the questionnaire. Further quantitative and qualitative findings were obtained from the survey.

To avoid any pressure arising from the teacher-student relationship, and to encourage honesty and interactivity of discussion, the focus group was moderated by a student. A senior (sixth year) student was chosen, who had already passed the exam in neurology and had displayed a special interest both in neurology and educational issues during activity in the Students' Scientific Club. The idea of the focus group and the research topic had been discussed with this senior student prior to obtaining her consent to moderate the discussion. Participants for the focus group were recruited through the website of students' societies. The invitation was addressed to all fifth year students, equally encouraging those engaged or not in any additional educational activity and those interested in neurology or those who had already decided on another speciality. Potential participants could contact the researcher or the moderator for more information. Nine students initially considered participation, with six eventually participating.

There was one meeting of the focus group that lasted for approximately two hours. At the beginning, the participants were given a list of 28 expressions (based on a relevant literature search) and asked to choose the five expressions that they most associated with neurology. At the end they were asked to review the initial version of the questionnaire and to comment on it. Their discussion was recorded and the transcript of the recording was analysed to enable the identification of particular themes. Subsequently, the moderator (and the willing participants) were asked to review the description of findings, and to provide feedback.

The questionnaire contained closed and open-ended items. The closed ones were either dichotomous (yes/no) or Likert-type format with five answers (including a neutral response), with easily completed tick-boxes. The initial version of the questionnaire was based on an extensive literature search and the combined experiences of the authors. Then it was piloted by several sixth year students (who had already completed the neurology course) and reviewed by several junior assistants in neurology (who still remembered the students' perspective but were already involved in teaching). Finally, the questionnaire was presented to the participants of the focus group for comment.

A paper version of the questionnaire (Polish and English versions for particular students' groups) was chosen for easier dissemination. The questionnaires were offered to the students before the onset of their classes and collected afterwards at the exit door, in order to maximise confidentiality and anonymity.

The data from the closed items were subjected to statistical analysis. The number of responses was calculated and their distribution was compared between genders and Polish/non-Polish participants, using the Chi-square test with Yate's correction. $P \leq 0.01$ was considered statistically significant, because of the multiple comparisons performed. The analysis was performed using EPIINFO software (Version 7.1.1.14, 2013).

For ethical reasons, special attention was paid within the design of the study to minimise pressure from hierarchical teacher-student relationships and to assure anonymity and confidentiality of data. The Bioethical Board of Wroclaw Medical University approved the project. Informed consent was obtained from all the subjects prior to their participation in the focus group or prior to responding to the questionnaire. The information contained an explanation of the aim and conduct of the study and assurances that participation would not affect the subjects' further participation in their degree or any form of assessment, and that the results would not be revealed or published before the end of the exam session. The informed consent forms were stored — for confidentiality reasons — separately from the transcripts of discussions and completed questionnaires.

Results

The focus group

The six participants in the focus group were fifth year students: three men and three women, aged 23–25 (mean 23.7). The moderator was a sixth year female student.

Attitudes towards neurology

General and specific aspects of neurology

From the list of expressions associated with neurology that we provided, the participants most often selected: 'logical', 'making progress' and '"interesting' (from the descriptive terms) and 'detailed examination', 'cognitive dysfunction', and 'chronic diseases' (from the related items) (Tab. 1).

The students mostly perceived neurology to be an interesting subject, with the diagnostic process based on logical thinking and supported by technology-based tools. They noted recent progress in terms of early recognition of the diseases and — to a lesser extent — within therapy. Still unsolved problems in neurology were regarded as scope for future investigation (Tab. 2).

Objections to neurology were associated with the type of disorders handled: their insidious onset or subtle signs hindering diagnosis, frequent speech or cognitive impairment resulting in communication problems, chronic course and adverse prognosis with still few treatment options available, with resultant frustration and emotional load for the physician (Tab. 2).

Neurology as future speciality

Three students considered neurology as their future career while the other three planned to pursue other specialities. The latter considered basic competence in neurology as necessary in their future work.

A neurologist's inpatient practice was perceived as interesting but demanding, with numerous consultations, including emergencies. The opportunity to deal with outpatients in an independent establishment was also appreciated for its greater stability and higher income. The prestige of being a neurologist was perceived as being underestimated by the public but valued by the patients who were treated. The following qualities were regarded as necessary for a good neurologist: calmness, accuracy, observation and reasoning skills, empathy, patience and an ability to maintain an emotional distance. Those planning to become neurologists were aware of the discussed drawbacks and challenges of this speciality, but felt ready to face them.

Factors affecting attitudes towards neurology

Demographics

Female students were anxious about problems with work-life balance and possible gender discrimination during training in neurology. However, the latter was attributed to the hierarchical structure of healthcare settings rather than to the speciality itself. Male students did not express concern in this field. There were no other gender-specific comments or statements from the focus group participants.

Table 1. Expressions associated with neurology chosen by the focus group participants

Expression	Number of choices	Expression	Number of choices
logical	7	detailed examination	3
making progress	4	cognitive dysfunction	3
interesting	3	chronic diseases	2
useful	2	rare disorders	1
difficult	2	neuroimaging	1
conservative	1	consultations	1
timid	1	rehabilitation	1
stressful	1	symptomatic treatment	1
emotional load	1	disability	0
complicated	0	emergency conditions	0
effective	0	topographic diagnostics	0
easy	0	electrophysiological studies	0
up-to-date	0		
palliative	0		
boring	0		
niche	0		

Table 2. Perceptions of positive and negative aspects of neurology

A: Positive	A: Negative
St.1: it's like an intriguing puzzle - you put together findings from history and examination, think logically - and work out the solution	**St. 5:** it's so stressful: you may overlook something important - the neurological signs seem so explicit in the textbook, but not at all in real patients
St.4: neurology is necessary in so many fields - when you deal with contusions, congenital failures, systemic diseases...	**St.6:** searching for the diagnosis is great - but then you should tell it to the patient (...) and often there is not much more to offer
St.2: there has been much progress in diagnostic methods - one can recognise the disease earlier (..), especially neuroimaging is very helpful (..), you may have a real insight into the brain	**St. 1:** I find it difficult to talk to the patients with aphasia or dementia. (...) It's such an emotional burden - these chronic and disabling diseases - think it may lead to burn-out syndrome
St. 5: with advanced technology, there are also more treatment options available	**St.4:** when you still meet similar patients - with stroke or headache - it's not so challenging any more
St. 3: there is still a lot to discover - the background and nature of disorders - a perfect area for research	
B: Positive	**B: Negative**
Interesting (functions of the brain, specificity of the nervous system).	Difficult: many complex issues, vast material for a narrow speciality.
Variety of problems and disorders.	Theory hardly applicable in practice (PL).
Based on logical thinking.	Type of diseases: mostly chronic, progressive and disabling, with poor outcomes.
Recent progress in diagnostics and treatment.	Specific patients: elderly, difficult to communicate with.
Challenging.	Too few treatment options, lack of effective procedures.
Scope for research (many unknown issues to explore).	Frustrating, emotional burden.
Various opportunities of job (ENG).	Little availability of residency posts (PL).
Narrow speciality - easy to become an expert (ENG).	Few opportunities for interesting jobs (PL).

A: by the focus group participants, B: by respondents to the survey.

Experiences preceding neurology course

The participants' earlier experiences related to neurology included meeting patients with neurological disorders during other clinical classes (emergency unit, internal diseases) or in their private lives, the opinions of other specialists (both positive and negative), and information acquired from the media.

The neurology course

The courses in neurosciences (preclinical years) and neurology formed the main source of the students' opinion about neurology. The former highlighted specificity and uniqueness of neurosciences, while the latter revealed clinical aspects of neurology and their usefulness in other specialities.

The survey

Respondents

290 Polish and 110 English versions of the questionnaire were handed out. The survey was responded to by 134 Polish students (PL) and 75 English speaking ones (ENG), with response rates of 46.2 % and 68.2 % respectively.

PL and ENG did not differ in gender (c. 40% men, 60% women). Mean age was slightly lower in ENG (23.7 *vs* 24.2; p = 0.008).

Among ENG, 22 were participants in ERASMUS and 53 were students of English Division. English was the native language for 14 persons (from Canada, USA, Ireland, and Sudan), while the remaining 61 came from Sweden (25), Italy (11), Germany (10), Spain (4), Ukraine (4), Portugal (2), Saudi Arabia (2), Slovenia (1) and Switzerland (1).

All the respondents answered the closed questions completely; 97.7% of PL and 90.7% of ENG provided free text comments invited by open questions.

Attitudes towards neurology

General perception of neurology

In both groups the majority of respondents regarded neurology as "somewhat" or "definitely" difficult, interesting and important for general medical education. A moderate proportion of respondents found it not relevant for their future speciality or remained undecided (Fig. 1 A-D).

Neurology as future speciality

Twenty four (17.9 %) PL and 14 (18.7%) ENG would consider neurology as their future speciality, which ranked it among the top five most preferred specialities (Tab. 3).

Specific aspects of neurology

The majority of respondents agreed with statements concerning the link between neurology and difficult basic neurosciences, progress in neurosciences, specificity of the diagnostic process (based on deductive thinking, perceived as difficult and challenging), and types of disorders (chronic,

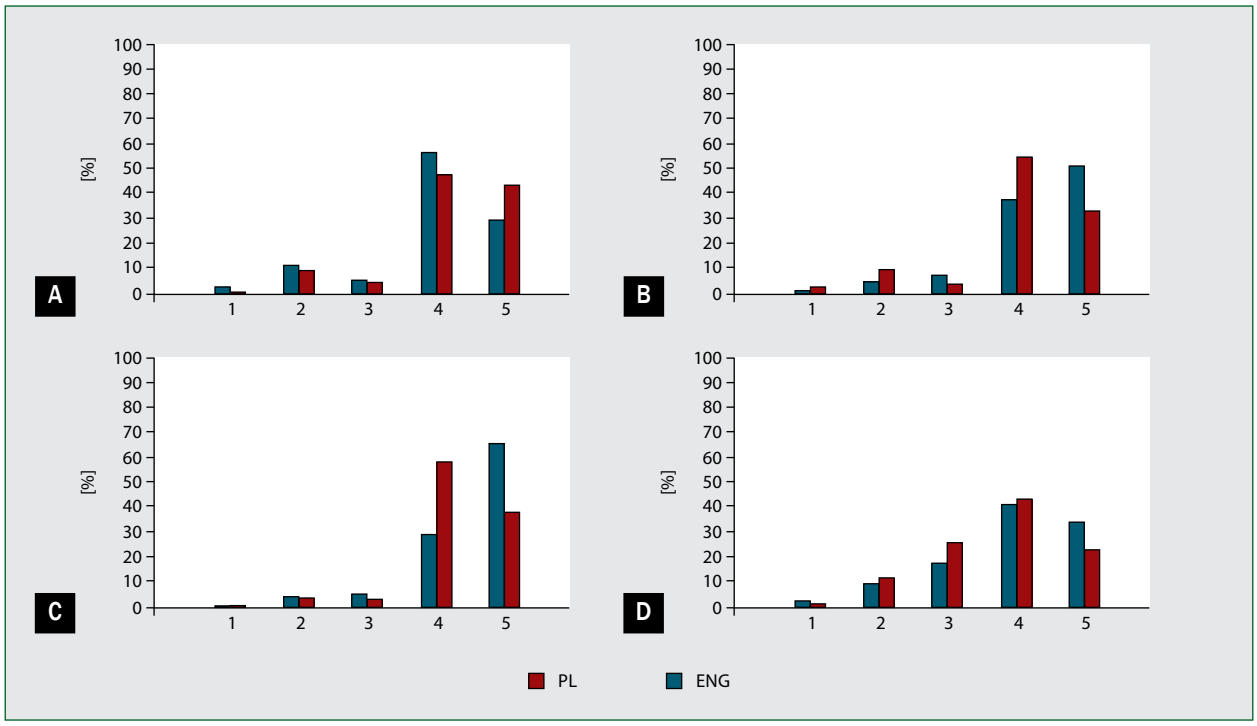


Figure 1. Distribution of responses to question regarding the general perception of neurology: Do you find neurology - A. difficult? B. interesting? C. important for medical education? D. relevant for your future speciality? 1- definitely not, 2- rather not, 3 - don't know, 4 - somewhat yes, 5 - definitely yes, PL- Polish students, ENG - English-speaking students

disabling) (Tab. 4). There was a greater diversity of responses concerning the difficulty of neurological examination, the incurability of neurological disorders, and emergency conditions covered by neurology. A large percentage of respondents expressed no opinion ("don't know") on the following issues: up-to-date diagnostic methods and therapeutic options used in neurology, unknown background and incurability of neurological disorders, and links between neurology and other specialities (Tab. 4).

In the open questions, the respondents were asked to describe briefly the reasons for their preference (or lack of it) for neurology as their future speciality. Among the latter, 29% PL and 38% ENG claimed "lack of interest" and "preference for other specialities" as the main reason, while 4.5% PL and 20% ENG added some potential aspects in favour of neurology (Tab. 2).

Factors affecting attitudes towards neurology

Demographics

Among PL there were no gender differences in responses reflecting attitudes towards neurology.

Among ENG, fewer men than women "definitely" agreed and more "rather" disagreed that neurological diagnostics is difficult and challenging ($\chi^2 = 10.9$, df = 3, p = 0.012).

Significant differences were found between PL and ENG in the responses reflecting their attitudes towards neurology (Fig. 1, Tab. 4).

Fewer PL than ENG "definitely" agreed and more "rather" disagreed with recognising neurology to be important for general medical education ($\chi^2 = 17.8$, df = 3, p = 0.0005).

More PL than ENG "definitely" agreed that up-to-date diagnostics are used in neurology, that neurological disorders are chronic and have unknown background, and that neurological patients require interdisciplinary care. Fewer PL than ENG "definitely" agreed and more "rather" disagreed that neurology deals with emergency conditions and symptoms secondary to systemic diseases, and may be associated with an emotional burden (Tab. 4).

Experiences preceding neurology course

The respondents had a range of neurology-related experiences preceding their course in neurology (Fig. 2).

ENG more often than PL had met a specialist or trainee in neurology (56% *vs* 37.3%, p = 0.014), learnt about a neurological problem from professional resources (86.7% *vs* 58.2%, p = 0.00004), and had heard more positive (22.7% *vs* 7.46%, p = 0.0002) and less negative (5.3% *vs* 22.4%, p = 0.0002) opinions about neurology.

No gender differences were found among the respondents within this domain.

Table 3. Preferences for the future specialty among the respondents to the survey

ENG (n = 75)		PL (n = 134)	
Considered future specialty	**Number (%) of students**	**Considered future specialty**	**Number (%) of students**
Gynecology/obstetrics	18 (24%)	Radiology	28 (20.9%)
Pediatrics	17 (22.7%)	Pediatrics	26 (19.4%)
Internal diseases	14 (18.7%)	Internal diseases	26 (19.4%)
Neurology	14 (18.7%)	Neurology	24 (17.9%)
Cardiology	13 (17.3%)	Anesthesiology	24 (17.9%)
Dermatology	13 (17.3%)	Family medicine	20 (14.9%)
Surgery	13 (17.3%)	Cardiology	18 (13.4%)
Family medicine	13 (17.3%)	Psychiatry	18 (13.4%)
Infectious diseases	11 (14.7%)	Gynecology/obstetrics	13 (9.7%)
Anesthesiology	9 (12%)	Endocrinology	13 (9.7%)
Emergency medicine	9 (12%)	Oncology	12 (8.9%)
Orthopedics	6 (8%)	Ophthalmology	11 (8.2%)
Radiology	5 (6.7%)	Dermatology	11 (8.2%)
Endocrinology	5 (6.7%)	Infectious diseases	10 (7.5%)
Cardiosurgery	5 (6.7%)	Surgery	10 (7.5%)
Neurosurgery	4 (5.3%)	Otolaryngology	10 (7.5%)
Plastic surgery	4 (5.3%)	Orthopedics	7 (5.2%)
Pediatric surgery	4 (5.3%)	Emergency medicine	6 (4.5%)
Gastroenterology	4 (5.3%)	Plastic surgery	5 (3.7%)
Otolaryngology	4 (5.3%)	Neurosurgery	4 (2.9%)
Ophthalmology	4 (5.3%)	Urology	3 (2.2%)
Urology	3 (4%)	Vascular surgery	2 (1.5%)
Psychiatry	3 (4%)	Nephrology	2 (1.5%)
Nephrology	2 (2.7%)	Rheumatology	2 (1.5%)
Hematology	2 (2.7%)	Pathology	2 (1.5%)
Oncology	2 (2.7%)	Hematology	1 (1.5%)
Forensic medicine	1 (2.7%)	Gastroenterology	1 (1.5%)
Already chosen specialty	31 (41.3%)	Already chosen specialty	54 (40.3%)

ENG – English speaking students; PL – Polish students

The neurology course

An equal percentage of PL and ENG (42.6%) claimed that they had changed their previous opinion on neurology having experienced the course, and for approximately one third of them (36.6% PL, 34.7% ENG), this was influenced by a teacher.

Among those who changed their opinion on neurology, the majority found it more interesting, or even enjoyable, than they had anticipated (three students expressed the opposite view). A more thorough knowledge of the nervous system and better understanding of the links between symptoms and their background made the learning less difficult and stressful. Several students claimed that they had a better overview of neurology (they recognised a wider spectrum of diseases and progress in therapy), realised its relevance for other specialities, and found it less frustrating than they had expected. Four students started to consider neurology as their future career. Teachers mostly influenced these positive attitudes by effective explanation of neurological problems, highlighting practical issues, evoking interest and an encouraging approach. However, a few PL students commented on a teacher's performance, which had discouraged them more than the course itself.

Discussion

Overview

A positive response rate to the survey, especially among non-Poles, allowed a representative sample of the fifth year undergraduates' opinion to be obtained. Although the focus

Table 4. Distribution of responses to the question: "How much do you agree with the statements (concerning various aspects of neurology)" and their comparison between Polish (PL) and English-speaking (ENG) students

		Definitely not %	Rather not %	Don't know %	Somewhat yes %	Definitely yes %	χ2	df	p
Learning neurology requires knowledge of difficult anatomy and physiology of the nervous system	PL	0	4.5	1.7	46.3	47.5	6.80	4	0.15
	ENG	1.3	1.3	0	38.7	58.7			
Neurosciences constitute an interesting and constantly developing knowledge domain	PL	0	6	6	42.5	45.5	11.3	3	0.01
	ENG	0	0	12	28	60			
Neurological examination is difficult to perform and interpret	PL	0.8	33.6	5.9	45.5	14.2	4.53	4	0.34
	ENG	5.3	33.3	6.7	42.7	12			
Diagnostics of neurological symptoms and signs is based on rational and deductive thinking	PL	0	6.7	11.3	44	38	0.91	3	0.82
	ENG	0	6.7	9.3	50.7	33.3			
Variety of up-to-date diagnostics methods are used in neurology	PL	0	4.5	8.9	36.6	50	10.6	3	0.01
	ENG	0	6.7	22.7	38.7	32			
Diagnosis of neurological disorders is often difficult and challenging	PL	0	3.7	4.5	51.5	40.3	2.77	3	0.43
	ENG	0	5.3	6.7	58.7	29.3			
The background of neurological diseases often remains unknown	PL	0	7.5	7.5	45.5	39.6	14.6	3	0.002
	ENG	0	6.7	22.7	50.7	20			
Neurological diseases are mostly incurable	PL	0	17.9	20.9	45.5	15.7	1.58	3	0.66
	ENG	0	12	25.3	48	14.7			
During the recent decade new therapeutic options have emerged for neurological disorders	PL	0	2.2	18.7	50	29.1	6.94	4	0.14
	ENG	1.3	0	29.4	40	29.3			
Neurology deals with patients with emergency and life-threatening conditions	PL	1.5	31.3	5.2	45.5	16.4	18.4	4	0.001
	ENG	0	13.3	4	42.7	40			
Neurological disorders are usually chronic ones and they substantially affect the patients' quality of life	PL	0	0	1.5	33.6	64.9	10.3	3	0.017
	ENG	0	1.3	4	50.7	44			
Consequences of neurological disorders often include disability and cognitive problems	PL	0	6.7	5.3	53.7	37.3	0.77	3	0.86
	ENG	0	4	2.7	54.6	38.7			
Managing the patients with neurological diseases carries an emotional burden for the physician	PL	0.8	6	2.2	47	44	36.5	4	0.0000
	ENG	2.7	14.7	24	38.7	20			
Patients with neurological diseases need interdisciplinary care	PL	0	4.5	3	43.3	49.3	28.7	3	0.0000
	EN	0	4	25.3	45.3	25.3			
Nervous system can often be involved in the course of diseases of other organs/systems	PL	0	13.4	14.9	53	18.7	11.4	3	0.0098
	ENG	0	9.3	5.3	48	37.3			

p = statistically significant

group influenced the final formulation of the questionnaire, the survey results did not exactly mirror the focus group opinion. Some meaningful differences between these findings justify the triangulation of data within a mixed methods approach.

Attitudes towards neurology

Approximately 80% of survey respondents regarded neurology as difficult, but also interesting and important for medical education. Nearly half of the students considered it relevant for their future speciality.

In the free text comments, the students valued neurology for its interesting content, variety of problems, constant progress, rationality, and providing opportunities for research. These were mostly consistent with the focus group findings, although its participants called neurology "logical" and "making progress" above all other descriptions, and emphasised its usefulness in other specialities.

Negative aspects of neurology described in the survey included: difficulties in learning (especially basic neurosciences), specificity of neurological disorders (chronic,

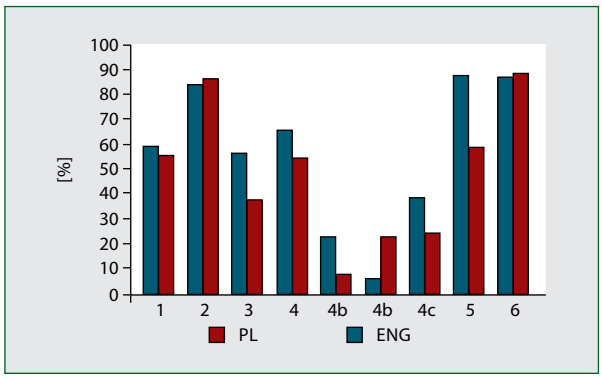


Figure 2. Percentage of respondents having experienced the following neurology-related issues: 1- neurological disorder among family or friends, **2** - meeting a patient with neurological disorder during other clinical classes, **3** - meeting a specialist in neurology; **4** - hearing opinion on neurology from an older student or physician (a - positive, b - negative, c - neutral or not specified), **5** - learning about neurological problem from professional resources, **6** - learning about neurological problem from popular media, PL- Polish students, ENG - English-speaking student

progressive, disabling) and patients (communication problems), insufficient treatment options, and an emerging emotional burden. Focus group participants noticed similar drawbacks to neurology and paid attention to the disorders' impact upon cognition. Although not discouraged by learning the theoretical basis, they perceived the interpretation of neurological examination and the diagnostic process to be more difficult and challenging.

The survey findings showed the greatest proportion of uncertainty regarding the issues of the unknown background of the diseases and their incurability. This might suggest these topics were not adequately addressed during the course.

Unlike the focus group findings, the results from the survey showed that two-thirds of students found neurological examinations difficult, up to 30% doubted if neurology covered emergencies, and approximately 20% were uncertain about progress in therapies or the links between neurology and other specialities. These differences could indicate that the focus group participants were more interested in neurology and better recognised its specificity.

Overall, the study participants expressed a more positive approach to neurology than has been described in the literature. Negative attitudes have been consistently shown in the studies on 'neurophobia'[3, 10–16], with the majority of students finding neurology difficult, a moderate proportion displaying some interest in it [11, 13, 16], and a minority admitting its importance for medical education [10]. However, specific drawbacks of neurology named in these studies are comparable with the findings of this study. Surprisingly, the unclear background of neurological disorders and insufficient treatment options had remained the main discouraging issues since the 1950s [17] or 1970s [7], a fact which brings into question the students' perception of progress in neurology. Positive aspects of neurology (similar to those perceived by participants in our study) have been addressed in studies on speciality choices [8–21].

Neurology as future speciality

Approximately 18% of the survey respondents (both Polish and English-speaking) considered neurology for their future career, which ranked it within the five most popular specialities. Although only half of the students claimed they had definitely made their choice, such an interest in neurology seemed surprisingly high. The reasons for selecting neurology included the positive aspects discussed above. Those considering other specialities more often declared other preferences, rather than explicitly rejecting neurology.

A half of the focus group participants planned to become neurologists, so had a positive approach to the subject. Their discussion showed that they had a thorough insight into the specificity of neurology, and felt ready to manage its shortcomings.

The studies on 'neurophobia' have highlighted a low proportion of students planning a career in neurology [3, 11–13, 15, 22]. The results of an Indian survey [18] stand out from these, with almost one-third of undergraduates considering a choice of neurology, which might indicate some local context for its popularity. Polish research [7–8] showed a similarly low percentage of students choosing to specialise in neurology (8% and 5.7%) despite progress in neurology and evolution in the postgraduate training model which had occurred between the 1970s and 2000s.

The high popularity of neurology within the survey findings has to be interpreted cautiously, considering the response rate (i.e. those who did not respond were probably less interested) and the possible intention of respondents of making a positive impression on the neurology teachers.

Factors affecting attitudes towards neurology

Gender

Few significant gender differences were found in this study. Female participants in the focus group expressed their concern with work-life balance and possible gender discrimination during postgraduate training. More female respondents of the survey were convinced that neurological diagnostics is difficult. In a UK survey [12] women were less prone than men to choose a career in neurology, and Arabic female students [15] found neurological examination more difficult than males. Overall, gender did not seem to affect the students' perception of neurology in this study.

Polish *vs* English-speaking students

The survey findings provided some differences in attitudes towards neurology between Poles and non-Poles. The latter were more convinced that neurology was important for

The focus group questions:

- what are your associations with neurology?
- in your opinion, what are the pros and cons of neurology ?
- would you consider neurology as future career? Why/why not?
- what do you think the neurologist's job looks like?
- had you had any experiences linked with neurology before the medical studies or during early years?
- how do you perceive the course in neurology (programme, organizational issues, teaching)?
- have you changed your previous opinion on neurology and in which manner? what were the reasons for this change?

The questionnaire

Age:

Gender:

Country of origin:

Native language:

Please tick relevant option: Erasmus English Division

Please tick ONE box which best corresponds with your view

1. In comparison to the other clinical subjects, do you find neurology:

	definitely not	rather not	don't know	somewhat yes	definitely yes
difficult ?	☐	☐	☐	☐	☐
interesting ?	☐	☐	☐	☐	☐
important part of general medical education ?	☐	☐	☐	☐	☐
relevant for your future specialty ?	☐	☐	☐	☐	☐

2. How much do you agree with the following statements:

	Definitely not	Rather not	Don't know	Somewhat yes	Definitely yes
learning neurology requires knowledge of difficult anatomy and physiology of the nervous system					
neurosciences constitute an interesting and constantly developing knowledge domain					
neurological examination is difficult to perform and interpret					
diagnostics of neurological symptoms and signs is based on rational and deductive thinking					
variety of up-to-date diagnostics methods are used in neurology					
diagnosis of neurological disorders is often difficult and challenging					
the background of neurological diseases often remains unknown					
neurological diseases are mostly incurable					
during the recent decade new therapeutic options have emerged for neurological disorders					
	Definitely not	Rather not	Don't know	Somewhat yes	Definitely yes
neurology deals with patients with emergency and life--threatening conditions					
neurological disorders are usually chronic ones and they substantially affect the patients' quality of life					
consequences of neurological disorders often include disability and cognitive problems					
managing the patients with neurological diseases carry an emotional burden for the physician					
patients with neurological diseases need interdisciplinary care					
nervous system can be often involved in the course of diseases of other organs/systems					

3. Please list up to three specialties you consider to choose for your career

.....

Please explain briefly why you would or would not choose neurology

.....

.....

If you have already chosen your future specialty, when did you make this choice?

.....

Please tick one of the boxes: YES or NO

4. Before attending the course in neurology, have you ever:	YES	NO
had any personal experience with neurological disease (among family, friends etc.)?	☐	☐
met patients with neurological disease during other clinical classes?	☐	☐
met a specialist in neurology or a physician during such specialization?	☐	☐
heard some opinion on neurology from senior students or residents/physicians of other specialties?	☐	☐

If **YES**, was it positive or negative one? .....

.....

learnt about any problem in the field of neurology or neurosciences from medical/professional resources (textbook, journal etc.)?	☐	☐
learnt about any neurological disorder from popular literature or media (movies, TV series, radio, website etc.)?	☐	☐

5. Please name 1-3 positive aspects

.....

.....

.....

and 1-3 negative aspects

.....

.....

.....

of the course in neurology you are currently attending.

Please tick ONE box which best corresponds with your view

6. Do you think the timing/schedule of neurology course is appropriate:

	definitely not	rather not	don't know	somewhat yes	definitely yes
two terms during the 5th year	☐	☐	☐	☐	☐
duration of mandatory blocks in each term (8)	☐	☐	☐	☐	☐
structure of single classes (1 h seminar, 2 h bedside classes)	☐	☐	☐	☐	☐
form of exam (verbal, theoretical)	☐	☐	☐	☐	☐

If "**rather not**" or "**definitely not**", what would you change?

.....

.....

7. Have you found the following forms of teaching helpful during course in neurology:

	definitely not	rather not	don't know	somewhat yes	definitely yes
seminars/tutorials	☐	☐	☐	☐	☐
bedside classes:					
• taking history	☐	☐	☐	☐	☐
• neurological examination	☐	☐	☐	☐	☐
• diagnostic tests review	☐	☐	☐	☐	☐
• case-based discussions	☐	☐	☐	☐	☐
• lectures/presentations	☐	☐	☐	☐	☐

8. Was your teacher(s) attitude supportive in learning neurology?

	definitely not	rather not	don't know	somewhat yes	definitely yes
	☐	☐	☐	☐	☐

9. Have you changed your previous opinion about neurology

not	rather not	don't know	somewhat yes	definitely yes	definitely
• during/after the course ?	☐	☐	☐	☐	☐
• influenced by the teacher?	☐	☐	☐	☐	☐

If "somewhat yes" or "definitely yes" please explain briefly

10. Which methods of learning do you use with regard to neurology?

	definitely not	rather not	don't know	somewhat yes	definitely yes
textbooks	☐	☐	☐	☐	☐
revision of notes made during the classes	☐	☐	☐	☐	☐
own notes (schemes, mind maps etc)	☐	☐	☐	☐	☐
tests	☐	☐	☐	☐	☐
online resources	☐	☐	☐	☐	☐
group learning	☐	☐	☐	☐	☐

Please give examples of online resources if you use any

.....

.....

Any other resources? Please specify

.....

.....

.....

11. Do you feel confident with the material you have learnt so far during the course in neurology

	definitely not	rather not	don't know	somewhat yes	definitely yes
theoretical knowledge	☐	☐	☐	☐	☐
practical skills	☐	☐	☐	☐	☐

Please tick ONE of the boxes: YES or NO

12. Have you undertaken (or are going to) any additional learning activity in neurology

	YES	NO
meetings of Students' Scientific Club	☐	☐
assisting the specialist/teacher during consultations	☐	☐

Any other? please specify

.....

.....

If YES please explain briefly the reason for choosing these activities .....

.....

.....

If NO please suggest if any form of additional learning in neurology would attract your attention

.....

.....

Thank you for the completion of the questionnaire.

medical education, covered emergency conditions, had interdisciplinary links and could be associated with an emotional burden. Polish students were more convinced that neurological disorders are chronic and often have an unknown background, and that modern diagnostic methods are available in neurology. However, a large proportion of both subgroups regarded neurology as interesting as well as difficult.

Although neurology was equally popular among Poles and non-Poles as a future speciality, some differences were noted in their motivation, probably conditioned by the cultures within particular countries. Polish students felt discouraged by the limited availability of residency posts, few opportunities for interesting jobs, and limited practical applicability of knowledge. On the other hand, non-Poles perceived neurology to be an interesting professional career as an expert in a narrow speciality.

The review of literature from various countries revealed similar perspectives on 'neurophobic' attitudes, and limited interest in a neurology career. However, the distinct findings from the UK [12] and Indian surveys [18], in which neurology was middle-ranked or high-ranked as a future speciality, may indicate the role of cultural and socio-economic background in shaping the students' approach.

Experiences preceding neurology course

The majority of the survey respondents had faced earlier neurology-related experiences. More than 80% had met patients with neurological disorders during other clinical courses and learnt about neurological problems from professional resources or popular media. More than 50% had heard some opinion on neurology and had encountered a neurological disorder among family or friends. The focus group participants mentioned similar experiences.

English-speaking respondents had more often met a neurologist, heard more positive than negative opinions on neurology, and used more professional resources.

These experiences did not seem to affect substantially the undergraduates' perception of neurology. Those focus group participants who planned to become neurologists were usually driven by an interest in neurosciences developed during preclinical years, had studied neurological problems on their own, and did not feel discouraged by negative opinions of this speciality.

These findings appear to contradict those from the UK and USA [12, 20], which revealed the impact of personal experiences upon an interest in neurology and its choice as a future career. Canadian authors [10] highlighted the role of 'preconceptions' in shaping negative attitudes towards neurology. Their findings showed that the most daunting experiences included contacts with patients with neurological disorders (without relevant knowledge about them), negative opinions of other specialists, and an unfavourable image of neurologists.

The course in neurology

Unlike previous experiences, the course in neurology did contribute to the students' perception of neurology. The focus group participants claimed the course was a valuable source of knowledge and allowed them to verify their idea of the speciality. More than 40% of the survey respondents changed their previous opinion on neurology, usually for the better. This change was caused by a deeper understanding of neurological issues and their relevance, and also by effective and supportive teaching. Sporadic contrary experiences included disappointment with the content of the course or with a poor teacher's performance.

Both these aspects are addressed in the literature. Many studies [10, 18–20, 23–24] have highlighted the potential of positive training experiences to overcome prejudices against neurology, improve its image, and encourage speciality choice. However, some authors [10, 15, 20] have indicated that negative experiences from the course might become the dominant reason for an adverse attitude towards neurology.

Implications and future directions

The strength of this study is its presentation of a range of attitudes towards neurology and perception of its various aspects within a representative group of undergraduates.

The limitations of this study include its local character (little possibility of generalisation) and lack of an English-speaking focus group (due to expected problems emerging from the language barrier). The findings from the survey might have been biased by its having been conducted just before the exam session. Despite efforts to limit pressures arising from the teacher-student relationship, some students might have refrained from expressing critical remarks, or responding to the survey. Addressing the survey to sixth year students or conducting it online might eliminate this bias, but presumably at the cost of a lower response rate.

Continuing studies within this field might involve further exploration of the students' perception of neurosciences, with regard to teaching and learning aspects. Their perspective might be evaluated during preclinical years and comparatively towards the end of their studies, to follow its dynamics. Other factors, including the socioeconomic status of the students and their migration plans, might be considered. Online surveys might be addressed to undergraduates from other medical faculties in Poland to compare the local findings with their opinions. The students' perspective might also be supplemented by the teachers' point of view.

Conclusions

Fifth year medical undergraduates expressed mostly positive attitudes towards neurology, perceived by the majority to be interesting and important for medical education, and it ranked highly as a prospective future speciality. However,

the majority of the survey participants regarded neurology as difficult and noticed specific drawbacks of this speciality.

In spite of a similar general perception of neurology, Polish and English-speaking students differed in their perception of particular aspects. This was conditioned by diversity in cultural background and earlier experiences associated with neurology.

The course in neurology affected attitudes towards the subject more than preceding experiences, mostly in a positive manner. This is an important message for clinical teachers and would be worth pursuing in other specialities. The feedback from undergraduates may contribute to improvements in the teaching of neurology, especially with regards to less frequently considered topics and the integration of neurology with other subjects.

Sources of funding / conflict of interests: *This article constitutes part of a dissertation for an MSc degree in Clinical Education at the University of Edinburgh. Attending the Clinical Education programme by Anna Pokryszko-Dragan was supported by a Polish School of Medicine Memorial Fund scholarship. Gill Aitken is the Director of the Clinical Education programme, and together with John Mottershead she supervised the dissertation. No conflict of interest existed for any of the authors.*

References

1. Neurological Disorders: Public Health Challenges. Neurol Disord Public Heal Challenges. 2006: 41–176, doi: 10.1001/archneurol.2007.19.
2. Jozefowicz RF. Neurophobia: the fear of neurology among medical students. Arch Neurol. 1994; 51(4): 328–329, indexed in Pubmed: 8155008.
3. Zinchuk A, Flanagan E, Tubridy N, et al. Attitudes of US medical trainees towards neurology education: "Neurophobia" - a global issue. BMC Medical Education. 2010; 10(1), doi: 10.1186/1472-6920-10-49.
4. Solorzano GE, Józefowicz RF. Neurophobia: a chronic disease of medical students. Neurology. 2015; 85(2): 116–117, doi: 10.1212/WNL.0000000000001751, indexed in Pubmed: 26070337.
5. McGee J, Maghzi AH, Minagar A. Neurophobia: a global and under-recognized phenomenon. Clin Neurol Neurosurg. 2014; 122: iii–iv, doi: 10.1016/j.clineuro.2014.03.023, indexed in Pubmed: 24726892.
6. Nicholl DJ, Appleton JP. Clinical neurology: why this still matters in the 21st century. J Neurol Neurosurg Psychiatry. 2015; 86(2): 229–233, doi: 10.1136/jnnp-2013-306881, indexed in Pubmed: 24879832.
7. Zieliński JJ, Bejnarowicz J, Drabrowska-Kaczmarek A, et al. [Place and role of clinical neurology in the opinion of students graduating from medical schools]. Neurol Neurochir Pol. 1979; 13(4): 411–416, indexed in Pubmed: 481693.
8. Trzeciak B, Siebert J, Kliszcz J, et al. Specialties' preferences of students of Medical University in Gdansk during the transformation period. Fam Med Prim Care Rev. 2006; 8: 77–81.
9. Ministry Health. http://www mz gov pl/system-ochrony-zdrowia/kadra-medyczna.
10. Fantaneanu TA, Moreau K, Eady K, et al. Neurophobia inception: a study of trainees' perceptions of neurology education. Can J Neurol Sci. 2014; 41(4): 421–429, indexed in Pubmed: 24878464.
11. Youssef FF. Neurophobia and its implications: evidence from a Caribbean medical school. BMC Med Educ. 2009; 9: 39, doi: 10.1186/1472-6920-9-39, indexed in Pubmed: 19570231.
12. Pakpoor J, Handel AE, Disanto G, et al. Association of British Neurologists. National survey of UK medical students on the perception of neurology. BMC Med Educ. 2014; 14: 225–229, doi: 10.1186/1472-6920-14-225, indexed in Pubmed: 25335431.
13. Matthias AT, Nagasingha P, Ranasinghe P, et al. Neurophobia among medical students and non-specialist doctors in Sri Lanka. BMC Med Educ. 2013; 13: 164, doi: 10.1186/1472-6920-13-164, indexed in Pubmed: 24321477.
14. Flanagan E, Walsh C, Tubridy N. ?Neurophobia?? attitudes of medical students and doctors in Ireland to neurological teaching. European Journal of Neurology. 2007; 14(10): 1109–1112, doi: 10.1111/j.1468-1331.2007.01911.x.
15. Lukas R, Albert D, Abulaban A, et al. Neurophobia among medical students. Neurosciences. 2015; 20(4): 404–404, doi: 10.17712/nsj.2015.4.20150500.
16. Schon F. Is clinical neurology really so difficult? Journal of Neurology, Neurosurgery & Psychiatry. 2002; 72(5): 557–559, doi: 10.1136/jnnp.72.5.557.
17. POSER CM. Undergraduate attitudes toward the specialty of neurology. Neurology. 1959; 9: 682–688, indexed in Pubmed: 14434363.
18. Khadilkar S, Bangar S, Patil T, et al. Neurology as career option among postgraduate medical students. Annals of Indian Academy of Neurology. 2013; 16(4): 478–482, doi: 10.4103/0972-2327.120427.
19. Albert D, Hoyle C, Yin H, et al. Why neurology? Factors which influence career choice in neurology. Neurological Research. 2016; 38(1): 10–14, doi: 10.1080/01616412.2015.1120444.
20. Kamour A, Han D, Mannino D, et al. Factors that impact medical student and house-staff career interest in brain related specialties. Journal of the Neurological Sciences. 2016; 369: 312–317, doi: 10.1016/j.jns.2016.08.046.
21. Humbert K, Chang B. In the beginning: How medical students choose (or do not choose) neurology. Annals of Neurology. 2014; 75(4): 487–489, doi: 10.1002/ana.24133.
22. Ridsdale L, Massey R, Clark L. Preventing neurophobia in medical students, and so future doctors. Pract Neurol. 2007; 7(2): 116–123, indexed in Pubmed: 17430877.
23. Fuller G. Neurophilia: a fascination for neurology—a new syndrome. Practical Neurology. 2012; 12(5): 276–278, doi: 10.1136/practneurol-2012-000400.
24. Giles J. Clinical neuroscience attachments: a student's view of 'neurophobia'. Clin Teach. 2010; 7(1): 9–13, doi: 10.1111/j.1743-498X.2009.00330.x, indexed in Pubmed: 21134136.

RESEARCH PAPERS

Neurologia i Neurochirurgia Polska
Polish Journal od Neurology and Neurosurgery
2019, Volume 53, no. 1, pages: 74–82
DOI: 10.5603/PJNNS.a2018.0006

ISSN 0028–3843

No association between MRI changes in the lumbar spine and intensity of pain, quality of life, depressive and anxiety symptoms in patients with low back pain

Anna Babińska[1], Wojciech Wawrzynek[1], Elżbieta Czech[2], Jarosław Skupiński[1], Jarosław Szczygieł[3], Beata Łabuz-Roszak[4]

[1]Department of Radiology, District Hospital of Orthopaedics and Trauma Surgery, Piekary Slaskie, Poland
[2]Department of Biostatistics, Faculty of Public Health in Bytom, Medical University of Silesia, Katowice, Poland
[3]1st Department of Neurological Rehabilitation, Upper Silesian Rehabilitation Centre "Repty", Tarnowskie Gory, Poland
[4]Department of Basic Medical Sciences, Faculty of Public Health, Medical University of Silesia, Katowice, Poland

ABSTRACT

Introduction. The association between changes in magnetic resonance imaging (MRI) and clinical symptoms in patients with low back pain (LBP) is unclear.

Aim. To evaluate correlations between combined MRI findings of the lumbar spine (LS) and pain intensity, depressive and anxiety symptoms and quality of life in patients with LBP.

Material and methods. 200 subjects (93 men and 107 women; mean age 51.42 ± 13.21 years) with LBP referred for MRI were enrolled in the study. All patients completed the Hospital Anxiety and Depression Scale (HADS), Quality of Life Scales (EQ-5D, EQ-VAS) and the Visual Analogue Scale (VAS). MRI scans were assessed according to a scoring system prepared by the authors, and the total MRI score was calculated.

Results. The mean total MRI score was 11.59 ± 6.73 points (range 0–50 points) and was higher in men than in women ($p = 0.015$). A correlation was observed between total MRI score and age ($p < 0.001$) and between total MRI score and BMI ($p = 0.005$). An association was found between total MRI score and EQ-5D ($p = 0.012$) and HADS-D results ($p = 0.003$). VAS and HADS-A results did not correlate with MRI score. When multivariate analysis was done, the total MRI score was only significantly related to age and BMI, and association between the total MRI score and EQ-5D or HADS-D results was not confirmed. Decreased quality of life was associated with increased intensity of pain and depressive and anxiety symptoms.

Conclusions. Combined MRI changes in LS do not correlate with pain intensity, depressive and anxiety syndromes or quality of life in patients with LBP.

Key words: low back pain, quality of life, depressive symptoms, anxiety, MRI examination
(*Neurol Neurochir Pol 2019; 53 (1): 74–82*)

Introduction

Low back pain (LBP) is an important and common public health problem which can lead to chronic pain syndromes and physical disability. It has also crucial socioeconomic implications due to the costs of diagnostic and therapeutic procedures, absence from work, and earlier retirement and pension [1]. Patients have sought medical help from general practitioners and specialists for many years. The consequences of chronic spinal pain such as physical disability, reduction

Address for correspondence: Anna Babińska, Department of Radiology, District Hospital of Orthopaedics and Trauma Surgery, e-mail: annababinska88@gmail.com

in professional efficiency and social disruption have negative impacts on quality of life in patients and can cause depressive and anxiety symptoms, affecting social relationships and family life [2–3].

While magnetic resonance imaging (MRI) is a sensitive diagnostic tool in patients with LBP, any associations between radiological findings of the lumbar spine (LS) and clinical symptoms remain controversial [4]. MRI is a nonspecific examination that reveals changes which often correlate poorly with clinical manifestations. Some authors have found a higher prevalence of spinal abnormalities in MRI in asymptomatic patients [5–7]. Disc herniation, disc degeneration, Modic type endplate changes and annular tears are common findings in LS MRI in patients with LBP, and also in asymptomatic patients since such changes may be due to the ageing process of the spine.

Although numerous studies have investigated the relationship between pain intensity and particular MRI abnormalities [4, 8, 9], it is still unclear how combined MRI can influence clinical symptoms. According to Chou et al. [10], patients with severe back pain tend to have a higher prevalence of the degenerative changes found in MRI. Previous studies [11–13] have focused on looking for an association between the combined MRI findings and clinical outcomes, comparing the degree of disability and pain intensity with the total number of radiological abnormalities. Similarly, in our study we considered extensive MRI changes in the LS in patients with LBP. However, unlike the above studies, we focused on different clinical and radiological aspects. We analysed whether the combined MRI changes in the LS (from L1 to S1 levels) were related to pain intensity, depressive and anxiety syndromes and quality of life. Previous studies have found no clear association between MRI findings and the degree of disability or pain. Additionally, associations between radiological changes and depression, anxiety and quality of life have been unclear [11–13].

Aim

The aim of our study was to evaluate the correlations between combined MRI findings in the LS and pain intensity, depressive and anxiety symptoms and quality of life in patients with LBP.

Material and methods

This study was conducted between May 2015 and December 2017**.** Patients with LBP referred for LS MRI were enrolled in the study.

According to the Bioethics Committee, the study was not a medical experiment. Therefore, no approval of the Committee was required. All patients provided informed written consent prior to study enrollment.

All participants were referred for MRI examination by orthopaedic surgeons, neurosurgeons, neurologists or general surgeons. In total, 200 patients met the following inclusion criteria: current or previous history of LBP, and age ≥ 18 years old. The exclusion criteria were as follows: previous surgery or interventional LS procedures, suspected or previous evidence of neoplasm or discitis, prior or active fractures of lumbar vertebrae, history of acute trauma to the lower back, structural vertebral changes (e.g. spondylolysis, spondylolisthesis, ankylosis, vertebral deformity), mild cognitive impairment, dementia or other mental illness. A Mini-Mental State Examination (MMSE) was performed to exclude patients with cognitive impairment. Eligible patients were requested to participate in the study.

Each subject was interviewed using a questionnaire prepared by the authors of the study. This questionnaire included questions related to the age, symptoms, education, professional activity, marital status, physical activity and socioeconomic status of the subjects. Neurological examination was performed by one of the authors of the study. The following questionnaires were used in the study: the Hospital Anxiety and Depression Scale (HADS), the Visual Analogue Scale (VAS) and Quality of Life Scales (EQ-5D, EQ-VAS). Medical history was obtained, physical examination was performed, and the questionnaires were completed prior to MRI examination.

Pain assessment

Intensity of pain was assessed using the Visual Analogue Scale (VAS). This scale determines pain intensity from 0 to 10 with the use of a 10 cm ruler where 0 means no pain, and 10 the worst pain imaginable [14].

Depressive and anxiety symptoms

Depressive and anxiety symptoms were assessed by the Hospital Anxiety and Depression Scale (HADS) which is a self-assessment screening questionnaire [15]. Patients were asked to select one response from four options for each question.

The questions related to anxiety marked with „A" (7 questions — HADS-A) and to depression marked with „D" (7 questions — HADS-D) were given alternately. The scores (from 0 to 3) for each question for "A" and separately for "D" were added together to obtain two results i.e. for anxiety and depression. A total score from 0 to 7 indicates no abnormality, 8–10 is borderline, and 11 and above suggests anxiety or depression.

Quality of life

Quality of life was assessed using a EuroQol 5D quality of life self-esteem questionnaire, which consists of two parts i.e. the EQ-5D and EQ-VAS. The EQ-5D covers five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Three responses to each question are possible. For the purposes of our study, the following scoring system was established: from 1 (no problem) to

3 points (considerable problems) for each question, and then the sum was calculated, giving a possible maximum score of 15 (i.e. the worst health status). The Polish validated version of the questionnaire was used [16]. A permission EuroQol Research Foundation was obtained to use it.

EQ-VAS is an analogue visual scale assessing general health status and disease activity from 0 (the worst imaginable health) to 100 (the best possible health). Most often it is presented as a vertical 100 mm-long line on which patients mark a horizontal line corresponding to their own judgment of disease severity. The result is obtained by measuring (in millimetres) the distance from the beginning of the scale to the place selected by the patient.

Magnetic resonance imaging

MR scans were performed using 3 T MR GE DISCOVERY 750W (57 patients) and 1.5 T ESPREE SIEMENS MR (143 patients). The following sequences of the LS (from L1 to S1 levels) were applied: sagittal T2-weighted images, sagittal T1-weighted images, sagittal T2-proton density weighted images, coronal T2-weighted images, and axial T2-weighted images angled parallel to individual disc spaces at each level between L1–S1. Slice thickness for 1.5T magnets was 4.0 mm with a 0.4 mm gap, the field of view (FOV) was 160 mm (axial T2) and 320 mm (other sequences); slice thickness for 3T magnets was between 3.0 and 4.0 mm with a 0.3–0.5 mm gap, FOV was 200 mm (axial T2) and 340 mm (other sequences).

Each MR examination was assessed by two radiologists independently, according to the protocol previously defined by the authors and classified for the presence or absence of the following abnormalities at each disc level of the LS: disc herniation, disc degeneration (according to the Pfirrmann scale), Modic type endplate changes, annular tears and nerve impingements (Fig. 1). If there was a disparity between assessments, a third independent radiological assessment was made and a consensus was reached. Prior to the analysis, a scoring system for the selected MRI findings was established (Tab. 1).

Disc herniation was classified as normal, 'bulging', protrusion, extrusion or sequestration (Fig. 2). We decided to rate 'bulging' lower than protrusion, extrusion and sequestration based on the recommendations proposed by Fardon et al. [17] that classified it not as a herniation, but rather as the first step in symmetric disc degeneration. Disc degeneration was assessed on sagittal T2-weighted images using a five-level grading system proposed by Pfirrmann which evaluates signal intensity changes in a disc, its internal

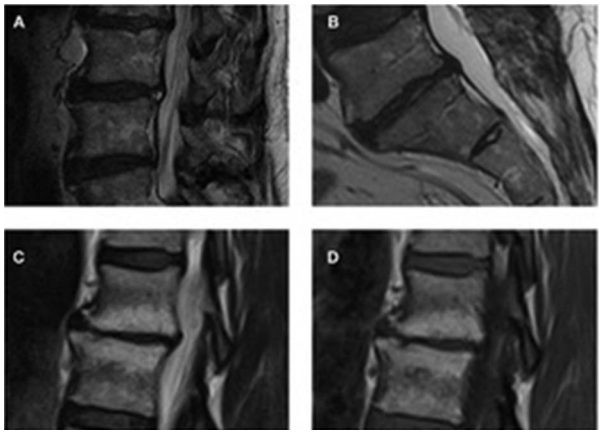


Figure 1. Examples of MRI findings evaluated in the study: A) HIZ and B) disc degeneration grade 5, according to the Pfirrmann scale on sagittal T2-weighted image; C) and D) Modic type 2 endplate changes on sagittal T2- and T1-weighted images

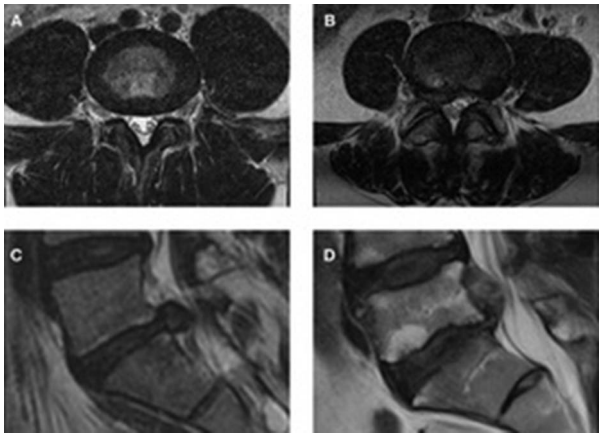


Figure 2. Typical features of lumbar disc pathology on T2-weighted images: **A**) disc bulge, **B**) protrusion, **C**) extrusion, and **D**) sequestration

Table 1. MRI scoring system

Radiological finding	0 points	1 point	2 points
Disc herniation	Normal	Bulging	Protrusion, extrusion, sequestration
Disc degeneration according to the Pfirrmann scale	Grade 1	Grades 2 and 3	Grades 4 and 5
Modic type endplate changes	Type 0	Types 2 and 3	Type 1
Annular tears	Absent	-	Present
Nerve root/spinal nerve	Normal	Displacement	Compression

structure, homogeneity and height [18]. Grade 1 was scored at 0 points as this represents the appearance of a regular disc. Modic type signal intensity changes in an adjacent endplate vertebral body were classified according to the scale as type 1: T1 hypointense and T2 hyperintense signal, type 2: T1 and T2 hyperintense signal, type 3: T1 and T2 hypointense signal intensity and type 0: no changes [19]. In this study, type 1 was rated higher than types 2 and 3. The most recent reports have indicated a significant relationship between pain intensity in patients with LBP and Modic changes type 1 [20–22]. According to other researches, types 2 and 3 did not show this relationship. Annular tear was defined as a high-signal intensity zone (HIZ) on T2-weighted images in the posterior part of the disc that was brighter than the nucleus pulposus. Posterior HIZ was rated as either present or absent. There is no transitional form for this finding, therefore it was scored at either 0 or 2 points. Nerve root changes were assessed as normal, displaced, or compressed.

The MRI scoring system ranged from 0 to 50 points. The maximum number of points was 10 for each intervertebral space level of the LS. The sum of all points at disc levels from L1 to S1 gave us the number (the total MRI score) which represented the severity of LS degeneration assessed in MRI.

Statistical analysis

Statistical analysis was performed using STATISTICA 12, Stat Soft Poland and R 3.3.2, GNU General Public License. Data were expressed as the mean with standard deviation and median (minimum÷maximum) and as the number and percentage. The following tests were used: the chi-square Pearson, Kruskal-Wallis, t-Student, U Mann-Whitney, multivariate analysis — general linear regression model (GLM). The Spearman's Rho correlation analysis was also performed. A p-value of < 0.05 was considered significant.

Results

The study comprised 200 patients (93 men and 107 women, mean age 51.42 ± 13.21 years). The average back pain duration was 66.68 (SD 78.92) months. The patient characteristics are presented in Table 2.

Neurological examination revealed unilateral or bilateral abnormalities (symptoms of irritation or damage to nerve roots) in 76 patients (38%). Stretching symptoms (Laseque sign) were present in 70 subjects (35%), nerve root sensory disorders in 18 (9%), distal muscle weakness in 13 (6.5%), (limited plantar or dorsal flexion of the foot) and absent knee or Achilles tendon reflexes were found in 15 patients (7.5%). Only one patient reported sphincter disorders. Local symptoms related to LS (increased paraspinal muscle tone and/or limitation of spinal mobility and/or pain on palpation of spinous processes and/or reactive scoliosis) were present in 126 cases (63%). Neurological examination revealed no other central or peripheral changes.

Abnormalities in neurological examinations correlated with MRI findings. Nerve root compression and/or severe or moderate spinal stenosis at any spinal level were seen on MRI scans in all patients with the symptoms of root damage in neurological examinations. Only six patients (8.6%) of all subjects with stretching symptoms had no nerve root changes related to the L1–S1 levels.

The results of the questionnaires are presented in Table 3. Analysis of the results between both genders showed only statistically significant higher results (but still within the range) of HADS-A in women compared to men ($p = 0.046$). The results of HADS-D, EQ-5D and EQ-VAS were statistically significantly associated with the age of patients ($p < 0.001$, $p = 0.024$, $p = 0.001$, respectively) and the BMI ($p = 0.005$, $p < 0.001$, $p < 0.001$, respectively). The VAS scale results related only to the BMI ($p = 0.014$). The results of EQ-5D correlated with the results of the VAS scale ($p < 0.001$, $R = 0.47$), HADS-A ($p < 0.001$, $R = 0.44$) and HADS-D ($p < 0.001$, $R = 0.55$), which meant that a decrease in quality of life in patients was associated with a higher intensity of back pain and depressive and anxiety symptoms.

The mean total MRI score was 11.59 ± 6.73 points, with a statistically significant difference between women and men (10.47 ± 6.46 and 12.88 ± 6.83 points, respectively; $p = 0.015$) (Tab. 4). Most of the radiological changes were related to the L4–L5 and L5–S1 levels. Correlations were found between the total MRI score and the age of patients ($p < 0.001$, $R = 0.55$) and BMI ($p = 0.005$, $R = 0.2$). The most common radiological finding in the study group was a disc bulge, and the least common was sequestration, which was observed only three times (Tab. 5).

The mean waiting time for MRI was 7.49 ± 5.81 (0÷31) months. The mean number of LS radiographs was 1.77 ± 1.75 (0÷10), CTs – 0.83 ± 0.99 (0÷6) and MRIs – 0.85 ± 0.96 (0÷4) of LS (done during the whole life by subjects).

An association was found between the total MRI score and EQ-5D results ($R = 0.18$, $p = 0.012$) as well as HADS-D results ($R = 0.21$, $p = 0.003$). The results of other questionnaires (VAS, HADS-A) did not correlate with the total MRI score (Tab. 6). But when multivariate analysis was done (with variables significantly related to the total MRI score: age, gender, BMI, EQ-5D score, HADS-D score), significant associations were only found for the total MRI score and age ($p < 0.001$), and the total MRI score and BMI ($p < 0.001$). Multivariate analysis did not confirm an association between the total MRI and EQ-5D scores, as well as between the total MRI and HADS-D scores observed in univariate analyses.

Being professionally active was related to decreased pain intensity ($p = 0.002$), lower scores in HADS-D ($p = 0.002$) and better quality of life ($p = 0.002$ for EQ5D, $p = 0.003$ for EQ-VAS; U Mann-Whitney test). Unlimited physical activity was also associated with decreased pain intensity ($p < 0.001$), lower scores in HADS-D ($p < 0.001$) and HADS-A ($p < 0.001$) and better quality of life ($p < 0.001$ for EQ5D and EQ-VAS;

Table 2. Patient characteristics

		Women N = 107	Men N = 93	All subjects N = 200	P women *vs* men
Age (years)*		51.08 ± 12.68	51.82 ± 13.86	51.42 ± 13.21	p = 0.949U
		54.0 (20÷75)	52.5 (21÷80)	54.0 (20÷80)	
BMI (kg/m^2)*		27.01 ± 4.47	27.99 ± 4.26	27.13 ± 4.89	p = 0.117t
		26.9 (17.1÷40.9)	27.8 (18.6÷41.6)	26.9 (18.6÷41.6)	
Education**	Elementary	30 (28.0%)	25 (26.9%)	55 (27.5%)	
	Secondary	41 (38.3%)	46 (49.5%)	87 (43.5%)	p = 0.206χ
	University	36 (33.7%)	22 (23.6%)	58 (29.0%)	
Marital status**	Married/in a partnership	71 (66.4%)	74 (79.6%)	145 (72.5%)	
	Single/divorced/ /widow/widower	36 (33.6%)	19 (20.4%)	55 (27.5%)	p = 0.037χ
Place of residence** N = 196 (no data in four subjects)	Village	20 (19.0%)	21 (23.0%)	41 (20.9%)	
	Town < 100,000 inhabitants	51 (48.6%)	45 (49.5%)	96 (49.0%)	p = 0.678χ
	City > 100,000 inhabitants	34 (32.4%)	25 (27.5%)	59 (30.1%)	
Professional activity** N = 196 (no data in four subjects)	Active	57 (54.8%)	49 (53.3%)	106 (54.1%)	
	Inactive	47 (45.2%)	43 (46.7%)	90 (45.9%)	p = 0.828χ
Physical activity**	Without problems	43 (40.2%)	32 (34.4%)	75 (37.5%)	
	Some movement-related problems	62 (57.9%)	54 (58.1%)	116 (58%)	p = 0.127F
	Unable to walk without help	2 (1.9%)	7 (7.5%)	9 (4.5%)	
Socioeconomic status** N = 189 (no data in 11 subjects)	Very good	9 (8.9%)	5 (5.7%)	14 (7.4%)	
	Good	35 (34.7%)	42 (47.7%)	77 (40.7%)	
	Average	48 (47.5%)	40 (45.5%)	88 (46.6%)	p = 0.029F
	Bad	0	0	0	
	No opinion	9 (8.9%)	1 (1.1%)	10 (5.3%)	

* Data are presented as: mean ± standard deviation [SD] and median (minimum÷maximum); ** Data presented as N (%); χ — Chi2 Pearson test; U — Mann-Whitney test; t — Student test ; F — Fisher Exact Test
BMI — body mass index

Table 3. Questionnaire results. Data are presented as mean ± standard deviation [SD] and median (minimum÷maximum)

Parameter	Women N = 107	Men N = 93	All subjects N = 200	p^U women *vs* men
Pain intensity	6.13 ± 2.09	5.90 ± 2.20	6.02 ± 2.14	p = 0.477
(VAS; 1-10)	6.0 (1÷10)	6.0 (0÷10)	6.0 (0÷10)	
Quality of life	8.05 ± 1.62	8.08 ± 1.73	8.06 ± 1.67	p = 0.891
(EQ-5D; 5-15)	8.0 (5÷13)	8.0 (5÷12)	8.0 (5÷13)	
Quality of life	61.38 ± 18.37	63.53 ± 18.77	62.40 ± 18.54	p = 0.413
(EQ-VAS; 1-100%)	60.0 (5÷100)	70.0 (10÷100)	70.0 (5÷100)	
Anxiety symptoms	6.87 ± 3.99	5.82 ± 3.99	6.38 ± 4.01	p = 0.046
(HADS-A; 0-21)	7.0 (0÷19)	5.0 (0÷17)	6.0 (0÷19)	
Depressive symptoms	4.66 ± 3.67	4.74 ± 3.65	4.70 ± 3.65	p = 0.849
(HADS-D; 0-21)	5.0 (0÷16)	5.0 (0÷16)	4.0 (0÷16)	

U — U Mann-Whitney test; VAS — Visual Analogue Scale for intensity of pain; EQ-5D — EuroQol 5D quality of life self-esteem questionnaire; EQ-VAS — quality of life — visual analogue scale; HADS-A — Hospital Anxiety and Depression Scale — Anxiety Symptoms; HADS-D — Hospital Anxiety and Depression Scale — Depressive Symptoms

Table 4. MRI scoring system. Data are presented as mean ± standard deviation [SD] and median (minimum÷maximum)

	Women N = 107	Men N = 93	All subjects N = 200	p^U women *vs* men
Level L1-L2	0.42 ± 1.06	0.94 ± 1.76	0.66 ± 1.45	p = 0.095
(points; 0-10)	0.0 (0÷5)	0.0 (0÷7)	0.0 (0÷7)	
Level L2-L3	0.85 ± 1.49	1.10 ± 1.84	0.97 ± 1.66	p = 0.471
(points; 0-10)	0.0 (0÷7)	0.0 (0÷8)	0.0 (0÷8)	
Level L3-L4	1.64 ± 1.98	2.48 ± 2.27	2.03 ± 2.16	p = 0.006
(points; 0-10)	1.0 (0÷8)	2.0 (0÷8)	1.0 (0÷8)	
Level L4-L5	3.79 ± 2.31	4.05 ± 2.20	3.91 ± 2.26	p = 0.371
(points; 0-10)	4.0 (0÷9)	4.0 (0÷8)	4.0 (0÷9)	
Level L5-S1	3.80 ± 2.92	4.42 ± 2.22	4.09 ± 2.63	p = 0.095
(points; 0-10)	4.0 (0÷9)	5.0 (0÷9)	4.0 (0÷9)	
Total MRI score (from L1 to S1)	10.47 ± 6.46	12.88 ± 6.83	11.59 ± 6.73	p = 0.015
(points; 0-50)	10.0 (0÷30)	12.0 (0÷34)	11.0 (0÷34)	

U — U Mann-Whitney test

Table 5. Prevalence of radiological findings in study group (from L1 to S1 levels)

Radiological finding	Total number (percentage)
Modic type 1	35 (3.5%)
Modic type 2	89 (8.9%)
Modic type 3	9 (0.9%)
Pfirrmann grade 2	156 (15.6%)
Pfirrmann grade 3	158 (15.8%)
Pfirrmann grade 4	123 (12.3%)
Pfirrmann grade 5	116 (11.6%)
Annular tear	112 (11.2%)
Bulging	259 (25.9%)
Protrusion	185 (18.5%)
Extrusion	64 (6.4%)
Sequestration	3 (0.3%)
Nerve root compression	103 (10.3%)
Nerve root displacement	198 (19.8%)

Table 6. Correlations between total MRI score and questionnaire results (Spearman's correlation)

	Total score
Pain intensity	R = 0.14
(VAS scale)	p = 0.053
Quality of life	R = 0.18
(EQ-5D)	p = 0.012
Quality of life	R = -0.09
(EQ-VAS)	p = 0.192
Anxiety symptoms	R = 0.02
(HADS-A)	p = 0.737
Depressive symptoms	R = 0.21
(HADS-D)	p = 0.003

VAS — Visual Analogue Scale for intensity of pain; EQ-5D — EuroQol 5D quality of life self-esteem questionnaire; EQ-VAS — quality of life — visual analogue scale; HADS-A — Hospital Anxiety and Depression Scale — Anxiety Symptoms; HADS-D — Hospital Anxiety and Depression Scale — Depressive Symptoms

U Mann-Whitney test). EQ-5D and EQ-VAS results were associated with the level of education (p = 0.045 and p = 0.004, respectively; Kruskal-Wallis test) and the nature of work (p < 0.001; U Mann-Whitney test) (self-esteemed quality of life was decreased in patients with lower education level and/or those who were manual workers). No association was found between MRI findings and the place of residence, education, socioeconomic status, marital status, nature of work or physical activity.

Discussion

Patients with LBP tend to have more radiological abnormalities on MRI scans, including disc degeneration, Modic type changes and herniations compared to controls without back pain [23]. Some previous studies of patients with LBP compared the sum of several MRI findings with clinical symptoms [11–13]. In the present study, we evaluated the association between total MRI changes of the LS (from L1 to S1) and pain intensity, quality of life, depressive and anxiety symptoms in patients with LBP. To the best of our knowledge, ours is the first study to investigate such relationships.

In the study of Mariconda et al. [13], the total number of degenerative changes in the LS seen on MRI scans showed a borderline correlation with disability scores ($p = 0.05$) and pain duration ($p = 0.011$). Each intervertebral disc space from L1-S1 was evaluated and the total degeneration score was calculated. On the other hand, Berg et al. [12] found no association between total MRI changes and the degree of disability or LBP intensity in candidates for lumbar disc prosthesis. The analysis evaluated the following: disc height decrease, Modic changes types I and II, HIZ and hypointense nucleus pulposus on L4–L5 and L5–S1 levels. Arana et al. [11] found a weak correlation between the combined MRI score and pain interference with work ($p = 0.04$), but no correlation with the degree of disability while evaluating disc and facet findings, spinal stenosis and other pathologies in the two most affected LS levels on MRI scans.

Although those results are not comparable to ours due to different MRI variables, other clinical measurement methods, and different patient samples, our findings showed no correlation between pain symptoms and the total MRI score. We did not investigate the degree of disability. We found no relationship between physical activity and total MRI changes.

Unlike other studies [11, 12], we decided to increase the extent of the assessed spine levels from L1 to S1 and to extend the number of evaluated radiological findings. Because there is no validated measurement or scoring system to assess MRI scans of the LS, we decided to prepare our own scoring system related to selected degenerative MRI findings. This concept has already been used by other authors [12]. However, in this study we created a completely different MRI scoring system which contained changes most commonly observed in degenerative LS disease [24].

The main advantage of our study is related to the fact that it is the first research exploring the above-mentioned correlations. Furthermore, we assessed a relatively large patient group and extended MRI findings evaluated by radiologists. Moreover, the study included standardised nomenclature and classification systems that are currently used for the diagnosis of degenerative disease of the spine [24, 25]. The MRI changes were classified according to a consensus reached between three radiologists. In our opinion, the total MRI score is an objective and measurable tool which represents the severity of degeneration of the LS. Furthermore, this study includes comprehensive assessments of pain intensity, depressive and anxiety syndromes and quality of life using validated instruments. Moreover, the neurological examination was conducted on the same day that the MRI examination was performed, and a detailed history provided wide clinical knowledge about the sample group.

We observed increasing morphological LS degeneration seen on MRI scans with increasing age and BMI, as was demonstrated by previous researches [13, 26]. We observed significantly more LS MRI changes in men compared to women, which is consistent with observations made by other authors [13, 27]. Most of the radiological findings were seen on L4–L5 and L5–S1 levels, which is also consistent with other reports [11, 27]. Hollingworth et al. [27] found that 45% of patients with LBP and sciatica pain had no nerve root impingement on MRI. In our results only six patients with stretching sign had no nerve root changes. The explanation of such an enormous difference is probably related to a different method of assessing the symptoms i.e. medical history *vs* neurological examination, which is more specific.

Our study confirmed previous observations related to the problem of decreased quality of life, depressive and anxiety symptoms in chronic pain syndromes [2]. Moreover, a relationship between physical and professional activity and clinical symptoms was observed. This finding suggested that reduced disability (e.g. due to physiotherapy) and a quick return to work are important in the management of patients with LBP; long sick leave is not recommended.

Our study confirmed a poor association between radiological findings and clinical symptoms. No relationship was observed between combined MRI findings and intensity of pain, depressive and anxiety syndrome or quality of life. We believe that these results are clinically relevant. Chou et al. [28] showed that immediate, routine LS imaging in patients with LBP with no features suggestive of serious underlying conditions (such as cancer, infection, cauda equina syndrome) did not improve clinical outcomes compared to usual clinical care without immediate imaging. Moreover, early MRI in acute LBP without indications provides no benefits and could result in worse outcomes such as 'iatrogenic' work disability and an unnecessary medical procedure [29]. Routine and immediate LS imaging in asymptomatic patients is not recommended and could result in worse outcomes [10, 28, 29]. The number of MRI examinations is still increasing, and this generates higher costs. On the other hand, patients expect advanced diagnostic imaging. We share the opinion of Chou et al. [28] that patient education is important in order to change the expectations of patients and avoid unnecessary examinations.

Lumbar spine pain syndrome is a complex psychological, physiological and behavioural problem. Despite numerous studies, management in LBP still remains a challenge for clinicians. Pain reduction is the priority in the therapeutic process. However, depressive and anxiety symptoms and poor quality of life need to be considered as well. Treatment of depression and anxiety may help in patients with chronic pain symptoms.

Our study is another step towards improving the understanding of the complexity of clinical-radiological correlations in LBP syndromes. Further studies are needed to improve management in LBP.

Limitations of the study

There are some limitations of our study. Firstly, we did not exclude patients with chronic diseases such as diabetes

mellitus, heart failure, hypertension, skin diseases or allergies. These diseases can affect quality of life and increase psychological distress in patients. Secondly, the clinical features of the disease and symptoms may have changed while waiting for MRI, as the average duration from referral to MRI examination was 7.49 ± 5.81 months.

It is crucial to stress that there was no asymptomatic control group. However, our aim was not to compare two samples, rather we focused only on patients with LBP. The MRI scanning conditions were different (1.5T and 3T). However, this did not affect the results, as different magnetic field strengths do not change the assessment of radiological changes in degenerative spine disease.

Conclusions

Combined degenerative MRI changes in the LS do not correlate with LBP intensity, anxiety and depressive symptoms or quality of life. The total MRI findings are only associated with age and BMI.

Acknowledgements. *The authors wish to thank Arkadiusz Badzinski, DHSc, Assistant Professor at the University of Silesia, authorised medical interpretator and translator, for language correction of this paper.*

References

1. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. Spine J. 2008; 8(1): 8–20, doi: 10.1016/j.spinee.2007.10.005, indexed in Pubmed: 18164449.
2. Pakpour AH, Nikoobakht M, Campbell P. Association of pain and depression in those with chronic low back pain: the mediation effect of patient sexual functioning. Clin J Pain. 2015; 31(1): 44–51, doi: 10.1097/AJP.0000000000000076, indexed in Pubmed: 25485954.
3. Bahouq H, Allali F, Rkain H, et al. Discussing sexual concerns with chronic low back pain patients: barriers and patients' expectations. Clin Rheumatol. 2013; 32(10): 1487–1492, doi: 10.1007/s10067-013-2299-y, indexed in Pubmed: 23743660.
4. Beattie PF, Meyers SP, Stratford P, et al. Associations between patient report of symptoms and anatomic impairment visible on lumbar magnetic resonance imaging. Spine (Phila Pa 1976). 2000; 25(7): 819–828, indexed in Pubmed: 10751293.
5. Jarvik JG, Hollingworth W, Heagerty PJ, et al. Three-year incidence of low back pain in an initially asymptomatic cohort: clinical and imaging risk factors. Spine (Phila Pa 1976). 2005; 30(13): 1541–8; discussion 1549, indexed in Pubmed: 15990670.
6. Chung CB, Vande Berg BC, Tavernier T, et al. End plate marrow changes in the asymptomatic lumbosacral spine: frequency, distribution and correlation with age and degenerative changes. Skeletal Radiol. 2004; 33(7): 399–404, doi: 10.1007/s00256-004-0780-z, indexed in Pubmed: 15138721.
7. Weishaupt D, Zanetti M, Hodler J, et al. MR imaging of the lumbar spine: prevalence of intervertebral disk extrusion and sequestration, nerve root compression, end plate abnormalities, and osteoarthritis of the facet joints in asymptomatic volunteers. Radiology. 1998; 209(3): 661–666, doi: 10.1148/radiology.209.3.9844656, indexed in Pubmed: 9844656.
8. Jensen OK, Nielsen CV, Sørensen JS, et al. Back pain was less explained than leg pain: a cross-sectional study using magnetic resonance imaging in low back pain patients with and without radiculopathy. BMC Musculoskelet Disord. 2015; 16: 374, doi: 10.1186/s12891-015-0827-4, indexed in Pubmed: 26635015.
9. Endean A, Palmer KT, Coggon D. Potential of magnetic resonance imaging findings to refine case definition for mechanical low back pain in epidemiological studies: a systematic review. Spine (Phila Pa 1976). 2011; 36(2): 160–169, doi: 10.1097/BRS.0b013e3181cd9adb, indexed in Pubmed: 20739918.
10. Chou D, Samartzis D, Bellabarba C, et al. Degenerative magnetic resonance imaging changes in patients with chronic low back pain: a systematic review. Spine (Phila Pa 1976). 2011; 36(21 Suppl): S43–S53, doi: 10.1097/BRS.0b013e31822ef700, indexed in Pubmed: 21952189.
11. Arana E, Martí-Bonmatí L, Vega M, et al. Relationship between low back pain, disability, MR imaging findings and health care provider. Skeletal Radiol. 2006; 35(9): 641–647, doi: 10.1007/s00256-006-0100-x, indexed in Pubmed: 16602016.
12. Berg L, Hellum C, Gjertsen Ø, et al. Norwegian Spine Study Group. Do more MRI findings imply worse disability or more intense low back pain? A cross-sectional study of candidates for lumbar disc prosthesis. Skeletal Radiol. 2013; 42(11): 1593–1602, doi: 10.1007/s00256-013-1700-x, indexed in Pubmed: 23982421.
13. Mariconda M, Galasso O, Imbimbo L, et al. Relationship between alterations of the lumbar spine, visualized with magnetic resonance imaging, and occupational variables. Eur Spine J. 2007; 16(2): 255–266, doi: 10.1007/s00586-005-0036-1, indexed in Pubmed: 16835739.
14. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health. 1990; 13(4): 227–236, indexed in Pubmed: 2197679.
15. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatrica Scandinavica. 1983; 67(6): 361–370, doi: 10.1111/j.1600-0447.1983.tb09716.x.
16. Sobczyk W, Gugała M, Rola R. Rozwój badań nad jakością życia w chorobach przewlekłych. Post Psychiatr Neurol. 2008; 17(4): 353–356.
17. Fardon DF, Milette PC. Combined Task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology. Nomenclature and classification of lumbar disc pathology. Recommendations of the Combined task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology. Spine (Phila Pa 1976). 2001; 26(5): E93–E9E113, indexed in Pubmed: 11242399.
18. Pfirrmann CW, Metzdorf A, Zanetti M, et al. Magnetic resonance classification of lumbar intervertebral disc degeneration. Spine (Phila Pa 1976). 2001; 26(17): 1873–1878, indexed in Pubmed: 11568697.
19. Modic MT, Masaryk TJ, Ross JS, et al. Imaging of degenerative disk disease. Radiology. 1988; 168(1): 177–186, doi: 10.1148/radiology.168.1.3289089, indexed in Pubmed: 3289089.
20. Rahme R, Moussa R. The modic vertebral endplate and marrow changes: pathologic significance and relation to low back pain and segmental instability of the lumbar spine. AJNR Am J Neuroradiol. 2008; 29(5): 838–842, doi: 10.3174/ajnr.A0925, indexed in Pubmed: 18272564.

21. Albert HB, Manniche C. Modic changes following lumbar disc herniation. Eur Spine J. 2007; 16(7): 977–982, doi: 10.1007/s00586-007-0336-8, indexed in Pubmed: 17334791.
22. Kuisma M, Karppinen J, Niinimäki J, et al. Modic changes in endplates of lumbar vertebral bodies: prevalence and association with low back and sciatic pain among middle-aged male workers. Spine (Phila Pa 1976). 2007; 32(10): 1116–1122, doi: 10.1097/01.brs.0000261561.12944.ff, indexed in Pubmed: 17471095.
23. Hancock M, Maher C, Macaskill P, et al. MRI findings are more common in selected patients with acute low back pain than controls? European Spine Journal. 2011; 21(2): 240–246, doi: 10.1007/s00586-011-1955-7.
24. Heuck A, Glaser C. Basic aspects in MR imaging of degenerative lumbar disk disease. Semin Musculoskelet Radiol. 2014; 18(3): 228–239, doi: 10.1055/s-0034-1375566, indexed in Pubmed: 24896740.
25. Waldt S, Gersing A, Brügel M. Measurements and classifications in spine imaging. Semin Musculoskelet Radiol. 2014; 18(3): 219–227, doi: 10.1055/s-0034-1375565, indexed in Pubmed: 24896739.
26. Liuke M, Solovieva S, Lamminen A, et al. Disc degeneration of the lumbar spine in relation to overweight. Int J Obes (Lond). 2005; 29(8): 903–908, doi: 10.1038/sj.ijo.0802974, indexed in Pubmed: 15917859.
27. Hollingworth W, Dixon AK, Todd CJ, et al. Self reported health status and magnetic resonance imaging findings in patients with low back pain. Eur Spine J. 1998; 7(5): 369–375, indexed in Pubmed: 9840469.
28. Chou R, Fu R, Carrino JA, et al. Imaging strategies for low-back pain: systematic review and meta-analysis. Lancet. 2009; 373(9662): 463–472, doi: 10.1016/S0140-6736(09)60172-0, indexed in Pubmed: 19200918.
29. Webster BS, Bauer AZ, Choi Y, et al. Iatrogenic consequences of early magnetic resonance imaging in acute, work-related, disabling low back pain. Spine (Phila Pa 1976). 2013; 38(22): 1939–1946, doi: 10.1097/BRS.0b013e3182a42eb6, indexed in Pubmed: 23883826.

RESEARCH PAPERS

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 1, pages: 83–89
DOI: 10.5603/PJNNS.a2019.0002

ISSN 0028–3843

Stroke and TIA mimics in patients referred to a neurological emergency department by non-ambulance physicians, ambulance physicians and paramedics

Dorota Kozera-Strzelińska[1], Michał Karliński[1], Grzegorz Rak[2], Magdalena Wojdacz[1], Halina Sienkiewicz-Jarosz[3], Iwona Kurkowska-Jastrzębska[1]

[1] 2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland
[2] 2nd Faculty of Medicine, Medical University of Warsaw, Poland
[3] 1st Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland

ABSTRACT

Introduction. Our aim was to compare the structure and management of conditions mimicking acute cerebrovascular events (ACE) defined as stroke or transient ischaemic attack between patients referred directly to a neurological emergency department (ED) by non-ambulance physicians, ambulance physicians and paramedics.

Methods. This is a retrospective study of 802 consecutive patients referred to a Polish urban neurological ED with a prehospital suspicion of ACE between January and December 2014.

Results. After proper neurological assessment, ACE was excluded in 258 (32.2%) patients. The ratios of neurological to non-neurological ACE mimics were similar across all groups (35:93 for non-ambulance physicians, 22:39 for ambulance physicians, and 28:39 for paramedics). The most frequent conditions mimicking ACE were vertigo (14.0%), headache (9.7%), seizures (7.0%), blood hypertension (7.0%), electrolyte and metabolic disturbances (5.4%), infections (4.7%) and syncope (4.3%). There were no major differences between patients with ACE-mimics referred by ambulance physicians and referred by paramedics in terms of demographic, previous medical history, extent of diagnostic workup, final diagnosis or further management (neurological admission in 42.6% and 28.4% of cases). However, the characteristics and management of ACE mimics referred by non-ambulance physicians were slightly different, including a lower need for hospital admission (neurological admission in 21.5% of cases).

Conclusions. There seem to be no major differences in the structure, early diagnostic approach or management of ACE mimics between referrals from ambulance physicians and ambulance paramedics, which provides reassurance to healthcare systems that rely solely on paramedics. Mimics referred by non-ambulance physicians appear different in structure and are less resource-consuming.

Key words: stroke, transient ischaemic attack, misdiagnosis, ambulance, paramedics, emergency department
(*Neurol Neurochir Pol 2019; 53 (1): 83–89*)

Introduction

Contemporary evidence-based acute stroke treatment is highly oriented around reperfusion therapies, and it aims at constant optimisation of treatment logistics, which particularly refers to shortening door-to-needle or door-to-groin time [1]. Such an approach exerts additional pressure on Emergency Department (ED) personnel and makes

Address for correspondence: Michal Karliński, 2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland
e-mail: mkarlinski@ipin.edu.pl

room for diagnostic mistakes [1]. Not all patients initially suspected of having acute stroke actually suffer from cerebral ischaemia [2–5]. Incorrect diagnoses are made mostly in the prehospital setting but may also happen in the ED, especially if the initially attending physician is not a neurologist or a stroke physician [6]. In addition, clinical signs and symptoms combined with computed tomography (CT) and basic laboratory tests may sometimes be insufficiently conclusive to establish a final diagnosis within the first few hours after presenting to the ED. They sometimes require prolonged observation or magnetic resonance (MR) of the brain, which is not always easily available 24/7 and not always feasible [1]. Previous studies have shown that stroke mimics may account for as much as half of all suspected strokes, with a very wide range (2% to 47%) depending on the setting and methodology [2, 7–11]. More importantly, up to 10% of patients treated with intravenous thrombolysis may actually suffer from a condition other than ischaemic stroke [2, 12]. Therefore, clinicians should be aware of the most common stroke mimics that need to be addressed in the acute diagnostic workup at the ED. It also seems reasonable to account for country-specific features of emergency healthcare and patients' attitude towards acute illnesses. In Poland, the great majority of patients suspected of stroke within the therapeutic window for thrombolysis or thrombectomy are brought to the hospital by the ambulance with either a physician or a paramedic onboard.

The aim of our study was to compare the structure and management of conditions misdiagnosed in the prehospital setting as acute cerebrovascular events (ACE), defined as stroke or transient ischaemic attack, between patients referred directly to neurological ED by non-ambulance physicians, ambulance physicians and paramedics.

Material and methods

Our ED provides neurological and stroke care for approximately 350,000 inhabitants of a highly urban area (the southern part of Warsaw and neighbouring Polish towns). The hospital's profile is solely neuropsychiatric, with a neurosurgical ward and interventional neuroradiology. The ED is staffed 24 hours a day and 7 days a week with either a senior neurologist or a neurologist in training. Patients reporting to the ED are referred directly by non-ambulance physicians (mostly general practitioners but also outpatient specialists), ambulance physicians, ambulance paramedics or by themselves without any formal referral.

Brain CT, brain MR or CT-angiography are easily available at the ED and, if medically justified, the imaging can be performed without the need for subsequent admission to the neurological ward.

Study design

We retrospectively reviewed both paper and electronic source medical documentation of consecutive patients who reported to our neurological ED between 1st January 2014 and 31st December 2014 to identify all cases with a prehospital diagnosis of ACE. Patients who reported without any formal referral were not included in the analysis.

Data were extracted using a predefined form that included information about patient gender, age, type of referring entity, prehospital diagnosis (stroke or transient ischaemic attack or syndrome description highly suggestive of ACE), history of stroke, history of seizures, diagnostic workup undertaken at the ED (brain imaging, blood test), final diagnosis and the decision about admission or further referral.

This paper follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [13].

Statistical analysis

Categorical variables were presented as a number of valid observations and proportions calculated with exclusion of unknown values from the denominator. Continuous variables due to non-normal distribution (a Shapiro-Wilk test) were presented as a median with interquartile range (1st quartile to 3rd quartile, Q1–Q3).

Comparisons between patients referred by non-ambulance physicians, ambulance physicians and paramedics were done using chi square test or Kruskal-Wallis test, as appropriate. Pairwise differences were additionally tested only if the overall test for significance was positive ($p < 0.05$). Such an approach allowed us to reduce the risk of type I error without losing power by applying the Bonferroni correction.

P values of < 0.05 were considered statistically significant. Calculations were carried out using Dell STATISTICA 13.0 software package (Dell, Round Rock, TX, USA).

Results

During the 12-month study period there were 639 admissions for stroke or TIA in total, including 51 patients who reported to the ED without any referral and 95 patients with a prehospital diagnosis other than ACE. Of 802 patients who were referred to our neurological ED with a suspicion of ACE, 258 (32.2%) had a final diagnosis other than stroke or TIA. Approximately half of ACE mimics (n = 130) was referred by outpatient physicians and the other half by ambulance physicians (n = 61) or ambulance paramedics (n = 67) (Fig. 1). The ratios of neurological to non-neurological conditions mimicking ACE were similar across all three abovementioned groups (35:93, 22:39 and 28:39, respectively).

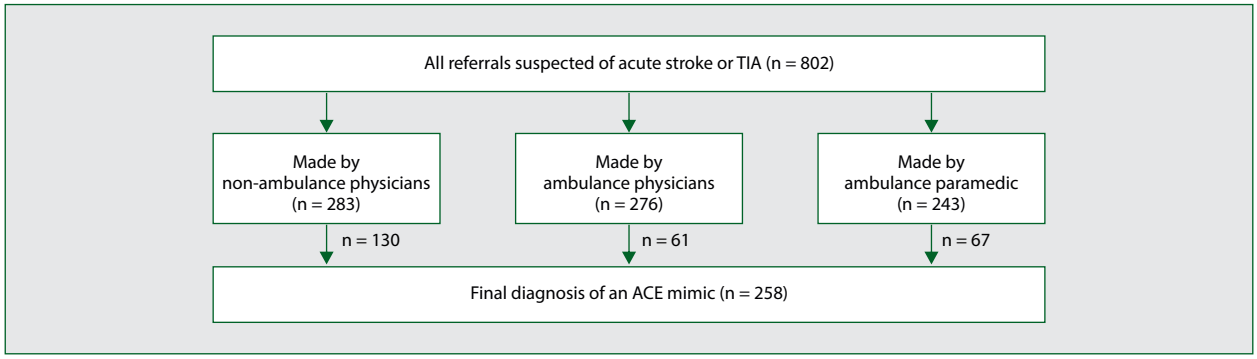


Figure 1. The structure of patients referred directly to neurological ED with a pre-hospital suspicion of ACE according to the type of the referring entity

Table 1. Conditions most frequently mimicking ACE

	n	Percentage within each group	Percentage overall (N = 258)
Neurological mimic (n = 171)	171	100%	66.3%
Vertigo	36	21.1%	14.0%
Headache	25	14.6%	9.7%
Seizures	18	10.5%	7.0%
Brain tumour	17	9.9%	6.6%
Sequels of cerebral infarction	14	8.2%	5.4%
Bell's palsy	13	7.6%	5.0%
Other neurological conditions	48	28.1%	18.6%
Non-neurological mimic (n = 87)	87	100%	33.7%
Very high blood pressure	18	20.7%	7.0%
Metabolic and electrolyte disturbances	14	16.1%	5.4%
Infections	12	13.8%	4.7%
Syncope	11	12.6%	4.3%
Cardiac condition	6	6.9%	2.3%
Alcohol abuse	5	5.7%	1.9%
Other non-neurological conditions	21	24.1%	8.1%

Patients incorrectly suspected of ACE were in 66.3% of cases eventually diagnosed with a neurological condition, most frequently vertigo (14.0%), headache (9.7%) and seizures (7.0%). Among non-neurological ACE mimics, the most frequent were blood hypertension (7.0%), electrolyte and metabolic disturbances (5.4%), infections (4.7%) and syncope (4.3%) (Tab. 1). The category of other neurological ACE mimics included a variety of conditions, mostly traumatic head injuries, side effects of neuroleptics or hypnotics, exacerbations of dementia or parkinsonism and single nerve pathologies. Other non-neurological ACE mimics were predominantly psychosomatic disturbances and exacerbations of chronic pulmonary or cardiac diseases.

There were no major differences between patients with ACE-mimics referred by ambulance physicians and paramedics in terms of demographics, previous medical history, extent of diagnostic workup, final diagnosis and the decision about admission to the neurological ward or direct referral to non-neurological ED in another hospital (Tab. 2).

However, ACE mimicking patients referred by non-ambulance physicians suffered significantly more frequently from headache and significantly less frequently from metabolic and electrolyte disturbances than patients referred either by paramedics or by ambulance physicians (Fig. 2). They also tended to have a less frequent history of seizures, less often required blood sample analyses to establish the final diagnosis, and less frequently were eventually admitted to the neurological ward or referred directly to a non-neurological ED in another hospital (Tab. 2). Additionally, compared to the ACE-mimics referred by ambulance physicians, they were

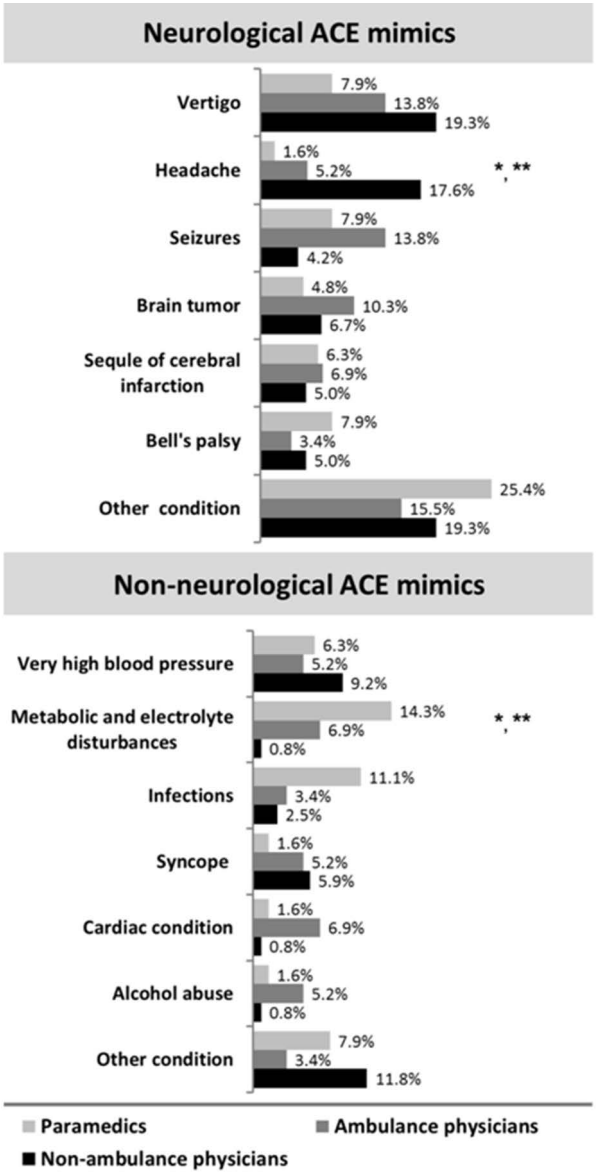


Figure 2. Most frequent ACE mimics according to the type of the referring entity. *, p<0.05 for comparison between non-ambulance physicians and ambulance physicians; **, p<0.05 for comparison between non-ambulance physicians and ambulance paramedics

more often female, less often had a history of stroke or TIA (transient ischaemic attack), and less often required admission to the neurological ward (Tab. 2). Patients referred by non-ambulance physicians were significantly younger and less often required brain imaging to exclude ACE than the patients referred by paramedics (Tab. 2). In terms of combined direct neurological admissions of ACE mimics or their re-referral to non-neurological EDs, both ambulance physicians and paramedics were superior to non-ambulance physicians (Tab. 2). However, the proportion of solely neurological admissions was significantly higher only among patients with ACE mimics referred by ambulance physicians (Tab. 2).

Discussion

To the best of our knowledge, this is the first study that has directly evaluated the structure and management of conditions incorrectly suspected in the prehospital setting of being acute stroke or TIA between three major types of referring entities in a healthcare system that employs ambulances with either onboard physicians or paramedics. In Poland, every patient suspected of stroke is immediately transported by emergency services to the nearest hospital with a stroke unit [1, 14]. Additionally, the Polish healthcare system economically promotes admissions of patients with TIA. According to the American Heart Association, TIA is episodic and transient neurological dysfunctions caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction but with a high short-term risk of subsequent stroke [15]. It is reasonable to admit to the hospital patients who present during the first 72 hours after TIA and have an $ABCD^2$ score ≥ 3. Hospital admission is also recommended if a diagnostic evaluation cannot be rapidly completed on an outpatient basis [16]. Moreover, in some TIA patients focal symptoms are still present at the time of prehospital evaluation or even initial contact with the ED. Therefore it is reasonable to approach them in the acute phase in a similar manner to patients with suspected stroke, combining those two groups into suspected ACE [6]. As the diagnosis of the ACE is mainly based on clinical symptoms, it may sometimes lead to initiation of intravenous thrombolysis in a non-stroke patient [1, 2, 12, 17]. For that reason, some authors propose MR as the first choice imaging modality in hyperacute and acute stages to actually visualise the responsible ischaemic lesion [8, 9, 18, 19]. However, MR is not always easily available 24/7, is not always feasible, and is more costly and time-consuming [1, 17, 20–22]. It may also be false negative in lacunar syndromes [23–25]. Therefore, guidelines still promote non-contrast CT as a simple tool for the exclusion of haemorrhage in otherwise clear cases [1]. In our material none of the ACE mimics received thrombolysis.

Our data shows that patients incorrectly suspected of ACE by non-ambulance physicians were in many respects different from the quite homogenous group of patients referred by the ambulance physicians and ambulance paramedics. Results from previous studies addressing the issue of ACE mimics are not uniform. The most frequent misdiagnoses have included seizures (7–21%), vertigo (2–5%), brain tumours (4–15%), metabolic and electrolyte disturbances (4–24%), infections (7–16%) and functional disorders (1–8%), which only partially overlap with our results (vertigo followed by metabolic and electrolyte disturbances, headache, seizures and brain tumours without any functional disorders) [10, 11, 26–31].

Such heterogeneity may reflect system- and patient-related differences that limit generalisability and complicate direct comparisons between particular studies. In our previous analysis of patients with ACE mimics referred by physicians in the year 2006/2007, non-ambulance physicians less often

Table 2. Characteristics of patients with a final diagnosis of ACE mimic according to type of referring entity

	Non-ambulance physicians (n = 130)	Ambulance physician (n = 61)	Ambulance paramedic (n = 67)	Overall P	Pairwise differences
General information					
Male sex, no. [%]	39 (30.0)	28 (45.9)	29 (43.3)	0.052	*
Age [years], median [IQR]	66 (54–79)	72 (62–79)	73 (61–84)	0.015	**
Known medical history					
Previous stroke or TIA, no. [%]	24 (18.5)	22 (36.1)	17 (25.4)	0.030	*
Previous seizures, no. [%]	2 (1.5)	5 (8.2)	5 (7.5)	0.056	*, **
Prehospital diagnosis, no. [%]					
Stroke	60 (46.2)	35 (57.4)	39 (58.2)	0.196	
TIA	58 (44.6)	24 (39.3)	21 (31.3)		
Syndrome description	12 (9.2)	2 (3.3)	7 (10.5)		
Diagnostic workup at Neurological ED					
Brain imaging, no. [%]					
None	64 (49.2)	28 (45.9)	21 (31.3)	0.074	
Non-contrast CT	46 (35.4)	25 (41.0)	38 (56.7)		
MR (or CT and then MR)	30 (15.4)	8 (13.1)	8 (11.9)		
Any brain imaging *(vs no imaging)*, no. [%]	66 (50.8)	33 (54.1)	46 (68.7)	0.053	**
Blood sample analysis, no. [%]	45 (34.6)	45 (73.8)	42 (62.7)	< 0.001	*, **
Discharge from Neurological ED					
Final decision, no. [%]					
Admission to neurological ward	28 (21.5)	26 (42.6)	19 (28.4)	0.006	*, **
Referral to another hospital	24 (18.5)	10 (16.4)	21 (31.3)		
Referral to outpatient clinic	55 (42.3)	19 (31.2)	14 (20.9)		
Referral to general practitioner	22 (16.9)	6 (9.8)	12 (17.9)		
Direct neurological admission (*vs other*), no. [%]	28 (21.5)	26 (42.6)	19 (28.4)	0.011	*
Admission or hospital referral (*vs other*), no. [%]	52 (40.0)	36 (59.0)	40 (59.7)	0.008	*, **

*, p < 0.05 for comparison between non-ambulance physicians and ambulance physicians; **, p < 0.05 for comparison between non-ambulance physicians and ambulance paramedics

confused ACE with vertigo (4%) and headache (2%) but more often referred patients with metabolic disturbances (8%) and cardiac conditions (11%). On the other hand, ambulance physicians less often misdiagnosed brain tumours (5%) but more often referred metabolic disturbances (15%). This shift suggests an overall improvement in the prehospital differential diagnosis between ACE and metabolic disturbances. It should be noted that at that time almost all ambulances were staffed with physicians.

Recent data shows that mimics may account for 2% to 47% of suspected strokes and up to 60% of suspected TIAs [2, 7, 9, 11, 19, 28, 29]. In our cohort, the overall proportion of ACE mimics was 32.2%, which is slightly lower than the 36.8% observed in our previous study [6]. Interestingly, this positive trend was present among ambulance physicians (22.1% now *vs* 32.4% previously) but not among non-ambulance physicians (45.9% now *vs* 46.3% previously) [6].

Prehospital diagnosis of TIA is particularly challenging because symptoms are transient and usually resolve by the time of proper neurological assessment. There are no laboratory tests for TIA so the diagnosis usually depends on the patient's history combined with the experience of the neurologist [30]. Metabolic and electrolyte disturbances or infections may be mistakenly interpreted as ACE, especially in older patients with multiple comorbidities [31].

Our study has several limitations. It is a retrospective analysis of consecutive cases and relies on standard source medical documentation. However, to maximise the chances of obtaining relevant information, both electronic and paper records were searched. Our findings could be biased towards a better performance of prehospital services than in other multi-profile hospitals. Considering ambulance standard operating procedures, we may safely assume that the great majority of patients from our catchment area suspected of

stroke by the prehospital services were actually brought in to our ED. However, it is possible that some patients with cardiac and other internal medicine conditions may have been referred to nearby multi-proflile hospitals with the vague label of TIA, especially if the ambulance staff was less certain of the diagnosis. For an assessment of external validity, one should note that in our cohort the prehospital diagnosis of TIA accounted for approximately 52% of ACE mimics and only 26% of all ACE referrals. One may also speculate that the ambulance dispatchers tend to send out physicians to more severe cases, which are more likely to be genuine strokes.

Conclusion

The structure of both neurological and non-neurological ACE mimics depend on the type of referring entity. One may assume that the early differential diagnostic approach towards ACE-labelled patients delivered to the ED by ambulance physicians or paramedics should be similar. This is of major importance considering that they are responsible for prehospital identification of candidates for acute stroke reperfusion therapies. It also gives reassurance to those healthcare systems that rely solely on paramedics. The mimics referred by outpatient physicians may require less diagnostic workup in the ED, and are probably least likely to require any type of hospital admission.

Conflict of interest. *None.*
Acknowledgement and financial support. *None.*

References

1. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018; 49: e46–e110.
2. Tsivgoulis G, Zand R, Katsanos AH, et al. Safety of Intravenous Thrombolysis in Stroke Mimics: Prospective 5-Year Study and Comprehensive Meta-Analysis. Stroke. 2015; 46(5): 1281–1287, doi: 10.1161/strokeaha.115.009012.
3. Nguyen PL, Chang JJ. Stroke Mimics and Acute Stroke Evaluation: Clinical Differentiation and Complications after Intravenous Tissue Plasminogen Activator. J Emerg Med. 2015; 49(2): 244–252, doi: 10.1016/j.jemermed.2014.12.072, indexed in Pubmed: 25802155.
4. Mehta S, Vora N, Edgell RC, et al. Stroke mimics under the drip-and--ship paradigm. J Stroke Cerebrovasc Dis. 2014; 23(5): 844–849, doi: 10.1016/j.jstrokecerebrovasdis.2013.07.012, indexed in Pubmed: 23954600.
5. Huff JS. Stroke mimics and chameleons. Emerg Med Clin North Am. 2002; 20(3): 583–595, indexed in Pubmed: 12379962.
6. Karliński M, Gluszkiewicz M, Członkowska A. The accuracy of prehospital diagnosis of acute cerebrovascular accidents: an observational study. Arch Med Sci. 2015; 11(3): 530–535, doi: 10.5114/aoms.2015.52355, indexed in Pubmed: 26170845.
7. Liberman AL, Prabhakaran S. Stroke Chameleons and Stroke Mimics in the Emergency Department. Curr Neurol Neurosci Rep. 2017; 17(15): 1–11.
8. Förster A, Griebe M, Wolf ME, et al. How to identify stroke mimics in patients eligible for intravenous thrombolysis? J Neurol. 2012; 259(7): 1347–1353, doi: 10.1007/s00415-011-6354-9, indexed in Pubmed: 22231865.
9. Vilela P. Acute stroke differential diagnosis: Stroke mimics. Eur J Radiol. 2017; 96: 133–144, doi: 10.1016/j.ejrad.2017.05.008, indexed in Pubmed: 28551302.
10. Harbison J, Hossain O, Jenkinson D, et al. Diagnostic accuracy of stroke referrals from primary care, emergency room physicians, and ambulance staff using the face arm speech test. Stroke. 2003; 34(1): 71–76, indexed in Pubmed: 12511753.
11. Rizos T, Ringleb PA, Huttner HB, et al. Evolution of stroke diagnosis in the emergency room–a prospective observational study. Cerebrovasc Dis. 2009; 28(5): 448–453, doi: 10.1159/000235989, indexed in Pubmed: 19738373.
12. Kostulas N, Larsson M, Kall TB, et al. Safety of thrombolysis in stroke mimics: an observational cohort study from an urban teaching hospital in Sweden. BMJ Open. 2017; 7(10): e016311, doi: 10.1136/bmjopen-2017-016311, indexed in Pubmed: 29084788.
13. Elm Ev, Altman D, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. The Lancet. 2007; 370(9596): 1453–1457, doi: 10.1016/s0140-6736(07)61602-x.
14. Postępowanie w udarze mózgu – wytyczne grupy ekspertów sekcji chorób naczyniowych polskiego towarzystwa neurologicznego. Neurologia i Neurochirurgia Polska. 2012; 46(1): 16–19.
15. Kernan W, Ovbiagele B, Black H, et al. Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. Stroke. 2014; 45(7): 2160–2236, doi: 10.1161/str.0000000000000024.
16. Easton J, Saver J, Albers G, et al. Definition and Evaluation of Transient Ischemic Attack. Stroke. 2009; 40(6): 2276–2293, doi: 10.1161/strokeaha.108.192218.
17. Guillan M, Alonso-Canovas A, Gonzalez-Valcarcel J, et al. Stroke mimics treated with thrombolysis: further evidence on safety and distinctive clinical features. Cerebrovasc Dis. 2012; 34(2): 115–120, doi: 10.1159/000339676, indexed in Pubmed: 22854315.
18. Girot M, Marc JB, Wiel E, et al. Impact on patient management of the implementation of a magnetic resonance imaging dedicated to neurological emergencies. J Eval Clin Pract. 2017: 1–7.
19. Nadarajan V, Perry RJ, Johnson J, et al. Transient ischaemic attacks: mimics and chameleons. Pract Neurol. 2014; 14(1): 23–31, doi: 10.1136/practneurol-2013-000782, indexed in Pubmed: 24453269.
20. Piliszek A, Witkowski G, Sklinda K, et al. Comprehensive imaging of stroke - Looking for the gold standard. Neurol Neurochir Pol. 2016; 50(4): 241–250, doi: 10.1016/j.pjnns.2016.04.009, indexed in Pubmed: 27375137.
21. Danière F, Edjlali-Goujon M, Mellerio C, et al. MR screening of candidates for thrombolysis: How to identify stroke mimics? J Neuroradiol. 2014; 41(5): 283–295, doi: 10.1016/j.neurad.2014.05.008, indexed in Pubmed: 25451670.
22. Khan NI, Chaku S, Goehl C, et al. Novel Algorithm to Help Identify Stroke Mimics. J Stroke Cerebrovasc Dis. 2017: 3–8.
23. Watts J, Wood B, Kelly A, et al. Stroke syndromes associated with DWI-negative MRI include ataxic hemiparesis and isolated internuc-

lear ophthalmoplegia. Neurol Clin Pract. 2013; 3(3): 186–191, doi: 10.1212/CPJ.0b013e318296f288, indexed in Pubmed: 29473634.
24. Morita S, Suzuki M, Iizuka K. False-negative diffusion-weighted MRI in acute cerebellar stroke. Auris Nasus Larynx. 2011; 38(5): 577–582, doi: 10.1016/j.anl.2011.01.017, indexed in Pubmed: 21330074.
25. Oppenheim C, Stanescu R, Dormont D, et al. False-negative diffusion--weighted MR findings in acute ischemic stroke. AJNR Am J Neuroradiol. 2000; 21(8): 1434–1440, indexed in Pubmed: 11003275.
26. Libman RB, Wirkowski E, Alvir J, et al. Conditions that mimic stroke in the emergency department. Implications for acute stroke trials. Arch Neurol. 1995; 52(11): 1119–1122, indexed in Pubmed: 7487564.
27. Hosseininezhad M, Sohrabnejad R. Stroke mimics in patients with clinical signs of stroke. Caspian J Intern Med. 2017; 8(3): 213–216, doi: 10.22088/cjim.8.3.213, indexed in Pubmed: 28932374.
28. Anathhanam S, Hassan A. Mimics and chameleons in stroke. Clin Med (Lond). 2017; 17(2): 156–160, doi: 10.7861/clinmedicine.17-2-156, indexed in Pubmed: 28365629.
29. Uchino K, Massaro L, Hammer M. Transient Ischemic Attack after Tissue Plasminogen Activator: Aborted Stroke or Unnecessary Stroke Therapy? Cerebrovascular Diseases. 2009; 29(1): 57–61.
30. Vargas M, Costa M, Melo TP, et al. Increase in the Admission of Stroke Mimics after Change in Emergency Shifts. Cerebrovascular Diseases. 2017; 44(1-2): 68–74, doi: 10.1159/000475823.
31. Gropen TI, Gokaldas R, Poleshuck R, et al. Factors related to the sensitivity of emergency medical service impression of stroke. Prehosp Emerg Care. 2014; 18(3): 387–392, doi: 10.3109/10903127.2013.864359, indexed in Pubmed: 24460036.

RESEARCH PAPERS

Neurologia i Neurochirurgia Polska
Polish Journal od Neurology and Neurosurgery
2019, Volume 53, no. 1, pages: 90–94
DOI: 10.5603/PJNNS.a2019.0003

ISSN 0028–3843

Prevalence and extent of right-to-left shunt on contrast--enhanced transcranial Doppler in patients with chronic hyperventilation syndrome: results of a case-control study

Jacek Staszewski, Kazimierz Tomczykiewicz, Anna Piusińska-Macoch, Adam Stępień

Clinic of Neurology, Military Medical Institute, Szaserow 128, 04-141 Warsaw, Poland

ABSTRACT

Aim. Chronic hyperventilation syndrome (CHVS) represents a frequent but poorly understood breathing pattern disorder. In a previous small pilot study, we reported a higher prevalence of right-to-left shunt (RLS) in CHVS patients than in healthy subjects. The aim of this study was to confirm those previous results from this larger and matched case-control study, and to evaluate the prevalence and grade of RLS in patients with CHVS in whom organic and psychiatric causes were excluded.

Clinical rationale for the study. Determining other types of CHVS triggers not related to organic or psychiatric causes which could be clinically useful.

Material and methods. 100 subjects (mean age 34 ± 6 years; 80% females), including 50 patients with CHVS and 50 age- and sex-matched healthy controls (CG), were prospectively recruited into this single-centre study. Vascular RLS was diagnosed using contrast-enhanced transcranial Doppler (c-TCD).

Results. RLS prevalence significantly increased in the CHVS group (n = 23) compared to the CG group (n = 8) (46% *vs* 16%; $p < 0.01$). Patients with CHVS and RLS tended to have more frequent permanent shunts compared to the CG (60% *vs* 25%; $p = 0.08$), but there was no difference regarding RLS grading between the groups.

Conclusions and clinical implications. This study confirmed our previous findings in which the prevalence of RLS in patients with CHVS was significantly higher than in an age- and sex-matched healthy control group. However, we could not confirm the results of our prior study, where RLS was larger in CHVS than in CG. The tentative association between RLS and CHVS needs to be further examined.

Key words: chronic hyperventilation syndrome, right-to-left shunt, transcranial Doppler
(*Neurol Neurochir Pol 2019; 53 (1): 90–94*)

Introduction

Chronic hyperventilation syndrome (CHVS) represents a frequent but poorly understood breathing pattern disorder that often goes undiagnosed due to its multi-systemic and apparently unrelated symptoms. CHVS can result in significant patient morbidity and an array of symptoms including breathlessness, chest tightness, dizziness, tremor, and paraesthesia; however, CHVS's underlying pathophysiology and effective management are not well understood [1]. CHVS is thought to be psychologically-based or physiologically-based. It involves breathing too deeply or too rapidly, resulting in hyperventilation which exceeds metabolic demands that lead to haemodynamic and chemical changes with characteristic clinical symptoms [2]. Approximately 6% of the general population, and 10% of patients in a general internal medicine practice, are reported to have CHVS. Patients with CHVS usually undergo extensive investigations, but in the majority of them, no organic causes can be found. Psychogenic hyperventilation is regarded as the main cause of CHVS; although CHVS and psychiatric disorders may overlap, only 25% of patients with CHVS have

Address for correspondence: Jacek Staszewski, Clinic of Neurology, Military Medical Institute, Warsaw, Poland, e-mail: jacekstaszewski@wp.pl

panic attacks, and many patients with CHVS do not manifest low partial pressure of carbon dioxide (PaCO2) during attacks [3]. Different stressors such as emotional distress, but also pharmacological agents such as sodium lactate, caffeine, and isoproterenol, can provoke an exaggerated respiratory response.

We hypothesised that similarly to patients with migraines with aura or transient global amnesia, various endogenic substances might enter the systemic circulation in CHVS. These endogenous substances could enter through a cardiac or pulmonary right-to-left shunt (RLS) instead of being trapped in the pulmonary capillaries, and they might trigger or contribute to CHVS [5]. We have previously reported an increase in RLS frequency (40% *vs* 8%) through the patent foramen ovale (PFO) in 25 patients with CHVS when compared to 25 controls in a small unmatched case-control pilot study which assessed feasibility of the approach using contrast-enhanced transcranial Doppler (c-TCD) and transoesophageal echocardiography examinations (TEE) [4]. TEE is considered the gold standard for RLS diagnosis through PFO, but c-TCD of the middle cerebral artery (MCA) has similar and high sensitivity (70–100%), is relatively cheap, well tolerated, and feasible for larger studies [6]. TCD also allowed us to classify the grade of severity of RLS using a microembolic signals grading score [7]. The aim of the current study was two-fold: (1) to confirm our previous findings using a larger cohort of patients with CHVS, and (2) to evaluate the association between CHVS and the presence and grade of RLS using an individual matched case-control design with prospective data collection.

Material and methods

Participants

Consecutive patients with previously diagnosed CHVS were recruited from the neurological Outpatient Department between 2012 and 2016 and prospectively included in the study. CHVS was recognised in patients with typical recurrent clinical symptoms (dizziness, numbness, paresthesia, and/or near syncope) reproduced by voluntary hyperventilation and confirmed by the presence of spontaneous electromyographic activity with ≥ 2 multiplets during provocative ischaemia and hyperventilation [8]. Subjects with asthma or other recognised pulmonary, cardiac, cerebrovascular, and/or psychiatric diseases were excluded. All patients with CHVS underwent psychiatric and cardiological consultations and had undergone brain neuroimaging (magnetic resonance imaging), EEG, carotid duplex ultrasonography, and TCD to exclude mental disorders and organic causes of the symptoms. Total and ionised calcium values were within normal reference range levels in all examined patients. The control group (CG) consisted of healthy volunteers matched with case subjects based on age and sex.

Ultrasound examination

Vascular RLS was diagnosed using c-TCD (Nicolet Companion III, Viasys) of the MCA to detect the presence of microbubble emboli (MB) following the standardised protocol recommended by the International Consensus Criteria (Figure 1) [7]. All patients had an adequate temporal window for performing a TCD examination. The appearance of at least one contrast-induced MB signal on the c-TCD trace was regarded as pathognomonic for RLS. Patients were prepared using an 18-gauge needle inserted into the cubital vein and were examined in the supine position. The Doppler signal indicating blood flow in the single MCA was located at a depth of 45 to 65 mm. The contrast agent was prepared using 9 ml isotonic saline solution and 1 ml air, which were then mixed with a three-way stopcock by exchange of the saline/air mixture between the syringes and injected as a bolus. The same physician prepared and injected the contrast into each patient. The MB were recorded with c-TCD at rest, and in case of no detection of MB in the MCA under basal conditions, the examination was repeated 5 sec post injection following the Valsalva manoeuvre (VM) with controlled duration (10 sec) and pressure (forced expiration against a manometer to 40 mmHg). The strength of the VM was considered sufficient when the MCA flow velocity amplitude decreased by 25%. Before the test, patients were asked to practice a standardised VM. All examinations were done using a single experienced operator who was blinded to the subject diagnosis. All examination data were stored internally and analysed offline afterwards. Grading or RLS was performed by counting the number of embolic tracks on the power M-mode and Doppler spectrogram in real time and offline. A four-level categorisation according to the MB count was applied: (1) 0 MB (negative result); (2) 1–10 MB (low-grade shunt); (3) > 10 MB and no curtain (medium-grade), and (4) curtain (large-grade) [7]. A curtain refers to a shower of MB in which a single bubble cannot be identified. RLS was considered permanent if it occurred during rest, and latent only if it occurred after a VM.

We evaluated the prevalence of RLS in addition to the shunt magnitude and permanent and latent RLS distributions in the study sample. We also compared migraine and migraine with aura frequencies in both studied groups. A migraine was diagnosed according to the International Classification of Headache Disorders, 3rd edition [9]. Quantitative and qualitative demographic characteristics were summarised, and the data tabulated and tested for normality using the Shapiro-Wilk test. Categorical data are presented as frequencies and were compared using the chi-squared or Fisher's exact tests in cases in which these tests were appropriate. Continuous data were reported as means ± standard deviations (SDs) and were compared using paired t-tests, while non-normal data were analysed using non-parametric tests. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

All analyses were performed using Statistica 17 software (StatSoft Inc, USA).

This study complied with the tenets of the Declaration of Helsinki. The protocol of the study was accepted by the local ethics committee (Komisja Bioetyczna Wojskowego Instytutu Medycznego w Warszawie). All subjects provided written informed consent before any study-related procedures were performed.

Results

A total of 100 individuals (mean age 34 ± 6 years; females 80%), including 50 with CHVS and 50 from the age- and sex-matched CG, were included in the analysis. The most common symptom in the CHVS group was vertigo or dizziness (66%) followed by paraesthesia (40%). The prevalence of migraines and migraines with aura was similar in both groups (Tab. 1). RLS was diagnosed in a significantly higher proportion of patients with CHVS (46%) than in controls (16%) (Tab. 2). There was a trend toward a higher proportion of permanent RLS in CHVS patients than in control subjects (60% *vs* 25%; p=0.08), but the grade of RLS did not differ between groups. Among all subjects with RLS, 13 (42%) had concomitant migraines with aura (nine with CHVS and four with CG), but the difference between CHVS and CG was not statistically significant.

Table 1. Baseline characteristics of the studied groups

Group	CHVS	Control	P
N (%)	50	50	
Mean age (±SD) years	33 ± 7	35 ± 9	0.7
Females	40 (80)	40 (80)	1
Vertigo	19 (38)	0	-
Dizziness	14 (28)	0	-
Paraesthesia	20 (40)	0	-
Near syncope	17 (34)	0	-
Any migraine	14 (28)	9 (18)	0.23
Migraine with aura	11 (22)	5 (10)	0.09

CHVS – chronic hyperventilation syndrome

Table 2. Right-to-left shunt in CHVS and control patients

Group	CHVS	Control	P
N (%)	50	50	
RLS in c-TCD	23 (46)	8 (16)	< 0.01
Permanent RLS	14 (60)	2 (25)	0.08
Grade of RLS			0.4
1–10 MB	6 (26)	5 (63)	
11–25 MB	12 (52)	2 (25)	
> 25 or curtain	5 (22)	1 (12)	
Migraine with aura	9 (39)	4 (50)	0.13

CHVS – chronic hyperventilation syndrome; RLS – right-to-left shunt; c-TCD – contrast transcranial Doppler; MB – microbubble emboli

Discussion

This study confirmed our previous findings and revealed a higher RLS prevalence in CHVS patients (46%) than in age- and sex-matched controls (16%). We also demonstrated that patients with CHVS tended to have more frequent permanent shunts than controls. This was a new finding, but we did not find any differences regarding RLS grading between groups. RLS aetiology in these patients was probably due to PFO, since other findings such as intrapulmonary or other intracardiac RLS are rare.

The underlying mechanism by which some patients develop hyperventilation syndrome is unknown. The incidence of CHVS is higher in first-degree relatives than in the general population, but no clear genetic factors have been identified. CHVS often represents a simple manifestation of anxiety, rarely related to endocrine and/or respiratory diseases (such as hypoparathyroidism, asthma, pulmonary embolism) or central nervous system disorders (such as brainstem lesions); however, other patients manifest an abnormal respiratory response to sodium lactate and other chemical and emotional triggers, which result in excess minute ventilation and hypocarbia. Inducing a decrease in PaCO2 through voluntary hyperventilation may provoke CHVS in some, but not all, patients [10].

The pathogenetic role of RLS is also unknown, and as far as we know the association between RLS and CHVS has not yet been reported. PFO represents one of the main causes of cardiac RLS. Findings from autopsies or population-based studies have shown that PFO prevalence in the general population ranges from 10% to 29% [11]. PFO has been linked to paradoxical embolisation of thrombi and/or other microparticles or vasoactive chemicals leading to cryptogenic stroke, and also a broad spectrum of neurological diseases (e.g. migraines or migraines with aura, transient global amnesia, cluster headaches, and decompression sickness in sport divers) [12–13]. The prevalence of both cardiac and pulmonary RLS is especially high in patients with migraines with aura. Anzola et al. reported in a TCD study that RLS was present in 48% of individuals with migraines with aura, compared to 20% of healthy controls and 23% of patients with migraines without aura [14]. Migraines were also more prevalent in patients with an RLS at rest compared to those with a provocable RLS, and RLS grade was larger in migraine patients than in controls [15–16]. In our cohort, we observed that 42% of subjects with RLS suffered from migraines with aura, but there was no significant difference between CHVS and control subjects. On the other hand, there was a trend toward a higher prevalence of

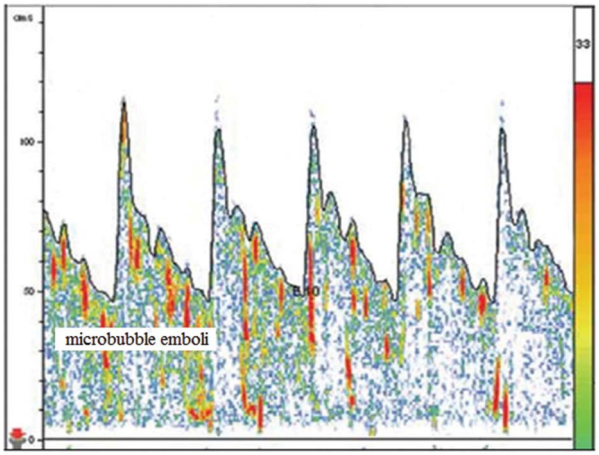


Figure 1. Transcranial Doppler recording showing multiple microbubbles

migraines with aura in patients with CHVD than in controls, which is in line with some previous reports showing a typical picture of CHVS in several patients with migraines at a headache phase [17–18].

Our study suggests an association between CHVS and RLS, but a causal relationship between these conditions remains speculative. Although we found more frequent permanent shunts in CHVS patients than in the CG, as we have previously reported, we did not demonstrate any differences in RLS grading between groups in the present study. As postulated in previous reports, RLS may allow venous-circulation of vasoactive chemicals that bypass the pulmonary filter and reach the cerebral circulation to induce a migraine and possible hyperventilation attack. But if this is so, the precise trigger has yet to be identified [19]. Whether or not chemical shunts or transient hypoxemia due to shunting of blood through the PFO plays a role in some patients with CHVS is unknown; however, CHVS is obviously related to a variety of mechanisms that may not be associated with hyperventilation alone [20]. While this putative mechanism accounts for some of the CHVS cases, it cannot account for all of them because not all CHVS patients have a shunt, and not all patients with an RLS have CHVS.

Our study has a number of limitations. It was a single-centre study with a limited number of patients. RLS was not confirmed by TEE, and we could not discriminate between RLS at the cardiac or pulmonary level based solely on c-TCD examination. In our previous report, we found extracardiac shunting via pulmonary arterio-venous malformation (AVM) in two patients with CHVS and none in the CG. This was an important finding because it suggests that the association of RLS with CHVD exists independently of shunt anatomy. We did not perform TEE or chest CT to diagnose extracardiac shunts because both procedures are invasive examinations, and they would possibly have had negative effects on recruitment. However, AVM in the general population is uncommon. In an autopsy study, only three pulmonary AVM cases were detected out of 15,000 consecutive autopsies [21]. TCD is considerably less invasive for the patient, and the VM, which significantly increases MB appearance, can be performed more accurately than TEE. Another limitation was the evaluation of a highly selective group of patients with CHVS. Patients with psychiatric or pulmonary diseases, frequently found in patients with CHVS, were excluded; thus, the study population may not be representative of the general CHVS patient population.

On the other hand, our study has some major advantages. The present case-control study is one of the first to address the prevalence of RLS in CHVS. We enrolled a relatively large number of well-characterised patients with rarely studied CHVS and compared them to age- and sex-matched controls. This is an important difference compared to the previous unmatched study because PFO prevalence and size may vary with age and sex, and also CHVS most commonly occurs among young women [22–24]. Although the age and sex distribution of this sample was comparable to the previously enrolled cohort, our current study design improved the efficiency of analysis by better distributing cases and controls between strata [25]. Another advantage is that all subjects had excluded cardiac and cerebrovascular diseases, and tests to detect RLS were performed in a blinded manner.

The reported association between CHVS and RLS is novel and difficult to explain, but whether it is functional or aetiological, it may improve the understanding of these conditions.

Conclusions

Our study suggests a possible link between RLS and CHVS. The prevalence of RLS in patients with CHVS was higher than in controls, but there was no difference between RLS grading or prevalence of migraine between groups. The clinical implications of these findings need to be determined.

References

1. Kern B, Rosh AJ. „Hyperventilation Syndrome." eMedicine. Eds. Ryland P Byrd, et al. 28 Nov. 2016. Medscape. 01 Sep. 2011. http://emedicine.com/emerg/topic270.htm.
2. Jones M, Harvey A, Marston L, et al. Breathing exercises for dysfunctional breathing/hyperventilation syndrome in adults. Cochrane Database Syst Rev. 2013(5): CD009041, doi: 10.1002/14651858.CD009041.pub2, indexed in Pubmed: 23728685.
3. Boulding R, Stacey R, Niven R, et al. Dysfunctional breathing: a review of the literature and proposal for classification. Eur Respir Rev. 2016; 25(141): 287–294, doi: 10.1183/16000617.0088-2015, indexed in Pubmed: 27581828.
4. Staszewski J, Tomczykiewicz K, Brodacki B, et al. An increased frequency of right-to-left shunt in patients with chronic hyperventilation syndrome. Perspectives in Medicine. 2012; 1(1-12): 241–243, doi: 10.1016/j.permed.2012.02.027.
5. Klötzsch C, Sliwka U, Berlit P, et al. An increased frequency of patent foramen ovale in patients with transient global amnesia. Analysis of

53 consecutive patients. Arch Neurol. 1996; 53(6): 504–508, indexed in Pubmed: 8660151.
6. Blersch WK, Draganski BM, Holmer SR, et al. Transcranial duplex sonography in the detection of patent foramen ovale. Radiology. 2002; 225(3): 693–699, doi: 10.1148/radiol.2253011572, indexed in Pubmed: 12461247.
7. Jauss M, Zanette E. Detection of right-to-left shunt with ultrasound contrast agent and transcranial Doppler sonography. Cerebrovasc Dis. 2000; 10(6): 490–496, doi: 10.1159/000016119, indexed in Pubmed: 11070388.
8. Valls-Solé J, Montero J. Role of EMG evaluation in muscle hyperactivity syndromes. J Neurol. 2004; 251(3): 251–260, doi: 10.1007/s00415-004-0380-9, indexed in Pubmed: 15015003.
9. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013; 33(9): 629–808, doi: 10.1177/0333102413485658, indexed in Pubmed: 23771276.
10. Hornsveld HK, Garssen B, Dop MJ, et al. Double-blind placebo-controlled study of the hyperventilation provocation test and the validity of the hyperventilation syndrome. Lancet. 1996; 348(9021): 154–158, indexed in Pubmed: 8684155.
11. Movsowitz C, Podolsky LA, Meyerowitz CB, et al. Patent foramen ovale: a nonfunctional embryological remnant or a potential cause of significant pathology? J Am Soc Echocardiogr. 1992; 5(3): 259–270, indexed in Pubmed: 1622617.
12. Homma S, Sacco RL. Patent foramen ovale and stroke. Circulation. 2005; 112(7): 1063–1072, doi: 10.1161/CIRCULATIONAHA.104.524371, indexed in Pubmed: 16103257.
13. Del Sette M, Angeli S, Leandri M, et al. Migraine with aura and right-to-left shunt on transcranial Doppler: a case-control study. Cerebrovasc Dis. 1998; 8(6): 327–330, doi: 10.1159/000015875, indexed in Pubmed: 9774749.
14. Anzola GP, Magoni M, Guindani M, et al. Potential source of cerebral embolism in migraine with aura: a transcranial Doppler study. Neurology. 1999; 52(8): 1622–1625, indexed in Pubmed: 10331688.
15. Blau JN, Dexter SL. Hyperventilation during migraine attacks. Br Med J. 1980; 280(6226): 1254, indexed in Pubmed: 7388493.
16. Razavi M, Razavi B, Fattal D, et al. Hemiplegic migraine induced by exertion. Arch Neurol. 2000; 57(9): 1363–1365, indexed in Pubmed: 10987906.
17. Wilmshurst PT, Nightingale S, Walsh KP, et al. Effect on migraine of closure of cardiac right-to-left shunts to prevent recurrence of decompression illness or stroke or for haemodynamic reasons. Lancet. 2000; 356(9242): 1648–1651, indexed in Pubmed: 11089825.
18. Jesurum JT, Fuller CJ, Velez CA, et al. Migraineurs with patent foramen ovale have larger right-to-left shunt despite similar atrial septal characteristics. J Headache Pain. 2007; 8(4): 209–216, doi: 10.1007/s10194-007-0396-5, indexed in Pubmed: 17901924.
19. Kerut EK, Norfleet WT, Plotnick GD, et al. Patent foramen ovale: a review of associated conditions and the impact of physiological size. J Am Coll Cardiol. 2001; 38(3): 613–623, indexed in Pubmed: 11527606.
20. Gardner WN. The pathophysiology of hyperventilation disorders. Chest. 1996; 109(2): 516–534, indexed in Pubmed: 8620731.
21. SLOAN RD, COOLEY RN. Congenital pulmonary arteriovenous aneurysm. Am J Roentgenol Radium Ther Nucl Med. 1953; 70(2): 183–210, indexed in Pubmed: 13065567.
22. Nedeltchev K, Wiedmer S, Schwerzmann M, et al. Sex differences in cryptogenic stroke with patent foramen ovale. Am Heart J. 2008; 156(3): 461–465, doi: 10.1016/j.ahj.2008.04.018, indexed in Pubmed: 18760126.
23. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc. 1984; 59(1): 17–20, indexed in Pubmed: 6694427.
24. Pfortmueller CA, Pauchard-Neuwerth SE, Leichtle AB, et al. Primary Hyperventilation in the Emergency Department: A First Overview. PLoS One. 2015; 10(6): e0129562, doi: 10.1371/journal.pone.0129562, indexed in Pubmed: 26110771.
25. Pearce Neil. Analysis of matched case-control studies BMJ. 2016; 352: i969.

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 1, pages: 95–97
DOI: 10.5603/PJNNS.a2019.0006

ISSN 0028–3843

Delayed onset of Takotsubo syndrome after epileptic seizure

Claudia Stöllberger, Josef Finsterer

Krankenanstalt Rudolfstiftung, Juchgasse 25, A-1030 Vienna, Austria

Key words: midventricular ballooning, neurogenic stunned myocardium
(*Neurol Neurochir Pol 2019; 53 (1): 95–97*)

Introduction

Takotsubo syndrome (TTS) is characterised by transient systolic left ventricular dysfunction. Its clinical presentation, electrocardiography (ECG) findings, and biomarker profiles are often similar to those of an acute coronary syndrome [1]. TTS predominantly affects elderly women and is often preceded by emotional or physical stress [1]. Epileptic seizures as triggering events of TTS have to date been described in nearly 100 cases [2, 3]. The temporal association between epileptic seizure and onset of TTC is frequently unknown due to postictal somnolence or lack of cardiologic surveillance after a seizure. Here we describe a patient who developed TTS only 48 hours after a witnessed epileptic seizure. This case report required no ethical approval because the data was collected retrospectively. The patient was informed that her case was being observed in terms of a scientific observation and she accepted the fact that her case would be described.

Case report

A 67 year-old Caucasian female, height 165 cm, weight 70 kg, was admitted because of three generalised, tonic-clonic seizures having occurred on the day of admission. She had a history of childhood onset epilepsy of generalised type starting at the age of 12 years which had not been well controlled due to poor adherence. Furthermore, she had a ten year history of arterial hypertension, pneumonia at age 26 and again at age 57, a fall-induced fracture of the humerus at age 62, and a bilateral ovarectomy because of benign cysts at age 66. In the four weeks prior to admission she had felt increasingly weak and had suffered several falls. She was on medication of lamotrigine 500 mg/d (for epilepsy), clonazepam 2 mg/d (for epilepsy), primidone 375 mg/d (for tremor), folic acid 5 mg/d, acetylsalicylic acid 100 mg/d and nebivolol 1.25 mg/d. She admitted that she had failed to take the medications according to the prescription on the days before admission.

On admission, she did not complain of cardiac or respiratory symptoms. Blood pressure was 104/70 mm Hg and heart rate 104/min. Clinical cardiological investigation did not disclose any abnormalities. The electrocardiogram (ECG) was normal except for sinus tachycardia (Fig. 1).

Blood tests showed hyponatremia, creatine kinase levels within the normal range, and an elevated troponin T level (Tab. 1). Clinical neurological exam on admission revealed deviation nystagmus, dysarthria, dyspraxia, hearing impairment, and postural tremor.

Electroencephalography revealed spikes in the frontal projections bilaterally. Magnetic resonance of the brain revealed a patchy T2-hyperintensity in the right parietal projection and multiple spot-like T2-hyperintensities, which were hypointense on T2-weighted images. Neuropsychological investigations revealed mild cognitive impairment (MMSE 25).

Over the following 24 hours, troponin levels decreased, CK levels increased slightly, and NT-pro-BNP levels were elevated (Tab. 1). 48 hours after admission, the patient complained for the first time of anginal chest pain. ECG, which had been normal on admission, now showed negative T waves and a prolonged QT interval (Fig. 1). Since a non-ST-elevation myocardial infarction was suspected, the patient received a loading dose of 600 mg clopidogrel, followed by clopidogrel 75 mg/d. Coronary angiography, carried out four days after the seizure and two days after the onset of chest pain, showed normal coronary arteries and midventricular ballooning, suggesting the diagnosis of TTS. Echocardiography after seven days showed normalisation of regional wall motion, a normal

Address for correspondence: Claudia Stöllberger, Krankenanstalt Rudolfstiftung, Juchgasse 25, A-1030 Wien, Austria, e-mail: claudia.stoellberger@chello.at

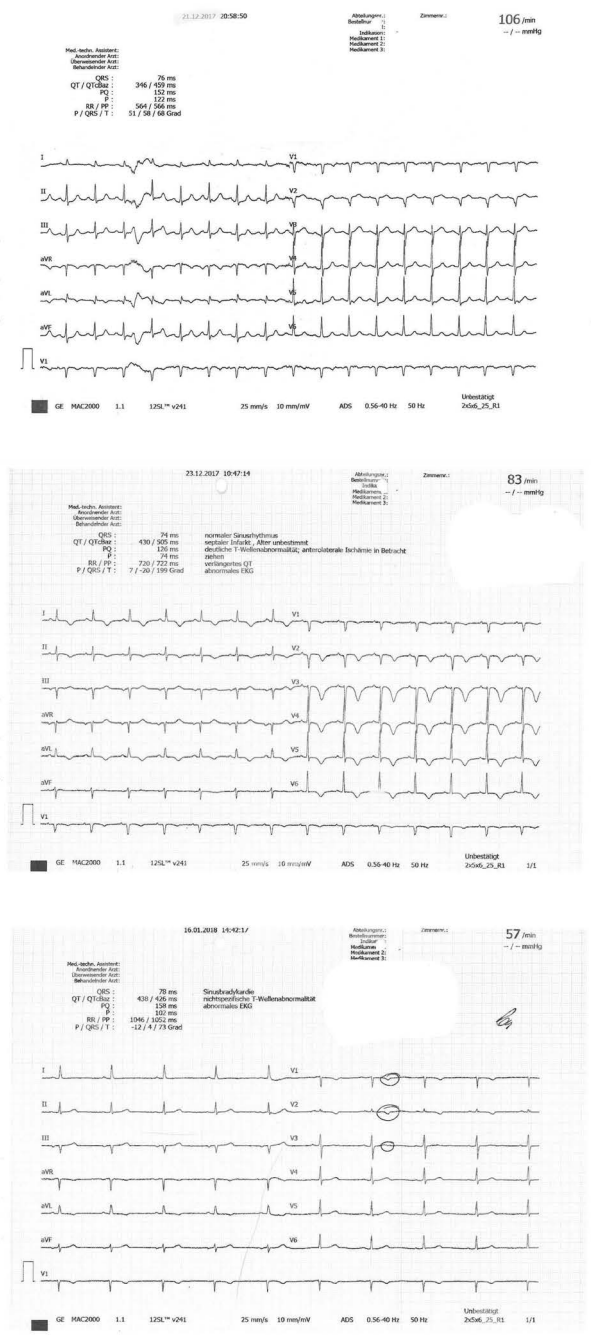


Figure 1. Electrocardiographic recordings immediately after the seizure (**A**), after 48 hours (**B**), and after 26 days (**C**). Whereas the initial ECG was normal, T-wave inversion was pronounced after 48 hours, and slightly visible after 26 days

systolic function, moderate (grade II) aortic regurgitation, and minimal mitral regurgitation. Since the patient showed symptoms of depression, antidepressive therapy was started. The patient was discharged with lamotrigine 400 mg/d, primidone 125 mg/d, clonazepam 3 mg/d, nebivolol 2.5 mg/d, acetylsalicylic acid 100 mg/d, valproic acid 1,500 mg/d, atorvastatin 40 mg/d, escitalopram 10 mg/d and mirtazapine 15 mg/d. One day after discharge, blood was taken to measure antiepileptic drug levels. Serum valproic level was 723 µmol/L (therapeutic range 350–700 µmol/L) and serum lamotrigine level was > 17.5 µmol/L (therapeutic range 2–10 µmol/L). Consequently, the antiepileptic therapy was modified by the treating neurologist. After 26 days, the ECG showed only slight negative T waves in leads V1–V3 and normalisation of the QT interval. At follow-up after 11 months, the patient did not report any cardiac symptoms. No epileptic seizures had occurred in the mean time. She is at present on antiepileptic medication with levetiracetam 3,000 mg/d.

Discussion

The most probable trigger for TTS in the presented patient was the epileptic seizure, since no other physical or emotional triggering events were detected. Why chest pain occurred only two days after the seizures remains unknown. The mechanism of the delay between seizure and TTS may be related to autonomic instability or more prolonged catecholamine release despite seizure control. Alternatively, it is possible that clinically silent seizures continued despite apparent resolution.

To date, the pathogenesis of TTS has not been completely clarified [1]. Elevated catecholamine levels seem to play an important role. In patients with an epileptic seizure, a significant increase in both plasma norepinephrine and epinephrine levels has been observed due to abnormal cerebral discharges [4]. Elevated serum catecholamine levels have been only described in two epilepsy-associated TTS cases to date [5, 6].

The negative T-waves in the ECG, together with chest pain and elevated troponin levels, led to the decision to perform coronary angiography and thus to the diagnosis of midventricular TTS. Negative T-waves in TTS are assumed to be due to myocardial oedema. This assumption is based on clinical observations such as the parallel time course of development and resolution of ventricular repolarisation abnormalities and myocardial oedema on initial and follow-up cardiac magnetic resonance images [7].

Interestingly, troponin was elevated on admission, although the patient showed no signs of myocardial ischaemia, neither clinically nor in the ECG at that time. Troponin elevations have been reported to occur in 6–12% of cases after epileptic seizures [8–10]. It is assumed that seizures lead to simultaneous increases in pulmonary and systemic resistance, hypoxemia, and catecholamine release, thus inducing myocardial damage [8]. Unfortunately, the ECG findings of patients from two of these series are not completely reported, thus it cannot be assessed how many of them eventually developed TTS [8, 9]. In the third study, however, the patients were investigated cardiologically more extensively and TTS was diagnosed in 27% of the troponin-positive patients [10].

Unfortunately, no serum levels of lamotrigine were assessed when the patient was admitted, but only after discharge.

Table 1. Results of blood tests of patient with seizure-associated Takotsubo syndrome

Parameter (normal range)	Admission	Day 1	Day 2	Day 3	Day 5
Leucocytes (4.0–9.0 g/L)	9.8	8.2	NM	NM	5.6
Erythrocytes (4.00–5.20 T/L)	4.37	3.08	NM	NM	12.3
Sodium (136–145 mmol/L)	133	128	NM	NM	125
Potassium (3.4–4.5 mmol/L)	4.4	4.2	NM	NM	4.2
Creatinine (0.50–0.90 mg/dL)	0.79	0.69	NM	NM	0.60
Creatinine kinase (< 170 U/L)	164	177	131	97	91
Troponin T (< 14 ng/L)	278	NM	109	82	28
NT-pro-BNP (< 285)	NM	2,608	NM	NM	NM
Cholesterol (< 200 mg/dL)	NM	160	NM	NM	NM
HDL-cholesterol (> 65 mg/dL)	NM	80	NM	NM	NM
LDL-cholesterol (< 130 mg/dL)	NM	68	NM	NM	NM
Haemoglobin A1C (4–6%)	NM	5.6	NM	NM	NM

NM — not measured

Thus, it cannot be assessed if TTS was encouraged by lamotrigine overdose, which is known to affect the cardiac conduction system [11]. TTS in epileptic patients, however, occurs also in patients without antiepileptic therapy, thus it cannot be explained exclusively as a side effect of antiepileptic drugs [2, 3].

From these findings and our case we conclude that TTS should be considered as a complication of epileptic seizures. Due to the fact that after epileptic seizures patients do not typically experience symptoms of angina pectoris or dyspnoea, TTS can easily be overlooked. After an epileptic seizure, an ECG and an assessment of troponin levels should be carried out. Where troponin is elevated, cardiological surveillance is recommended including a follow-up ECG, an assessment of brain natriuretic peptides, and echocardiography. Cases with wall motion abnormalities or ECG abnormalities should undergo coronary angiography.

References

1. Lyon AR, Bossone E, Schneider B, et al. Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2016; 18(1): 8–27, doi: 10.1002/ejhf.424, indexed in Pubmed: 26548803.
2. Finsterer J, Bersano A. Seizure-triggered Takotsubo syndrome rarely causes SUDEP. Seizure. 2015; 31: 84–87, doi: 10.1016/j.seizure.2015.07.015, indexed in Pubmed: 26362382.
3. Belcour D, Jabot J, Grard B, et al. Prevalence and Risk Factors of Stress Cardiomyopathy After Convulsive Status Epilepticus in ICU Patients. Crit Care Med. 2015; 43(10): 2164–2170, doi: 10.1097/CCM.0000000000001191, indexed in Pubmed: 26237133.
4. Simon RP, Aminoff MJ, Benowitz NL. Changes in plasma catecholamines after tonic-clonic seizures. Neurology. 1984; 34(2): 255–257, indexed in Pubmed: 6538024.
5. Sakuragi S, Tokunaga N, Okawa K, et al. A case of takotsubo cardiomyopathy associated with epileptic seizure: reversible left ventricular wall motion abnormality and ST-segment elevation. Heart Vessels. 2007; 22(1): 59–63, doi: 10.1007/s00380-006-0931-3, indexed in Pubmed: 17285449.
6. Shimizu M, Kagawa A, Takano T, et al. Neurogenic stunned myocardium associated with status epilepticus and postictal catecholamine surge. Intern Med. 2008; 47(4): 269–273, indexed in Pubmed: 18277028.
7. Migliore F, Zorzi A, Perazzolo Marra M, et al. Myocardial edema as a substrate of electrocardiographic abnormalities and life-threatening arrhythmias in reversible ventricular dysfunction of takotsubo cardiomyopathy: Imaging evidence, presumed mechanisms, and implications for therapy. Heart Rhythm. 2015; 12(8): 1867–1877, doi: 10.1016/j.hrthm.2015.04.041, indexed in Pubmed: 25937439.
8. Nass RD, Meiling S, Andrié RP, et al. Laboratory markers of cardiac and metabolic complications after generalized tonic-clonic seizures. BMC Neurol. 2017; 17(1): 187, doi: 10.1186/s12883-017-0965-4, indexed in Pubmed: 28927394.
9. Chatzikonstantinou A, Ebert AD, Hennerici MG. Temporal seizure focus and status epilepticus are associated with high-sensitive troponin I elevation after epileptic seizures. Epilepsy Res. 2015; 115: 77–80, doi: 10.1016/j.eplepsyres.2015.05.013, indexed in Pubmed: 26220381.
10. Schneider F, Kadel C, Pagitz M, et al. Takotsubo cardiomyopathy and elevated troponin levels following cerebral seizure. Int J Cardiol. 2010; 145(3): 586–587, doi: 10.1016/j.ijcard.2010.05.072, indexed in Pubmed: 20580097.
11. Chavez P, Casso Dominguez A, Herzog E. Evolving Electrocardiographic Changes in Lamotrigine Overdose: A Case Report and Literature Review. Cardiovasc Toxicol. 2015; 15(4): 394–398, doi: 10.1007/s12012-014-9300-0, indexed in Pubmed: 25448877.