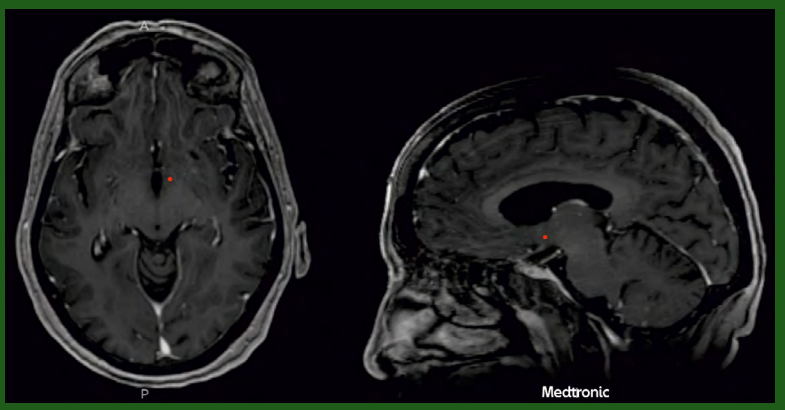
Neurologia i Neurochirurgia Polska, 2021, vol. 55, no. 5

NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF NEUROLOGY AND NEUROSURGERY

The Official Journal of Polish Neurological Society

2021, vol. 55, no. 5



Established: 1938

VIA MEDICA

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

www.journals.viamedica.pl/neurologia_neurochirurgia_polska

The option to opt-in is for Healthcare Professionals only. You may change your mind at any time by either accessing www.zogenixoptin.eu or by emailing eudataprivacy @zogenix.com. Our privacy policy can be accessed at www.zogenixresources.eu/Zogenix-Privacy-Policy-Master.pdf

ZOGENIX

SET A NEW STANDARD IN SEIZURE CONTROL FOR DRAVET SYNDROME

For many families living with **Dravet syndrome** the concept of 'normal' life is forgotten. The frequency and severity of seizures means that relationships are difficult to maintain, and the child and their parents are likely to become socially isolated.[2]

Fintepla▼ (fenfluramine) offers hope of seizure freedom that could open up a whole new world to those living with Dravet syndrome.

About Zogenix
Zogenix is a global biopharmaceutical company committed to developing and commercialising therapies with the potential to transform the lives of patients and their families living with rare diseases.

If you would like to learn more about Fintepla you can email our Key Account Manager, Olivia Guzicki, at oguzicki@zogenix.com to arrange a call, or you can scan the QR code on the left to let us know your channel and content preferences.

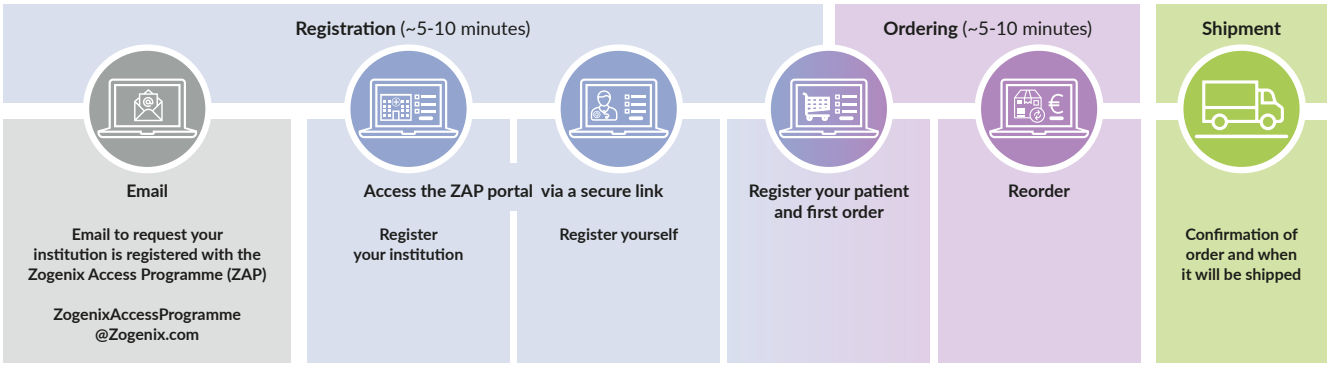
Fintepla is indicated for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.[1]

PL-FIN1-2100009 September 2021

ZOGENIX ACCESS PROGRAMME – AVAILABLE IN POLAND

Doctors in Poland can order Fintepla through the Zogenix Access Programme.
Email – **ZogenixAccessProgramme@Zogenix.com**

The ordering process is straightforward and illustrated below.



Polish Hospital Price is €2417 per 120ml bottle (ex.Vat). Shipment is included.

Fintepla▼ (fenfluramine) Prescribing information

Please refer to the full Summary of Product Characteristics (SmPC) before prescribing. **Indications:** Treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older. **Presentation:** 2.2 mg/mL oral solution. Each mL contains 2.2mg of fenfluramine (as fenfluramine hydrochloride). **Dosage and Administration:** Please refer to SmPC for full information/dosing tables. *Patients who are **not** taking stiripentol:* Starting dose is 0.1 mg/kg twice daily (0.2 mg/kg/day). After 7 days, if tolerated, can increase dose to 0.2 mg/kg twice daily (0.4 mg/kg/day). After an additional 7 days, if tolerated and further seizure reduction required, can increase dose to a maximum of 0.35 mg/kg twice daily (0.7 mg/kg/day), which is the recommended maintenance dose. Patients requiring more rapid titration may increase the dose every 4 days. Do not exceed maximum daily dose of 26 mg (13 mg twice daily). *Patients who are taking stiripentol:* Starting dose is 0.1 mg/kg twice daily (0.2 mg/kg/day). After 7 days, if tolerated, can increase dose to 0.2 mg/kg twice daily (0.4 mg/kg/day), which is the recommended maintenance dose. Patients requiring more rapid titration may increase the dose every 4 days. Do not exceed a total dose of 17 mg (8.6 mg twice daily). *Discontinuation:* When discontinuing treatment, decrease the dose gradually. As with all anti-epileptic medicines, avoid abrupt discontinuation when possible to minimize the risk of increased seizure frequency and status epilepticus. *Special populations: Renal impairment:* No clinical data available. *Hepatic impairment:* No clinical data available. Not recommended in moderate or severe liver impairment. *Elderly:* No data available. *Paediatric population:* Safety and efficacy in children below 2 years of age not yet established. No data available. **Contraindications:** Hypersensitivity to active substance or any excipients. Aortic or mitral valvular heart disease and pulmonary arterial hypertension. Within 14 days of the administration of monoamine oxidase inhibitors due to an increased risk of serotonin syndrome. **Warnings and Precautions:** *Aortic or mitral valvular heart disease and pulmonary arterial hypertension:* Prior to starting treatment, patients must undergo an echocardiogram to establish a baseline and exclude any pre-existing valvular heart disease or pulmonary hypertension. Conduct echocardiogram monitoring every 6 months for the first 2 years and annually thereafter. If an echocardiogram indicates pathological valvular changes, consider follow-up earlier to evaluate whether the abnormality is persistent. If pathological abnormalities seen on echocardiogram, evaluate the benefit versus risk of continuing fenfluramine treatment with the prescriber, caregiver and cardiologist. If echocardiogram findings suggestive of pulmonary arterial hypertension, perform a repeat echocardiogram as soon as possible and within 3 months to confirm these findings. If echocardiogram finding is confirmed suggestive of an increased probability of pulmonary arterial hypertension defined as intermediate probability, conduct a benefit-risk evaluation of continuation of Fintepla by the prescriber, carer and cardiologist. If echocardiogram suggests a high probability, it is recommended fenfluramine treatment should be stopped. *Decreased appetite and weight loss:* Fenfluramine can cause decreased appetite and weight loss - an additive effect can occur in combination with other anti-epileptic medicines such as stiripentol. Monitor the patient's weight. Undertake risk-benefit evaluation before starting treatment if history of anorexia nervosa or bulimia nervosa. *Fintepla controlled access programme*. A controlled access programme has been created to 1) prevent off-label use in weight management in obese patients and 2) confirm that prescribing physicians have been informed of the need for periodic cardiac monitoring in patients taking Fintepla. *Somnolence*: Fenfluramine can cause somnolence which could be potentiated by other central nervous system depressants. *Suicidal behaviour and ideation.* Suicidal behaviour and ideation have been reported in patients treated with anti-epileptic medicines in several indications. Advise patients and caregivers to seek medical advice should any signs of suicidal behaviour and ideation emerge. *Serotonin syndrome:* Serotonin syndrome, a potentially life-threatening condition, may occur with fenfluramine treatment, particularly with concomitant use of other serotonergic agents; with agents that impair metabolism of serotonin such as MAOIs; or with antipsychotics that may affect the serotonergic neurotransmitter systems. Carefully observe the patient, particularly during treatment initiation and dose increases. *Increased seizure frequency:* A clinically relevant increase in seizure frequency may occur during treatment, which may require adjustment in the dose of fenfluramine and/or concomitant anti-epileptic medicines, or discontinuation of fenfluramine, should the benefit-risk be negative. *Cyproheptadine:* Cyproheptadine is a potent serotonin receptor antagonist and may therefore decrease the efficacy of fenfluramine. If cyproheptadine is added to treatment with fenfluramine, monitor patient for worsening of seizures. If fenfluramine treatment is initiated in a patient taking cyproheptadine, fenfluramine's efficacy may be reduced. *Glaucoma.* Fenfluramine can cause mydriasis and can precipitate angle closure glaucoma. Discontinue therapy in patients with acute decreases in visual acuity. Consider discontinuation if ocular pain of unknown origin. *Strong CYP1A2 or CYP2B6 inducers*. Co-administration with strong CYP1A2 inducers or CYP2B6 inducers may decrease fenfluramine plasma concentrations. Consider an increase in fenfluramine dosage when co-administered with a strong CYP1A2 or CYP2B6 inducer; do not exceed the maximum daily dose. *Excipients*. Contains sodium ethyl para-hydroxybenzoate (E 215) and sodium methyl para-hydroxybenzoate (E 219) - may cause allergic reactions (possibly delayed). It also contains sulfur dioxide (E 220) which may rarely cause severe hypersensitivity reactions and bronchospasm. Patients with rare glucose-galactose malabsorption should not take this medicine. The product contains less than 1 mmol sodium (23 mg) per the maximum daily dose of 12 mL; essentially 'sodium-free'. Contains glucose - may be harmful to teeth. **Drug interaction**: Pharmacodynamic interactions with other CNS depressants increase the risk of aggravated central nervous system depression. Examples of such depressants are other serotonergic agents (including SSRIs, SNRIs, tricyclic antidepressants, or triptans); agents that impair metabolism of serotonin such as MAOIs; or antipsychotics that may affect the serotonergic neurotransmitter systems. Co-administration with CYP2D6 substrates or MATE1 substrates may increase their plasma concentrations. Co-administration with CYP2B6 or CYP3A4 substrates may decrease their plasma concentrations **Pregnancy and lactation**: *Pregnancy:* Limited data in pregnant women. As a precaution, avoid use of Fintepla in pregnancy. *Breast-feeding:* It is unknown whether fenfluramine/metabolites are excreted in human milk. Animal data have shown excretion of fenfluramine/metabolites in milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Fintepla taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **Ability to drive and use machines:** Fintepla has moderate influence on the ability to drive/ use machines as it may cause somnolence and fatigue. Advise patients not to drive or operate machinery until they have sufficient experience to gauge whether it adversely affects their abilities. **Undesirable effects:** *Very common (≥1/10):* Bronchitis, upper respiratory tract infection, decreased appetite, lethargy, somnolence, status epilepticus, tremor, constipation, diarrhoea, vomiting, pyrexia, fatigue, blood glucose decreased, echocardiogram abnormal (trace regurgitation), weight decreased and fall. *Common (≥1/100 to <1/10):* Ear infection, abnormal behaviour and irritability. Refer to SmPC for other adverse reactions. **Overdose:** Limited data concerning clinical effects and management of overdose. Agitation, drowsiness, confusion, flushing, tremor (or shivering), fever, sweating, abdominal pain, hyperventilation, and dilated non-reactive pupils were reported at much higher doses of fenfluramine than those included in the clinical trial program. Treatment should include gastric lavage. Monitor vital functions closely, and administer supportive treatment in case of convulsions, arrhythmias, or respiratory difficulties. **Package quantities and Marketing Authorisation number**: Fintepla is presented in a white bottle with oral syringes included which should be used to administer the prescribed dose. Bottle sizes of 60 mL, 120 mL and 360 mL. EU/1/20/1491/001, EU/1/20/1491/002 and EU/1/20/1491/004. **Legal Category:** POM. **Marketing Authorisation Holder:** Zogenix ROI Ltd, Trinity House, Charleston Road, Ranelagh, Dublin 6 D06 C8X4 Ireland.

Job Code: EU-FIN1-2000087 **Date of Preparation:** December 2020

Adverse events should be reported. Please refer to section 4.8 of the SmPC for national reporting requirements in your country.

Adverse events should also be reported to Zogenix International Limited at medinfo.eu@zogenix.com

References

1. Fintepla Summary of Product Characteristics.
2. Lagae L, Irwin J, Gibson E, Battersby A. *Seizure: European Journal of Epilepsy.* 2019;**65**:72-79.

Adverse events must be reported. If you wish to report an adverse event, please write to medinfo.eu@zogenix.com. Adverse events should also be reported to Departament Monitorowania Niepożądanych Działań Produktów Leczniczych Urzędu Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych: https://smz.ezdrowie.gov.pl

Fintepla®▼
(fenfluramine)
2.2 mg/mL oral solution

NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF NEUROLOGY AND NEUROSURGERY

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

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

NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF NEUROLOGY AND NEUROSURGERY

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

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

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

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

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

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

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

Cover photo: Sobstyl M. et al., Visualisation of NAc in 1.5 MRI contrast enhanced T1-weighted image (see figure on page 445).

20-0824.005.001

NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF NEUROLOGY AND NEUROSURGERY

The Official Journal of Polish Neurological Society

2021, vol. 55, no. 5

Table of Contents

EDITORIAL NOTE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 5, pages: 415–415
DOI: 10.5603/PJNNS.2021.0076

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

Professor Jarosław Sławek elected Secretary of the International Association of Parkinsonism and Related Disorders

Zbigniew K. Wszolek[1], Łukasz Stolarczyk[2]

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

With great pleasure, we announce that Professor Jarosław Sławek, Co-Editor-in-Chief of the *Polish Journal of Neurology and Neurosurgery* (PJNNS, *Neurologia i Neurochirurgia Polska*) has just been elected to the position of Secretary of the International Association of Parkinsonism and Related Disorders (IAPRD). Prof. Sławek holds the positions of Professor of Neurology at the Medical University of Gdansk, Poland and Head of the Neurology & Stroke Department at the Saint Adalbert Hospital, also in Gdansk. Last month, he completed his four-year tenure as President of the Polish Neurological Society.

The IAPRD is a professional society of movement disorders specialists from around the world. It was formally incorporated in 2010, but the IAPRD has evolved from the earlier World Federation of Neurology Research Group on Parkinsonism and Related Disorders. IAPRD supports publishing of two subspecialty journals, *Parkinsonism & Related Disorders* and *Clinical Parkinsonism and Related Disorders*. The Association organises biannual international scientific and educational congresses, and holds teaching and educational symposia / meetings in the years in between.

We wish Professor Sławek great success in his new international position.

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

INVITED EDITORIAL

This Invited Editorial accompanies a Short Communication, see page 494

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 5, pages: 416–417
DOI: 10.5603/PJNNS.a2021.0070

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

To drip or to mothership — the ongoing race for stroke thrombectomy

Michał Karliński

2nd Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland

Key words: acute stroke, mothership, drip-and-ship, thrombolysis, mechanical thrombectomy

(*Neurol Neurochir Pol 2021; 55 (5): 416–417*)

Modern acute stroke care is firmly oriented on reperfusion therapies. In Europe, intravenous thrombolysis (IVT) has been the gold standard of care for almost 20 years. Several years ago, this standard was augmented by the introduction of evidence-based mechanical thrombectomy (MT) for patients with large vessel occlusion (LVO). The pace of implementation of MT depends on the financial and organisational capabilities of particular healthcare systems, and thus varies across the continent [1–4].

Both IVT and MT are highly time-sensitive, and this remains true even in the era of late window thrombectomy. Delays in delivering endovascular thrombectomy to stroke patients can result in lower recanalisation rates and definitely results in substantial loss of healthy life-years [5, 6].

This is why door-to-needle time and door-to-groin puncture time have joined the simple rate of treated patients as the key performance indicators of each stroke unit [1–4]. The necessary struggle for optimisation of logistics exerts additional pressure on the whole system. For an acute stroke patient, the first critical point in the medical pathway is to raise among the ambulance crews a suspicion of stroke that (i) will turn out to be a stroke that (ii) qualifies for reperfusion therapy [7]. The next critical point is to transfer the patient to the right hospital. Given the organisational requirements, costs and the availability of properly trained personnel, MT is delivered only in comprehensive stroke centres (CSC), whilst all stroke units are able to administer IVT. This discrepancy results in two distinct treatment paradigms.

The default model, widely known as 'drip-and-ship' (DAS), implies that all patients with suspected acute stroke are transferred to the nearest stroke-ready hospital (i) to identify whether they are eligible for IVT or MT based on their history, clinical presentation, brain and vessel imaging; (ii) to initiate IVT; and (iii) to transfer to the cooperating CSC for MT.

The second model, commonly known as 'mothership' (MS), implies selection of patients with a high probability of acute ischaemic stroke caused by LVO at the scene, followed by a direct transfer to the CSC, thus bypassing the nearest stroke-ready hospital. Such patients may benefit from (i) earlier MT and (ii) shorter in-hospital delays to IVT. However, this is at the costs of (i) possibly overloading CSCs with patients not suitable for MT; (ii) the risk of not giving IVT to patients who would still be within the therapeutic window at their nearest hospital; and (iii) the consumption of additional resources from the ambulance service. The evidence overall points in favour of MS, but it is derived mostly from observational studies and does not refer to a uniform triage paradigm [8–12]

In this issue of *Neurologia i Neurochirurgia Polska*, Luchowski et al. attempt to answer the question of whether the MS pathway might be superior in patients suffering from acute stroke in the Polish healthcare system [13]. This is a retrospective analysis of 400 consecutive patients admitted for MT to a single CSC located in Lublin, Poland that coordinates a regional stroke network of 12 stroke units. The MS group (n = 267, 67%) and the DAS group (n = 133, 33%) were balanced in terms of basic demographic factors, comorbidities and stroke severity. Patients delivered in the MS model had a significantly shorter time form onset to groin puncture (179 min *vs.* 264 min) and a shorter time from picture to puncture (62 min *vs.* 146 min) at the cost of a longer time from door to groin (86 min *vs.* 35 min). There were no significant differences in terms of successful recanalisation (TICI 2b-3), symptomatic intracranial haemorrhages, NIHSS at discharge from CSC, 3-month mortality, or functional independence (mRS 0–2).

Address for correspondence: Michał Karliński, Institute of Psychiatry and Neurology, Sobieskiego 9 Str., 02–957 Warsaw, Poland; e-mail: mkarlinski@ipin.edu.pl

Received: 13.09.2021 Accepted: 1.10.2021 Early publication date: 12.10.2021

However, the authors observed a statistically significant and clinically relevant difference favouring MS (33% *vs.* 23%) in terms of excellent functional outcome (mRS 0–1).

Luchowski et al.'s study does not resolve the question of whether to 'drip' or to 'mothership'. One should note that the presented results reflect a scenario in which all patients transferred in the MS model actually undergo MT, and in which the primary stroke centres have long 'door-in door-out' times. The only large randomised clinical trial, carried out in Catalonia in Spain, failed to prove the superiority of the MS model in terms of clinical outcome partly because of the very good efficiency of the primary hospitals and partly because the proportion of patients undergoing MT was 50% (compared to 41% in DAS) at the cost of 20% relative reduction of IVT rate (RACECAT, presented at ESOC 2020, not yet published). However, the study by Luchowski et al. adds to the ongoing discussion another important piece of evidence in favour of the MS model. Noteworthy, the Polish healthcare system can be briefly described as developed but modestly financed and suboptimally organised, which slowed the widespread implementation of MT [14]. Therefore, the results may be usefully extrapolated to other countries in Central and Eastern Europe.

It the context of other studies, it seems important to underline that 'one size does not fit all'. The decision whether to implement a particular stroke system should depend not only on the general evidence. It should also be tailored for particular regions, depending on their geography and the capabilities of their stroke services, including the challenges around interhospital transfers and prenotification.

Conflict *of interest: None.*

References

1. Błażejewska-Hyżorek B, Czernuszenko A, Członkowska A, et al. Wytyczne postępowania w udarze mózgu. Polski Przegląd Neurologiczny. 2019; 15(A): 1–156, doi: 10.5603/ppn.2019.0001.
2. Powers W, Rabinstein A, Ackerson T, et al. et al.. Guidelines for the Early Management of Patients with Acute Ischemic Stroke. 2019; 50: e344–418.
3. Turc G, Bhogal P, Fischer U, et al. European Stroke Organisation (ESO) – European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischaemic StrokeEndorsed by Stroke Alliance for Europe (SAFE). Eur Stroke J. 2019; 4(1): 6–12, doi: 10.1177/2396987319832140, indexed in Pubmed: 31165090.
4. Berge E, Whiteley W, Audebert H, et al. De, Fonseca AC, Padiglioni C, European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. ; 2021: 6I–LXII.
5. Nowak K, Derbisz J, Jagiełła J, et al. Time from stroke onset to groin puncture affects rate of recanalisation after mechanical thrombectomy: a real-life single centre experience. Neurol Neurochir Pol. 2020; 54(2): 156–160, doi: 10.5603/PJNNS.a2020.0024, indexed in Pubmed: 32242914.
6. Almekhlafi MA, Goyal M, Dippel DWJ, et al. HERMES Trialists Collaboration. Healthy Life-Year Costs of Treatment Speed From Arrival to Endovascular Thrombectomy in Patients With Ischemic Stroke: A Meta-analysis of Individual Patient Data From 7 Randomized Clinical Trials. JAMA Neurol. 2021; 78(6): 709–717, doi: 10.1001/jamaneurol.2021.1055, indexed in Pubmed: 33938914.
7. Kozera-Strzelińska D, Karliński M, Rak G, et al. Stroke and TIA mimics in patients referred to a neurological emergency department by non-ambulance physicians, ambulance physicians and paramedics. Neurol Neurochir Pol. 2019; 53(1): 83–89, doi: 10.5603/PJNNS.a2019.0002, indexed in Pubmed: 30614515.
8. Romoli M, Paciaroni M, Tsivgoulis G, et al. Mothership versus Drip-and-Ship Model for Mechanical Thrombectomy in Acute Stroke: A Systematic Review and Meta-Analysis for Clinical and Radiological Outcomes. J Stroke. 2020; 22(3): 317–323, doi: 10.5853/jos.2020.01767, indexed in Pubmed: 33053947.
9. Schlemm L, Endres M, Scheitz JF, et al. Comparative Evaluation of 10 Prehospital Triage Strategy Paradigms for Patients With Suspected Acute Ischemic Stroke. J Am Heart Assoc. 2019; 8(12): e012665, doi: 10.1161/JAHA.119.012665, indexed in Pubmed: 31189395.
10. Cabal M, Machova L, Vaclavik D, et al. New Prehospital Triage for Stroke Patients Significantly Reduces Transport Time of EVT Patients Without Delaying IVT. Front Neurol. 2021; 12: 676126, doi: 10.3389/fneur.2021.676126, indexed in Pubmed: 34220685.
11. Xu Y, Parikh N, Jiao B, et al. Decision Analysis Model for Prehospital Triage of Patients With Acute Stroke. Stroke. 2019; 50(4): 970–977, doi: 10.1161/strokeaha.118.023272.
12. Holodinsky JK, Patel AB, Thornton J, et al. Drip and ship versus direct to endovascular thrombectomy: The impact of treatment times on transport decision-making. Eur Stroke J. 2018; 3(2): 126–135, doi: 10.1177/2396987318759362, indexed in Pubmed: 31008345.
13. Luchowski P, Wojczal J, Prus K, et al. Direct admission vs. secondary transfer for mechanical thrombectomy: long-term clinical outcomes from a single Polish Comprehensive Stroke Centre. Neurol Neurochir Pol. 2021 [Epub ahead of print], doi: 10.5603/PJNNS.a2021.0050, indexed in Pubmed: 34346053.
14. Słowik A, Wnuk M, Brzegowy P, et al. Polish Thrombectomy Initiative. Mechanical thrombectomy in acute stroke — Five years of experience in Poland. Neurol Neurochir Pol. 2017; 51(5): 339–346, doi: 10.1016/j.pjnns.2017.05.004, indexed in Pubmed: 28756015.

REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 5, pages: 418–428
DOI: 10.5603/PJNNS.a2021.0056

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

Alzheimer's disease and type 2 diabetes mellitus: similarities in pathomechanisms lead to therapeutic opportunities

Krzysztof Bednarz, Joanna Siuda

Department of Neurology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland

ABSTRACT

Introduction. Type 2 diabetes mellitus is a metabolic disease the development of which depends on both environmental and genetic factors. The rapid increase in the number of cases observed in recent decades has been associated with the lifestyle predominant in the West, characterised by a high-calorie diet rich in carbohydrates and saturated fatty acids as well as little physical activity and chronic stress. Another disease with growing morbidity is Alzheimer's disease, a neurodegenerative disorder characterised by progressive dementia**.**

State of the art. The results of numerous studies indicate many similarities between these two diseases in terms of their pathomechanisms, especially changes in the activity of enzymatic pathways, accumulation of peptides with altered structure, and chronic inflammation. Amyloid β, hyperphosphorylated tau protein, amylin, and apolipoprotein J are involved in both pathologies. The reasons for their excessive accumulation are not fully understood, but cellular metabolism disorders associated with insulin resistance and diabetes mellitus may play a key role in this process.

It is highly probable that the changes observed at cellular level, which translate into the clinical state of patients, are caused by many abnormalities common to both diseases.

Clinical implications. The discovery of pathophysiological similarities has resulted in attempts to use antidiabetic drugs in Alzheimer's disease therapy. While animal studies have revealed the potential benefits of oral antidiabetic drugs, studies on humans have not provided clear data regarding their effectiveness. Most clinical trial results are promising, but there have also been studies that have shown no significant, or even adverse, effects of these drugs on Alzheimer's disease course.

Future directions. Undoubtedly, further research is needed to better understand the mechanisms by which the medications used in diabetes treatment affect the nervous system, and further clinical trials to compare the effectiveness of this therapy in patients presenting different clinical conditions at different stages of Alzheimer's disease.

Key words: Alzheimer's disease, type 2 diabetes mellitus, insulin resistance, dementia, antidiabetic drugs

(*Neurol Neurochir Pol 2021; 55 (5): 418–428*)

Introduction

Diabetes mellitus is a significant problem for healthcare systems worldwide due to the rapidly growing number of patients diagnosed with this metabolic disease. The estimated number of patients in 1995, approximately 135 million, increased to c. 171 million in 2000, and 285 million in 2010. Estimates indicate that by 2030 the number will reach 578 million, and by 2045 c.700 million [1]. The more common type is Type 2 diabetes mellitus (T2DM) occurring in 85–95% of cases. This is more frequent in middle and older age and strongly associated with excessive amounts of adipose tissue, especially the abdominal obesity that induces increased synthesis of compounds, including inflammatory mediators, contributing to progressive insulin resistance of tissues [2]. Metabolic disorders in T2DM are a complex problem. The disease affects the metabolism of carbohydrates, lipids and proteins, leading to dysfunction of almost all systems and organs of the body including the cardiovascular system, kidneys, eyes, peripheral and central nervous system (CNS) [3]. The influence of factors related to T2DM on the CNS can be observed as atrophic changes in brain tissue in magnetic resonance imaging (MRI) [4].

Address for correspondence: Joanna Siuda, Medical University of Silesia, Katowice, Poland; e-mail: jsiuda@sum.edu.pl

Received: 30.01.2021 Accepted: 24.05.2021 Early publication date: 6.08.2021

Diabetes mellitus increases the risk of various types of dementia, including Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI), by promoting the formation of vascular lesions and ischaemia, altering metabolic processes of neurons and glial cells, and maintaining chronic inflammation. Changes in cognitive abilities can appear at any age and be noticeable even in children with diabetes [4–6]. Untreated or improperly treated diabetes increases the risk of developing dementia and maintaining the physiological level of glycaemia improves cognitive functions, which is why it is so important to restore proper glucose metabolism with appropriately selected pharmacotherapy [7, 8].

According to WHO data, various types of dementia affect about 50 million people worldwide. AD is the cause of 50–75% of dementia cases [7]. There is a rare, early-onset form (age under 65) associated with genes of the amyloid precursor protein (APP) and presenilin 1 and 2. The most common is the sporadic form occurring in the elderly, the causes of which can be found in environmental and genetic factors such as carrying at least one ε4 allele of the apolipoprotein E gene (ApoE-ε4) [9]. The exact pathomechanism of AD is unclear. It is known that as a result of excessive accumulation of amyloid beta (Aβ) and hyperphosphorylated tau protein as well as damage to mitochondria, oxidative stress and many other mechanisms, nerve cell death and reduced neurotransmission occur. This leads to increasing cognitive impairment, mood disorders, general disability and, eventually, death [10].

AD is usually diagnosed based on the patient's medical history, neurological examination and behavioural observations with screening tests, including the commonly used Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). These scales are useful for the assessment of a patient's cognitive functions and determining whether more detailed evaluation is needed. Recently, in a study which included 281 participants aged over 60 (91 without neurocognitive disorders (NCD) and the other 190 diagnosed with mild NCD), the Polish version of MoCA 7.2 was confirmed to be more sensitive than MMSE in the detection of mild NCD [11]. Structural and functional brain imaging also plays an important role in AD differential diagnosis. MRI shows atrophy in the cerebral cortex, especially in the medial part of the temporal lobe and the hippocampus. Functional studies with positron emission tomography (PET) detect changes at the early stage of the disease. Neuronal damage in areas such as posterior cingulate gyrus, precuneus, posterior, lateral and medial temporal-parietal association cortex and lateral frontal cortex, are associated with decreased glucose metabolism detected with 18F-fluorodeoxy-glucose (18F-FDG). Other radiotracers that bind to Aβ (florbetapir) or tau protein (flortaucipir) are used in the detection of neurotoxic peptides deposits [12].

As with T2DM, the number of people with AD will increase due to the ageing population. The common feature of both diseases is treatment based on slowing progression of the disease without being able to stop it completely. Growing knowledge about alterations at the cellular level is revealing more common features in terms of enzymatic pathway insufficiency, chronic inflammation and metabolic disorders [13]. The association between both diseases seems to be particularly strong in the case of carriers of the ApoE-ε4 allele in whom reduced glucose metabolism was observed in the posterior cingulate, precuneus and lateral parietal cortex [7, 14]. In addition, carriage of this allele in diabetic patients is associated with increased Aβ accumulation [7].

The many similarities between AD and T2DM are why some researchers have dubbed the metabolic disorders underlying the development of AD as 'type 3 diabetes' [8, 13–16].

Common pathophysiological mechanisms underlying T2DM and AD

Insulin and insulin resistance

The main feature of T2DM is insulin resistance of tissues leading to impaired glucose transport into cells, changes in intracellular carbohydrates, lipids and protein metabolism, a decrease in glycogen synthesis and an increase in hepatic gluconeogenesis (Fig. 1). A large amount of adipose tissue causes increased production of compounds acting as inflammation mediators, including TNF-α and interleukin-6, as well as alterations in the amounts of hormones secreted by adipose tissue, such as leptin and adiponectin. These compounds in physiological concentrations regulate carbohydrates and lipids metabolism and play a significant role in the regulation of satiety and hunger. Besides, these hormones influence the

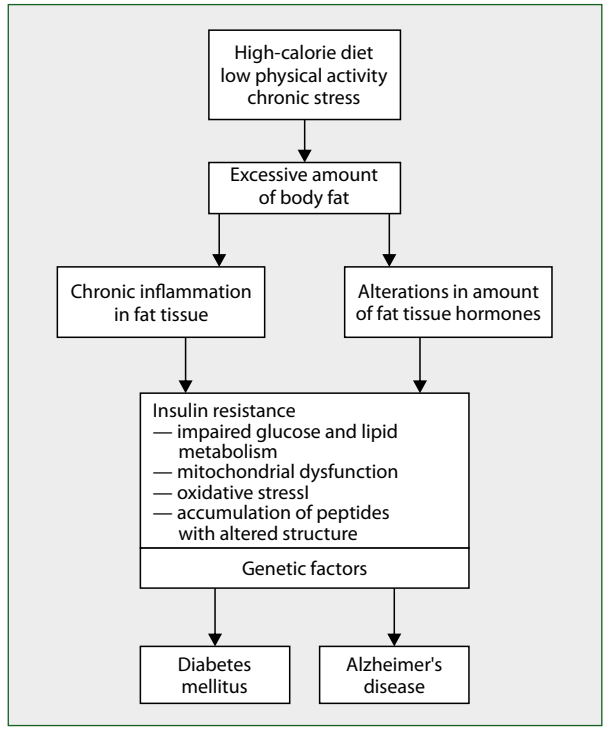


Figure 1. Pathophysiological relations between diabetes mellitus and alzheimer's disease

CNS. Leptin decreases Aβ deposition by inhibiting β-secretase and increasing the removal of amyloid deposits from nervous tissue, and also reduces the activity of glycogen synthase kinase 3 (GSK-3β) associated with excessive tau protein phosphorylation. Adiponectin, the concentration of which is reduced in the case of obesity and diabetes, has the ability to inhibit inflammation [17]. Insulin exerts its effect on cells through the transmembrane insulin receptor (IR) consisting of two α and two β subunits [8]. When an insulin molecule binds to one of the α-subunits, autophosphorylation of the β-subunits occurs because of its tyrosine kinase activity. This leads to activation of other enzymes which are part of the signalling pathways. The two most important are the MAPK-related pathway (mitogen-activated protein kinase) and the PI3K-Akt-GSK-3β pathway [18–20]. When the balance of cytokines and hormones secretion is disturbed, a detrimental effect on the cells of the liver and other tissues begins to lead to impairment of IR and the associated enzymatic signalling pathways function [13]. Research shows that disorders related to insulin resistance affect not only peripheral tissues but also take place in the central nervous system, and insulin resistance is a phenomenon that occurs in the course of AD [21, 22].

Insulin can cross the blood-brain barrier (BBB). This is evidenced by its presence in the cerebrospinal fluid where insulin concentration increases proportionally to the increase in blood concentration [8, 19]. Transport of the hormone across the BBB is mediated by receptors on vascular endothelial cells and depends on factors such as inflammation or triglyceride concentration related to obesity [23]. Long-term hyperinsulinaemia, caused by peripheral insulin resistance, also can reduce the transport of insulin across the BBB [24]. Additionally, transport of insulin takes place in structures such as the hypothalamus where the BBB is more permeable. This is confirmed by the increase of insulin activity in these regions after peripheral administration [24, 25]. In studies of human and rat brains, the presence of insulin mRNA has been detected in PCR tests. The presence of C-peptide in human CSF has also been observed, which may indicate a possible central synthesis of this hormone, but these studies require confirmation [9, 19]. It is also not known how much central insulin synthesis could contribute to the effect of this hormone on nerve cells [26].

In the CNS, insulin performs many important functions, but its role is not as well researched as is its influence on peripheral tissues [18]. There are numerous IRs in the hippocampus and medial temporal cortex which are related to the role of this hormone in memory processes [27]. These receptors are located both presynaptically and postsynaptically and their number, like the concentration of insulin itself, decreases with age [19]. Also, in patients with AD decreased expression of IRs within the CNS has been observed [20, 27]. Insulin plays a significant role in creating and strengthening new synaptic connections including the formation of long-term potentiation (LTP). Therefore, it is an important factor in the learning process and impairment of its function in the brain may be one reason behind impaired new memory traces formation in AD [8, 13]. Additionally, insulin is related to other cognitive functions including attention and executive functions. It is also one of the factors responsible for regulation of neurotransmitters, such as dopamine, acetylcholine and noradrenaline, by influencing secretion and reuptake [13, 18, 19, 28]. It also acts like a growth factor because of its involvement in neurogenesis, nerve cell development and neuroprotection [7, 25]. Insulin acts on the blood vessels through receptors in endothelial cells and can increase the production of nitric oxide, which causes vasodilatation. In high concentrations, insulin also stimulates the production of endothelin-1, which by constricting blood vessels increases blood pressure, which adversely affects the functioning of many organs including the brain [18]. Insulin resistance of cells or hormone deficiency increases the accumulation of Aβ and the hyperphosphorylated tau protein. Tau protein stabilises the structure of microtubules in neurons, essential for the correct transport of compounds along axons to synapses. This function depends on tau phosphorylation, as the hyperphosphorylated protein does not bind properly with microtubules leading to destabilisation of the cytoskeleton and cell death. Tau protein phosphorylation depends on the activity of kinases including GSK-3β. The activity of this enzyme increases due to disruption of the PI3K/Akt signalling pathway when IR stimulation is reduced. High GSK-3β activity leads to a significant increase in tau protein phosphorylation, its function impairment and formation of the neurofibrillary tangles being one of the causes of neuron death in AD [7, 29].

Another important element of insulin's impact on neurons is Insulin Degrading Enzyme (IDE) which is also responsible for the breakdown of other molecules including glucagon, atrial natriuretic peptide, Aβ and amylin [30]. The insulin resistance-induced hyperinsulinaemia in T2DM leads to insufficient enzyme activity against amyloid, due to competition between its substrates, resulting in excessive accumulation of Aβ and damage to nerve cells [31]. Reduction of the Akt activity, caused by decreased stimulation of IRs, can also lead to decreased IDE activity, with all of the consequences mentioned above [32].

On the other hand, it has been observed that Aβ oligomers impair intracellular signalling related to IR, leading to a vicious cycle of increasing insulin resistance and Aβ accumulation [7, 33].

Amylin

Amylin, also known as islet amyloid polypeptide (IAPP), is produced and secreted with insulin by β cells of the pancreatic islets [34]. It plays an important regulatory function by reducing insulin and glucagon secretion, inhibiting gastric emptying and suppressing appetite. Increase in amylin production and accumulation in pancreatic islets, observed in T2DM, leads to β-cell damage and decrease in insulin production [35, 36]. Amylin has numerous similarities to Aβ in terms of physicochemical properties such as a similar secondary structure and the mechanism of cytotoxicity [2, 34]. Both peptides form cell-damaging oligomers and fibrillary deposits which,

due to their low solubility, cannot be effectively removed from tissues. After penetrating the BBB, amylin can form deposits with Aβ and leads to inflammation, intensification of oxidative stress, mitochondrial dysfunction and nerve cell death [37, 38]. Tissue tests of the pancreas and brain of patients with AD have shown the presence of Aβ and tau protein in pancreatic islet β cells in T2DM patients, and even in some non-diabetic patients [39, 40]. Moreover, it has been shown that amylin can co-deposit with both Aβ and tau protein in the pancreas and CNS. This may indicate that amylin, Aβ and tau are together involved in the development of both T2DM and AD [41].

Another compound associated with both AD and T2DM is clusterin (apolipoprotein J). This is a protein involved in the regulation of processes such as cell apoptosis, inflammation and lipid transport [9, 42]. In view of the fact that the concentration of clusterin in blood is elevated in AD, in pre-diabetes and diabetes mellitus it is possible that clusterin is not only a biomarker but also a factor involved in the course of these diseases [43]. One study showed that the concentration of clusterin correlates negatively with MMSE scores and correlates positively with the concentration of glycosylated haemoglobin (HbA1C), the HOMA-IR index and the concentration of C-peptide. It is also associated with structural changes in the CNS imaging examinations. Clusterin can cross the BBB and is also produced by nerve cells in CNS where it influences the formation of Aβ deposits and its concentration increases with exacerbation of AD and diabetes [43]. Clearly, the role of clusterin in the course of both diseases requires further research.

Mitochondrial dysfunction, inflammation and oxidative stress

Dysfunction of mitochondria is an important element of the pathomechanisms of many diseases including T2DM and AD [9, 44, 45]. The problem is caused by disruption of enzymatic pathways related to the IR and by Aβ accumulation. These phenomena are further intensified by progressive mitochondrial dysfunction which leads to a vicious circle [7]. Impaired function of these organelles results in decreased synthesis of ATP, the main energy carrier in cells, which contributes to cell death [44]. On the other hand, there is increased production of reactive oxygen species (ROS) which are responsible for alterations in the chemical structure of proteins and lipids [7, 46]. Oxidative stress is especially intense in T2DM because of reduced antioxidant compounds activity. Damage to the mitochondria also leads to disturbances in cellular calcium homeostasis, another factor associated with cell apoptosis [7, 9, 47].

Chronic inflammation occurs in both AD and T2DM and leads to IR dysfunction and insulin resistance of tissues. It is associated with increased adipose tissue volume and high concentration of lipid compounds in the blood. Fatty acids can cross the BBB and are taken up by nerve and glial cells. This process is intensified in people with increased body weight [48]. Saturated fatty acids bind to TLR 4 receptors (toll-like receptor 4) which are associated with the removal of Aβ from the extracellular space in the early stages of AD [33].

Over time, their activation leads to increased cytokine synthesis in astrocytes and inflammatory response in various structures of the CNS [49]. Chronic activation of microglial cells, associated with the presence of Aβ deposits in the brain tissue, leads to exacerbation of neurodegeneration due to continuous release of inflammatory mediators, including TNF-α and Interleukin-6, as well as neurotoxic ROS by activated glial cells [50]. However, inflammation is associated not only with glial cells. Increased activity of peripheral inflammatory cells in AD has been observed in the early stages of the disease, and studies indicate an association between the severity of inflammation and cognitive impairment [51, 52].

High levels of cytokines in the brain lead to a decreased response of CNS cells to insulin, similarly as in peripheral tissues [37]. Moreover, a high concentration of pro-inflammatory cytokines leads to impaired LTP formation in the dentate gyrus, which results in impaired memory functions [16].

Antidiabetic drugs in AD therapy

Metabolic disorders, both systemic and directly related to the CNS, lead to progressive loss of nerve cells. This results in impaired functioning of extensive neural networks, largely associated with a significant reduction of neurotransmission. Drugs such as galantamine and rivastigmine inhibit the action of acetylcholinesterase and lead to increased acetylcholine concentration. Memantine exerts neuroprotective activity by NMDA receptor antagonism [13, 53]. However, this type of therapy is aimed at eliminating the effects of massive neural cell death. On the other hand, attempts to neutralise the causes of neurodegeneration with drugs, such as monoclonal Aβ antibodies (solanezumab, aducanumab, crenezumab) or β-secretase inhibitors (verubecestat), have not been effective [54–57].

Therefore, it is possible that effective therapy should focus on influencing the metabolic genesis of AD associated with insulin resistance, inflammation and mitochondrial dysfunction [13]. Connections between AD and T2DM indicate that drugs used in diabetes therapy may point to a new therapeutic direction in the fight against dementia.

Insulin

Exogenous insulin is the main agent used in treatment of patients with Type 1 Diabetes Mellitus, and in some situations it is also administered to patients with T2DM. Due to the consequences of insulin deficiency for nerve cells, researchers have drawn attention to the use of insulin in the treatment of AD and MCI.

One study, in which 13 non-diabetic AD or MCI patients were administered intranasal insulin for 21 days, showed improvements in memory function and attention compared to a placebo group [58]. Another study with MCI and AD participants showed that short-term (21 days) long-acting insulin administration is more effective with higher doses (40 IU compared to 20 IU)

[59]. Moreover, long-term insulin administration (4-month therapy) resulted in improvement of memory functions associated with slowing of atrophic changes in MRI and an improvement in the tau-P181/ Aβ42 ratio, but in this case the effects were noticeable with the use of short-acting insulin [60]. A recent study, in which patients with MCI or AD were administered insulin in daily doses of 40 IU for 12 months, showed no positive changes in terms of cognitive functions [61]. In clinical trials, insulin is administered intranasally and transport to CNS along the trigeminal nerve and the olfactory tract [62]. This route of administration is intended to minimise the risk of systemic side effects, such as hypoglycaemia, that could be the result of peripheral injections.

Moreover, the nasal route of administration is associated with more effective delivery of appropriate doses to the CNS [62, 63]. Insulin has an effect on tau protein phosphorylation and Aβ removal as well as APP metabolism, and by these effects is probably responsible for a positive impact on the AD patients who take it [64]. A positive response to insulin therapy, in terms of improving cognitive abilities in these patients, is gender-related, with males responding better to higher doses (40 IU) than females [65]. The result seems to be influenced also by the carriage of the ApoE-ε4 allele. At high insulin doses, ApoE-ε4 (-) males achieved a better response to treatment than APOE-ε4 (+). The opposite effect was observed in high-dose group females. ApoE ε4 (-) females had the worst cognitive performance while ApoE ε4 (+) remained stable. ApoE ε4 (+) males and females with high insulin dose obtained results without significant improvements or decreases [65]. These differences could be a result of interaction of ApoE4 with the IR, observed in mice, causing the impairment of IR transport to the cell membrane by trapping it in endosomes which results in decreased insulin response in ApoE-ε4 allele carriers [66].

Metformin

Metformin is the first-line medication in T2DM therapy [19]. It is orally administered and has the ability to penetrate to the brain tissue across the BBB [67]. The mechanism of its action is based on increasing cells sensitivity to insulin. A significantly reduced risk of dementia has been reported in metformin users [68]. Observations of diabetic patients taking metformin show a positive effect of this drug on cognitive functions [64]. Clinical trials have confirmed the safety of metformin and its penetration into the CNS as well as the association with improvements in executive functions, memory and attention in patients with MCI and AD [58]. An improvement in the ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive subscale) score, which measures cognitive abilities, was also observed in patients with MCI who were overweight or obese, but not diabetic [69]. Another study showed that only participants taking metformin in monotherapy achieved significant improvements in cognitive function measured by neuropsychological tests [70].

However, there is some evidence that metformin may also cause cognitive decline, and that prolonged use could even increase the risk of AD [71, 72]. Certainly, further studies are needed to find the cause of these contradictions in the results of previous research and to set optimal doses and durations of therapy as well as to identify patients who could achieve significant benefits from metformin therapy. The MAP study (Metformin in Alzheimer's Dementia Prevention, ClinicalTrials.gov Identifier: NCT04098666) was planned to start in early 2021. This is a multicentre, randomised, phase II / III study in 370 male and female participants with early-stage MCI and without diabetes. The study will provide new data about the role of metformin in inhibiting the progression of dementia.

Liraglutide

Liraglutide is an antidiabetic drug from the group of GLP-1 analogues (Glucagon-like peptide-1). In the CNS, receptors for GLP-1 are located in many areas including temporal cortex and hippocampus [73]. Studies have shown enhanced learning abilities in mice with high expression of GLP-1 receptors within the hippocampus [74]. Liraglutide has a positive effect on CNS glucose transport and metabolism observed with FDG-PET in AD patients [75]. In rodents, the drug increased neurogenesis, had a neuroprotective effect by reducing the amount of Aβ and hyperphosphorylated tau reducing inflammation, and also had a positive effect on memory by participating in LTP formation [76–79]. Studies on a mouse model of AD have shown that liraglutide can improve memory functions and increase the number of nerve cells in the hippocampus [80].

Most of these effects have been observed in studies on animal models, therefore clinical trials in large groups of patients are necessary to assess the long-term efficacy of liraglutide in reducing AD symptoms. The effect of liraglutide on the human nervous system has already been observed as detected in fMRI improvement of connectivity within the Default Mode Network (DMN) seen after 12 weeks of liraglutide therapy [81]. However, the participants were not diagnosed with dementia and the study found no changes in cognitive function. The influence of liraglutide on the course of AD was also the subject of the ELAD study (Evaluating the effects of the novel GLP-1 analogue Liraglutide in Alzheimer's Disease) [82]. Its purpose was to evaluate changes in cerebral glucose metabolism in AD patients after 12 months of daily administration of liraglutide compared to a placebo group. Participants were examined by PET of medial temporal lobe, posterior part of cingulate cortex and hippocampus. Changes in the condition of the study participants were also assessed with scales measuring the severity of AD symptoms (Alzheimer's Disease Assessment Scale, Executive Domain Scores of the Neuropsychological Test Battery, Clinical Dementia Rating Sum of Boxes, and Alzheimer's Disease Cooperative Study — Activities of Daily Living), MRI scans and several other parameters. Unfortunately, during the CTAD (Clinical Trials on Alzheimer's Disease) congress in November 2020, it was reported that no changes in glucose metabolism were observed in studied regions of the brain between the groups administered the drug and the placebo.

Dipeptidyl peptidase-4 (DPP-4) inhibitors

DPP-4 inhibitors are a class of medications that act on the enzyme responsible for the inactivation of incretin compounds including GLP-1. The inhibition of DPP-4 increases GLP-1 level in the blood, thus enhances not only the antidiabetic properties of incretins but also those associated with a beneficial effect on the CNS.

In animal models of AD, linagliptin, a highly specific and potent inhibitor of DPP-4, improved cognitive function, and decreased inflammatory markers, tau phosphorylation and Aβ aggregation [55, 83]. A study of the neuroprotective properties of linagliptin on human nerve cells has shown that the drug can protect neurons from the effects of Aβ on mitochondrial damage, oxidative stress and impairment of IR signalling. Restoring the proper functioning of the IR pathways is caused by inhibition of GSK-3β activity, which leads to a reduction in tau protein phosphorylation [84]. These effects could be useful in AD therapy [55].

Sitagliptin also may improve the condition of patients with AD. In one study, 253 elderly patients with T2DM (205 participants, including 52 with AD, completed the study) were divided into a sitagliptin and a non-drug group [85]. After six months of therapy, the group taking the drug not only required lower doses of insulin (improved glycaemic control in diabetes) but also achieved better MMSE scores. Improvement was seen in both AD patients and those without dementia.

Thiazolidinediones

This is a class of antidiabetic agents which act by peroxisome proliferator-activated receptors (PPAR-γ) and result in increased insulin sensitivity of tissues. These drugs not only normalise blood glucose level, but also have a positive effect on the lipid profile, which is very beneficial for patients with T2DM [86]. Pioglitazone, in addition to the above-mentioned effects, also has many properties that could be helpful in the treatment of AD [87]. This drug has the ability to reduce the amount of Aβ deposits. *In vitro* studies on rat nerve cells have shown that pioglitazone can inhibit the phosphorylation of the PPAR-γ which regulates the expression of IDE, an enzyme responsible for Aβ degradation. PPAR-γ also influences expression of β-secretase involved in APP processing leading to generation of Aβ [88]. The neuroprotective role of pioglitazone could also be related to a decrease in TNF-α concentration [89]. In mice treated for two weeks with pioglitazone and leptin, a positive effect of this form of therapy on spatial memory and on the amount of Aβ deposits was observed [90]. In healthy, elderly patients treated with low doses of pioglitazone (0.6 mg) for two weeks, an increase in fMRI-measured hippocampal cells activity was observed during tasks involving memory functions [91]. Subsequent studies have shown an improvement in cognitive functions after pioglitazone therapy in patients with T2DM as well as MCI and AD, as well as an increase in cerebral blood flow within the parietal lobe in patients with T2DM and AD [92, 93].

Rosiglitazone improves spatial memory tested in the Morris water maze and increases removal of Aβ deposits, similarly to pioglitazone, by increasing IDE expression in diabetic and AD-induced mice [94]. The positive effect of rosiglitazone on nerve cells and formation of LTP in the dentate gyrus of rodents can also be a consequence of drug-associated decreased production of proinflammatory cytokines including IL-1β and IFNγ [95]. There are many conflicting results from clinical trials regarding the efficacy of rosiglitazone in dementia treatment. Some trials indicate that the drug may improve cognitive performance in patients with MCI and AD [96]. However, later studies do not confirm such an effect [97].

Drugs affecting amylin receptors

Pramlintide is a synthetic amylin analogue for use in the treatment of Types 1 and 2 Diabetes Mellitus. It works by slowing gastric emptying and reducing glucagon secretion which results in improved glycaemic control [38]. It does not show the ability to form deposits which in the case of amylin impair physiological functions [98]. In studies on animal models, it has been observed that administration of amylin or pramlintide reduces the amount of Aβ deposits and phosphorylated tau protein, decreases inflammation, and improves cognitive functions [38, 99].

Amylin receptor antagonists act by blocking amylin receptor (AMYR). Substances such as AC253 weaken the harmful effects of amylin and Aβ oligomers on cells via these receptors [38]. Injection of AC253 into the brain ventricles improves spatial memory and decreases microglia activity. It has been observed that the cyclic form of AC253 has better stability, better accessibility to brain tissue, and higher affinity for AMYR than the original form of AC253 [100]. Interestingly, pramlintide and AMYR antagonists have a similar effect on the nervous system, although their actions on AMYR are in opposite directions [38].

As can be seen, the results of clinical trials do not provide a clear answer to the question of therapeutic effectiveness in AD. Some conflicting conclusions drawn from these studies may be related to the high heterogeneity of participants. Patients at different stages of disease can react differently to the same treatment. It is also important to stress that we still do not know all of the pathophysiological mechanisms of both metabolic and neurodegenerative disorders, so we cannot comprehend all the variables that could potentially affect the treatment outcomes in patients with apparently similar clinical conditions.

Conclusions and future directions

T2DM and AD present major challenges to healthcare systems. This challenge will continue to grow due to increases in the main risk factors for both diseases observed in the population. Despite the differences in clinical presentation, diabetes and AD appear to have many similarities in terms of metabolic alterations in cells. Some studies show a positive effect of antidiabetic drugs in improving cognitive function in people with dementia, although some results have been less positive (Tab. 1).

Table 1. Summary of studies with AD and MCI participants taking antidiabetic drugs

Drug	Study	Trial type	Participants	Outcomes
Intranasal insulin	Reger et al. 2008 [58]	Randomized Double-blind Placebo--Controlled, Parallel Group	25 with early stage AD or MCI, without diabetes	Improvement of memory and attention, increase in Aβ40/Aβ42 ratio in group taking regular insulin 40 IU/day
	Claxton et al. 2013 [65]	Randomized Double-blind Placebo--Controlled, Parallel Group	104 (64 with amnestic MCI and 40 with mild to moderate AD, no diabetes)	Males responded better to higher doses (40 IU) than females. At high doses, APOE-ε4 (–) males responded better to treatment than APOE-ε4 (+). The ApoE ε4 (–) females had the worst cognitive performance, while the ApoE ε4 (+) remained stable. Males and females ApoE ε4 (+) at high dose obtained results without significant improvement or decrease
	Claxton et al. 2015 [59]	Randomized Double-blind Placebo--Controlled, Parallel Group	60 with AD or MCI, without diabetes	Improvement of verbal and visual-spatial memory on high dose (40 IU). No effect on cognition on low dose (20 IU)
	Craft et al. 2017 [60]	Randomized Double-blind Placebo--Controlled, Parallel Group	37 with AD or MCI, without diabetes	Improvement of verbal memory, MRI and tau-P181/Aβ42 ratio (group with 40 IU, short-acting insulin). No effect on cognition, MRI or biomarkers (group with 40 IU, long-acting insulin)
	Craft et al. 2020 [61]	Randomized Double-blind Placebo--Controlled, Parallel Group	240 with AD or MCI, without diabetes	No significant effect on cognitive functions, general functioning or AD biomarkers and small but significant reduction in hippocampal volume. In group taking regular insulin
Metformin	Imfeld et al. 2012 [72]	Case-control study	7086 with AD and the same number without dementia	Suggestion that there is a higher risk of AD from long-term use of metformin
	Moore et al. 2013 [71]	Randomized Placebo-Controlled	480 with AD, 187 with MCI, 687 without cognitive impairment	Cognitive impairment associated with metformin therapy. Vitamin B12 and calcium supplements can improve vitamin B12 deficiency caused by metformin and are associated with better cognitive functions
	Luchsinger et al. 2016 [69]	Randomized Double-blind Placebo--Controlled	80 with MCI overweight or obese, without diabetes	Improvement of the ADAS-Cog score on verbal memory in group taking metformin 2.000 mg/day
	Herath et al. 2016 [70]	Population-based cohort study	1814 without dementia, with or without diabetes	Significant effect of diabetes treatment on cognitive functions only with participants using metformin in monotherapy, who demonstrated a significant protective effect of metformin in verbal memory, working memory and executive functions
	Koenig et al. 2017 [67]	Randomized Double-blind Placebo--Controlled, Crossover Study	20 with early-stage AD or MCI, without diabetes	Improvement of executive functions, memory and attention after metformin therapy
Liraglutide	Gejl et al. 2016 [75]	Randomized Double-blind Placebo--Controlled, Parallel Group	38 with AD, without diabetes	Preserved glucose metabolism in group taking liraglutide 1.8 mg/day compared to decrease in the placebo group. No changes in cognitive functions
	Watson et al. 2019 [81]	Randomized Double-blind Placebo--Controlled, Parallel Group	43 with subjective cognitive impairment without AD and MCI	Improvement of the functioning of nerve connections in fMRI and no changes in cognitive functions in group taking liraglutide 1.8 mg/day
	Femminella et al. 2019 [82]	Randomized Double-blind Placebo--Controlled	206 with AD and without treated diabetes	No changes in glucose metabolism in observed brain regions between the drug and placebo groups
Sitagliptin	Isik et al. 2017 [85]	Prospective and Observational	253 with diabetes mellitus, some with AD	In addition to its effects on glycaemic control, sitagliptin therapy may be associated with improved cognitive functions in elderly T2DM patients with and without AD
Pioglitazone	Hanyu et al. 2009 [92]	Randomized Double-blind Placebo--Controlled, Parallel Group	32 with AD or MCI, with diabetes	Improvement in ADAS-Cog and no significant changes in MMSE in drug group
	Hanyu et al. 2010 [89]	Randomized Double-blind Placebo--Controlled, Parallel Group	34 with AD and diabetes	Reduction of TNF- α levels after pioglitazone treatment associated with cognitive improvement
	Sato et al. 2011 [93]	Randomized Double-blind Placebo--Controlled, Parallel Group	42 with AD and diabetes	In drug group: improvement of cognitive functions in MMSE, ADAS-Cog, increase in blood flow in the parietal lobe, no changes in the Aβ40/Aβ42 ratio
Rosiglitazone	Risner et al. 2006 [96]	Randomized Double-blind Placebo--Controlled, Parallel Group	518 with non-diabetic AD	Improvement of cognitive functions in apoE4 (–) subject taking rosiglitazone 8 mg/day
	Gold et al. 2010 [97]	Randomized Double-blind Placebo--Controlled	693 with AD with or without diabetes	No cognitive improvement with rosiglitazone in either the overall sample or within APOE4 subgroups

Clearly, further research and observations are needed. This seems to be promising area to investigate, and the amount of medications used in the therapy of diabetes that could affect the condition of dementia patients is considerable.

The future will reveal whether the knowledge obtained through laboratory studies and clinical trials will result in improvements in the condition of patients.

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

References

1. Saeedi P, Salpea P, Karuranga S, et al. IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9 edition. Diabetes Res Clin Pract. 2019; 157: 107843, doi: 10.1016/j.diabres.2019.107843, indexed in Pubmed: 31518657.
2. Akash MS, Rehman K, Chen S, et al. Role of inflammatory mechanisms in pathogenesis of type 2 diabetes mellitus. J Cell Biochem. 2013; 114(3): 525–531, doi: 10.1002/jcb.24402, indexed in Pubmed: 22991242.
3. Papatheodorou K, Papanas N, Banach M, et al. Complications of Diabetes 2016. J Diabetes Res. 2016; 2016: 6989453, doi: 10.1155/2016/6989453, indexed in Pubmed: 27822482.
4. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nat Rev Endocrinol. 2018; 14(10): 591–604, doi: 10.1038/s41574-018-0048-7, indexed in Pubmed: 30022099.
5. Rönnemaa E, Zethelius B, Sundelöf J, et al. Impaired insulin secretion increases the risk of Alzheimer disease. Neurology. 2008; 71(14): 1065–1071, doi: 10.1212/01.wnl.0000310646.32212.3a, indexed in Pubmed: 18401020.
6. S Roriz-Filho J, Sá-Roriz TM, Rosset I, et al. (Pre)diabetes, brain aging, and cognition. Biochim Biophys Acta. 2009; 1792(5): 432–443, doi: 10.1016/j.bbadis.2008.12.003, indexed in Pubmed: 19135149.
7. Sun Y, Ma C, Sun H, et al. Metabolism: a novel shared link between diabetes mellitus and Alzheimer's disease. J Diabetes Res. 2020; 2020: 4981814, doi: 10.1155/2020/4981814, indexed in Pubmed: 32083135.
8. Nguyen TT, Ta QT, Nguyen TK, et al. Type 3 diabetes and its role implications in Alzheimer's disease. Int J Mol Sci. 2020; 21(9), doi: 10.3390/ijms21093165, indexed in Pubmed: 32365816.
9. Neth BJ, Craft S. Insulin resistance and Alzheimer's disease: bioenergetic linkages. Front Aging Neurosci. 2017; 9: 345, doi: 10.3389/fnagi.2017.00345, indexed in Pubmed: 29163128.
10. Weller J, Budson A. Current understanding of Alzheimer's disease diagnosis and treatment. F1000Res. 2018; 7, doi: 10.12688/f1000research.14506.1, indexed in Pubmed: 30135715.
11. Sokołowska N, Sokołowski R, Oleksy E, et al. Usefulness of the Polish versions of the Montreal Cognitive Assessment 7.2 and the Mini-Mental State Examination as screening instruments for the detection of mild neurocognitive disorder. Neurol Neurochir Pol. 2020; 54(5): 440–448, doi: 10.5603/PJNNS.a2020.0064, indexed in Pubmed: 32808669.
12. Barc K, Kuźma-Kozakiewicz M. Positron emission tomography neuroimaging in neurodegenerative diseases: Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Neurol Neurochir Pol. 2019; 53(2): 99–112, doi: 10.5603/PJNNS.a2019.0013, indexed in Pubmed: 30855701.
13. De Sousa RA, Harmer AR, Freitas DA, et al. An update on potential links between type 2 diabetes mellitus and Alzheimer's disease. Mol Biol Rep. 2020; 47(8): 6347–6356, doi: 10.1007/s11033-020-05693-z, indexed in Pubmed: 32740795.
14. Knopman DS, Jack CR, Wiste HJ, et al. 18F-fluorodeoxyglucose positron emission tomography, aging, and apolipoprotein E genotype in cognitively normal persons. Neurobiol Aging. 2014; 35(9): 2096–2106, doi: 10.1016/j.neurobiolaging.2014.03.006, indexed in Pubmed: 24702820.
15. Monte Sd, Wands J. Alzheimer's Disease is type 3 diabetes–evidence reviewed. Journal of Diabetes Science and Technology. 2008; 2(6): 1101–1113, doi: 10.1177/193229680800200619.
16. Meng L, Li XY, Shen L, et al. Type 2 diabetes mellitus drugs for alzheimer's disease: current evidence and therapeutic opportunities. Trends Mol Med. 2020; 26(6): 597–614, doi: 10.1016/j.molmed.2020.02.002, indexed in Pubmed: 32470386.
17. Van Dyken P, Lacoste B. Impact of metabolic syndrome on Neuroinflammation and the blood-brain barrier. Front Neurosci. 2018; 12: 930, doi: 10.3389/fnins.2018.00930, indexed in Pubmed: 30618559.
18. Kellar D, Craft S. Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. Lancet Neurol. 2020; 19(9): 758–766, doi: 10.1016/S1474-4422(20)30231-3, indexed in Pubmed: 32730766.
19. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. Nat Rev Neurol. 2018; 14(3): 168–181, doi: 10.1038/nrneurol.2017.185, indexed in Pubmed: 29377010.
20. Gabbouj S, Ryhänen S, Marttinen M, et al. Altered Insulin Signaling in Alzheimer's Disease Brain - Special Emphasis on PI3K-Akt Pathway. Front Neurosci. 2019; 13: 629, doi: 10.3389/fnins.2019.00629, indexed in Pubmed: 31275108.
21. de la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes-evidence reviewed. J Diabetes Sci Technol. 2008; 2(6): 1101–1113, doi: 10.1177/193229680800200619, indexed in Pubmed: 19885299.
22. Sims-Robinson C, Kim B, Rosko A, et al. How does diabetes accelerate Alzheimer disease pathology? Nat Rev Neurol. 2010; 6(10): 551–559, doi: 10.1038/nrneurol.2010.130, indexed in Pubmed: 20842183.
23. Banks WA, Owen JB, Erickson MA. Insulin in the brain: there and back again. Pharmacol Ther. 2012; 136(1): 82–93, doi: 10.1016/j.pharmthera.2012.07.006, indexed in Pubmed: 22820012.
24. Rhea EM, Banks WA. Role of the blood-brain barrier in central nervous system insulin resistance. Front Neurosci. 2019; 13: 521, doi: 10.3389/fnins.2019.00521, indexed in Pubmed: 31213970.
25. Kleinridders A, Ferris HA, Cai W, et al. Insulin action in brain regulates systemic metabolism and brain function. Diabetes. 2014; 63(7): 2232–2243, doi: 10.2337/db14-0568, indexed in Pubmed: 24931034.
26. Ahn KC, Learman CR, Baker GB, et al. Regulation of diabetes: a therapeutic strategy for Alzheimer's disease? J Korean Med Sci. 2019; 34(46): e297, doi: 10.3346/jkms.2019.34.e297, indexed in Pubmed: 31779058.
27. Frazier HN, Ghoweri AO, Anderson KL, et al. Broadening the definition of brain insulin resistance in aging and Alzheimer's disease. Exp Neurol. 2019; 313: 79–87, doi: 10.1016/j.expneurol.2018.12.007, indexed in Pubmed: 30576640.

28. Zilliox LA, Chadrasekaran K, Kwan JY, et al. Diabetes and cognitive impairment. Curr Diab Rep. 2016; 16(9): 87, doi: 10.1007/s11892-016-0775-x, indexed in Pubmed: 27491830.
29. Rankin CA, Sun Q, Gamblin TC. Tau phosphorylation by GSK-3beta promotes tangle-like filament morphology. Mol Neurodegener. 2007; 2: 12, doi: 10.1186/1750-1326-2-12, indexed in Pubmed: 17598919.
30. Haque R, Nazir A. Insulin-degrading enzyme: a link between Alzheimer's and type 2 diabetes mellitus. CNS Neurol Disord Drug Targets. 2014; 13(2): 259–264, doi: 10.2174/18715273113126660139, indexed in Pubmed: 24059320.
31. Zhao L, Teter B, Morihara T, et al. Insulin-degrading enzyme as a downstream target of insulin receptor signaling cascade: implications for Alzheimer's disease intervention. J Neurosci. 2004; 24(49): 11120–11126, doi: 10.1523/JNEUROSCI.2860-04.2004, indexed in Pubmed: 15590928.
32. Tundo GR, Sbardella D, Ciaccio C, et al. Multiple functions of insulin-degrading enzyme: a metabolic crosslight? Crit Rev Biochem Mol Biol. 2017; 52(5): 554–582, doi: 10.1080/10409238.2017.1337707, indexed in Pubmed: 28635330.
33. Madhusudhanan J, Suresh G, Devanathan V. Neurodegeneration in type 2 diabetes: Alzheimer's as a case study. Brain Behav. 2020; 10(5): e01577, doi: 10.1002/brb3.1577, indexed in Pubmed: 32170854.
34. Mietlicki-Baase EG. Amylin-mediated control of glycemia, energy balance, and cognition. Physiol Behav. 2016; 162: 130–140, doi: 10.1016/j.physbeh.2016.02.034, indexed in Pubmed: 26922873.
35. Brito-Moreira J, Lourenco MV, Oliveira MM, et al. Interaction of amyloid-β (Aβ) oligomers with neurexin 2α and neuroligin 1 mediates synapse damage and memory loss in mice. J Biol Chem. 2017; 292(18): 7327–7337, doi: 10.1074/jbc.M116.761189, indexed in Pubmed: 28283575.
36. Lutz TA, Meyer U. Amylin at the interface between metabolic and neurodegenerative disorders. Front Neurosci. 2015; 9: 216, doi: 10.3389/fnins.2015.00216, indexed in Pubmed: 26136651.
37. Stanciu GD, Bild V, Ababei DC, et al. Link between diabetes and Alzheimer's disease due to the shared amyloid aggregation and deposition involving both neurodegenerative changes and neurovascular damages. J Clin Med. 2020; 9(6), doi: 10.3390/jcm9061713, indexed in Pubmed: 32503113.
38. Grizzanti J, Corrigan R, Servizi S, et al. Neuroprotective effects of amylin analogues on Alzheimer's disease pathogenesis and cognition. J Alzheimers Dis. 2018; 66(1): 11–23, doi: 10.3233/JAD-180433, indexed in Pubmed: 30282360.
39. Martinez-Valbuena I, Valenti-Azcarate R, Amat-Villegas I, et al. Amylin as a potential link between type 2 diabetes and alzheimer disease. Ann Neurol. 2019; 86(4): 539–551, doi: 10.1002/ana.25570, indexed in Pubmed: 31376172.
40. Miklossy J, Qing H, Radenovic A, et al. Beta amyloid and hyperphosphorylated tau deposits in the pancreas in type 2 diabetes. Neurobiol Aging. 2010; 31(9): 1503–1515, doi: 10.1016/j.neurobiolaging.2008.08.019, indexed in Pubmed: 18950899.
41. Despa F, Goldstein LB, Biessels GJ. Amylin as a potential link between type 2 diabetes and Alzheimer disease. Ann Neurol. 2020; 87(3): 486, doi: 10.1002/ana.25668, indexed in Pubmed: 31916276.
42. Kim N, Yoo JC, Han JY, et al. Human nuclear clusterin mediates apoptosis by interacting with Bcl-XL through C-terminal coiled coil domain. J Cell Physiol. 2012; 227(3): 1157–1167, doi: 10.1002/jcp.22836, indexed in Pubmed: 21567405.
43. Ha J, Moon MK, Kim H, et al. Plasma clusterin as a potential link between diabetes and Alzheimer disease. J Clin Endocrinol Metab. 2020; 105(9), doi: 10.1210/clinem/dgaa378, indexed in Pubmed: 32561922.
44. Wang W, Zhao F, Ma X, et al. Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances. Mol Neurodegener. 2020; 15(1): 30, doi: 10.1186/s13024-020-00376-6, indexed in Pubmed: 32471464.
45. Wijesekara N, Gonçalves RA, De Felice FG, et al. Impaired peripheral glucose homeostasis and Alzheimer's disease. Neuropharmacology. 2018; 136(Pt B): 172–181, doi: 10.1016/j.neuropharm.2017.11.027, indexed in Pubmed: 29169962.
46. Rigotto G, Basso E. Mitochondrial dysfunctions: a thread sewing together Alzheimer's disease, diabetes, and obesity. Oxid Med Cell Longev. 2019; 2019: 7210892, doi: 10.1155/2019/7210892, indexed in Pubmed: 31316720.
47. Wang CH, Wei YH. Role of mitochondrial dysfunction and dysregulation of Ca homeostasis in the pathophysiology of insulin resistance and type 2 diabetes. J Biomed Sci. 2017; 24(1): 70, doi: 10.1186/s12929-017-0375-3, indexed in Pubmed: 28882140.
48. Karmi A, Iozzo P, Viljanen A, et al. Increased brain fatty acid uptake in metabolic syndrome. Diabetes. 2010; 59(9): 2171–2177, doi: 10.2337/db09-0138, indexed in Pubmed: 20566663.
49. Gupta S, Knight AG, Gupta S, et al. Saturated long-chain fatty acids activate inflammatory signaling in astrocytes. J Neurochem. 2012; 120(6): 1060–1071, doi: 10.1111/j.1471-4159.2012.07660.x, indexed in Pubmed: 22248073.
50. Pugazhenthi S, Qin L, Reddy PH. Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. Biochim Biophys Acta Mol Basis Dis. 2017; 1863(5): 1037–1045, doi: 10.1016/j.bbadis.2016.04.017, indexed in Pubmed: 27156888.
51. Zhang R, Miller RG, Madison C, et al. Systemic immune system alterations in early stages of Alzheimer's disease. J Neuroimmunol. 2013; 256(1-2): 38–42, doi: 10.1016/j.jneuroim.2013.01.002, indexed in Pubmed: 23380586.
52. Ferreira ST, Clarke JR, Bomfim TR, et al. Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease. Alzheimers Dement. 2014; 10(1 Suppl): S76–S83, doi: 10.1016/j.jalz.2013.12.010, indexed in Pubmed: 24529528.
53. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimers Res Ther. 2014; 6(4): 37, doi: 10.1186/alzrt269, indexed in Pubmed: 25024750.
54. Egan MF, Kost J, Voss T, et al. Randomized trial of verubecestat for prodromal Alzheimer's disease. N Engl J Med. 2019; 380(15): 1408–1420, doi: 10.1056/NEJMoa1812840, indexed in Pubmed: 30970186.
55. Egan MF, Kost J, Tariot PN, et al. Randomized trial of verubecestat for mild-to-moderate Alzheimer's disease. N Engl J Med. 2018; 378(18): 1691–1703, doi: 10.1056/NEJMoa1706441, indexed in Pubmed: 29719179.
56. Egan MF, Mukai Y, Voss T, et al. Further analyses of the safety of verubecestat in the phase 3 EPOCH trial of mild-to-moderate Alzheimer's disease. Alzheimers Res Ther. 2019; 11(1): 68, doi: 10.1186/s13195-019-0520-1, indexed in Pubmed: 31387606.
57. Linnemann C, Lang UE. Pathways connecting late-life depression and dementia. Front Pharmacol. 2020; 11: 279, doi: 10.3389/fphar.2020.00279, indexed in Pubmed: 32231570.

58. Reger MA, Watson GS, Green PS, et al. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurology. 2008; 70(6): 440–448, doi: 10.1212/01.WNL.0000265401.62434.36, indexed in Pubmed: 17942819.
59. Craft S, Claxton A, Baker LD, et al. Long-acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease dementia. J Alzheimers Dis. 2015; 44(3): 897–906, doi: 10.3233/JAD-141791, indexed in Pubmed: 25374101.
60. Craft S, Claxton A, Baker LD, et al. Effects of regular and long-acting insulin on cognition and alzheimer's disease biomarkers: a pilot clinical trial. J Alzheimers Dis. 2017; 57(4): 1325–1334, doi: 10.3233/JAD-161256, indexed in Pubmed: 28372335.
61. Craft S, Raman R, Chow TW, et al. Safety, efficacy, and feasibility of intranasal insulin for the treatment of mild cognitive impairment and alzheimer disease dementia: a randomized clinical trial. JAMA Neurol. 2020; 77(9): 1099–1109, doi: 10.1001/jamaneurol.2020.1840, indexed in Pubmed: 32568367.
62. Chapman CD, Schiöth HB, Grillo CA, et al. Intranasal insulin in Alzheimer's disease: Food for thought. Neuropharmacology. 2018; 136(Pt B): 196–201, doi: 10.1016/j.neuropharm.2017.11.037, indexed in Pubmed: 29180222.
63. Schmid V, Kullmann S, Gfrörer W, et al. Safety of intranasal human insulin: A review. Diabetes Obes Metab. 2018; 20(7): 1563–1577, doi: 10.1111/dom.13279, indexed in Pubmed: 29508509.
64. Tumminia A, Vinciguerra F, Parisi M, et al. Type 2 diabetes mellitus and Alzheimer's disease: role of insulin signalling and therapeutic implications. Int J Mol Sci. 2018; 19(11), doi: 10.3390/ijms19113306, indexed in Pubmed: 30355995.
65. Claxton A, Baker LD, Wilkinson CW, et al. Sex and ApoE genotype differences in treatment response to two doses of intranasal insulin in adults with mild cognitive impairment or Alzheimer's disease. J Alzheimers Dis. 2013; 35(4): 789–797, doi: 10.3233/JAD-122308, indexed in Pubmed: 23507773.
66. Zhao Na, Liu CC, Van Ingelgom AJ, et al. Apolipoprotein E4 Impairs Neuronal Insulin Signaling by Trapping Insulin Receptor in the Endosomes. Neuron. 2017; 96(1): 115–129.e5, doi: 10.1016/j.neuron.2017.09.003, indexed in Pubmed: 28957663.
67. Koenig AM, Mechanic-Hamilton D, Xie SX, et al. Effects of the insulin sensitizer metformin in Alzheimer disease: pilot data from a randomized placebo-controlled crossover study. Alzheimer Dis Assoc Disord. 2017; 31(2): 107–113, doi: 10.1097/WAD.0000000000000202, indexed in Pubmed: 28538088.
68. Chiang MC, Cheng YC, Chen SJ, et al. Metformin activation of AMPK-dependent pathways is neuroprotective in human neural stem cells against Amyloid-beta-induced mitochondrial dysfunction. Exp Cell Res. 2016; 347(2): 322–331, doi: 10.1016/j.yexcr.2016.08.013, indexed in Pubmed: 27554603.
69. Luchsinger JA, Perez T, Chang H, et al. Metformin in amnestic mild cognitive impairment: results of a pilot randomized placebo controlled clinical trial. J Alzheimers Dis. 2016; 51(2): 501–514, doi: 10.3233/JAD-150493, indexed in Pubmed: 26890736.
70. Herath PM, Cherbuin N, Eramudugolla R, et al. The effect of diabetes medication on cognitive function: evidence from the PATH through life study. Biomed Res Int. 2016; 2016: 7208429, doi: 10.1155/2016/7208429, indexed in Pubmed: 27195294.
71. Moore EM, Mander AG, Ames D, et al. AIBL Investigators. Increased risk of cognitive impairment in patients with diabetes is associated with metformin. Diabetes Care. 2013; 36(10): 2981–2987, doi: 10.2337/dc13-0229, indexed in Pubmed: 24009301.
72. Imfeld P, Bodmer M, Jick SS, et al. Metformin, other antidiabetic drugs, and risk of Alzheimer's disease: a population-based case-control study. J Am Geriatr Soc. 2012; 60(5): 916–921, doi: 10.1111/j.1532-5415.2012.03916.x, indexed in Pubmed: 22458300.
73. Hamilton A, Hölscher C. Receptors for the incretin glucagon-like peptide-1 are expressed on neurons in the central nervous system. Neuroreport. 2009; 20(13): 1161–1166, doi: 10.1097/WNR.0b013e32832fbf14, indexed in Pubmed: 19617854.
74. During MJ, Cao L, Zuzga DS, et al. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nat Med. 2003; 9(9): 1173–1179, doi: 10.1038/nm919, indexed in Pubmed: 12925848.
75. Gejl M, Gjedde A, Egefjord L, et al. In alzheimer's disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: randomized, placebo-controlled, double-blind clinical trial. Front Aging Neurosci. 2016; 8: 108, doi: 10.3389/fnagi.2016.00108, indexed in Pubmed: 27252647.
76. Batista AF, Forny-Germano L, Clarke JR, et al. The diabetes drug liraglutide reverses cognitive impairment in mice and attenuates insulin receptor and synaptic pathology in a non-human primate model of Alzheimer's disease. J Pathol. 2018; 245(1): 85–100, doi: 10.1002/path.5056, indexed in Pubmed: 29435980.
77. Zhang Y, Xie JZ, Xu XY, et al. Liraglutide ameliorates hyperhomocysteinemia-induced Alzheimer-like pathology and memory deficits in rats via multi-molecular targeting. Neurosci Bull. 2019; 35(4): 724–734, doi: 10.1007/s12264-018-00336-7, indexed in Pubmed: 30632006.
78. McClean PL, Parthsarathy V, Faivre E, et al. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. J Neurosci. 2011; 31(17): 6587–6594, doi: 10.1523/JNEUROSCI.0529-11.2011, indexed in Pubmed: 21525299.
79. McClean PL, Parthsarathy V, Faivre E, et al. The novel GLP-1 analogue liraglutide has neuroprotective properties in a mouse model of Alzheimer's disease. Regulatory Peptides. 2010; 164(1): 40, doi: 10.1016/j.regpep.2010.07.102.
80. Hansen HH, Fabricius K, Barkholt P, et al. The GLP-1 receptor agonist liraglutide improves memory function and increases hippocampal CA1 neuronal numbers in a senescence-accelerated mouse model of Alzheimer's disease. J Alzheimers Dis. 2015; 46(4): 877–888, doi: 10.3233/JAD-143090, indexed in Pubmed: 25869785.
81. Watson KT, Wroolie TE, Tong G, et al. Neural correlates of liraglutide effects in persons at risk for Alzheimer's disease. Behav Brain Res. 2019; 356: 271–278, doi: 10.1016/j.bbr.2018.08.006, indexed in Pubmed: 30099030.
82. Femminella GD, Frangou E, Love SB, et al. Evaluating the effects of the novel GLP-1 analogue liraglutide in Alzheimer's disease: study protocol for a randomised controlled trial (ELAD study). Trials. 2019; 20(1): 191, doi: 10.1186/s13063-019-3259-x, indexed in Pubmed: 30944040.
83. Kosaraju J, Holsinger RM, Guo L, et al. Linagliptin, a dipeptidyl peptidase-4 inhibitor, mitigates cognitive deficits and pathology in the 3xTg-AD mouse model of Alzheimer's disease. Mol Neurobiol. 2017; 54(8): 6074–6084, doi: 10.1007/s12035-016-0125-7, indexed in Pubmed: 27699599.
84. Kornelius E, Lin CL, Chang HH, et al. DPP-4 inhibitor linagliptin attenuates Aβ-induced cytotoxicity through activation of AMPK in neuronal cells. CNS Neurosci Ther. 2015; 21(7): 549–557, doi: 10.1111/cns.12404, indexed in Pubmed: 26010513.
85. Isik AT, Soysal P, Yay A, et al. The effects of sitagliptin, a DPP-4 inhibitor, on cognitive functions in elderly diabetic patients with or without Alzheimer's disease. Diabetes Res Clin Pract. 2017; 123: 192–198, doi: 10.1016/j.diabres.2016.12.010, indexed in Pubmed: 28056430.

86. Landreth G, Jiang Q, Mandrekar S, et al. PPARgamma agonists as therapeutics for the treatment of Alzheimer's disease. Neurotherapeutics. 2008; 5(3): 481–489, doi: 10.1016/j.nurt.2008.05.003, indexed in Pubmed: 18625459.
87. Muñoz-Jiménez M, Zaarkti A, García-Arnés JA, et al. Antidiabetic drugs in Alzheimer's disease and mild cognitive impairment: A systematic review. Dement Geriatr Cogn Disord. 2020; 49(5): 423–434, doi: 10.1159/000510677, indexed in Pubmed: 33080602.
88. Quan Q, Qian Y, Li Xi, et al. Pioglitazone reduces β amyloid levels inhibition of PPARγ phosphorylation in a neuronal model of Alzheimer's disease. Front Aging Neurosci. 2019; 11: 178, doi: 10.3389/fnagi.2019.00178, indexed in Pubmed: 31379559.
89. Hanyu H, Sato T, Sakurai H, et al. The role of tumor necrosis factor-alpha in cognitive improvement after peroxisome proliferator-activator receptor gamma agonist pioglitazone treatment in Alzheimer's disease. J Am Geriatr Soc. 2010; 58(5): 1000–1001, doi: 10.1111/j.1532-5415.2010.02841.x, indexed in Pubmed: 20722838.
90. Fernandez-Martos CM, Atkinson RAK, Chuah MI, et al. Combination treatment with leptin and pioglitazone in a mouse model of Alzheimer's disease. Alzheimers Dement (N Y). 2017; 3(1): 92–106, doi: 10.1016/j.trci.2016.11.002, indexed in Pubmed: 29067321.
91. Knodt AR, Burke JR, Welsh-Bohmer KA, et al. Effects of pioglitazone on mnemonic hippocampal function: A blood oxygen level-dependent functional magnetic resonance imaging study in elderly adults. Alzheimers Dement (N Y). 2019; 5: 254–263, doi: 10.1016/j.trci.2019.05.004, indexed in Pubmed: 31304231.
92. Hanyu H, Sato T, Kiuchi A, et al. Pioglitazone improved cognition in a pilot study on patients with Alzheimer's disease and mild cognitive impairment with diabetes mellitus. J Am Geriatr Soc. 2009; 57(1): 177–179, doi: 10.1111/j.1532-5415.2009.02067.x, indexed in Pubmed: 19170800.
93. Sato T, Hanyu H, Hirao K, et al. Efficacy of PPAR-γ agonist pioglitazone in mild Alzheimer disease. Neurobiol Aging. 2011; 32(9): 1626–1633, doi: 10.1016/j.neurobiolaging.2009.10.009, indexed in Pubmed: 19923038.
94. Li H, Wu J, Zhu L, et al. Insulin degrading enzyme contributes to the pathology in a mixed model of Type 2 diabetes and Alzheimer's disease: possible mechanisms of IDE in T2D and AD. Biosci Rep. 2018; 38(1), doi: 10.1042/BSR20170862, indexed in Pubmed: 29222348.
95. Xu S, Guan Q, Wang C, et al. Rosiglitazone prevents the memory deficits induced by amyloid-beta oligomers via inhibition of inflammatory responses. Neurosci Lett. 2014; 578: 7–11, doi: 10.1016/j.neulet.2014.06.010, indexed in Pubmed: 24933538.
96. Risner ME, Saunders AM, Altman JFB, et al. Rosiglitazone in Alzheimer's Disease Study Group. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. Pharmacogenomics J. 2006; 6(4): 246–254, doi: 10.1038/sj.tpj.6500369, indexed in Pubmed: 16446752.
97. Gold M, Alderton C, Zvartau-Hind M, et al. Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. Dement Geriatr Cogn Disord. 2010; 30(2): 131–146, doi: 10.1159/000318845, indexed in Pubmed: 20733306.
98. Grizzanti J, Corrigan R, Casadesus G. Neuroprotective effects of amylin analogues on Alzheimer's disease pathogenesis and cognition. J Alzheimers Dis. 2018; 66(1): 11–23, doi: 10.3233/JAD-180433, indexed in Pubmed: 30282360.
99. Zhu H, Wang X, Wallack M, et al. Intraperitoneal injection of the pancreatic peptide amylin potently reduces behavioral impairment and brain amyloid pathology in murine models of Alzheimer's disease. Mol Psychiatry. 2015; 20(2): 252–262, doi: 10.1038/mp.2014.17, indexed in Pubmed: 24614496.
100. Soudy R, Patel A, Fu W, et al. Cyclic AC253, a novel amylin receptor antagonist, improves cognitive deficits in a mouse model of Alzheimer's disease. Alzheimers Dement (N Y). 2017; 3(1): 44–56, doi: 10.1016/j.trci.2016.11.005, indexed in Pubmed: 29067318.

REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 5, pages: 429–439
DOI: 10.5603/PJNNS.a2021.0063

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

Vigabatrin — new data on indications and safety in paediatric epilepsy

Weronika Golec[1], Elżbieta Sołowiej[1], Jolanta Strzelecka[1], Elżbieta Jurkiewicz[2], Sergiusz Jóźwiak[1]

[1]Department of Child Neurology, Medical University of Warsaw, Poland
[2]Department of Diagnostic Imaging, The Children's Memorial Health Institute, Warsaw, Poland

ABSTRACT

Introduction: Vigabatrin (VGB), a second-generation antiepileptic drug, is effective for the treatment of infantile spasms and focal seizures, primarily in tuberous sclerosis complex (TSC) patients. However, reports of adverse events of VGB, including VGB-associated visual field loss and brain abnormalities in neuroimaging, have raised concerns about the broader use of VGB and thus significantly limited its application.

Aim of the study: The goal of this review was to summarise the recent therapeutic guidelines, the use of VGB in focal seizures and new VGB applications as a disease-modifying treatment in TSC patients. Moreover, we discuss the current opinions on potential VGB-associated toxicity and the safety of VGB.

Key words: vigabatrin, infantile spasms, focal seizures, tuberous sclerosis complex, preventive treatment, VGB-associated visual field loss, VGB-associated brain abnormalities

(*Neurol Neurochir Pol 2021; 55 (5): 429–439*)

Introduction

Vigabatrin (VGB) (Sabril®) is a second-generation antiepileptic drug (AED) of which the therapeutic effect results from an increase in the level of gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the central nervous system (CNS), through the selective, irreversible inactivation of GABA transaminase (GABA-T) [1]. A study by Yang et al. suggests that VGB reduces glutamate/glutamine cycling between astrocytes and neurons. These findings imply a glutamatergic effect, which could also be related to VGB's anticonvulsant effect [2]. VGB is an antiseizure medication with proven efficacy in the treatment of infantile spasms (IS) and focal onset seizures, mainly in tuberous sclerosis complex (TSC) patients, but its use has been limited due to concerns about visual toxicity [3–5].

Despite its long history and some safety issues regarding the possibility of visual-field defects (VFDs), VGB retains a significant status in paediatric epileptology. This study reports recent recommendations and new indications for the use of VGB in focal seizures, trials of VGB application as a disease-modifying treatment in TSC, and current opinions on vigabatrin-dependent VFDs in epileptic patients.

Registered indications and clinical guidelines

VGB was first registered in the United Kingdom (UK) in 1989 for the treatment of IS and as a second-line treatment for uncontrolled focal seizures [1]. A growing number of reports of visual changes emerging for both paediatric and adult patients caused the European Medicines Agency (EMA) to update guidelines on VGB usage in 1999. The EMA limited VGB use to adjunctive therapy for refractory focal epilepsy in both adults and children and as monotherapy for IS [6]. Current therapeutic guidelines for VGB in Europe include: IS, an adjunctive therapy of refractory focal onset epilepsy, and in TSC patients as therapy in all types of seizures [7, 8].

Due to concerns over the safety of VGB treatment, the drug was not approved in the United States (US) until 2009. Nowadays, there are differences in the indications for VGB therapy guidelines in the US, including IS monotherapy in patients aged from 1 month to 2 years, and as adjunctive therapy in patients with refractory focal onset epilepsy ≥ 10 years whose seizures have inadequately responded to several alternative treatments. For patients with TSC, indications include only IS monotherapy [9].

Address for correspondence: Sergiusz Jóźwiak, Department of Child Neurology, Medical University of Warsaw, Żwirki i Wigury 63A, 02-091 Warsaw, Poland; e-mail: sergiusz.jozwiak@gmail.com

Received: 17.05.2021 Accepted: 2.06.2021 Early publication date: 20.09.2021

VGB is particularly effective in epileptic seizures in patients in whom the epilepsy is caused by a genetic disorder, as in TSC cases [10]. In addition, recent data suggests that VGB may have not only antiseizure, but also antiepileptogenic or disease-modifying, properties in TSC [11]. This effect may be caused by the possible additional mechanism of action of VGB consisting in partial inhibition of the mTOR (mammalian target of rapamycin) pathway, which is dysregulated in the course of TSC [12].

Therapeutic effectiveness of VGB

VGB has proven to be highly effective in the treatment of IS especially in patients with TSC [13, 14]. Data considering the effectiveness of VGB in focal seizures among paediatric patients is limited [15–17]. It seems certain that VGB therapy extends beyond IS in the paediatric population. Jackson et al. carried out a retrospective evaluation of the efficacy of VGB beyond the current U.S. Food and Drug Administration (FDA) approval recommendations [18]. Their study included 103 patients with different aetiologies and types of seizures (epileptic spasms, focal seizures, tonic seizures, tonic-clonic seizures), including a large percentage of treatment-resistant seizures under 11 years of age treated with VGB monotherapy and or adjuvant therapy. In this study, VGB has been shown to provide good seizure control: in short-term seizure outcome (median of 1.6 months), the seizure frequency decreased by 83.3% from baseline, and 72.7% of patients achieved ≥ 50% seizure reduction. The improved seizure outcome was maintained also for long-term follow-up (median of 12.1 months), with 96.7% seizure frequency reduction and 72.7% of patients experiencing a reduction in seizure frequency of ≥ 50%. In addition, a low relapse rate (6.5%) following VGB therapy was demonstrated [18].

VGB treatment efficacy in IS

Infantile spasm is severe epileptic encephalopathy appearing with a frequency of 0.01 to 0.58/1,000 live births which mainly affects children under the age of 2 years, peaking between 3 and 7 months [19, 20]. Historically, the classic West syndrome triad has included the characteristic clinical seizures — epileptic spasms (ES) — sudden contraction of the trunk and extremities lasting less than one second, most frequently occurring in series, an abnormal interictal electroencephalographic (EEG) pattern (hypsarrhythmia), and developmental abnormalities. However, developmental delay and hypsarrhythmia do not always occur, especially at the beginning, which has led to the updating and broadening of the IS definition by the International League Against Epilepsy (ILAE) and the West Delphi Consensus Statement, according to which IS is recognised when characteristic ES are present, with or without the presence of hypsarrhythmia in EEG [21, 22].

VGB is recommended as the first line treatment for IS, together with adrenocorticotropic hormone (ACTH) or corticosteroids. The effectiveness of the drug has been confirmed in several randomised controlled trials [13, 23]. Favourable long-term neurodevelopmental outcomes are associated with early ES cessation. It has been shown that the duration of hypsarrhythmia is a sensitive prognostic parameter in IS, and the risk of mental retardation increases after three weeks of hypsarrhythmia persistence in the EEG [24, 25].

Efficient diagnostics and quick treatment initiation have the greatest impact on the long-term outcomes of IS patients. In the United Kingdom Infantile Spasms Study (UKISS), O'Callaghan et al. presented the risk of delayed IS treatment [26]. Their study showed an inverse relationship between the length of treatment delay and the results of the Vineland Adaptive Behaviour Scales (VABS) in patients aged 4 years. A 3.9 point reduction in VABS score was associated with each successive delay interval as follows: 8–14 days; 2–4 weeks; 4–8 weeks; > 8 weeks [26]. Widjaja et al. conducted a meta-analysis that included studies confirming the relationship between IS treatment delay and long-term outcomes. The authors proved that a lead time to treatment (LTTT) of < 4 weeks was associated with a 51.9% improvement in neurodevelopmental outcome compared to a > 4 weeks LTTT [25].

Several randomised, multicentre trials have been conducted to compare different IS therapeutic options. According to ILAE, short-term VGB response rates range from 35% to 54%, much less than with hormonal treatment (76–87%) [22]. In the UKISS study, Lux et al. showed that infants assigned to hormonal therapy had a greater chance of not having ES on days 13 and 14 of treatment compared to those treated with VGB at the minimum dose of 100 mg/kg/day (73% compared to 54%) [27]. The same authors assessed patients aged 12–14 months, showing that long-term ES control in both treatment options was similar (hormonal vs VGB treatment, 75% vs. 76%) [28]. Moreover, the VABS neurological development score showed that in patients with an unknown IS aetiology, hormonal therapy promotes a better initial ES control which can lead to improved development [28].

The study by Djuric et al. also reported that long-term developmental outcomes in patients treated with VGB were similar to those in patients treated with ACTH or corticosteroids [29]. However, the continuation of the UKISS study with paediatric patients at mean age 4 years with a telephone epilepsy questionnaire and a VABS assessment showed that in cases of seizures without identified aetiology, patients treated with prednisolone or ACTH had better development than those treated with VGB [30]. The study by Knupp et al. proved that ACTH (all doses combined) was associated with a higher rate of early (at two weeks) response than VGB (55% of infants receiving ACTH as initial treatment versus 36% for VGB). The sustained response rate in patients treated with ACTH, after relapse rates were taken into account, was still

significantly higher compared to those treated with VGB at three months of therapy [31].

The International Collaborative Infantile Spasms Study (ICISS) was the first prospective work to evaluate the efficacy of combination therapy. This study determined that combination therapy (ACTH or high-dose steroids with VGB) was more effective and faster in achieving clinical and electroclinical responses in children with IS compared to treatment with hormonal therapy alone. Combination therapy has been proven to be much more effective in stopping ES (between 14 and 42 days of treatment inclusive) than hormonal therapy alone (71.9% vs. 56.6%). Furthermore, this study also supports the fact that earlier ES termination correlates with better long-term epilepsy outcomes [32]. The patients from the ICISS were next evaluated after 18 months of treatment: combination therapy showed no improvement in developmental or treatment outcomes for epilepsy. [33]. Retrospective analysis by Hahn et al. also showed a similar result: patients receiving combination therapy with VGB and prednisolone showed a significantly better response to initial treatment than with VGB monotherapy (55.3% vs. 39.1%) [34].

VGB treatment efficacy in focal non-TSC seizures

It is assumed that the administration of VGB in paediatric patients expands beyond IS. Although the available data is limited, several studies have demonstrated good efficacy of VGB in focal epilepsy in nonTSC patients [16, 17, 35]. A recent (2020) meta-analysis by Bresnahan et al. included 11 randomised, double-blind, placebo-controlled, fully published trials of VGB involving 756 people, which investigated VGB as an add-on treatment of drug-resistant focal epilepsy. This study included nonTSC patients aged 10 to 64 years. It has been shown that patients given VGB may be two to three times more likely to experience a 50% or greater reduction in seizure frequency compared to those treated with a placebo, and it is also suggested that patients given VGB may be up to three times more likely to stop treatment than people given a placebo. However, it has been evaluated that the results should not be related to children aged under 10, and also that all studies had a significant risk of bias [36]. VGB treatment effectiveness in focal epilepsy in nonTSC and TSC paediatric patients is set out in Table 1.

VGB in patients with TSC

TSC is a genetic neurocutaneous disease caused by mutations of *TSC1* or *TSC2* suppressor genes, coding for the proteins hamartin and tuberin. Both of these proteins function as the mTOR inhibitory complex, which is involved in a number of cellular processes necessary for growth, metabolism and regulation of cell division. Mutations in any of the genes lead to upregulation of the mTOR pathway, resulting in uncontrolled cell growth and the formation of typical TSC changes [37, 38]. Epilepsy is the most common neurological symptom of TSC, occurring in 70–90% of patients, with a peak occurrence in the first year of life [39, 40]. Patients with TSC can present almost any type of seizure, although focal seizures and ES are the most common. Moreover, subtle focal seizures may precede or coexist with ES [41, 42]. VGB is recognised as the most effective drug for all type of seizures in TSC patients. Moreover, it is more effective in treating IS than ACTH, eliminating ES in about 95% of TSC patients [40]. VGB therapy is recommended in TSC both in IS and focal seizures because treatment can prevent the evolution of focal seizures into IS during the first year of life. According to the study by Overwater et al., focal seizures develop before infantile spasms in 58% of paediatric patients [40]. The recommendations of the International Tuberous Sclerosis Complex Consensus (2012 and 2018), in Europe, but not in the US, indicate VGB as a first-line drug for all seizures in paediatric patients with TSC under the age of 1 year. Furthermore, VGB therapy should also be considered for a variety of seizure types in older children and adults [8, 43]. Accessible, mainly retrospective, studies have indicated the effectiveness of VGB treatment in TSC children with focal epilepsy [15–17, 35, 44]. A study conducted in 2015 showed that VGB is more effective when introduced as an initial treatment for TSC-related seizures [40]. A delay to VGB treatment is associated with unfavourable long-term outcomes, while early and aggressive treatment correlates with a lower percentage of refractory seizures [45]. Early seizure control plays a key role in reducing cognitive and behavioural function, and minimising the risk of autism and intellectual disability [46, 47]. Permanent remission of seizures seems to be a necessary condition for better development, including cognitive function, in patients with TSC [48]. In view of the above, Hussain et al. attempted to plan an effective strategy for the prevention of IS relapses. Their prospective study conducted on a group of patients with IS and TSC showed that each increase in the VGB dose by 50 mg/kg/day was associated with a 61% reduction in the risk of IS recurrence. In addition, the authors found that the risk of IS recurrence is exceptionally low with a VGB dose of at least 150 mg/kg/day. The results of this study suggest that treatment with high doses of VGB may reduce the risk of IS recurrence in TSC patients [49].

VGB is an example of a drug with individualised efficacy for seizures in TSC. The high efficacy of the drug in TSC is not yet clarified. In recent years, a vast amount of research has been conducted to explain the mechanism of the above correlation. Some of the investigators have indicated that the mTOR complex 1 (mTORC1) is involved in epileptogenesis in TSC and VGB can inhibit mTOR pathway [12, 50]. Deregulation of the mTOR pathway could have a potential antiepileptogenic effect or disease-modifying properties of VGB in TSC [11].

The recent reports on the possibility of preventing epilepsy in patients with TSC seem to be groundbreaking. Increased awareness of TSC symptoms, together with significant progress in early diagnosis, allows for implementation of regular

Table 1. VGB treatment effectiveness in focal epilepsy in nonTSC and TSC paediatric patients

Clinical study	Number of patients	Age	Seizure aetiology (TSC or nonTSC)	Only VGB or other treatment	Treatment duration range	Effectiveness of VGB treatment	References
Retrospective study	121 — 60 focal-onset alone — 41 focal-onset in association with IS — 4 focal-onset in association with other — 12 IS alone — 4 other seizure types alone	1.8 years, range 0.1–29.2 years	TSC 100 non-TSC 21	Lack of detailed data, some patients with drug-resistant epilepsy	0.7–101.0 months — evaluated short--term(≤ 6 months) and long-term (≥ 5 years) efficacy	— short-term: improvement 3.7 ± 0.6 S.D. to 8 ± 1.6 S.D. — long-term: improvement 3.7 ± 0.7 S.D. to 2.4 ± 1.6 S.D.	Greiner et al., 2012 [16]
Retrospective study	13	11 months, range 0–48 months	TSC	first-line VGB monotherapy second-line VGB add-on therapy	12 months	— 3/9 (33.3%) complete control — 3/4 (75%) complete control	Yum et al., 2013 [44]
Retrospective study	49	5.4 ± 7.7 years	TSC	two or more AEDs	49.5 ± 45.9 months (0–173 months), with a median duration of exposure of 40 months	— 13 (24.5%) complete control (8/13) or experienced a > 90% decrease in seizure frequency	Friedman et al., 2013 [15]
Retrospective study	59 — 16 focal-seizures alone — 43 uncontrolled focal-seizures in association with IS	0–12 months	non-TSC and TSC	add-on therapy	≥ 6 months	— responders 20/59 (34%): — 10/59 (17%) complete control — 10/59 (17%) reduction in seizure frequency > 50% — TSC patients higher responded (40%) than other aetiologies (21%)	Camposano et al., 2008 [35]
Retrospective study	175	1 week –19 years	non-TSC and TSC	66% of patients two or more AEDs	6 months to 6.7 years (mean 29 months)	— 54/178 (30%) complete control — 125/178 (70%) reduction in seizure frequency > 50% — 27/32 (85%) TSC patients responded	Nabbout et al., 1997 [17]

video-EEG surveillance and the introduction of VGB treatment before clinical seizures [51, 52]. In the study by Jóźwiak et al., the initiation of VGB treatment (100–150 mg/kg/day) at the presence of subclinical epileptiform EEG before the onset of clinical seizures was associated at the 24th month of life with a lower percentage of epilepsy (43% vs. 71%), a lower incidence of drug-resistant epilepsy, and a lower rate of intellectual disability (48% vs. 14%) compared to the group of patients treated conventionally after the onset of clinical seizures [45]. A longer follow-up of the same group demonstrated that the effects of preventive antiepileptic treatment introduced in infancy persisted until school age. Preventive treatment reduced the risk of clinical seizures (50% vs. 96% in the conventionally treated group) and intellectual disability (21% vs. 72%) in school-aged children with TSC [53].

Currently, two major prospective, randomised trials are evaluating the preventive use of VGB in TSC: the EPISTOP project (a long-term, prospective study evaluating clinical and molecular biomarkers of epileptogenesis in a genetic model of epilepsy — tuberous sclerosis complex, NCT02098759) and the PREVeNT trial (Preventing Epilepsy Using Vigabatrin in Infants With Tuberous Sclerosis Complex, NCT02849457) [54, 55]. The PREVeNT study results are not yet available. The EPISTOP project focused not only on the prevention of epilepsy, but also on the identification of clinical and molecular biomarkers of epileptogenesis in patients with TSC. The project ended in 2018 and the clinical part of its results were published in 2021 [56]. They demonstrated that preventive treatment of VGB was associated with a more than two-fold reduction in the risk of drug-resistant epilepsy compared to conventional treatment (28% vs. 64%). The time to the first clinical seizure was longer (approximately 4x) with preventive treatment. Moreover, the incidence of neurodevelopmental delay at age 2 years in the group with preventive treatment compared to conventional treatment was substantially lower (33% vs. 50%). Most importantly, none of the EPISTOP patients had a severe learning disability (cognitive-developmental quotient < 50) at age 2 years. None of the children who received preventive treatment developed IS throughout the course of the study, while 40% of patients on conventional treatment have. Furthermore, no adverse events related to preventive treatment were noted [56].

In conclusion, the results of the EPISTOP study showed that prophylactic antiepileptic treatment significantly reduces the risk of epilepsy, as well as its severity and the risk of drug resistance. Apart from the clinical part, for the first time, the EPISTOP project has undertaken comprehensive research with the use of currently available molecular methods aimed at detecting the mechanisms of epilepsy and its impact on the development of children. Work on this part of the project is still ongoing.

Adverse events of VGB

VGB is a well-tolerated drug; the most commonly reported adverse reactions are somnolence, sedation, irritability, and restlessness, but these are usually transient and dose-related [57, 58]. Despite the recognised efficacy of the drug, the use of VGB has been limited by reports of rare, but significant and characteristic of VGB, side effects. The main one is retinopathy resulting in permanent defects of the peripheral visual field defects (pVFDs), termed Vigabatrin-associated visual field loss (VAVFL), and the other is toxicity presented in neuroimaging.

Vigabatrin-associated visual field loss

Retrospective studies describing visual field constrictions in both adult and paediatric patients are available, but the results are still inconclusive [59–62]. The meta-analysis by Maguire et al. demonstrated that the prevalence of VAVFL among patients treated for focal epilepsy was higher in adults (52%) than in older children (34%) [63]. In contrast, two other studies have reported visual fields loss in school-age children who had received VGB in infancy. The results of these studies showed a lower prevalence of pVFDs at school age, with mild pVFDs measured by Goldmann kinetic perimetry being observed in only 6–7% of children [64, 65]. In a recently published cohort study, 21% of children treated with VGB for IS had a significant amplitude reduction in 30 Hz flicker electroretinogram (ERG) [66]. However, whether changes in ERG are a relevant marker of pVFD is debatable because ERG results change with development, and the reliability of the results in infants remains questionable.

In a study by Moskowitz et al., paediatric patients were assessed by both ERG and perimetry. This work demonstrated that there was no relationship between the amplitude of the 30 Hz flicker response and visual field defects on perimetry [67]. The onset of VAVFL is presumed to occur in the periphery (outside of the central 30-degree field of view), to progress centrally, and to persist after VGB has been discontinued [68, 69]. The risk of vision loss is considered to be low with early exposure to VGB [70]. This risk may increase with age, higher cumulative doses of VGB, and with duration of treatment [71, 72]. However, a systematic review by Maguire et al. demonstrated the association between VGB therapy and ocular toxicity to be minor and not sufficient to alter treatment decisions [63].

Due to the potentially serious side effect of permanent pVFDs, in accordance with the requirements of the FDA, VGB is available under a limited distribution programme known as the Risk Evaluation and Mitigation Strategy (REMS) which includes a mandatory registry and monitoring of patients treated with VGB (sabril.net/hcp/prescribing_sabril/) [5, 9]. The REMS recommendations require an eye assessment at the start of treatment, every three months during treatment, and for 3-6 months after treatment. The recommended screening test is perimetry. For patients incapable of performing perimetry due to chronological age, developmental age, or cognitive difficulties, the recommended screening strategy consists of confrontational testing with ERG and optical coherence tomography (OCT) [73].

Based on the REMS registry of patients treated with VGB between 2009 and 2016, two studies were published describing demographics, disease characteristics and vision changes in 9,423 paediatric and adult patients [74, 75]. These studies demonstrated that almost 30% of all patients enrolled in the VGB registry were exempt from ophthalmological testing. The drug registry received ophthalmological test results from only 1,509 patients, of whom 37% had preexisting, baseline clinically significant pathology affecting the visual system that was not related to VGB. The described data was next reviewed by two independent neuro-ophthalmologists who identified only 30 patients (2.0%) with a potential VGB-associated effect on vision [76].

To further assess the influence of VGB on the visual system, Sergott et al. initiated in 2010 a prospective, longitudinal, single-arm, open-label phase IV study (NCT01278173) [77]. In this study, the effect of therapy was evaluated in VGB-naive patients during one year of adjunctive VGB treatment. The obtained results demonstrated that a substantial proportion of adult patients with refractory focal impaired awareness seizures had preexisting vision abnormalities prior to receiving VGB [32% of patients had an abnormally thin retinal nerve fibre layer (RNFL), 15% had abnormal visual acuity, and 20% had abnormal near visual fields], and did not reveal statistically significant changes in population mean change from reference in central 30-degree visual field measurements. Moreover, in contrast to previous publications, the authors showed significant increases in RNFL thickness in spectral-domain optical coherence tomography (SD-OCT). The clinical relevance of retinal thickening is unclear, but the authors suggested that it may be caused by intra-axonal and intracellular oedema. Retrospective studies suggest that retinal toxicity occurs only after months to years of VGB therapy, therefore the short duration of follow-up (only one year) could be the limitation of this particular study [77].

There is more data concerning visual deficits in epileptic patients not exposed to VGB. In 2011, Plant and Sergott reported that bilateral constrictions of the visual field occur also in epilepsy patients who had not previously been treated with VGB [78]. In 2015, Balestrini et al. demonstrated that epilepsy patients treated with several AEDs (without VGB) and/or vagus nerve stimulator also exhibited abnormally thin RNFL compared to healthy controls, which could indicate that an abnormally thin RNFL may be associated with refractory epilepsy, sequelae, or possibly treatment-related with non-vigabatrin AEDs [79]. A study by Schwarz et al. did not detect any clinically apparent vision loss when evaluating 143 IS patients treated with VGB [80]. A recent study by McFarlane et al. demonstrated retinal toxicity with ERG in nearly a quarter of infants with IS who had not previously been treated with VGB. This study indicated an association of abnormal ERG (retinal damage) with the aetiology of IS which is a structurally-acquired (perinatal) subgroup, included a hypoxic-ischaemic defect. This was the first study on the incidence of retinal abnormalities in a large group of children with IS unrelated to VGB treatment. The authors found that nearly a quarter of children with IS not treated with VGB showed symptoms of a retinal defect identified in ERG responses. Nearly a quarter of the children in this study had structural perinatal brain damage [81].

The results of prospective observations which did not reveal new visual deficits led the FDA, in 2013, to lower the age (from 17 to 10) at which VGB can be prescribed to patients with refractory focal onset impaired awareness seizures. Moreover, in 2016, the wording in the package insert regarding eye examinations to monitor for drug toxicity was changed from "required" to "recommended". In addition, the "30 per cent or more" part of the ocular section of the black box warning has been omitted since 2016 compared to the previous prescribing information [76].

VGB-associated brain abnormalities on magnetic resonance imaging (MRI)

Another, poorly understood but definitely important, side effect is the risk of VGB-associated brain abnormalities on MRI (VABAM) in the form of predominantly asymptomatic and reversible high T2-weighted signal and restricted diffusion in the thalami, basal ganglia, brainstem tegmentum, and cerebellar dentate nuclei [82]. It is estimated that the risk of asymptomatic VABAM in infants is approximately 20–30%, and so far no data in older children and adults is available [82, 83]. The pathophysiological mechanism of VABAM is unclear. Initially MRI changes were thought to correlate with intramyelinic oedema [82]. However, there have been reports that MRI abnormalities are more likely due to axonal degeneration [84, 85]. According to previous reports, VABAM correlates with high doses of VGB, younger age, and the 'cryptogenic' aetiology of IS [82, 86]. Moreover, isolated cases of VABAM are associated with hyperkinetic movement disorders as well as acute life-threatening encephalopathy and breathing difficulties, although the pathophysiology of these phenomena is unknown [85, 87, 88]. The study by Fong et al. undermined previously reported movement disorders related to VGB exposure, as there were identified cases where movement disorders occurred without MRI changes or VGB exposure, and in patients whose symptoms persisted despite VGB withdrawal, or resolved despite continuation of VGB [89]. Due to the high prevalence of asymptomatic VABAM in infants, and the rare but potentially life threatening effects of symptomatic VABAM, Hussain et al. designed a retrospective study in which the predictors of both symptomatic and asymptomatic VABAM were identified in IS patients [85]. The obtained results indicate that the risk of asymptomatic VABAM was dose-dependent and that peak (but not cumulative) VGB dose was strongly associated with asymptomatic VABAM. In addition, only four patients from a study group of 104 had symptomatic VABAM. It appears that the risk of symptomatic VABAM is dose-independent and potentially related to combining VGB with hormonal therapy [85].

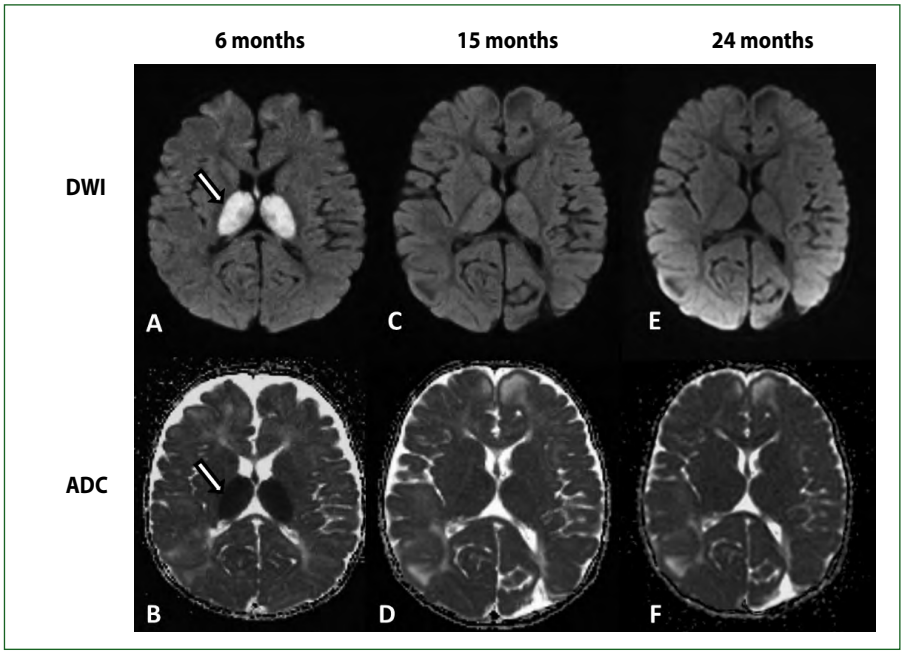


Figure 1. MRI abnormalities related to VGB. First column (**A**, **B**) shows MRI brain examination at age 6 months, second column (**C**, **D**) at age 15 months, and third column (**E**, **F**) at age 24 months. Treatment of VGB was continued. **A**. Diffusion-weighted images (DWI) with b = 1,000 shows strong hyperintensity and symmetrical increased volume of both thalami; **B**. Corresponding apparent diffusion coefficient (ADC) map demonstrates hypointense signal consistent with restricted diffusion; **C**. Hyperintense signal of thalami slightly visible still on DWI, but signal on ADC map is normalised (**D**); **E**, **F**. Follow-up examination demonstrates resolution of diffusion abnormalities; images courtesy of Prof. Elżbieta Jurkiewicz, Department of Diagnostic Imaging, The Children's Memorial Health Institute, Warsaw, Poland

Individual reports of patients with concomitant encephalopathy and changes in neuroimaging during combination therapy have been reported in the literature [87]. A recent report describes an 8-month-old girl with IS treated with ACTH and high dose VGB (182 mg/kg/day), who developed encephalopathy and movement disorders with associated changes in imaging [90]. It seems that combination therapy, despite its better effectiveness, may carry a greater risk of VGB-related toxicity seen on MRI. The results of a study by the National Infantile Spasms Consortium which aims to compare combination therapy with hormonal therapy alone and VGB alone (ClinicalTrials.gov NCT03347526), may answer this question [91]. Figure 1 sets out reversible MRI abnormalities related to VGB.

It is important to distinguish between brain MRI results related to VGB from other aetiologies, including metabolic, infectious and ischaemic. In symptomatic VABAM, the symptoms should be confronted with the effects of epilepsy itself, which may lead to encephalopathy and developmental regression [85]. It is important to take into account the side effects of VGB, as misdiagnosis can lead to increased iatrogenic symptoms.

Conclusions

VGB is an antiepileptic drug used as first-line therapy in IS, a severe epileptic encephalopathy leading to developmental delay which frequently is a precursor of other forms of epilepsy (e.g. Lennox–Gastaut syndrome) [5, 13, 22]. In IS treatment, VGB's therapeutic effectiveness is weaker than other first line options such as ACTH and corticosteroids [22]. However, combined therapy of VGB and ACTH is significantly more effective and faster in achieving clinical and electroclinical responses in children with IS [32]. Nonetheless, in TSC epilepsy patients, VGB is highly effective both in IS treatment (eliminating ES in about 95% of patients) and for other seizure types including focal seizures that may occur prior to IS [40].

There have been groundbreaking recent reports on VGB's efficacy as a preventive epilepsy treatment. The results of several clinical studies and major prospective trials such as EPISTOP suggest that VGB may not only demonstrate antiseizure, but also antiepileptogenic, properties in TSC patients [11, 56]. In fact, currently VGB is the only AED which has been proven effective in the prevention or modification of epilepsy.

It is clear that the use of VGB has been limited over the years due to reports of potential adverse effects. This was particularly noticeable in the US, where the drug was introduced with limited use in 2009, with the recommendation of regular monitoring of patients receiving VGB in the form of the REMS programme [9, 74, 75]. However, the suggestion of ocular toxicity originates from retrospective studies which did not include a pre-treatment ocular evaluation. Additionally,

performing visual field examination in younger patients, especially those with neurological deficits, can be challenging and the peripheral nature of the field loss means there is no one ideal technique to assess VAVFL. Furthermore, prospective studies in the form of the VGB drug registry and the phase IV vision study by Sergott et al. did not demonstrate patients with symptomatic visual loss associated with VGB [74, 75, 77]. Considering the latest reports, it seems that the fear of severe adverse effects associated with VGB therapy, such as ocular toxicity, may be unfounded.

Despite multiple reports, VGB's therapeutic indications and possible antiepileptogenic properties are not ultimately established. Moreover, the risk and course of VGB's adverse effects are ambiguous. There are still many unanswered questions in the form of the frequency and severity of visual deficits caused by VGB. There is a need for more randomised, prospective and sufficiently extended trials which could definitively answer these important questions.

Acknowledgments: *this work was supported by Medical Research Agency grant ViRAP No 2019/ABM/01/00034/P/06 and grant EPIMARKER of the Polish National Center for Research and Development No STRATEGMED3/306306/4/2016.*
Conflict of interest: *None.*

References

1. Ben-Menachem E. Mechanism of action of vigabatrin: correcting misperceptions. Acta Neurol Scand Suppl. 2011(192): 5–15, doi: 10.1111/j.1600-0404.2011.01596.x, indexed in Pubmed: 22061176.
2. Yang J, Shen J. Elevated endogenous GABA concentration attenuates glutamate-glutamine cycling between neurons and astroglia. J Neural Transm (Vienna). 2009; 116(3): 291–300, doi: 10.1007/s00702-009-0186-0, indexed in Pubmed: 19184333.
3. Iannetti P, Spalice A, Perla FM, et al. Visual field constriction in children with epilepsy on vigabatrin treatment. Pediatrics. 2000; 106(4): 838–842, doi: 10.1542/peds.106.4.838, indexed in Pubmed: 11015531.
4. Wohlrab G, Boltshauser E, Schmitt B, et al. Visual field constriction is not limited to children treated with vigabatrin. Neuropediatrics. 1999; 30(3): 130–132, doi: 10.1055/s-2007-973477, indexed in Pubmed: 10480207.
5. Elterman RD, Shields WD, Bittman RM, et al. Vigabatrin for the treatment of infantile spasms: final report of a randomized trial. J Child Neurol. 2010; 25(11): 1340–1347, doi: 10.1177/0883073810365103, indexed in Pubmed: 20404353.
6. European Medicines Agency. Opinion of the committee for proprietary medicinal products pursuant to article 12 of council directive 75/319/EEC as amended, for vigabatrin. 1999.
7. Specchio N, Pietrafusa N, Ferretti A, et al. Treatment of infantile spasms: why do we know so little? Expert Rev Neurother. 2020; 20(6): 551–566, doi: 10.1080/14737175.2020.1759423, indexed in Pubmed: 32316776.
8. van der Poest Clement E, Jansen FE, Braun KPJ, et al. Update on Drug Management of Refractory Epilepsy in Tuberous Sclerosis Complex. Paediatr Drugs. 2020; 22(1): 73–84, doi: 10.1007/s40272-019-00376-0, indexed in Pubmed: 31912454.
9. Sabril [package insert]. Deerfield, IL: Lundbeck LLC; 2013. n.d.
10. Hancock E, Osborne JP. Vigabatrin in the treatment of infantile spasms in tuberous sclerosis: literature review. J Child Neurol. 1999; 14(2): 71–74, doi: 10.1177/088307389901400201, indexed in Pubmed: 10073425.
11. Klein P, Friedman A, Hameed MQ, et al. Repurposed molecules for antiepileptogenesis: Missing an opportunity to prevent epilepsy? Epilepsia. 2020; 61(3): 359–386, doi: 10.1111/epi.16450, indexed in Pubmed: 32196665.
12. Zhang Bo, McDaniel SS, Rensing NR, et al. Vigabatrin inhibits seizures and mTOR pathway activation in a mouse model of tuberous sclerosis complex. PLoS One. 2013; 8(2): e57445, doi: 10.1371/journal.pone.0057445, indexed in Pubmed: 23437388.
13. Wilmshurst JoM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. Epilepsia. 2015; 56(8): 1185–1197, doi: 10.1111/epi.13057, indexed in Pubmed: 26122601.
14. Thodeson D, Sogawa Y. Practice experience in the treatment of infantile spasms at a tertiary care center. Pediatr Neurol. 2014; 51(5): 696–700, doi: 10.1016/j.pediatrneurol.2014.07.019, indexed in Pubmed: 25175384.
15. Friedman D, Bogner M, Parker-Menzer K, et al. Vigabatrin for partial-onset seizure treatment in patients with tuberous sclerosis complex. Epilepsy Behav. 2013; 27(1): 118–120, doi: 10.1016/j.yebeh.2012.12.033, indexed in Pubmed: 23399947.
16. Greiner HM, Lynch ER, Fordyce S, et al. Vigabatrin for childhood partial-onset epilepsies. Pediatr Neurol. 2012; 46(2): 83–88, doi: 10.1016/j.pediatrneurol.2011.11.020, indexed in Pubmed: 22264701.
17. Nabbout RC, Chiron C, Mumford J, et al. Vigabatrin in partial seizures in children. J Child Neurol. 1997; 12(3): 172–177, doi: 10.1177/088307389701200304, indexed in Pubmed: 9130090.
18. Jackson MC, Jafarpour S, Klehm J, et al. Effect of vigabatrin on seizure control and safety profile in different subgroups of children with epilepsy. Epilepsia. 2017; 58(9): 1575–1585, doi: 10.1111/epi.13836, indexed in Pubmed: 28691157.
19. Jia JL, Chen S, Sivarajah V, et al. Latitudinal differences on the global epidemiology of infantile spasms: systematic review and meta-analysis. Orphanet J Rare Dis. 2018; 13(1): 216, doi: 10.1186/s13023-018-0952-x, indexed in Pubmed: 30486850.
20. Talwar D, Baldwin MA, Hutzler R, et al. Epileptic spasms in older children: persistence beyond infancy. Epilepsia. 1995; 36(2): 151–155, doi: 10.1111/j.1528-1157.1995.tb00974.x, indexed in Pubmed: 7821272.
21. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017; 58(4): 512–521, doi: 10.1111/epi.13709, indexed in Pubmed: 28276062.
22. Messer R, Knupp KG. Infantile Spasms: Opportunities to Improve Care. Semin Neurol. 2020; 40(2): 236–245, doi: 10.1055/s-0040-1705121, indexed in Pubmed: 32143232.
23. Elterman RD, Shields WD, Bittman RM, et al. US Infantile Spasms Vigabatrin Study Group. Randomized trial of vigabatrin in patients with infantile spasms. Neurology. 2001; 57(8): 1416–1421, doi: 10.1212/wnl.57.8.1416, indexed in Pubmed: 11673582.
24. Primec ZR, Stare J, Neubauer D. The risk of lower mental outcome in infantile spasms increases after three weeks of hypsarrhythmia duration. Epilepsia. 2006; 47(12): 2202–2205, doi: 10.1111/j.1528-1167.2006.00888.x, indexed in Pubmed: 17201726.
25. Widjaja E, Go C, McCoy B, et al. Neurodevelopmental outcome of infantile spasms: A systematic review and meta-analysis. Epilepsy Res. 2015; 109: 155–162, doi: 10.1016/j.eplepsyres.2014.11.012, indexed in Pubmed: 25524855.

26. O'Callaghan FJK, Lux AL, Darke K, et al. The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study. Epilepsia. 2011; 52(7): 1359–1364, doi: 10.1111/j.1528-1167.2011.03127.x, indexed in Pubmed: 21668442.
27. Darke K, Edwards SW, Hancock E, et al. trial steering committee on behalf of participating investigators, United Kingdom Infantile Spasms Study. The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. Lancet. 2004; 364(9447): 1773–1778, doi: 10.1016/S0140-6736(04)17400-X, indexed in Pubmed: 15541450.
28. Lux AL, Edwards SW, Hancock E, et al. United Kingdom Infantile Spasms Study. The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. Lancet Neurol. 2005; 4(11): 712–717, doi: 10.1016/S1474-4422(05)70199-X, indexed in Pubmed: 16239177.
29. Djuric M, Kravljanac R, Tadic B, et al. Long-term outcome in children with infantile spasms treated with vigabatrin: a cohort of 180 patients. Epilepsia. 2014; 55(12): 1918–1925, doi: 10.1111/epi.12847, indexed in Pubmed: 25377998.
30. Darke K, Edwards SW, Hancock E, et al. trial steering committee on behalf of participating investigators. Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multi-centre randomised trial. Arch Dis Child. 2010; 95(5): 382–386, doi: 10.1136/adc.2009.160606, indexed in Pubmed: 20457702.
31. Knupp KG, Coryell J, Nickels KC, et al. Pediatric Epilepsy Research Consortium. Response to treatment in a prospective national infantile spasms cohort. Ann Neurol. 2016; 79(3): 475–484, doi: 10.1002/ana.24594, indexed in Pubmed: 26704170.
32. O'Callaghan FJK, Edwards SW, Alber FD, et al. participating investigators. Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial. Lancet Neurol. 2017; 16(1): 33–42, doi: 10.1016/S1474-4422(16)30294-0, indexed in Pubmed: 27838190.
33. O'Callaghan FJK, Edwards SW, Alber FD, et al. International Collaborative Infantile Spasms Study (ICISS) investigators. Vigabatrin with hormonal treatment versus hormonal treatment alone (ICISS) for infantile spasms: 18-month outcomes of an open-label, randomised controlled trial. Lancet Child Adolesc Health. 2018; 2(10): 715–725, doi: 10.1016/S2352-4642(18)30244-X, indexed in Pubmed: 30236380.
34. Hahn J, Park G, Kang HC, et al. Optimized treatment for infantile spasms: Vigabatrin versus Prednisolone versus combination therapy. J Clin Med. 2019; 8(10), doi: 10.3390/jcm8101591, indexed in Pubmed: 31581698.
35. Camposano SE, Major P, Halpern E, et al. Vigabatrin in the treatment of childhood epilepsy: a retrospective chart review of efficacy and safety profile. Epilepsia. 2008; 49(7): 1186–1191, doi: 10.1111/j.1528-1167.2008.01589.x, indexed in Pubmed: 18479386.
36. Bresnahan R, Gianatsi M, Maguire MJ, et al. Vigabatrin add-on therapy for drug-resistant focal epilepsy. Cochrane Database Syst Rev. 2020; 7: CD007302, doi: 10.1002/14651858.CD007302.pub3, indexed in Pubmed: 32730657.
37. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. The Lancet. 2008; 372(9639): 657–668, doi: 10.1016/s0140-6736(08)61279-9.
38. Stafstrom CE, Staedtke V, Comi AM. Epilepsy mechanisms in neurocutaneous disorders: tuberous sclerosis complex, neurofibromatosis type 1, and Sturge-Weber syndrome. Front Neurol. 2017; 8: 87, doi: 10.3389/fneur.2017.00087, indexed in Pubmed: 28367137.
39. Curatolo P, Nabbout R, Lagae L, et al. Management of epilepsy associated with tuberous sclerosis complex: Updated clinical recommendations. Eur J Paediatr Neurol. 2018; 22(5): 738–748, doi: 10.1016/j.ejpn.2018.05.006, indexed in Pubmed: 29880258.
40. Overwater IE, Bindels-de Heus K, Rietman AB, et al. Epilepsy in children with tuberous sclerosis complex: Chance of remission and response to antiepileptic drugs. Epilepsia. 2015; 56(8): 1239–1245, doi: 10.1111/epi.13050, indexed in Pubmed: 26046563.
41. Chu-Shore CJ, Major P, Camposano S, et al. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia. 2010; 51(7): 1236–1241, doi: 10.1111/j.1528-1167.2009.02474.x, indexed in Pubmed: 20041940.
42. Kingswood JC, Belousova E, Benedik MP, et al. TOSCA Consortium and TOSCA Investigators. Epilepsy in tuberous sclerosis complex: Findings from the TOSCA study. Epilepsia Open. 2019; 4(1): 73–84, doi: 10.1002/epi4.12286, indexed in Pubmed: 30868117.
43. Krueger DA, Northrup H, Northrup H, et al. International Tuberous Sclerosis Complex Consensus Group, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 Iinternational Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013; 49(4): 243–254, doi: 10.1016/j.pediatrneurol.2013.08.001, indexed in Pubmed: 24053982.
44. Yum MS, Lee EH, Ko TS. Vigabatrin and mental retardation in tuberous sclerosis: infantile spasms versus focal seizures. J Child Neurol. 2013; 28(3): 308–313, doi: 10.1177/0883073812446485, indexed in Pubmed: 22752486.
45. Jóźwiak S, Kotulska K, Domańska-Pakieła D, et al. Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex. Eur J Paediatr Neurol. 2011; 15(5): 424–431, doi: 10.1016/j.ejpn.2011.03.010, indexed in Pubmed: 21507691.
46. Bombardieri R, Pinci M, Moavero R, et al. Early control of seizures improves long-term outcome in children with tuberous sclerosis complex. Eur J Paediatr Neurol. 2010; 14(2): 146–149, doi: 10.1016/j.ejpn.2009.03.003, indexed in Pubmed: 19369101.
47. Cusmai R, Moavero R, Bombardieri R, et al. Long-term neurological outcome in children with early-onset epilepsy associated with tuberous sclerosis. Epilepsy Behav. 2011; 22(4): 735–739, doi: 10.1016/j.yebeh.2011.08.037, indexed in Pubmed: 22142783.
48. Riikonen RS. Favourable prognostic factors with infantile spasms. Eur J Paediatr Neurol. 2010; 14(1): 13–18, doi: 10.1016/j.ejpn.2009.03.004, indexed in Pubmed: 19362867.
49. Hussain SA, Schmid E, Peters JM, et al. Tuberous Sclerosis Complex Autism Center of Excellence Network. High vigabatrin dosage is associated with lower risk of infantile spasms relapse among children with tuberous sclerosis complex. Epilepsy Res. 2018; 148: 1–7, doi: 10.1016/j.eplepsyres.2018.09.016, indexed in Pubmed: 30296632.
50. Galanopoulou AS, Gorter JA, Cepeda C. Finding a better drug for epilepsy: the mTOR pathway as an antiepileptogenic target. Epilepsia. 2012; 53(7): 1119–1130, doi: 10.1111/j.1528-1167.2012.03506.x, indexed in Pubmed: 22578218.
51. Słowińska M, Jóźwiak S, Peron A, et al. Early diagnosis of tuberous sclerosis complex: a race against time. How to make the diagnosis before seizures? Orphanet J Rare Dis. 2018; 13(1): 25, doi: 10.1186/s13023-018-0764-z, indexed in Pubmed: 29378663.
52. Słowińska M, Golec W, Jóźwiak S. Prevention of epilepsy in humans - truth or myth? The experience from Sturge-Weber syndrome and Tube-

rous Sclerosis Complex. Neurol Neurochir Pol. 2019; 53(3): 190–193, doi: 10.5603/PJNNS.a2019.0022, indexed in Pubmed: 31166003.
53. Jozwiak S, Słowińska M, Borkowska J, et al. Preventive antiepileptic treatment in tuberous sclerosis complex: A long-term, prospective trial. Pediatr Neurol. 2019; 101: 18–25, doi: 10.1016/j.pediatrneurol.2019.07.008, indexed in Pubmed: 31481332.
54. Preventing Epilepsy Using Vigabatrin In Infants With Tuberous Sclerosis Complex - Full Text View - ClinicalTrials.gov n.d. https://clinicaltrials.gov/ct2/show/NCT02849457 (February 21, 2021).
55. Long-term, Prospective Study Evaluating Clinical and Molecular Biomarkers of Epileptogenesis in a Genetic Model of Epilepsy - Tuberous Sclerosis Complex - Full Text View - ClinicalTrials.gov n.d. https://clinicaltrials.gov/ct2/show/NCT02098759 (February 21, 2021).
56. Kotulska K, Kwiatkowski DJ, Curatolo P, et al. EPISTOP Investigators. Prevention of epilepsy in infants with tuberous sclerosis complex in the EPISTOP trial. Ann Neurol. 2021; 89(2): 304–314, doi: 10.1002/ana.25956, indexed in Pubmed: 33180985.
57. Carmant L. Vigabatrin therapy for infantile spasms: review of major trials in Europe, Canada, and the United States; and recommendations for dosing. Acta Neurol Scand Suppl. 2011(192): 36–47, doi: 10.1111/j.1600-0404.2011.01599.x, indexed in Pubmed: 22061179.
58. Moavero R, Pisani LR, Pisani F, et al. Safety and tolerability profile of new antiepileptic drug treatment in children with epilepsy. Expert Opin Drug Saf. 2018; 17(10): 1015–1028, doi: 10.1080/14740338.2018.1518427, indexed in Pubmed: 30169997.
59. Eke T, Talbot JF, Lawden MC. Severe persistent visual field constriction associated with vigabatrin. BMJ. 1997; 314(7075): 180–181, doi: 10.1136/bmj.314.7075.180, indexed in Pubmed: 9022432.
60. Krauss GL, Johnson MA, Miller NR. Vigabatrin-associated retinal cone system dysfunction: electroretinogram and ophthalmologic findings. Neurology. 1998; 50(3): 614–618, doi: 10.1212/wnl.50.3.614, indexed in Pubmed: 9521245.
61. Vanhatalo S, Pääkkönen L, Nousiainen I. Visual field constriction in children treated with vigabatrin. Neurology. 1999; 52(8): 1713–1714, doi: 10.1212/wnl.52.8.1713, indexed in Pubmed: 10331710.
62. Vanhatalo S, Nousiainen I, Eriksson K, et al. Visual field constriction in 91 Finnish children treated with vigabatrin. Epilepsia. 2002; 43(7): 748–756, doi: 10.1046/j.1528-1157.2002.17801.x, indexed in Pubmed: 12102679.
63. Maguire MJ, Hemming K, Wild JM, et al. Prevalence of visual field loss following exposure to vigabatrin therapy: a systematic review. Epilepsia. 2010; 51(12): 2423–2431, doi: 10.1111/j.1528-1167.2010.02772.x, indexed in Pubmed: 21070215.
64. Gaily E, Jonsson H, Lappi M. Visual fields at school-age in children treated with vigabatrin in infancy. Epilepsia. 2009; 50(2): 206–216, doi: 10.1111/j.1528-1167.2008.01961.x, indexed in Pubmed: 19215279.
65. Wohlrab G, Leiba H, Kästle R, et al. Vigabatrin therapy in infantile spasms: solving one problem and inducing another? Epilepsia. 2009; 50(8): 2006–2008, doi: 10.1111/j.1528-1167.2009.02167.x, indexed in Pubmed: 19682036.
66. Westall CA, Wright T, Cortese F, et al. Vigabatrin retinal toxicity in children with infantile spasms: An observational cohort study. Neurology. 2014; 83(24): 2262–2268, doi: 10.1212/WNL.0000000000001069, indexed in Pubmed: 25381295.
67. Moskowitz A, Hansen RM, Eklund SE, et al. Electroretinographic (ERG) responses in pediatric patients using vigabatrin. Doc Ophthalmol. 2012; 124(3): 197–209, doi: 10.1007/s10633-012-9320-7, indexed in Pubmed: 22426576.
68. Moseng L, Sæter M, Mørch-Johnsen GH, et al. Retinal nerve fibre layer attenuation: clinical indicator for vigabatrin toxicity. Acta Ophthalmol. 2011; 89(5): 452–458, doi: 10.1111/j.1755-3768.2010.02077.x, indexed in Pubmed: 21251242.
69. Nousiainen I, Mäntyjärvi M, Kälviäinen R. No reversion in vigabatrin-associated visual field defects. Neurology. 2001; 57(10): 1916–1917, doi: 10.1212/wnl.57.10.1916, indexed in Pubmed: 11723291.
70. Chiron C, Dulac O. Epilepsy: Vigabatrin treatment and visual field loss. Nat Rev Neurol. 2011; 7(4): 189–190, doi: 10.1038/nrneurol.2011.25, indexed in Pubmed: 21364521.
71. Hardus P, Verduin WM, Engelsman M, et al. Visual field loss associated with vigabatrin: quantification and relation to dosage. Epilepsia. 2001; 42(2): 262–267, doi: 10.1046/j.1528-1157.2001.15000.x, indexed in Pubmed: 11240600.
72. Wild JM, Chiron C, Ahn H, et al. Visual field loss in patients with refractory partial epilepsy treated with vigabatrin: final results from an open-label, observational, multicentre study. CNS Drugs. 2009; 23(11): 965–982, doi: 10.2165/11317650-000000000-00000, indexed in Pubmed: 19845417.
73. Sergott R, Wheless J, Smith M, et al. Evidence-based review of recommendations for visual function testing in patients treated with vigabatrin. Neuro-Ophthalmology. 2010; 34(1): 20–35, doi: 10.3109/01658100903582498.
74. Pellock JM, Faught E, Foroozan R, et al. Which children receive vigabatrin? Characteristics of pediatric patients enrolled in the mandatory FDA registry. Epilepsy Behav. 2016; 60: 174–180, doi: 10.1016/j.yebeh.2016.03.030, indexed in Pubmed: 27208827.
75. Krauss G, Faught E, Foroozan R, et al. Sabril® registry 5-year results: Characteristics of adult patients treated with vigabatrin. Epilepsy Behav. 2016; 56: 15–19, doi: 10.1016/j.yebeh.2015.12.004, indexed in Pubmed: 26807550.
76. Foroozan R. Vigabatrin: lessons learned from the United States experience. J Neuroophthalmol. 2018; 38(4): 442–450, doi: 10.1097/WNO.0000000000000609, indexed in Pubmed: 29280765.
77. Sergott RC, Johnson CA, Laxer KD, et al. Retinal structure and function in vigabatrin-treated adult patients with refractory complex partial seizures. Epilepsia. 2016; 57(10): 1634–1642, doi: 10.1111/epi.13495, indexed in Pubmed: 27580566.
78. Plant GT, Sergott RC. Understanding and interpreting vision safety issues with vigabatrin therapy. Acta Neurol Scand Suppl. 2011(192): 57–71, doi: 10.1111/j.1600-0404.2011.01601.x, indexed in Pubmed: 22061181.
79. Balestrini S, Clayton LMS, Bartmann AP, et al. Retinal nerve fibre layer thinning is associated with drug resistance in epilepsy. J Neurol Neurosurg Psychiatry. 2016; 87(4): 396–401, doi: 10.1136/jnnp-2015-310521, indexed in Pubmed: 25886782.
80. Schwarz MD, Li M, Tsao J, et al. A lack of clinically apparent vision loss among patients treated with vigabatrin with infantile spasms: The UCLA experience. Epilepsy Behav. 2016; 57(Pt A): 29–33, doi: 10.1016/j.yebeh.2016.01.012, indexed in Pubmed: 26921595.
81. McFarlane MT, Wright T, McCoy B, et al. Retinal defect in children with infantile spasms of varying etiologies: An observational study. Neurology. 2020; 94(6): e575–e582, doi: 10.1212/WNL.0000000000008686, indexed in Pubmed: 31792095.
82. Dracopoulos A, Widjaja E, Raybaud C, et al. Vigabatrin-associated reversible MRI signal changes in patients with infantile spasms.

Epilepsia. 2010; 51(7): 1297–1304, doi: 10.1111/j.1528-1167.2010.02564.x, indexed in Pubmed: 20384718.
83. Wheless JW, Carmant L, Bebin M, et al. Magnetic resonance imaging abnormalities associated with vigabatrin in patients with epilepsy. Epilepsia. 2009; 50(2): 195–205, doi: 10.1111/j.1528-1167.2008.01896.x, indexed in Pubmed: 19054414.
84. Simao GN, Zarei Mahmoodabadi S, Snead OC, et al. Abnormal axial diffusivity in the deep gray nuclei and dorsal brain stem in infantile spasm treated with vigabatrin. AJNR Am J Neuroradiol. 2011; 32(1): 199–203, doi: 10.3174/ajnr.A2224, indexed in Pubmed: 20801762.
85. Hussain SA, Tsao J, Li M, et al. Risk of vigabatrin-associated brain abnormalities on MRI in the treatment of infantile spasms is dose-dependent. Epilepsia. 2017; 58(4): 674–682, doi: 10.1111/epi.13712, indexed in Pubmed: 28230253.
86. Pearl PL, Vezina LG, Saneto RP, et al. Cerebral MRI abnormalities associated with vigabatrin therapy. Epilepsia. 2009; 50(2): 184–194, doi: 10.1111/j.1528-1167.2008.01728.x, indexed in Pubmed: 18783433.
87. Dill P, Datta AN, Weber P, et al. Are vigabatrin induced T2 hyperintensities in cranial MRI associated with acute encephalopathy and extrapyramidal symptoms? Eur J Paediatr Neurol. 2013; 17(3): 311–315, doi: 10.1016/j.ejpn.2012.10.009, indexed in Pubmed: 23199677.
88. Hernández Vega Y, Kaliakatsos M, U-King-Im JM, et al. Reversible vigabatrin-induced life-threatening encephalopathy. JAMA Neurol. 2014; 71(1): 108–109, doi: 10.1001/jamaneurol.2013.1858, indexed in Pubmed: 24247994.
89. Fong CYi, Osborne JP, Edwards SW, et al. An investigation into the relationship between vigabatrin, movement disorders, and brain magnetic resonance imaging abnormalities in children with infantile spasms. Dev Med Child Neurol. 2013; 55(9): 862–867, doi: 10.1111/dmcn.12188, indexed in Pubmed: 23789722.
90. Lotan E, Bluvstein J, Zan E. Vigabatrin toxicity in a patient with infantile spasms treated with concomitant hormonal therapy. Isr Med Assoc J. 2020; 22(7): 461–462.
91. A Novel Approach to Infantile Spasms - Full Text View - ClinicalTrials.gov n.d. https://clinicaltrials.gov/ct2/show/NCT03347526 (February 21, 2021).

REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 5, pages: 440–449
DOI: 10.5603/PJNNS.a2021.0065

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

Nucleus accumbens as a stereotactic target for the treatment of addictions in humans: a literature review

Michał Sobstyl[1], Anna Kupryjaniuk[1], Paweł Mierzejewski[2]

[1]Department of Neurosurgery, Institute of Psychiatry and Neurology, Warsaw, Poland
[2]Department of Pharmacology, Institute of Psychiatry and Neurology, Warsaw, Poland

ABSTRACT

Introduction: Deep brain stimulation (DBS) has achieved substantial success as a treatment for movement disorders such as Parkinson's Disease (PD), essential tremor (ET), and dystonia. More recently, a limited number of basic and clinical studies have indicated that DBS of the nucleus accumbens (NAc) and other neighbouring structures of the reward circuit may be an effective intervention for patients with treatment-refractory addiction.

Material and methods: We performed a structured literature review of human studies of DBS for addiction outlining the clinical efficacy and adverse events. We found 14 human studies targeting mostly the NAc with neighbouring structures such as anterior limb of the internal capsule (ALIC). Five studies including 12 patients reported the outcomes for alcohol dependence. Nine studies including 18 patients reported the outcomes for addictions to various psychoactive substances. The most common indication was addiction to heroin, found in 13 patients, followed by methamphetamine, 3 patients, cocaine, one patient, and polysubstance drug abuse in one patient.

Conclusions: The limited clinical data available indicates that DBS may be a promising therapeutic modality for the treatment of intractable addiction. In general, the safety profile of DBS in patients with addiction is good. Based on the data published in the literature, the NAc is the most often targeted, and is probably the most effective, structure of the reward circuit in the treatment of addiction in humans. Given the ever-expanding understanding of the psychosurgery of addiction, DBS could in the future be a treatment option for patients suffering from intractable addictive disorders.

Key words: addiction, alcohol dependence, anterior limb of the internal capsule, deep brain stimulation

(*Neurol Neurochir Pol 2021; 55 (5): 440–449*)

Introduction

Drug addiction, also called substance use disorder, is a disease that affects a person's brain and behaviour and leads to an inability to control the use of a legal or illegal drug or medication. Drug addiction is a complex, chronic, relapsing illness [1]. Addictive disorders are among the most common mental disorders in developed countries. Drug addiction is composed of physical and psychosocial dependence. Physical dependence is related to the withdrawal syndrome with coexistent noradrenergic hyperactivity in the locus coeruleus. The treatment of physical dependence (withdrawal syndrome) may be successfully achieved by means of substantive therapies or other therapies such as dopamine transporter blockers, non-dopaminergic drugs, or cannabinoid antagonists. Psychological dependence has been closely associated with drug-seeking behaviour which correlates with dopaminergic activity in the mesolimbic pathway, especially in the nucleus accumbens (NAc) [2].

The treatment of psychological dependence is much more difficult than physiological detoxification and elimination of withdrawal syndrome. Psychological dependence can be treated by a drug substitute therapy, cognitive-behavioural therapy (CBT), and surgical treatment. Surgical treatment, mainly the ablative neuropsychiatric procedures for drug addiction, has been utilised in a large cohort of patients since

Address for correspondence: Anna Kupryjaniuk, Department of Neurosurgery, Institute of Psychiatry and Neurology, Sobieskiego 9, 02–957, Warsaw, Poland; e-mail: kupryjaniukanna@gmail.com

Received: 30.05.2021 Accepted: 10.08.2021 Early publication date: 11.10.2021

the 1970s. Ablative procedures have been largely replaced in recent years by deep brain stimulation (DBS) procedures not only for movement disorders, but also for neuropsychiatric indications such as obsessive-compulsive disorder (OCD), major depressive disorder (MDD), Tourette's Syndrome, and drug abuse and addiction [3–7].

The primary aim of this review was to present the clinical outcomes of nucleus accumbens (NAc) DBS for alcohol and psychoactive drug addictions. We also present the role of the NAc in the psychological mechanism of drug addiction.

Nucleus accumbens as target within reward system for addiction

Recent advances in neuroimaging have brought about better understanding of the functions of the reward system in humans and its disturbances in addicted patients [8]. The most prominent neuroanatomically defined structures of the reward pathway include the anterior cingulate cortex (AAC), the orbitofrontal cortex, the NAc within the ventral striatum (VS), and the ventral tegmental area (VTA) [9].

The reward pathway, sometimes referred to as the mesolimbic pathway, connects the VTA in the midbrain to the VS of the basal ganglia in the forebrain. The release of dopamine from the mesolimbic pathway into the NAc regulates motivation and desire for rewarding stimuli and facilitates reinforcement and reward-related motor function learning [10]. Dysregulation of the mesolimbic pathway and its output neurons in the NAc plays a significant role in the development and maintenance of an addiction [11].

The NAc is subdivided into limbic and motor subregions known as the NAc shell and the NAc core. The shell of the NAc occupies its medial, ventral, and lateral parts, whereas the core occupies its central and dorsal parts. The medium spiny neurons in the NAc receive input from both the dopaminergic neurons of the VTA and the glutamatergic neurons of the hippocampus, amygdala, and medial prefrontal cortex. When they are activated by these inputs, the medium spiny neurons' projections release GABA onto the ventral striatum. The NAc attains a central position between limbic and mesolimbic dopaminergic structures, basal ganglia, and limbic prefrontal cortices. This central position of the NAc influences reward-related and drug self-administration behaviours, as well as motivation, learning and adaptive behaviours [10, 11].

Commonly abused substances, such as cocaine, alcohol, and nicotine, have been shown to increase extracellular levels of dopamine within the mesolimbic pathway, preferentially within the NAc [12]. These dopaminergic activations of the mesolimbic pathway are accompanied by the perception of reward. This stimulus-reward association shows a resistance to extinction and creates an increased motivation to repeat the same behaviour that caused it. Neurosurgical procedures directed at the mesolimbic system have reduced or modulated NAc activity. These have included stereotactic ablation of the NAc with the VS, and more recently implantation of DBS electrodes into the NAc to treat intractable addictive disorders.

Ablative surgery and DBS procedures for addictive disorders

Surgery as treatment for drug addiction has been carried out since the 1970s, when many patients were addicted to heroin and other drugs as partial consequences of the 'hippie' revolution. The failed attempts of substitute therapy or CBT for drug addicts, and extremely high drug relapse rates, have generated interest in the ablative neurosurgical procedures done at that time for psychiatric disorders and drug addictions.

One of the first ablative stereotactic operations for the treatment of various psychiatric illnesses, including mood disorders, anxiety disorders and OCD, was cingulotomy [13]. Cingulotomy was shown to be not only effective for psychiatric conditions, but also for chronic intractable pain in patients addicted to narcotics [14]. Foltz et al. presented in 16 patients, (11 patients had bilateral and five had unilateral lesions in cingulum) that all 14 addicted to narcotics required no more drugs 72 hours after unilateral or bilateral cingulotomy [15]. In 1978, Kanaka and Balasubramaniam reported the clinical outcomes of 73 patients with drug addiction treated with anterior cingulotomy [16]. They analysed the results of surgical treatment of these 73 patients with morphine, pethidine and alcohol addictions. Follow-up varied from 1-6 years. According to the authors, excellent results were achieved in 60-80% of patients [16].

The largest study, of 348 addicted patients after bilateral cingulotomy, was reported by Medvedev et al. At 2-years follow-up, 187 patients had complete cessation of drug use and termination of drug craving [17]. Stereotactic lesions targeting ventromedial hypothalamic nucleus or hypothalamus have also been applied in the neurosurgical treatment of drug addiction, but with only limited clinical value [18]. The main limitation of the abovementioned studies was the lack of precision of lesion placement when compared to neurosurgical procedures for alcohol or drug addiction that are performed today. Direct targeting with magnetic resonance imaging (MRI) has enabled the detailed documentation of lesion placement in the NAc or post-operative accurate verification of the position of a DBS electrode in the NAc.

In 2003, Gao et al. presented encouraging results in 28 patients with NAc ablation for opiate addiction [19]. Over the ensuing months, the relapse rates increased and at 6 months reached 58%. The side effects included temporary memory loss in four patients and personality changes in two. The authors stated that the side effects apparently did not affect the patients' daily functioning or intellectual ability. These results sparked the rise of NAc ablations for addicted patients in China. It was estimated that around 1,000 NAc bilateral ablations had been performed by 2004. Well-controlled clinical trials were not done to support the claim that NAc ablation was a safe and effective neurosurgical treatment for drug addiction in humans. As a consequence, the widespread clinical use of NAc ablation was halted by China's Ministry of Health.

Table 1. Case reports and pilot studies showing effects of bilateral NAc DBS in treatment of severe alcohol dependency. In all case reports and case series for alcohol addiction, NAc was chosen as a stereotactic target

Authors and year of publication	Number of patients	Study design	Stimulation parameters	Prevailed indication for DBS procedure	Outcomes	Follow-up	Side effects of stimulation
Kuhn et al. 2007 [20]	1	Case report	3 V, 90 µsec, 130 Hz	Severe anxiety disorder, secondary depressive disorder and comorbid alcohol dependency	Slight reduction of anxiety disorder, no effect on depression, remarkable change in alcohol dependency	1 year	Not reported
Mullner et al. 2009 [21]	3	Case series	3.5–4.5 V, 90 µsec, 130 Hz	Primary alcohol dependency	2 patients remained abstinent, 1 patient showed reduction in alcohol dependency	1 year	Transient hypomanic period of 1 week's duration in 1 patient
Kuhn et al. 2011 [22]	1	Case report	5.5 V, 120 µsec, 130 Hz	Primary alcohol dependency	Complete cessation of alcohol dependency	1 year	Not reported
Voges et al. 2013 [24]	5	Pilot study Case series	4.5 V, 120 µsec, 130 Hz	Primary alcohol dependency	2 patients remained abstinent, 3 relapsed with reduced alcohol consumption	2 years average follow-up to 38 months	Transient hypomania. One case of electrode dislocation
Mullner at al. 2016 [25]	5 (3 patients included from previous publication)	Pilot study Case series	3.5–4.5 V, 90 µsec, 130 Hz	Primary alcohol dependency	All patients reported persistent disappearance of craving, 2 patients remained abstinent for 7 years and 3 patients showed a marked reduction of alcohol consumption	Follow-up to 8 years	No patient reported any negative overall psychological well-being or psychopathological symptoms due to DBS

NAc — nucleus accumbens; V — volts; µsec — microseconds; Hz — frequency

Ablative surgery has in recent years been replaced by DBS procedures in mentally ill patients. Patients with neurological and psychiatric disorders who have undergone DBS procedures with comorbid addictive disorders have also noticed improvements in addictive behaviours towards alcohol, nicotine or psychoactive drugs.

DBS for alcohol addiction

In 2007, Kuhn et al. presented the first patient with severe anxiety disorder including agoraphobia and secondary depressive disorder who also had alcohol dependence [20]. After bilateral NAc DBS at 1-year follow-up, despite the lack of desired improvement in anxiety, the authors observed a remarkable, although not primarily intended, alleviation of the patient's comorbid alcohol dependency. This case demonstrated the extremely effective treatment of alcohol dependency by means of bilateral NAc DBS [20].

Müllner et al. also confirmed the efficacy of NAc DBS in three alcohol-dependent patients [21]. At 1-year follow-up, two patients remained abstinent, while the third showed a remarkable reduction in the number of days on which he drank, and none had any significant adverse effects [21]. Another case of severe alcohol dependence with psychiatric comorbidities was presented by Kuhn et al. in 2011 [22]. The authors noted that the NAc DBS normalised addictive behaviour and craving.

The authors concluded that their case supports the hypothesis that DBS of the NAc could have a positive effect on addiction through normalisation of the craving associated with anterior mid-cingulate cortex (aMCC) functioning [22].

Also, Voges et al. presented five patients treated off-label by bilateral NAc DBS for severe alcohol addiction with an average follow-up of 38 months [24]. All patients experienced significant and ongoing improvement of craving. Two patients remained completely abstinent for more than four years. These authors assessed not only the clinical efficacy of bilateral NAc DBS, but also investigated recording of local field potentials from the target area and surface electroencephalography (EEG) [24]. Subsequently, Müllner et al. reported on the long-term clinical outcome (up to 8 years) of five patients who received bilateral NAc DBS to treat long-lasting and treatment-resistant alcohol addiction [25]. All patients reported a complete absence of craving for alcohol; two patients remained abstinent for seven years and the other three patients showed a marked reduction in their alcohol consumption. Table 1 sets out the clinical outcomes of DBS procedures in patients with alcohol dependency.

DBS for opiate addiction

The first report of NAc DBS for heroin addiction was presented by Zhou et al. [26]. The patient after surgery with a 6-year follow-up was relapse-free, with improvements in his

anxiety and depression. An additional case of a heroin-addicted patient was presented by Valencia-Alfonso [27]. Bilateral NAc DBS produced a decrease of heroin usage and craving over a 6-month postoperative period [26]. Kuhn et al. presented two additional patients with heroin addiction who achieved decreased heroin consumption with amelioration of depressive and anxiety symptoms and an increase in their subjectively perceived quality of life [28].

The largest study so far reporting the outcomes of NAc DBS for eight heroin-addicted patients was presented by Chen et al. [29]. DBS electrodes were implanted through the anterior limb of internal capsule (ALIC) into the NAc. Five patients were abstinent for more than three years, two relapsed after abstaining for six months, and one was lost to follow-up at three months. Simultaneous DBS of the NAc and ALIC improved the quality of life, alleviated psychiatric symptoms, and increased glucose metabolism in addiction-related brain regions revealed by positron emission tomography (PET) studies.

Zhang at al. presented a case of primary opioid addiction treated by bilateral stimulation of ventral capsule (VC)/VS. In the postoperative period, a mild hypomanic episode forced lowering of the stimulation parameters, which resulted in increased cravings and repeated relapses. The patient fatally overdosed on heroin three months after the initial surgery [30].

DBS for cocaine addiction

The first case report of a patient with cocaine addiction was presented by Gonzales-Ferreira [31]. DBS electrodes were placed in the posteromedial part of the NAc neighbouring the bed nucleus of stria terminalis (BNST). Six months after the surgery, the use of cocaine and craving were markedly reduced. At 2-years follow-up, there was still improvement in cocaine addiction, but this was a smaller improvement than that witnessed at six months postoperatively [31].

DBS for methamphetamine/amphetamine (MA/A) addiction

Zhang et al. described a methamphetamine-addicted patient after DBS of the NAc and the VC without co-morbid psychiatric and substance-use disorders [31]. One year after surgery, the patient had become methamphetamine-free and his social functioning had improved. Ge et al. reported two additional patients with MA addiction [32]. At the final follow-up (ranging from 1.5 to 2.5 years) one patient was MA abstinent, but the other patient did not respond and subsequently relapsed. This discrepancy of clinical outcomes was attributed to misplaced DBS leads in the other patient [32]. A recently published case has featured multidrug addiction combining NAc DBS with anterior capsulotomy [33]. After placing radiofrequency lesions bilaterally in the anterior capsule, the DBS leads were implanted into the NAc. This patient had no drug cravings and had stopped using drugs at 12 months follow-up. Moreover, the patient's comorbid depression and anxiety showed progressive improvements during the follow-up. The patient had no adverse events related to the combined surgery, and also showed improvements in memory, learning, and cognitive functions.

According to these authors, the excellent results of combined simultaneous ablative and DBS lead implantations for drug addiction with comorbid psychiatric problems should prompt larger well-controlled clinical studies [33]. Table 2 sets out the clinical outcomes of DBS procedures in patients with various dependencies to psychoactive drugs.

Inclusion and exclusion criteria for DBS in patients with addictions

The worldwide experience in DBS for addiction is limited, and there are no definitive guidelines on patient selection criteria. Some authors have formulated protocols for the use of DBS in addiction to alcohol or psychoactive substances [20, 23, 25, 30–33]. In all of the proposed studies, the main inclusion criterion is a primary diagnosis of addiction according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, and the International Classification of Diseases, 10th edition. Qualification for DBS should be carried out by a psychiatrist who has experience in treating addicted patients. Furthermore, the whole procedure should assume the presence of a multidisciplinary team, including a psychiatrist and a neuropsychologist. Moreover, a neurosurgeon and a psychiatrist should be involved in programming the device. There are separate specific inclusion criteria for alcohol addictionand for different drug addictions.

Patients with alcohol addiction should fulfill the following criteria: age 25–60 years, inpatient detoxification with at least two weeks of abstinence before surgery, and the presence of alcoholism for at least 10 years [21]. Patients should try at least two long-term inpatient therapies of at least six months in total with at least one anticraving medication [21]. Patients with drug addictions should meet the following inclusion criteria: age 18–50 years, addiction to psychoactive drugs for at least three years, and at least three relapses with previous conservative treatments including ineffective substitute medication therapies [28].

Patients' cravings for alcohol or drugs have a profound influence on their health and severely affect the quality of their lives and the lives of their family members [23, 25, 30–33]. The final important issue regarding the inclusion criteria is that the consequences of the procedure are understood by the patient and his or her family member in order for an informed choice without coercion to be made and written informed consent for the procedure to be given [23, 28]. A reasonable amount of time should be given in which the patient and their family can fully consider the benefits and risks before signing a written informed consent.

Such patients must have a suitable living environment and sufficient postoperative care and support to participate in an early postoperative stimulation settings optimisation period, as well as in the scheduled follow-up visits postoperatively.

Table 2. Case reports and pilot studies showing effects of bilateral NAc DBS or combination of NAc and ALIC DBS in treatment of severe drug addiction including heroin, cocaine, methamphetamine and benzodiazepines

Authors and year of publication	Number of patients	Study design	Stereotactic target/targets	Stimulation parameters	Prevailed indication for DBS procedure	Outcomes	Follow-up	Side effects of stimulation
Zhou et al. 2011 [25]	1	Case report	Bilateral stimulation of NAc	2.5 V, 90 µsec, 125 Hz	Primary heroin addiction	Complete drug addiction withdrawal for 6 years	For 2.5 years with stimulation, up to 6 years without stimulation	Transient mild confusion and urinary incontinence. On request of family, pulse generator was turned off at 2.5 years after surgery, and at 3 years removed
Valencia--Alfonso et al. 2012 [26]	1	Case report	Bilateral stimulation of NAc and anterior limb of internal capsule (ALIC)	3.5 V, 90 µsec, 180 Hz	Primary heroin addiction	6 months drug--free except for 14 days relapse	6 months	Not reported
Kuhn et al. 2014 [27]	2	Case series	Bilateral stimulation of NAc	4.5–5 V, 90–120 µsec, 140–150 Hz	Primary heroin addiction. Secondary addictions included amphetamines, alcohol, benzodiazepines, anxiety and depression	Both patients abandoned heroin use, improvements in anxiety and depressive symptoms	2 years	1 postoperative epileptic seizure in patient with previous epilepsy
Chen at al. 2018 [28]	8	Open label pilot study	Bilateral stimulation of NAc and ALIC	1.5–7 V, 150-240 µsec, 130–185 Hz	Primary heroin addiction	5 patients abstinent for more than 3 years, 2 patients relapsed after 6 months, 1 patient lost to follow-up after 3 months	2 years	1 patient had clinically--silent haemorrhage at DBS lead tip. Stimulation-related transient adverse events included dizziness, agitation, irritability, sweating. 1 case of slight memory decline
Zhang at al. 2018 [29]	1	Case report	Bilateral stimulation of VC/VS	3.5 V, 90 µs, 130 Hz	Primary heroin addiction	Reduced opioid cravings and decreased discomfort	12 moths	Transient hypomania due to stimulation settings increase. Death 3 months after surgery due to heroin overdose
Gonzales--Ferreira et al. 2016 [30]	1	Case report with double--blind randomised control	Bilateral stimulation of postero--medial part of NAc with neighbouring BNST	2.5–4 V, 150 µsec, 150 Hz	Primarycocaine addiction, secondary addictions to heroin, cannabis, alcohol	At 2,5 years follow-up, there was still improvement in cocaine addiction, but it was smaller than at 6 months	2.5 years	Transient stimulation induced unpleasant warmness, sweating and flushing
Zhang et al. 2019 [31]	1	Case report	Bilateral stimulation of NAc and ventral capsule	Not reported	Primary methamphetamine addiction	Complete cessation of methamphetamine addiction	1 year	Not reported
Ge et al. 2019 [32]	2	Case series	Bilateral stimulation of NAc	2.5–3.3 V, 210–240 µsec, 150–165 Hz	Primary methamphetamine addiction	First patient experienced complete cessation of addiction, second patient failed due to DBS lead deviation	2 years	Lead deviation caused failure of NAc DBS resulting in hypomania and anxiety
Zhu et al. 2019 [33]	1	Case report	Bilateral stimulation of NAc combined with capsulotomy	2.7 V, 90 µsec, 145–160 Hz	Polysubstance use disorder (bucinnazine, morphine, hypnotics)	Cessation of all drug cravings and drug addiction	1 year	Not reported

ALIL — anterior limb of internal capsule; BNST — bed nucleus of stria terminalis; NAc — nucleus accumbens; VS/VC — ventral striatum/ventral capsule

Moreover, the local ethics committee and the committee for neurosurgery for psychiatric disorders should review each case individually, and decide whether an addicted patient is suitable for a DBS procedure.

Based on the scientific literature, this is a list of the most frequently described criteria that exclude addicted patients from the DBS procedure: a positive history of withdrawal seizure during pharmacological detoxification for alcohol dependence; an active psychiatric disorder such as schizophrenia; a history of psychosis; active bipolar disorder; and an antisocial personality disorder. Patients with structural changes visible on MRI should be excluded from undergoing DBS surgery. In addition, contraindications for MRI examinations, such as the presence of metal or of a pacemaker, and pregnancy, are exclusion criteria for DBS. Mental retardation or mental handicap is regarded as an exclusion criterion. Presurgically confirmed dementia by neuropsychological tests should be regarded as an exclusion criterion. An IQ in intelligence tests of less than 80 also remains an exclusion criterion. Inability to understand the procedure, lack of cooperation (e.g. non-compliance with scheduled follow-up visits), and inability to provide written informed consent constitute additional exclusion criteria. The abovementioned inclusion/exclusion criteria protocol may promote DBS procedures for alcohol and drug addictions [21, 23, 28].

A proposal to qualify patients with addictions for a DBS procedure

We present our proposal to qualify patients with addictions based on the current knowledge in this field.

As the main qualification criterion, we propose that a psychiatrist diagnoses the presence of addiction resistant to pharmacological treatment. Psychotherapeutic measures (including addiction therapy) should have been undertaken, which did not bring about the desired therapeutic effect. There should have been at least 10 years of alcohol dependence and/or at least three years of addiction to psychoactive substances. The prognosis without surgery must be unfavourable. The patient must make informed constent to the entire treatment procedure, not only to the surgery itself, but also to postoperative visits. Moreover, the patient should have access to a social support system in the form of family/friends. This social support system will enable the patient to cope in the postoperative period and will constitute another source of data on the patient's health, for instance whether there is aggravation, simulation, or dissimulation of symptoms. Moreover, the family environment will be another element of the treatment system in this difficult psychiatric diagnosis. Patients after succesful surgery (withdrawal symptoms of addiction) will have to face new challenges (i.e. starting work, returning to society), and thanks to the help of relatives this will be easier to achieve.

Another issue surrounds informed consent. Patients suffering from, for example, Korsakoff's Syndrome, would be excluded from the study due to an overly large memory loss that could influence their making an informed decision. On the other hand, in the criteria for assessing the cognitive profile, it should be taken into account that the treatment should concern the sick and not the healthy (and that therefore, some cognitive deficits can be acceptable in the qualification criteria). For this reason, it is extremely important that a multidisciplinary team participates in the patient's qualification, and that decisions about qualification are made unanimously.

One disqualification criterion would be a concomitant psychiatric diagnosis (except for mild/moderate depression, which is often a concomitant symptom in addictions). It should be considered whether the personality disorder constitutes a comorbid psychiatric diagnosis. On the one hand, a personality disorder, for instance borderline personality disorder, could be a significant hindrance to the entire research procedure, as a person with borderline personality disorder could make an impulsive decision to stop attending follow-up visits. Therefore, in our opinion, decisions in this matter should be made individually, based on the knowledge and experience of the research team. A definite criterion excluding from surgical treatment would be the presence of a brain tumour, arteriovenous malformation, or progressive neurodegenerative disease. In addition, the presence of an implanted metal device for stimulation anywhere in the body (e.g. pacemaker, spinal cord stimulator) or a metal implant in the head (e.g. aneurysm clip, cochlear implant) would also be an exclusion criterion. Another exclusion criterion would be a positive pregnancy test, as it is not known how the surgery would affect the patient and whether it might contribute to the occurrence of negative factors (e.g. stress) affecting the foetus. The last important disqualification factor for DBS surgery is significant internal burden, excluding surgery lasting up to five hours under local and thereafter general anaesthesia. Postoperatively, patients should have a follow-up visit scheduled soon afterwards. The programme should be performed by a team, as a neurosurgeon alone is untrained in interpreting different patient behaviours, while on the other hand a psychiatrist inexperienced in DBS cannot interpret properly the over-stimulation or stimulation of surrounding structures.

The result is that team work both before and after surgery is needed to care for patients with implanted DBS for addictions.

Adverse events related to dbs procedures for severe refractory addiction

The adverse events related to a DBS procedure can be divided into three categories. These complications are primarily surgery-related, i.e. haemorrhagic complications (bleeding, venous infarction), stimulation-induced complications (i.e. mood changes, the appearance of new or worsening comorbid psychiatric symptoms), and hardware-related complications (i.e. infections, erosions, the fracture of a DBS lead, or the failure of an internal pulse generator).

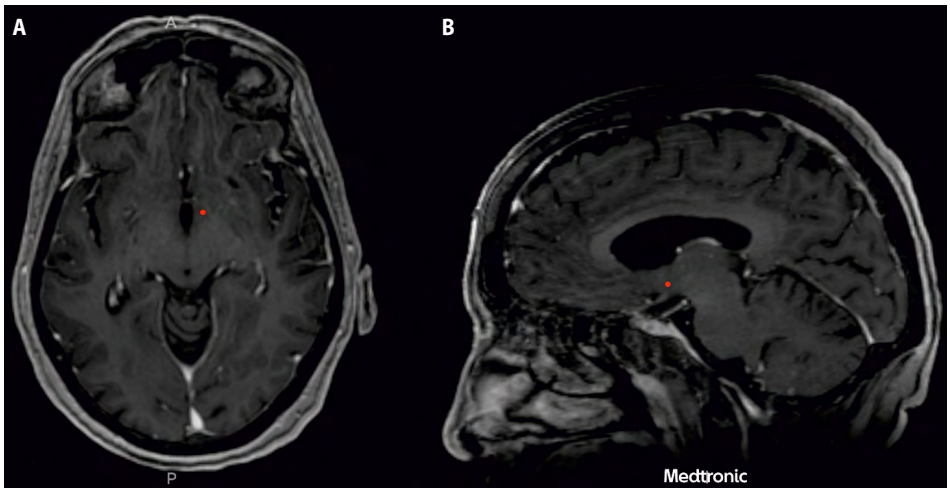


Figure 1. A. Visualisation of nucleus accumbens (NAc) in 1.5 MRI contrast enhanced T1-weighted image in axial orientation. Right NAc is marked with red dot. NAc lies medial to ventral capsule; **B.** Visualization of NAc in 1.5 MRI contrast enhanced T1-weighted image in para-sagittal orientation. Location of NAc is marked with red dot

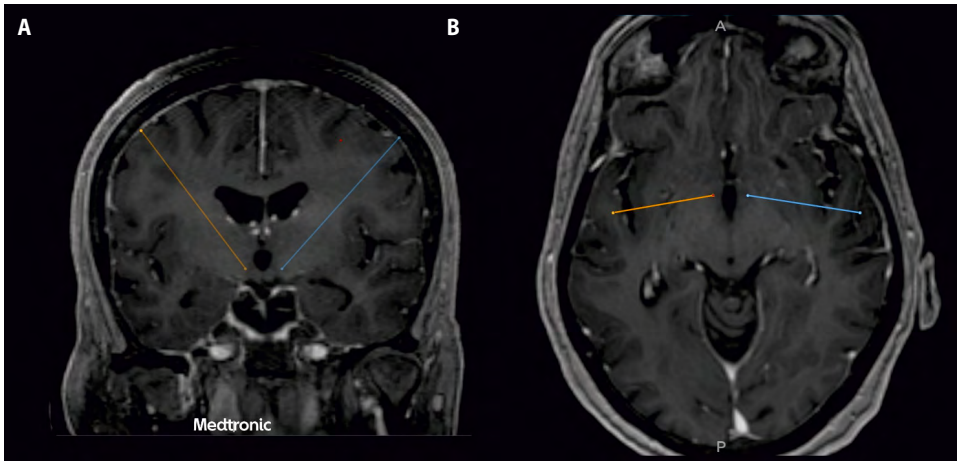


Figure 2. A. Coronal 1.5 MRI contrast enhanced T1-weighted image representing stereotactic trajectories from entry points on brain surface to NAc bilaterally. Stereotactic trajectories are planned to avoid passage of brain sulci, vessels, and ventricles to minimise intraoperative haemorrhagic complications; **B.** Same stereotactic trajectories shown in axial contrast enhanced T1-weighted image

A DBS procedure is usually carried out by members of a multidisciplinary team, which includes an experienced functional stereotactic team with DBS expertise in movement disorders, OCD, MDD, and other psychiatric DBS indications [34, 35]. Modern stereotactic operations are supported by navigation systems, and these have significantly reduced the number of intraoperative haemorrhagic complications by allowing the visualisation of stereotactic trajectories from the entry points at the brain surface to the stereotactic targets. This advantage in terms of preoperative planning of stereotactic trajectories enables the passing the electrodes through cerebral sulci, vessels or ventricular system to be avoided, and thereby enhances the safety of the stereotactic procedures (Fig. 1, 2).

The surgery-related adverse events that have been reported have been transient, and did not result in any immediate neurological deficit or death related to a DBS procedure for addiction [20–33]. To date, only one patient treated by NAc DBS has experienced a clinically silent haemorrhagic complication located near the DBS electrode tip [28]. The most commonly reported adverse events due to NAc DBS have been stimulation-related and have appeared mostly in the early postoperative period during the optimisation of DBS stimulation settings. These stimulation-related adverse events are probably due to the overstimulation of the NAc and neighbouring structures. These have included transient hypomanic episodes, obsessive-compulsive traits, insomnia, anxiety, dizziness, agitation, irritability, and difficulties falling asleep [21, 23, 28]. All of these symptoms were transitory due to the adjustment of the stimulation parameters [21, 23].

The main factors behind acute stimulation-related adverse events in the early postoperative period have been different stimulation parameters and the mode of stimulation [20, 22, 24, 29–31]. Stimulation settings have not been standardised among the studies [20–33]. The stimulation parameters were adjusted throughout the studies and individualised as per patient response. In most studies, drug use and drug craving were decreased [20–25, 28, 30, 32, 33].

No hardware-related adverse events of DBS procedures for addiction, such as DBS lead fracture, or internal pulse generator malfunction, have been reported in the literature [20–33]. Interestingly, no patients suffered from skin erosion over implanted DBS hardware with a possible subsequent hardware infection. This situation may be partially explained by the still small number of patients addicted to alcohol or drugs treated by DBS with relatively short follow-up periods, reaching 1-2 years in most studies [20–23, 26, 27, 31–33].

Generally, the safety profile of DBS in patients with addictions is considered to be good, with a very low rate of mostly transient adverse events [21, 23, 25, 27, 28, 32]. Moreover, most of the patients have gained significant improvements in concomitant depressive symptoms or anxiety [21, 24, 26–28]. Moreover, DBS of the NAc, ALIC and BNST has been reported to have beneficial effects on attention, memory, sleep, and social and occupational functioning in addicted patients [20–33].

Closing remarks

The most relevant and today the most widely used DBS surgical target for the treatment of addiction is the NAc [23, 24]. It plays a central role in the reward circuit, remaining the main structure of an initial reinforcement effect to alcohol and most drug abuse (8.9). Dysfunction of the brain reward circuit which includes the NAc, the bed nucleus of stria terminalis (BNST), anterior limb of the internal capsule (ALIC), and medial forebrain bundle (MFB), is thought to underlie addiction [10, 30, 36].

The NAc has been used in several studies to treat addiction by DBS, showing good results and preventing a relapse [20–28, 30–33]. The relatively close proximity of ALIC and BNST to NAc, structures involved in pathophysiology of several psychiatric disorders (OCD, MDD, anxiety disorders), may also play a pivotal role in the effects of DBS in addiction [26, 28–31, 33]. The ALIC contains white-matter bundles such as anterior thalamic radiation and MFB connecting the core reward circuit structures. The ALIC with its passing fibres also constitutes a promising DBS target for addiction. The anatomical neighbourhood of NAc and ALIC makes it feasible to plan a stereotactic trajectory through both structures with simultaneous neurostimulation [26, 28, 29].

Indeed, the largest to date, open-label pilot study revealed the effectiveness of both structures stimulation in preventing heroin relapse [28]. The latest case report presented a combined NAc DBS with anterior capsulotomy in a patient with polysubstance use disorder, showing convenient relapse prevention [33]. These two structures are central to the reward circuit and addiction pathophysiology, highlighting the fact that multi-site neuromodulation or a combined approach of NAc DBS with capsulotomy may be more efficacious than single-site neuromodulation [28, 33]. The recent case report selecting the postero-medial part of NAc with neighbouring BNST showed this to be very effective in a patient with cocaine dependence [30].

Taking into account the relatively small number of individuals treated with DBS for addiction, it remains unclear whether the stimulation of the NAc itself or in combination with white-matter bundles is associated with the greater clinical benefit to patients. Shifting the target more posteriorly and ventrally closer to BNST may be more efficient for addiction, based on a clinical response to bilateral BNST for intractable OCD [37–39].

The limited worldwide experience of DBS in addiction precludes the drawing of conclusions regarding the most effective target, although the NAc is the most commonly selected target [20–25, 28, 30, 32, 33]. Moreover, the stimulation parameters and the mode of stimulation are not standardised among the studies. The stimulation parameters are corrected throughout the studies and individualised as per individual patient responses.

Addiction is a serious global problem. According to the National Survey on Drug Use and Health (NSDUH), 19.7 million American adults (aged 12 and older) battled a substance use disorder in 2017. In the same year, 8.5 million American adults suffered from both a mental health disorder and a substance use disorder, or a co-occurring disorder. Drug abuse and addiction cost American society alone more than $740 billion annually in lost workplace productivity, healthcare expenses, and crime-related costs. These facts should lead to the promotion of more well designed studies to better understand the underlying mechanism of DBS for addiction, and to define the selection criteria for addicted patients who might benefit from DBS procedures. Addiction with comorbid mental disorders may become a new established indication for DBS in the future, in the same way that movement disorders are nowadays.

Acknowledgments: *This manuscript was written without financial funding. We would like to thank Mr. Stanisław Choński for his help in searching the literature that was used to write this manuscript.*

Conflict of the interest: *None.*

References

1. van den Bosch LMc, Verheul R. Patients with addiction and personality disorder: Treatment outcomes and clinical implications. Curr Opin Psychiatry. 2007; 20(1): 67–71, doi: 10.1097/YCO.0b013e328011740c, indexed in Pubmed: 17143086.
2. Di Chiara G, Bassareo V, Fenu S, et al. Dopamine and drug addiction: the nucleus accumbens shell connection. Neuropharmacology. 2004;

47 Suppl 1: 227–241, doi: 10.1016/j.neuropharm.2004.06.032, indexed in Pubmed: 15464140.
3. Greenberg BD, Gabriels LA, Malone DA, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. Mol Psychiatry. 2010; 15(1): 64–79, doi: 10.1038/mp.2008.55, indexed in Pubmed: 18490925.
4. Nuttin B, Wu H, Mayberg H, et al. Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders. J Neurol Neurosurg Psychiatry. 2014; 85(9): 1003–1008, doi: 10.1136/jnnp-2013-306580, indexed in Pubmed: 24444853.
5. Zyss T, Zieba A, Hese RT, et al. [Deep brain stimulation--the newest physical method of treatment of depression]. Psychiatr Pol. 2010; 44(3): 301–317, indexed in Pubmed: 20672511.
6. Antosik-Wójcińska AZ, Święcicki Ł. The use of DBS stimulation in mental disorders - opportunities and risks. Psychiatr Pol. 2015; 49(4): 791–800, doi: 10.12740/PP/25162, indexed in Pubmed: 26488354.
7. Beszłej JA, Wieczorek T, Kobyłko A, et al. Deep brain stimulation: new possibilities for the treatment of mental disorders. Psychiatr Pol. 2019; 53(4): 789–806, doi: 10.12740/PP/OnlineFirst/103090, indexed in Pubmed: 31760410.
8. Adinoff B. Neurobiologic processes in drug reward and addiction. Harv Rev Psychiatry. 2004; 12(6): 305–320, doi: 10.1080/10673220490910844, indexed in Pubmed: 15764467.
9. Ikemoto S. Brain reward circuitry beyond the mesolimbic dopamine system: a neurobiological theory. Neurosci Biobehav Rev. 2010; 35(2): 129–150, doi: 10.1016/j.neubiorev.2010.02.001, indexed in Pubmed: 20149820.
10. Berridge KC, Kringelbach ML. Pleasure systems in the brain. Neuron. 2015; 86(3): 646–664, doi: 10.1016/j.neuron.2015.02.018, indexed in Pubmed: 25950633.
11. Olsen CM. Natural rewards, neuroplasticity, and non-drug addictions. Neuropharmacology. 2011; 61(7): 1109–1122, doi: 10.1016/j.neuropharm.2011.03.010, indexed in Pubmed: 21459101.
12. Blum K, Werner T, Carnes S, et al. Sex, drugs, and rock 'n' roll: hypothesizing common mesolimbic activation as a function of reward gene polymorphisms. J Psychoactive Drugs. 2012; 44(1): 38–55, doi: 10.1080/02791072.2012.662112, indexed in Pubmed: 22641964.
13. Jung HHo, Kim CH, Chang JH, et al. Bilateral anterior cingulotomy for refractory obsessive-compulsive disorder: Long-term follow-up results. Stereotact Funct Neurosurg. 2006; 84(4): 184–189, doi: 10.1159/000095031, indexed in Pubmed: 16912517.
14. Pouratian N, Sharim J. Anterior cingulotomy for the treatment of chronic intractable pain: A systematic review. Pain Physician. 2016; 19(8): 537–550, doi: 10.36076/ppj/2016.19.537, indexed in Pubmed: 27906933.
15. Foltz EL, White LE. Pain "relief" by frontal cingulumotomy. J Neurosurg. 1962; 19: 89–100, doi: 10.3171/jns.1962.19.2.0089, indexed in Pubmed: 13893868.
16. Kanaka TS, Balasubramaniam V. Stereotactic cingulumotomy for drug addiction. Appl Neurophysiol. 1978; 41(1-4): 86–92, doi: 10.1159/000102404, indexed in Pubmed: 365103.
17. Medvedev SV, Anichkov AD, Polyakov II. Physiological mechanisms of the effectiveness of bilateral stereotactic cingulotomy against strong psychological dependence in drug addicts. Fiziol Cheloveka . 2003; 29(4): 117–123, indexed in Pubmed: 13677207.
18. Müller D, Roeder F, Orthner H. Further results of stereotaxis in the human hypothalamus in sexual deviations. First use of this operation in addiction to drugs. Neurochirurgia (Stuttg). 1973; 16(4): 113–126, doi: 10.1055/s-0028-1090504, indexed in Pubmed: 4581040.
19. Gao G, Wang X, He S, et al. Clinical study for alleviating opiate drug psychological dependence by a method of ablating the nucleus accumbens with stereotactic surgery. Stereotact Funct Neurosurg. 2003; 81(1-4): 96–104, doi: 10.1159/000075111, indexed in Pubmed: 14742971.
20. Kuhn J, Lenartz D, Huff W, et al. Remission of alcohol dependency following deep brain stimulation of the nucleus accumbens: valuable therapeutic implications? J Neurol Neurosurg Psychiatry. 2007; 78(10): 1152–1153, doi: 10.1136/jnnp.2006.113092, indexed in Pubmed: 17878197.
21. Müller UJ, Sturm V, Voges J, et al. Successful treatment of chronic resistant alcoholism by deep brain stimulation of nucleus accumbens: first experience with three cases. Pharmacopsychiatry. 2009; 42(6): 288–291, doi: 10.1055/s-0029-1233489, indexed in Pubmed: 19924591.
22. Kuhn J, Gründler TOJ, Bauer R, et al. Successful deep brain stimulation of the nucleus accumbens in severe alcohol dependence is associated with changed performance monitoring. Addict Biol. 2011; 16(4): 620–623, doi: 10.1111/j.1369-1600.2011.00337.x, indexed in Pubmed: 21762290.
23. Voges J, Müller U, Bogerts B, et al. Deep brain stimulation surgery for alcohol addiction. World Neurosurg. 2013; 80(3-4): S28.e21–S28.e31, doi: 10.1016/j.wneu.2012.07.011, indexed in Pubmed: 22824557.
24. Müller UJ, Sturm V, Voges J, et al. Nucleus accumbens deep brain stimulation for alcohol addiction - safety and clinical long-term results of a pilot trial. Pharmacopsychiatry. 2016; 49(4): 170–173, doi: 10.1055/s-0042-104507, indexed in Pubmed: 27145161.
25. Zhou H, Xu J, Jiang J. Deep brain stimulation of nucleus accumbens on heroin-seeking behaviors: a case report. Biol Psychiatry. 2011; 69(11): e41–e42, doi: 10.1016/j.biopsych.2011.02.012, indexed in Pubmed: 21489407.
26. Valencia-Alfonso CE, Luigjes J, Smolders R, et al. Effective deep brain stimulation in heroin addiction: a case report with complementary intracranial electroencephalogram. Biol Psychiatry. 2012; 71(8): e35–e37, doi: 10.1016/j.biopsych.2011.12.013, indexed in Pubmed: 22281120.
27. Kuhn J, Möller M, Treppmann JF, et al. Deep brain stimulation of the nucleus accumbens and its usefulness in severe opioid addiction. Mol Psychiatry. 2014; 19(2): 145–146, doi: 10.1038/mp.2012.196, indexed in Pubmed: 23337942.
28. Chen L, Li N, Ge S, et al. Long-term results after deep brain stimulation of nucleus accumbens and the anterior limb of the internal capsule for preventing heroin relapse: An open-label pilot study. Brain Stimul. 2019; 12(1): 175–183, doi: 10.1016/j.brs.2018.09.006, indexed in Pubmed: 30245163.
29. Zhang C, Huang Y, Zheng F, et al. Death from opioid overdose after deep brain stimulation: A case report. Biol Psychiatry. 2018; 83(1): e9–ee10, doi: 10.1016/j.biopsych.2017.07.018, indexed in Pubmed: 28882316.
30. Gonçalves-Ferreira A, do Couto FS, Rainha Campos A, et al. Deep brain stimulation for refractory cocaine dependence. Biol Psychiatry. 2016; 79(11): e87–e89, doi: 10.1016/j.biopsych.2015.06.023, indexed in Pubmed: 26235303.
31. Zhang C, Wei H, Zhang Y, et al. Increased dopamine transporter levels following nucleus accumbens deep brain stimulation in methamphetamine use disorder: A case report. Brain Stimul. 2019; 12(4):

1055–1057, doi: 10.1016/j.brs.2019.02.023, indexed in Pubmed: 30853339.

32. Ge S, Chen Y, Li N, et al. Deep brain stimulation of nucleus accumbens for methamphetamine addiction: Two case reports. World Neurosurg. 2019; 122: 512–517, doi: 10.1016/j.wneu.2018.11.056, indexed in Pubmed: 30448569.
33. Zhu R, Zhang Y, Wang T, et al. Deep brain stimulation of nucleus accumbens with anterior capsulotomy for drug addiction: A case report. Stereotact Funct Neurosurg. 2020; 98(5): 345–349, doi: 10.1159/000509313, indexed in Pubmed: 32846423.
34. Zrinzo L, Foltynie T, Limousin P, et al. Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. J Neurosurg. 2012; 116(1): 84–94, doi: 10.3171/2011.8.JNS101407, indexed in Pubmed: 21905798.
35. Fenoy AJ, Simpson RK. Risks of common complications in deep brain stimulation surgery: management and avoidance. J Neurosurg. 2014; 120(1): 132–139, doi: 10.3171/2013.10.JNS131225, indexed in Pubmed: 24236657.
36. Luigjes J, van den Brink W, Feenstra M, et al. Deep brain stimulation in addiction: a review of potential brain targets. Mol Psychiatry. 2012; 17(6): 572–583, doi: 10.1038/mp.2011.114, indexed in Pubmed: 21931318.
37. Luyten L, Hendrickx S, Raymaekers S, et al. Electrical stimulation in the bed nucleus of the stria terminalis alleviates severe obsessive-compulsive disorder. Mol Psychiatry. 2016; 21(9): 1272–1280, doi: 10.1038/mp.2015.124, indexed in Pubmed: 26303665.
38. Greenberg BD, Gabriels LA, Malone DA, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. Mol Psychiatry. 2010; 15(1): 64–79, doi: 10.1038/mp.2008.55, indexed in Pubmed: 18490925.
39. Naesström M, Hariz M, Strömsten L, et al. Deep brain stimulation in the bed nucleus of stria terminalis in obsessive-compulsive disorder-1-year follow-up. World Neurosurg. 2021; 149: e794–e802, doi: 10.1016/j.wneu.2021.01.097, indexed in Pubmed: 33540102.

REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 5, pages: 450–461
DOI: 10.5603/PJNNS.a2021.0058

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

Cerebral microbleeds in neurological practice: concepts, diagnostics and clinical aspects

Aleksandra Wach-Klink[1], Ewa Iżycka-Świeszewska[2, 3], Grzegorz Kozera[4], Piotr Sobolewski[1, 5]

[1]Department of Neurology and Stroke Unit in Sandomierz, Jan Kochanowski University, Kielce, Poland
[2]Department of Pathology and Neuropathology, Medical University of Gdansk, Poland
[3]Department of Pathomorphology, Copernicus Hospitals Gdansk, Poland
[4]Medical Simulation Centre, Medical University of Gdansk, Poland
[5]Collegium Medicum, Jan Kochanowski University, Kielce, Poland

ABSTRACT

Introduction: Due to the widespread use of magnetic resonance imaging (MRI) in neurological diagnostics, the number of patients detected as having cerebral microbleeds (CMBs) continues to increase. However, their clinical impact still remains controversial, especially the question of whether CMBs significantly increase the risk of life-threatening intracerebral haemorrhage (ICH) in patients undergoing intravenous thrombolysis (IVT) or endovascular thrombectomy (EVT), or in patients on anticoagulant therapy or statins.

State of the art: The term 'CMB' is a radiological concept that aims to illustrate microscopic pathology of perivascular hemosiderin deposits corresponding most probably to small foci of past bleeding. MRI images in sequence T2*-GRE and susceptibility-weighted imaging (SWI) are used for a diagnosis of a CMB. This review summarises the current knowledge regarding the definition, prevalence, genetics, risk factors, radiological diagnosis and differential diagnosis of a CMB. We discuss its role as an indicator of future ischaemic or haemorrhagic events in high risk patients or those on antiplatelet or anticoagulant therapy, and its prognostic value for reperfusion strategies and for the development of dementia.

Future direction: The place of CMBs in current guidelines is explored herein. It must be emphasised that the recommendations relating to CMBs are expert opinions. Therefore, at the end of this review, we pose a number of questions that future clinical trials should answer.

Key words: cerebral microbleed, small vessel disease, intravenous thrombolysis, endovascular thrombectomy, antithrombotic therapy

(*Neurol Neurochir Pol 2021; 55 (5): 450–461*)

Introduction

Due to the ever-increasing use of head magnetic resonance imaging (MRI), the population of patients being diagnosed with cerebral microbleeds (CMBs) continues to increase [1, 2]. The term CMB is a radiological concept that aims to illustrate microscopic pathology of perivascular hemosiderin deposits corresponding to small foci of past bleeding. The detection of CMBs in neuroimaging mainly concerns the older population, patients with previous haemorrhagic and ischaemic strokes, patients with various types of dementia, patients with neurogenerative diseases of the nervous system, and patients with hypertension and amyloid angiopathy [2–4].

The most important clinical question is whether CMBs increase the risk of a life-threatening intracerebral haemorrhage (ICH), especially in patients undergoing intravenous thrombolysis (IVT), endovascular thrombectomy (EVT) or who are being treated with anticoagulants or statins. However,

Address for correspondence: Aleksandra Wach-Klink, Department of Neurology and Stroke Unit of UJK and of Holy Spirit Specialist Hospital in Sandomierz, 13 Schinzla Str., 27-600 Sandomierz, Kielce, Poland; e-mail: aleksandrawach4@gmail.com

Received: 15.02.2021 Accepted: 21.06.2021 Early publication date: 11.08.2021

these important clinical problems in patients with CMBs are not yet fully understood, which means that the published recommendations are mainly based on observational studies or on the experience of experts [5–9].

This review summarises today's evidence-based clinical data regarding CMBs and their impact on IS and ICH risk.

State of the art

Definition and prevalence

Signs of small vessel disease (SVD) on conventional MRI include recent small subcortical infarcts, white matter magnetic resonance (MR) hyperintensities, lacunes, prominent perivascular spaces, cerebral microbleeds, and atrophy [10]. The term 'CMB' is in fact a radiological concept that aims to illustrate microscopic pathology of perivascular hemosiderin deposits corresponding to small foci of past bleeding [10, 11]. Support for this notion has been provided in post mortem correlative MR and histopathological studies. Histopathologically, areas of signal loss on gradient echo T2*-weighted sequences in the brains of deceased patients represent hemosiderin deposits indicating previous extravasation of blood [Supplementary reference 1, 2]. CMBs develop alongside small arteries, arterioles or capillaries, usually demonstrating fibrolipohyalinosis or amyloid microangiopathy. Therefore, hemosiderin-laden macrophages are presented in their proximity [Supplementary reference 3]. In the population-based Mayo Clinic Study of Ageing, the age- and sex-specific prevalence of core cerebrovascular disease lesions (infarctions, cerebral microbleeds, and white-matter hyperintensities detected with magnetic resonance imaging) were assessed. Among 1,462 participants without dementia, core cerebrovascular disease features increased with age. The prevalence of CMBs was 13.6%, of infarcts 11.7%, and of abnormal white-matter hyperintensities 10.7%. Infarcts and cerebral microbleeds are more common among men. In contrast, abnormal white-matter hyperintensities are more common among women aged 60 to 79 and men aged 80+ [10].

Hemosiderin deposits are superparamagnetic, and thus they show considerable internal magnetisation and magnetic susceptibility into the MRI magnetic field [10]. Their detection on MRI demands proper selection of appropriate sequences. CMBs are not visible in computed tomography. Consequently, the sensitivity of CMB detection varies with the MRI parameter i.e. pulse sequence, spatial resolution, magnetic field strength, and post-processing method [11]. It is estimated that CMBs occur in 3–7% of healthy people aged 45 to 50. Their presence increases with age: in people 80+, the prevalence of CMBs varies from 17.8% to 38.3% [1, 2] and is higher in men [Supplementary reference 3, 4]. In the Mayo Clinic Study of Ageing, CMB frequency increased with age with each succeeding decade (11% aged 60–69, 22% aged 70–79, and 39% aged 80+) [Supplementary reference 5]. A higher presence of CMBs in also reported in patients with first-ever and recurrent haemorrhagic or ischaemic stroke, Alzheimer's Disease, vascular cognitive impairment or vascular dementia, hypertensive vasculopathy and cerebral amyloid angiopathy (CAA) [2, 12–15]. Apart from dementia, the presence of multiple CMBs is also associated with a global neuropsychiatric disorder burden, in particular symptoms of depression and disinhibition [Supplementary reference 6]. A high extent of CMBs may also induce parkinsonism and other motor symptoms such as gait disturbances. CMBs occur more commonly in PD patients with dementia than in those without dementia [Supplementary reference 7, 8].

Risk factors for CMBs

CMBs can be associated with some of the classical cerebrovascular risk factors, including male gender, advancing age, arterial hypertension (AH), and cigarette smoking [3, 16, 17]. However, any association between CMBs and diabetes [18] and dyslipidemia [19] has been inconsistent across published reports. In a population of patients from the Rotterdam Scan Study, the prevalence of CMBs gradually increased with age, from 6.5% in persons aged 45 to 50 to 35.7% in participants aged 80+ [2].

The number of CMBs is positively correlated with blood pressure values, and CMBs can be interpreted as a type of target organ damage due to chronic hypertension [20]. The results of a study on a general population in Sweden showed that both lobar and non-lobar CMBs were associated with the presence of AH [17]. Among cardiovascular risk factors determining the presence of CMBs in the lobar location, amyloid angiopathy and increased diastolic blood pressure have been identified [2]. A correlation between the duration of atrial fibrillation (AF) and the progression of CMBs during the observation period has been also reported [21].

Alcohol overuse may induce CMBs. In the AGES-Reykjavik study, heavy alcohol consumption increased the presence of CMBs in deep structures when compared to light or moderate consumption [1]. CMBs also constitute a ubiquitous manifestation of traumatic brain injury of all severities, and their presence is strongly associated with that of traumatic axonal injury (TBI). About 40% of the patients who died during the acute phase of TBI, and 47% of those who survived 12 months after a TBI, showed multifocal, perivascular and parenchymal CMBs in the grey matter [22].

CMBs develop in a high percentage of patients with brain tumours treated with radiation therapy within the first years after treatment. Significant factors for the development of a CMB include younger age at time of proton beam radiation therapy (PBT), a higher maximum radiation therapy dose, and a higher percentage and a higher volume of brain exposed to ≥ 30 Gy [23]. Bacterial endocarditis is also a condition often associated with the presence of CMBs [24]. A negative impact of obesity, and a positive impact of fish oil consumption, on the occurrence of CMBs have been observed [25]. The mere presence of a CMB is also a risk factor for its further progression [2, 26].

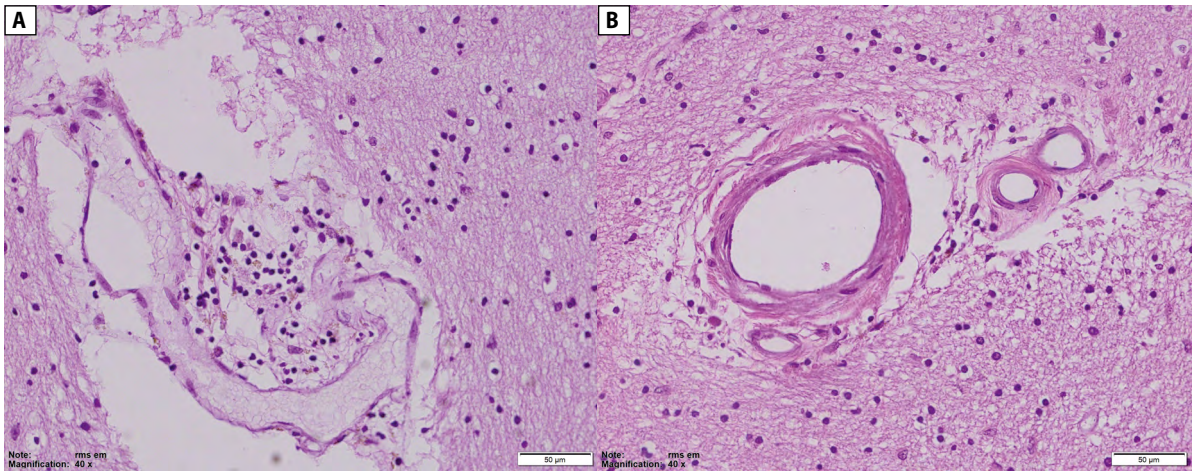


Figure 1. A. Perivenular space widening with accumulation of hemosiderin-laden macrophages and lymphocytes (HE, 400x) (Department of Pathology and Neuropathology, Medical University of Gdansk); **B.** Cerebral arterioles of different diameters presenting sclerotic changes and early perivascular space widening with single macrophages (HE, 400x) (Department of Pathology and Neuropathology, Medical University of Gdansk)

Neuropathology

Neuropathologically, SVD has been referred to using a wide range of terms, such as *status fibrosus*, *status lacunaris* or entity of hypertensive Binswanger's encephalopathy [27]. Age, vascular risk factors, and genetic predispositions are connected to neuro-vascular unit and cerebral small blood vessel (diameter 30–400 um) wall alterations. There are rare inherited forms and, sporadic types prevalent in older patients, with the most common being hypertensive arteriopathy (deep perforator arteriopathy) and cerebral amyloid arteriopathy (CAA).

Pathological changes of blood vessels in hypertensive arteriopathy include arteriosclerosis, fibrinoid necrosis and, although this is a term now less commonly used, lypohyalinosis. These changes are caused initially by endothelial and blood-brain barrier dysfunction. The molecular pathogenesis of arteriolosclerosis is not well understood, but its main steps encompass structural changes of the basement membranes, progressive loss of smooth myocytes, intimal thickening, replacement by collagen fibres (fibrosis), and protein depositions.

A second form, sporadic CAA, can occur in or outside an AD setting, and is characterised by blood vessel wall deposition of amyloid B protein (mainly AB40). AB in the soluble form is eliminated from the brain within the interstitial fluid along the vessels and along glial water channels of the glymphatic system. CAA intensity and presence have been shown to correlate with APOE specific alleles, and cerebral B-amyloid burden in PET studies.

CMBs correspond to perivascular hemosiderin-laden macrophages, hemosiderin deposits, iron-positive siderophages and small erythrocytic extravasations (Fig. 1A, B). They are identified in the setting of ICH and ischaemic stroke, and in AD, and are more frequently seen with increasing age. Some studies show also relations to the ischaemic mechanisms. In hypertensive arteriopathy, CMBs are found in the deep grey matter, white matter, and infratentorially, while lobar (cortico-subcortical) mainly occipital or frontal lesions correspond to CAA.

The mixed type of CMB distribution points to the coexistence of both types of vascular pathology; in addition, some authors have proposed that these two diseases create a continuum of age-related vascular pathology [28]. Some studies have shown no neuropathological evidence for a topographical relation between CMB and CAA [29]. However, there have been few radiological-neuropathological correlation studies in CMB . Pathophysiologically, the causes and consequences of CMB are multifactorial: impaired vasodilatation and autoregulation, loss of elasticity, vessel stiffening, aberrant blood flow, interstitial fluid drainage, fluctuation in blood flow, hypoperfusion, inflammation (microglial activation), myelin dysfunction, and finally neurodegeneration [30, 31].

Genetics

Genetic factors determining the presence of CMBs include polymorphisms linked with sporadic CMBs and less common mutations seen with familial conditions. The most common gene polymorphism associated with sporadic CMBs is the apolipoprotein E (APOE) gene on chromosome 19. Apolipoprotein E (ApoE) is genetically associated with cerebral β-amyloidosis (Aβ). ApoE has a determining role in the progression of Aβ deposition, since having the APOE ε2 and APOEε4 alleles is the major risk factor for CAA and Alzheimer's Disease (AD). APOE ε2 and APOE ε4 have each been independently associated with lobar CMBs [31]. Essential hypertension is a disease with a complex and multifactorial aetiology inherited by poligenes. Allelic variants, so-called 'candidate genes', only predispose to higher pressure values,

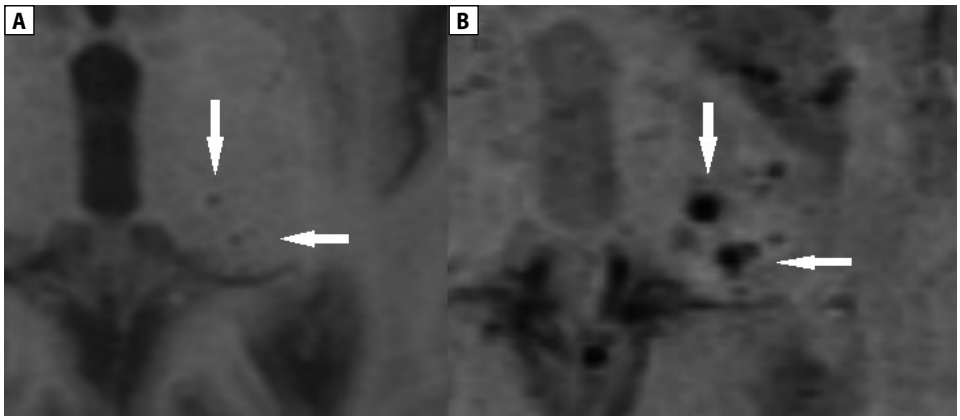


Figure 2. 'Blooming effect' in T1 (**A**) and T2* GRE (**B**) images (Department of Radiology of Holy Spirit Specialist Hospital in Sandomierz)

and only their combined action with environmental factors leads to an increase in blood pressure [32].

MRI diagnostics

The basis of blood-breakdown product detection in patients with CMBs is sequence T2*-GRE. MRI images in this sequence are typically larger than the physical size of the underlying hemosiderin deposits. This phenomenon is called the 'blooming effect' and significantly aids visual interpretation of CMBs [Fig. 2A, B]. The extent of blooming varies according to the MRI sequence parameter, especially echo, but also magnetic field strength (7T > 3T > 1,5T), slice thickness, flip angle, spatial resolution (3D > 2D) and image postprocessing technique (susceptibility-weighted imaging, SWI) [10, 15, 34]. SWI is another particularly effective diagnostic technique in the detection of CMBs (Fig 2A, B) [3, 34]. Studies have shown that SWI can detect significantly more CMBs (at least 67% more) compared to conventional T2*-GRE [35]. CMBs are characterised by a lack of signal hyperintensity in the T1 and T2 sequences.

According to the current consensus, CMBs are defined as: hypointense lesions (black) on T2*-GRE MRI, round or ovoid, well defined, small, not seen well on T1- or T2-weighted MRI, with the necessary exclusion of clinical history of traumatic diffuse axonal injury, and where at least half of the lesion is surrounded by brain parenchyma [15, 34].

Differential diagnosis

CMBs are by definition smaller than 5-10 mm in diameter. CMBs should be distinguished from mimics and artifacts. Various structures in the brain can give small, dot-like, low-signal areas on T2*-GRE or SWI MRI e.g. blood vessels in the subarachnoid space, calcifications of the basal ganglia, cavernous malformations, haemorrhagic micrometastases especially from melanoma or renal cell carcinoma, and post-traumatic changes. Hence, the diagnostician must carefully review contiguous scans using different MRI sequences and sometimes compare the suspected areas using CT scans [15, 36].

Distribution on MRI

Yakushiji et al. analysed data from 8,595 stroke-free individual participants aged between 55 and 75 from 11 studies for the presence and distribution of CMBs. The authors compared eastern (East Asian) and western (Caucasian) populations. They found that Eastern and Western general populations have different anatomical distributions of CMBs. In their analysis, Eastern populations had higher odds of deep and/or infratentorial or mixed CMBs [37]. CMBs in the lobar and deep locations are associated with hypertensive arteriopathy [20] [Supplementary figure 1a]. Age and APOE4 carrier status act through amyloid load to increase the risk of lobar CMBs, especially located in the occipital and parietal regions of the brain [38], although in patients with amyloid angiopathy CMBs have also been observed located infratentorially [39] [Supplementary figure 1b]. Mixed-location CMBs have been found to be a biomarker of neurodegeneration in a memory clinic population [40]. Also, the Framingham population study showed that hypertension increased the risk of any CMB and, in deep and mixed locations, low total cholesterol and APOE ε4 increased the risk of lobar CMB, and that statin use increased the risk of lobar and mixed location CMB [Supplementary reference 4]. Different distributions of CMBs have been observed in patients with Parkinson's Disease [4], although some studies have indicated an occurrence of strict lobar CMBs in patients with non-dementia Parkinson's Disease [41].

In order to assess the location of, and increase in, the number of CMBs, scales called 'MARS' (*Microbleed Anatomical Rating Scale*, Tab. 2, Supplementary reference 1) and 'BOMBS' (*Brain Observer Microbleed Scale*, Tab. 2, Supplementary reference 2) have been created with the possibility of mapping brain structures.

Clinical implications

Risk of ischaemic and haemorrhagic stroke

In patients with ischaemic stroke (IS), the presence of CMBs is associated with advanced age, diabetes and the previous use of antithrombotics. CMBs located in deep structures

are also associated with the presence of arterial hypertension [18, 42]. An increased risk of ischaemic and haemorrhagic stroke itself has been also reported in patients with CMBs [21, 43, 44]. In a meta-analysis of 13,864 patients from five population-based studies, CMB presence was significantly associated with the incidence of IS and ICH. Pooled analysis of 7,672 patients with ischaemic stroke/TIA (CMBs vs.no CMBs) from 19 studies showed that CMB was associated with an increased risk of recurrent IS and a crude risk of ICH during follow-up [36]. Patients with IS or TIA with CMBs are three times more likely to have a subsequent ICH [21, 45] or recurrent IS [45]. The predictors of ICH in AIS are age, high NIHSS score, and deep, lobar and cortico-subcortical distribution of CMBs. The risk and mortality of ICH increase with the quantity of CMBs [21, 46].

An observational prospective study based on 168 ICH survivors who underwent 1.5T MRI at ICH onset (median follow up 3.4 years) showed that prognostic and associated factors of incident CMBs differed according to the index ICH location. Whereas in lobar ICH, incident CMBs were associated with haemorrhagic biomarkers, in non-lobar ICH the ischaemic burden increased [47]. In the MISTRAL study (MIcrobleeds predict STRoke in ALzheimer's) carried out in 333 patients with AD (in one in three of whom a CMB was imaged), the main measures were stroke-related mortality, incident stroke, and ICH. Patients with AD with lobar CMBs had an increased risk of stroke and stroke-related mortality, and the presence of non-lobar CMBs was associated with an increased risk of cardiovascular events and cardiovascular mortality [48].

Dementia and neurodegenerative diseases

No strong association between the presence of CMBs and the development of dementia has been shown in prospective studies. However, adjusted meta-analysis of three population-based studies (Rotterdam, Framingham Heart and AGES Reykjavik), which included dementia-free participants at baseline, revealed that CMBs were independently associated with a marginally increased risk of all-cause incidence of dementia [5, 49]. In studies on an elderly population, CMB presence at baseline was associated with a doubled risk of dementia in the crude meta-analysis, although this was not confirmed in the adjusted meta-analysis [50, 51].

In a Japanese observational study, the presence of CMBs in patients with dementia was not associated with deterioration of memory function. But the presence of more than one CMB, and their mixed location, affected the development of dementia regardless of its clinical picture [52]. A report concerning stroke clinic patients showed that CMBs were consistently associated with frontal-executive impairment and had prognostic relevance for long-term cognitive outcome [53].

CMBs are associated with decreased cerebrospinal fluid amyloid levels and are related to the ApoE e4 allele, as well as other imaging manifestations typical of small vessel disease [Supplementary reference 9]. CMBs are found in c.24-33% of Alzheimer's Disease dementia patients [Supplementary reference 10–12]. In patients with AD or vascular dementia, those with lobar-only CMBs have a higher amyloid burden than those with mixed lobar and deep CMBs or deep-only CMBs. Apolipoprotein E ε4 homozygosity is associated with a greater risk of lobar CMBs [Supplementary reference 13].

The mixed location of CMBs is thought to be associated with neurodegenerative diseases of the nervous system [54]. CMBs are often detected in Parkinson's Disease, but different localisations of CMBs, including deep brain hemispheres, are more often given in this disease [4]. Kim et al. compared the occurrence of CMBs in patients with PD and multiple system atrophy (MSA), and found no difference between the number and distribution of CMBs in both groups of patients [55]. No reports of CMBs in other neurodegenerative diseases have been found.

Chronic Kidney Disease and haemodialysis

Chronic kidney disease is mentioned as one of the risk factors for CMBs, especially in patients treated with haemodialysis. A decrease in eGFR (estimated glomerular filtration rate) is associated with the occurrence of CMBs and an increase in their number [56]. MRI studies of cohorts of dialysed patients have shown asymptomatic markers of small vessel disease, including silent cerebral infarction, white matter hypersensitivity, and CMBs. However, all studies evaluating the problem of CMBs in dialysis patients to date have been conducted in Asian populations. The presence of these changes was associated with the future occurrence of strokes, memory impairment, and dementia [57]. Among 180 patients examined by Qian et al., 36.1% had detected CMBs. Deeply located CMBs were significantly associated with haemodialysis treatment, mean arterial pressure (MAP) and the number of lacunar infarctions, but were not associated with dialysis modality or heparin use [58].

Stroke course and treatment

Global risk and outcome

Sakuta et al. found that the presence of CMBs is predicts poor outcome in minor ischaemic stroke patients [59]. Among 1,963 participants of the Framingham Heart Study, with an average follow-up of 7+ years, CMBs were not strongly associated with increased mortality of any cause, and after adjusting for cardiovascular risk factors and preventative medication, there was no statistical significance [60]. In the Rotterdam Study, 3,979 participants were observed for 5+ years. Localisation of CMBs in deep structures of the brain and subtentorial areas was significantly associated with an increased risk of mortality of any cause, regardless of cardiovascular risk factors. The risk of mortality increased with the number of CMBs [61].

The results of the PROspective Study of Provastatin in the Elderly at Risk (PROSPER) showed that in the 7-years follow up, the presence of CMBs was associated with a six-times

greater risk of stroke-related death. Individuals with lobar CMBs had a seven-fold increase in stroke-related deaths (but not cardiovascular deaths), and individuals with non-lobar CMBs had a doubled risk of cardiovascular (but not stroke-related) death [62].

Data from the prospective study by Soo et al. showed that the risk of increase in mortality from ICH with quantity of CMBs was as follows: 0.6% (no CMBs); 0.9% (1 CMB); 1.5% (2–4 CMBs); and 3.8% (5 or more CMBs). Mortality from IS and myocardial infarction did not increase with quantity of CMBs [46].

In an overall meta-analysis including studies across different populations (IS/TIA; memory clinic high risk elderly cohort and patients from population-based studies) of 14,433 participants, CMB presence was an independent predictor of all-cause mortality [46]. In the MISTRAL study, in a cohort of patients with Alzheimer's Disease, lobar CMBs increased the risk of fatal stroke by more than 30 times, and CMBs located in deep structures of the brain led to a 12-fold increased risk of cardiovascular death [48].

Outcome after reperfusion strategies

Due to the destruction of the walls of the small arteries and arterioles adjacent to CMBs by lipohyalinosis, formed microaneurysms, hypertension and/or cerebral amyloid angiopathy, there is a predisposition towards brain haemorrhage. The risk of intracerebral haemorrhage increases if the patient is undergoing reperfusion therapy or is being treated with anticoagulants.

Therefore, multiple CMBs should serve as an especially loud warning of a potential risk for major brain bleeding when thrombolytics and antithrombotic agents are being considered [Supplementary reference 14].

IV-thrombolysis

Intravenous thrombolysis with rt-PA is the most widely used treatment for AIS [8, 9] Clinical studies and meta-analyses evaluating the association of CMBs with outcomes of AIS patients treated with IVT have shown contradictory results [63–70]. Some of these studies did not indicate a relationship between high CMB burden and poor long-term outcome [66, 67], but in contrast other studies did point to such an association [68–70]. A multicentre prospective European study and a meta-analysis by Arca et al. showed that only a high number of CMBs (≥ 10) was associated with higher mortality in patients treated with intravenous thrombolysis (IVT) [63]. Similar conclusions resulted from the multistep algorithm to model 90-day modified Rankin Scale scores in patients with ≤10 vs. >10 CMBs who did or did not receive IVT developed by Schlemm et al. [64]. In the meta-analysis by Wang et al., no effect of CMBs on mortality in IVT patients was found [65].

The results of studies in the context of occurrence of sICH after IVT in patients with CMBs detected before treatment are also contradictory [71, 72]. Zand et al. indicated that a high CMB burden (> 10) is associated with a higher risk of sICH [73]. The same conclusion was confirmed by other studies and meta-analyses [65, 73]. The recent meta-analysis by Yan et al. of 2,407 participants from nine studies showed that pretreatment CMBs were associated with increased incidence of sICH in AIS patients receiving IVT. However, these results were not convincing enough to establish the presence of a CMB as a contraindication to IVT [74].

Endovascular thrombectomy (EVT)

Prospective data regarding the impact of CMBs on the safety and efficacy of mechanical thrombectomy in patients with ASI remains limited. Choi and al. analysed the impact of CMBs on long-term outcome following recanalisation in patients with AIS. They found that the presence of a CMB, and high burden and lobar location, are independent predictors of poor outcomes, and may increase sICH especially in patients with recanalisation after large vessel occlusion, more than in those without recanalisation [75]. In the study by Shi et al., 6.8% had ≥ 2 CMBs, and only 1 patient had ≥ 5 CMBs. The authors showed that the presence of a CMB did not increase haemorrhagic transformation (HT) and mortality following EVT for AIS [76].

To date, only one meta-analysis based on the results of four studies with a total of 598 patients has been published. CMBs were present in 18%, and ≥ 5 CMBs in only 1% of patients. The risk of ICH after EVT did not significantly differ between patients with and without CMBs [77].

Carotid endarterectomy (CEA) and angioplasty with stenting (CAS)

Only two reports have discussed the problematic presence of CMBs in patients undergoing CAS. Among the whole group of patients treated by Kakumato et al., 20.5% had CMBs initially, and 8% developed new CMBs straight after CAS. New CMBs appeared on the same side of CAS in all patients. New CMBs appeared significantly more frequently in the CMB-positive group than in the CMB-negative one [78]. This observation confirmed the results of the study conducted by Ito et al., which found that new CMBs also developed after CAS, mostly in the territory of the treated carotid artery [79].

In a multicentre European study, 162 patients were treated with CEA or CAS. In both groups, there was no manifestation of ICH after surgery. CMBs appeared in only 6.0% of patients after CAS, and in 6.4% after CEA, without statistical significance between the groups [80].

Antithrombotic therapies

Antiplatelets

There has been long-running uncertainty as to whether during chronic use of antiplatelet agents there is incidence of CMBs or an increase in the number of them, and what their location is, and whether IS and/or ICH occurs more frequently.

Many studies have been carried out on this subject, but they have mainly been observational studies.

There have been some systemic reviews and meta-analyses discussing the relationship between antiplatelet drug use and CMBs [81–83]. The meta-analysis by Liu et al., based on 11 studies involving 10,429 participants, revealed a significant relationship between antiplatelet therapy and the occurrence of CMBs in both ICH and IS patients. In the case of stratification based on ethnicity, the relationship between antiplatelet therapy and CMBs was at a similar level of significance for ICH and IS for an Asian population, but was not significant for ICH and IS for patients from European countries [81]. A review of the literature including 1,460 patients with ICH and 3,817 with IS/TIA showed that CMBs were almost three times more common in the group of ICH, and almost six times more often seen in patients using antiplatelet drugs [82]. The meta-analysis conducted by Wang at al., based on the results of 10 studies, showed that patients with multiple CMBs had an almost quadrupled risk of developing ICH compared to patients with a single CMB. A very strong relationship has been found between the presence of CMBs and the subsequent occurrence of ICH in patients treated with antiplatelet agents [83]. The meta-analysis by Qui et al. was based on the results of 37 studies with a total of 20,988 participants. The analysis showed that CMBs were more frequent in antiplatelet users, and in those in strictly lobar rather than in than deep or infratentorial locations. ICH was higher in participants with CMBs than in those without CMBs [84].

The results of a recently conducted study emphasise that the duration of antiplatelet therapy can influence the prevalence of CMBs and the incidence of ICH [85].

Oral anticoagulants

Atrial fibrillation (AF) quintuples the risk of IS. Therefore, to reduce this risk, anticoagulants are indicated [86]. For this reason, for many years vitamin K antagonists (VKAs) have been used. We have had the results of several studies assessing the risk of ICH in patients using VKAs, although most of these studies did not take into account the presence of CMBs. NOACs (novel oral anticoagulants) have been used for several years, but the issue of any correlation between the occurrence of a CMB and the safety of treatment has not been properly studied.

Previous studies, not assessing the presence of CMBs in the MRI, showed that NOAC-related ICH patients had lower baseline haematoma volume and were less likely to have severe neurological deficits (> 10 points according to NIHSS-National Institutes of Health Stroke Scale score) on admission than VKA-ICH patients [87].

In turn, in the international collaborative multicentre pooled analysis CROMIS-2 (Clinical Relevance of Microbleeds In Stroke), no differences in baseline ICH volume, haematoma expansion, 90-day mortality, or functional outcome in ICH-patients treated with NOAC and VKA were found [88].

Graff-Radford et al. showed that anticoagulant use correlated with the presence of CMBs in the general population, and that the predictors for presence/absence of CMBs included older age at magnetic resonance imaging and male sex. The predictors of CMB count in the CMB-positive group were male sex and amyloid load detected with positron emission tomography (PET) [Supplementary reference 15].

In the multicentre prospective, observational study RASUNOA (Rationale and Design of the Registry of Acute Stroke Under Novel Oral Anticoagulants) location and counts of CMBs in patients with IS and ICH prior treated with NOAC were analysed. The proportion of patients with at least one CMB, and the absolute number of CMBs, were higher in the ICH group [89]. Lioutas et al. evaluated the incidence of CMBs in ICH patients treated with anticoagulants before stroke onset. In the study group, CMB prevalence was 51% (52% in VKA, 48% in NOAC). NOAC patients had a lower CMB count, and ≥ 5 CMBs were less prevalent in the NOAC group [90].

Balancing the risks of recurrent ischaemic stroke and intracranial haemorrhage is important for patients treated with antithrombotic therapy after ischaemic stroke or transient ischaemic attack.

In the aforementioned CROMIS-2 study of patients with atrial fibrillation anticoagulated after recent IS or TIA, CMBs were independently associated with sICH risk [91]. The results of the meta-analysis by Charidimou et al. based on a group of 1,552 patients pointed to a particular risk of ICH in patients in whom ≥ 5 CMBs had been detected [92].

In the pooled analysis of individual patient data from the Microbleeds International Collaborative Network (MICON), which includes 38 hospital-based prospective cohort studies from 18 countries, the authors found the novel MICON-intracranial haemorrhage (MICON-ICH) and MICON-ischaemic stroke (MICON-IS) risk scores — which include clinical variables and MRI-detected cerebral microbleeds — to predict intracranial haemorrhage in patients taking antithrombotic therapy after ischaemic stroke or transient ischaemic attack. These scores are new means by which to assess the long-term risk of intracranial haemorrhage and ischaemic stroke [Supplementary reference 16]. In Greenberg's opinion, the MICON-ICH risk score is substantially better than the discrimination offered by scales such as HASBLED that do not incorporate CMBs [Supplementary reference 17].

Statins

The results of studies assessing the impact of lipid levels and the effect of drugs used to regulate their level are inconsistent [19, 93]. Some of them have indicated that low serum cholesterol level and/or triglyceride level is associated with an increased risk of ICH. A meta-analysis based on 43 studies with a combined total of 317,291 patient-years of follow-up indicated that, in patients with ICH, statins did not increase recurrent ICH. In survivors of IS, although statins substantially and significantly reduced IS, there was a non-significant increase

Table 1. Cerebral microbleeds in the guidelines of expert groups and scientific societies

American Heart Association/ American Stroke Association: Scientific rationale for inclusion and exclusion criteria for intravenous alteplase in acute ischaemic stroke [97]	Intravenous alteplase has not been shown to increase sICH rates in patients with CMBs. Intravenous alteplase administration in these patients is therefore reasonable (Class IIa; benefit > risk)
American Heart Association/ American Stroke Association: Prevention of stroke in patients with silent cerebrovascular disease [98]	We suggest that, for patients with nonvalvular atrial fibrillation in whom anticoagulation is indicated but who are considered at particularly high risk of future ICH on basis of microbleed number and location, it may be reasonable to administer dabigatran, rivaroxaban, apixaban, or edoxaban in preference to warfarin. Another alternative to warfarin anticoagulation that might be considered is percutaneous closure of left atrial appendage
American Heart Association/ American Stroke Association: 2018 guidelines for early management of patients with acute ischaemic stroke [9]	In eligible patients who have previously had a small number (10 or fewer) of CMBs demonstrated on MRI, administration of IV alteplase is reasonable (Class IIa; benefit > risk); In eligible patients who have previously had a high burden of CMBs (more than 10) demonstrated on MRI, treatment with IV alteplase may be associated with an increased risk of sICH, and benefits of treatment are uncertain (Class IIb; benefit ≥ risk)
European Stroke Organisation — Karolinska Stroke Update Conference: Consensus statements and recommendations from ESO Karolinska Stroke Update Conference [99]	Routine MRI assessment of small vessel disease including CMBs is not recommended (Grade C; benefits outweigh risk); Oral anticoagulants in patients with evidence of CMBs should not be withheld (Grade C); NOACs should preferentially be used over VKA in NVAF (Grade C)
European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke [Supplementary reference 23]	For patients with acute ischaemic stroke of <4.5 h duration, for whom cerebral microbleed burden is unknown or is known to be low (< 10), we suggest intravenous thrombolysis with alteplase. Quality of evidence: Low; Strength of recommendation: Weak For patients with acute ischaemic stroke of < 4.5 h duration, for whom cerebral microbleed burden has been previously reported to be high (> 10), we suggest no intravenous thrombolysis. Quality of evidence: Low; Strength of recommendation: Weak
Decision algorithms for direct oral anticoagulant use in patients with nonvalvular atrial fibrillation: a practical guide for neurologists [100]	In patients after ICH, when anticoagulation is contraindicated (among other things on detection of > 5 cortical CMBs), surgical ablation or percutaneous left atrial appendage closure should be considered
European Society of Cardiology (ESC) guidelines for management of atrial fibrillation developed in collaboration with EACTS [8]	Among factors supporting lack of return to anticoagulation in patients with atrial fibrillation after ICH, numerous (> 10) CMBs are listed

of ICH. Nonetheless, statins show clear benefits in reducing mortality and improving functional outcome, irrespective of stroke subtype [94]. The conclusion of the Rotterdam Study was that low serum triglyceride level was associated with the presence of deep or infratentorial CMBs [95].

A recent review based on seven studies of 3,671 participants presented the hypothesis that statins treatment is not associated with CMBs overall, but may increase the risk of lobar CMBs formation [96].

Current guidelines

Nowadays, reperfusion therapy is widely used in AIS patients, and stroke prevention relies on chronic anticoagulation with a tendency towards aggressively initiating treatment. Unfortunately, the eligibility criteria for reperfusion procedures and the scales currently used to qualify for secondary stroke prevention, do not take the presence of CMBs into account [Supplementary reference 18–24].

All recommendations regarding the use of antiplatelet, anticoagulant or IVT and EVT in patients with CMBs are experts' opinions mostly based on the results of observational studies or on randomised clinical trials with relatively small groups of patients. However, despite omitting the issue of CMBs, they constitute a guideline for managing patients in various clinical cases.

In 2013, Fisher proposed MRI screening for chronic anticoagulation in AF [Supplementary reference 25]. The algorithm developed by Fisher recommends MRI screening in patients aged 60+. Among those patients who have CMBs demonstrable on MRI, a distinction is made between cortical vs. subcortical CMBs, and between findings of five or more subcortical vs. less than five subcortical CMBs. According to this algorithm, treatment should be considered in patients with cortical CMBs or at least five subcortical CMBs [97].

Following the current AHA/ASA Guidelines, no RCT of IVT and EVT in AIS with baseline MRI to identify CMBs have been conducted, so no determination of effect of baseline CMBs on the treatment safety and efficacy of alteplase and EVT with CMBs is available. In the absence of any evidence that IVT and EVT provide no benefit or cause harm in eligible patients with CMBs, withholding treatment on the basis of the presence of CMBs could lead to the exclusion of patients who would benefit from it.

The AHA/ASA also recommend the use of antiplatelet drugs and oral anticoagulants in the prevention of cardiovascular events in patients with CMBs [8, 97, 98]. The problem of CMBs in the European Stroke Organisation (ESO) [99, Supplementary reference 26] and European Association of Cardiology (ESC) [7] documents and in the Practical Guide for Neurologists published in 2019 by Canavero et al. [100] is under discussion. The current recommendations are set out in Table 1.

Therefore, future studies should determine the number of CMBs above which we should not perform reperfusion therapy and not use anticoagulant therapy, and also answer the questions as to whether the number is the same for different CMB locations and whether the presence of other cardiovascular risk factors could correct this number. It is also important to identify those groups of patients that should be scanned by MRI before making therapeutic decisions.

Conflict of interest: *None.*

References

1. Ding J, Sigurdsson S, Garcia M, et al. Risk factors associated with incident cerebral microbleeds according to location in older people: the age, gene/environment susceptibility (AGES)-Reykjavik study. JAMA Neurol. 2015; 72(6): 682–688, doi: 10.1001/jamaneurol.2015.0174, indexed in Pubmed: 25867544.
2. Poels MMF, Vernooij MW, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: an update of the Rotterdam scan study. Stroke. 2010; 41(10 Suppl): S103–S106, doi: 10.1161/STROKEAHA.110.595181, indexed in Pubmed: 20876479.
3. Kakar P, Charidimou A, Werring DJ. Cerebral microbleeds: a new dilemma in stroke medicine. JRSM Cardiovasc Dis. 2012; 1(8): 2048004012474754, doi: 10.1177/2048004012474754, indexed in Pubmed: 24175079.
4. Yamashiro K, Tanaka R, Shimo Y, et al. The prevalence and risk factors of cerebral microbleeds in patients with Parkinson's disease. Parkinsonism Relat Disord. 2015; 21(9): 1076–1081, doi: 10.1016/j.parkreldis.2015.06.019, indexed in Pubmed: 26142208.
5. Charidimou A, Shoamanesh A, Al-Shahi Salman R, et al. Cerebral amyloid angiopathy, cerebral microbleeds and implications for anticoagulation decisions: The need for a balanced approach. Int J Stroke. 2018; 13(2): 117–120, doi: 10.1177/1747493017741384, indexed in Pubmed: 29125055.
6. Choi KH, Kim JH, Kang KW, et al. Impact of microbleeds on outcome following recanalization in patients with acute ischemic stroke. Stroke. 2018 [Epub ahead of print]: STROKEAHA118023084, doi: 10.1161/STROKEAHA.118.023084, indexed in Pubmed: 30580721.
7. Kirchhof P, Benussi S, Kotecha D, et al. ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37(38): 2893–2962, doi: 10.1093/eurheartj/ehw210, indexed in Pubmed: 27567408.
8. Powers W, Rabinstein A, 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 Association. Stroke. 2018; 49(3): e46–99, doi: 10.1161/STR.0000000000000158, indexed in Pubmed: 29367334.
9. Błażejewska-Hyżorek B, Czernuszenko A, Członkowska A, et al. Wytyczne postępowania w udarze mózgu. Polski Przegląd Neurologiczny. 2019; 15(supl. A): 30–92, doi: 10.5603/PPN.2019.0001.
10. Graff-Radford J, Aakre JA, Knopman DS, et al. Prevalence and heterogeneity of cerebrovascular disease imaging lesions. Mayo Clin Proc. 2020; 95(6): 1195–1205, doi: 10.1016/j.mayocp.2020.01.028, indexed in Pubmed: 32498775.
11. Janaway BM, Simpson JE, Hoggard N, et al. MRC Cognitive Function and Ageing Neuropathology Study. Brain haemosiderin in older people: pathological evidence for an ischaemic origin of magnetic resonance imaging (MRI) microbleeds. Neuropathol Appl Neurobiol. 2014; 40(3): 258–269, doi: 10.1111/nan.12062, indexed in Pubmed: 23678850.
12. Vernooij MW, Ikram MA, Wielopolski PA, et al. Cerebral microbleeds: accelerated 3D T2*-weighted GRE MR imaging versus conventional 2D T2*-weighted GRE MR imaging for detection. Radiology. 2008; 248(1): 272–277, doi: 10.1148/radiol.2481071158, indexed in Pubmed: 18490493.
13. Cordonnier C, van de, Sluimer JD, et al. Prevalence and severity of microbleeds in a memory clinic setting. Neurology. 2006; 66(9): 1356–1360, doi: 10.1212/01.wnl.0000210535.20297.ae, indexed in Pubmed: 16682667.
14. Fazekas F, Kleinert R, Roob G, et al. Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. AJNR Am J Neuroradiol. 1999; 20(4): 637–642, indexed in Pubmed: 10319975.
15. Greenberg SM, Vernooij MW, Cordonnier C, et al. Microbleed Study Group. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol. 2009; 8(2): 165–174, doi: 10.1016/S1474-4422(09)70013-4, indexed in Pubmed: 19161908.
16. Jeerakathil T, Wolf PA, Beiser A, et al. Cerebral microbleeds: prevalence and associations with cardiovascular risk factors in the Framingham Study. Stroke. 2004; 35(8): 1831–1835, doi: 10.1161/01.STR.0000131809.35202.1b, indexed in Pubmed: 15155954.
17. Elmståhl S, Ellström K, Siennicki-Lantz A, et al. Association between cerebral microbleeds and hypertension in the Swedish general population "Good Aging in Skåne" study. J Clin Hypertens (Greenwich). 2019; 21(8): 1099–1107, doi: 10.1111/jch.13606, indexed in Pubmed: 31274244.
18. Nighoghossian N, Hermier M, Adeleine P, et al. Old microbleeds are a potential risk factor for cerebral bleeding after ischemic stroke: a gradient-echo T2*-weighted brain MRI study. Stroke. 2002; 33(3): 735–742, doi: 10.1161/hs0302.104615, indexed in Pubmed: 11872897.
19. Orken DN, Kenangil G, Uysal E, et al. Lack of association between cerebral microbleeds and low serum cholesterol in patients with acute intracerebral hemorrhage. Clin Neurol Neurosurg. 2010; 112(8): 668–671, doi: 10.1016/j.clineuro.2010.05.004, indexed in Pubmed: 20627554.
20. Lyu L, Shen J, Zeng C, et al. Cerebral microbleeds are associated with blood pressure levels in individuals with hypertension. Clin Exp Hypertens. 2020; 42(4): 328–334, doi: 10.1080/10641963.2019.1665673, indexed in Pubmed: 31542967.
21. Horstmann S, Möhlenbruch M, Wegele C, et al. Prevalence of atrial fibrillation and association of previous antithrombotic treatment in patients with cerebral microbleeds. Eur J Neurol. 2015; 22(10): 1355–1362.
22. Liu J, Kou Z, Tian Y. Diffuse axonal injury after traumatic cerebral microbleeds: an evaluation of imaging techniques. Neural Regen Res. 2014; 9(12): 1222–1230, doi: 10.4103/1673-5374.135330, indexed in Pubmed: 25206786.
23. Wahl M, Anwar M, Hess CP, et al. Relationship between radiation dose and microbleed formation in patients with malignant glioma. Radiat Oncol. 2017; 12(1): 126, doi: 10.1186/s13014-017-0861-5, indexed in Pubmed: 28797254.
24. Murai R, Kaji S, Kitai T, et al. The clinical significance of cerebral microbleeds in infective endocarditis patients. Semin Thorac Cardiovasc

Surg. 2019; 31(1): 51–58, doi: 10.1053/j.semtcvs.2018.09.020, indexed in Pubmed: 30287247.
25. van Bussel BCT, Henry RMA, Schalkwijk CG, et al. Fish consumption in healthy adults is associated with decreased circulating biomarkers of endothelial dysfunction and inflammation during a 6-year follow-up. J Nutr. 2011; 141(9): 1719–1725, doi: 10.3945/jn.111.139733, indexed in Pubmed: 21753064.
26. Lee SH, Lee ST, Kim BJ, et al. Dynamic temporal change of cerebral microbleeds: long-term follow-up MRI study. PLoS One. 2011; 6(10): e25930, doi: 10.1371/journal.pone.0025930, indexed in Pubmed: 22022473.
27. Lammie GA. Pathology of small vessel stroke. Br Med Bull. 2000; 56(2): 296–306, doi: 10.1258/0007142001903229, indexed in Pubmed: 11092081.
28. Schreiber S, Wilisch-Neumann A, Schreiber F, et al. Invited Review: The spectrum of age-related small vessel diseases: potential overlap and interactions of amyloid and nonamyloid vasculopathies. Neuropathol Appl Neurobiol. 2020; 46(3): 219–239, doi: 10.1111/nan.12576, indexed in Pubmed: 31386773.
29. Kövari E, Charidimou A, Herrmann FR, et al. No neuropathological evidence for a direct topographical relation between microbleeds and cerebral amyloid angiopathy. Acta Neuropathol Commun. 2015; 3: 49, doi: 10.1186/s40478-015-0228-9, indexed in Pubmed: 26268348.
30. Kalaria RN. Neuropathological diagnosis of vascular cognitive impairment and vascular dementia with implications for Alzheimer's disease. Acta Neuropathol. 2016; 131(5): 659–685, doi: 10.1007/s00401-016-1571-z, indexed in Pubmed: 27062261.
31. Yates PA, Villemagne VL, Ellis KA, et al. Cerebral microbleeds: a review of clinical, genetic, and neuroimaging associations. Front Neurol. 2014; 4(205), doi: 10.3389/fneur.2013.00205, indexed in Pubmed: 24432010.
32. Wise IA, Charchar FJ. Epigenetic modifications in essential hypertension. Int J Mol Sci. 2016; 17(4): 451, doi: 10.3390/ijms17040451, indexed in Pubmed: 27023534.
33. Conijn MMA, Geerlings MI, Biessels GJ, et al. Cerebral microbleeds on MR imaging: comparison between 1.5 and 7T. AJNR Am J Neuroradiol. 2011; 32(6): 1043–1049, doi: 10.3174/ajnr.A2450, indexed in Pubmed: 21546463.
34. Nandigam RNK, Viswanathan A, Delgado P, et al. MR imaging detection of cerebral microbleeds: effect of susceptibility-weighted imaging, section thickness, and field strength. AJNR Am J Neuroradiol. 2009; 30(2): 338–343, doi: 10.3174/ajnr.A1355, indexed in Pubmed: 19001544.
35. Greenberg SM, Nandigam RN, Delgado P, et al. Microbleeds versus macrobleeds: evidence for distinct entities. Stroke. 2009; 40(7): 2382–2386, doi: 10.1161/STROKEAHA.109.548974, indexed in Pubmed: 19443797.
36. Charidimou A, Shams S, Romero JR, et al. International META-MICROBLEEDS Initiative. Clinical significance of cerebral microbleeds on MRI: A comprehensive meta-analysis of risk of intracerebral hemorrhage, ischemic stroke, mortality, and dementia in cohort studies (v1). Int J Stroke. 2018; 13(5): 454–468, doi: 10.1177/1747493017751931, indexed in Pubmed: 29338604.
37. Yakushiji Y, Wilson D, Ambler G, et al. Distribution of cerebral microbleeds in the East and West: Individual participant meta-analysis. Neurology. 2019; 92(10): e1086–e1097.
38. Graff-Radford J, Lesnick T, Rabinstein AA, et al. Cerebral microbleed incidence, relationship to amyloid burden: The Mayo Clinic Study of Aging. Neurology. 2020; 94(2): e190–e199, doi: 10.1212/WNL.0000000000008735, indexed in Pubmed: 31801832.
39. Renard D, Tatu L, Thouvenot E. Infratentorial cerebral microbleeds in patients with cerebral amyloid angiopathy. J Stroke Cerebrovasc Dis. 2018; 27(9): 2534–2537, doi: 10.1016/j.jstrokecerebrovasdis.2018.05.015, indexed in Pubmed: 29861129.
40. Gyanwali B, Shaik MA, Venketasubramanian N, et al. Mixed-location cerebral microbleeds: An imaging biomarker for cerebrovascular pathology in cognitive impairment and dementia in a memory clinic population. J Alzheimers Dis. 2019; 71(4): 1309–1320, doi: 10.3233/JAD-190540, indexed in Pubmed: 31524167.
41. Kim KJ, Bae YJ, Kim JM, et al. The prevalence of cerebral microbleeds in non-demented Parkinson's disease patients. J Korean Med Sci. 2018; 33(46): e289, doi: 10.3346/jkms.2018.33.e289, indexed in Pubmed: 30416409.
42. Yakushiji Y, Yokota C, Yamada N, et al. Clinical characteristics by topographical distribution of brain microbleeds, with a particular emphasis on diffuse microbleeds. J Stroke Cerebrovasc Dis. 2011; 20(3): 214–221, doi: 10.1016/j.jstrokecerebrovasdis.2009.12.001, indexed in Pubmed: 20621512.
43. Lim JS, Hong KS, Kim GM, et al. Cerebral microbleeds and early recurrent stroke after transient ischemic attack: results from the Korean Transient Ischemic Attack Expression Registry. JAMA Neurol. 2015; 72(3): 301–308, doi: 10.1001/jamaneurol.2014.3958, indexed in Pubmed: 25580844.
44. Akoudad S, Portegies MLP, Koudstaal PJ, et al. Cerebral microbleeds are associated with an increased risk of stroke: the Rotterdam study. Circulation. 2015; 132(6): 509–516, doi: 10.1161/CIRCULATIONAHA.115.016261, indexed in Pubmed: 26137955.
45. Imaizumi T, Horita Y, Hashimoto Y, et al. Dotlike hemosiderin spots on T2*-weighted magnetic resonance imaging as a predictor of stroke recurrence: a prospective study. J Neurosurg. 2004; 101(6): 915–920, doi: 15597750, indexed in Pubmed: 10.3171/jns.2004.101.6.0915.
46. Soo YOY, Yang SR, Lam WWM, et al. Risk vs benefit of anti-thrombotic therapy in ischaemic stroke patients with cerebral microbleeds. J Neurol. 2008; 255(11): 1679–1686, doi: 10.1007/s00415-008-0967-7, indexed in Pubmed: 19156486.
47. Pasquini M, Benedictus MR, Boulouis G, et al. Incident cerebral microbleeds in a cohort of intracerebral hemorrhage. Stroke. 2016; 47(3): 689–694, doi: 10.1161/STROKEAHA.115.011843, indexed in Pubmed: 26839348.
48. Benedictus MR, Prins ND, Goos JDC, et al. Microbleeds, mortality, and stroke in Alzheimer disease: The MISTRAL study. JAMA Neurol. 2015; 72(5): 539–545, doi: 10.1001/jamaneurol.2015.14, indexed in Pubmed: 25798556.
49. Akoudad S, Wolters FJ, Viswanathan A, et al. Association of cerebral microbleeds with cognitive decline and dementia. JAMA Neurol. 2016; 73(8): 934–943, doi: 10.1001/jamaneurol.2016.1017, indexed in Pubmed: 27271785.
50. Miwa K, Tanaka M, Okazaki S, et al. Endoscopic follow-up of 3 cases with gastrointestinal tract involvement of mantle cell lymphoma. Intern Med. 2010; 49(3): 231–235, doi: 10.2169/internalmedicine.49.2766, indexed in Pubmed: 20118601.
51. van Uden IWM, van der Holst HM, Tuladhar AM, et al. White matter and hippocampal volume predict the risk of dementia in patients with cerebral small vessel disease: The RUN DMC study. J Alzheimers Dis. 2016; 49(3): 863–873, doi: 10.3233/JAD-150573, indexed in Pubmed: 26529206.

52. Miwa K, Tanaka M, Okazaki S, et al. Endoscopic follow-up of 3 cases with gastrointestinal tract involvement of mantle cell lymphoma. Intern Med. 2010; 49(3): 231–235, doi: 10.2169/internalmedicine.49.2766, indexed in Pubmed: 20118601.
53. Gregoire SM, Smith K, Jäger HR, et al. Cerebral microbleeds and long-term cognitive outcome: longitudinal cohort study of stroke clinic patients. Cerebrovasc Dis. 2012; 33(5): 430–435, doi: 10.1159/000336237, indexed in Pubmed: 22456577.
54. Gyawali B, Shaik MA, Tan CS, et al. Mixed-location cerebral microbleeds as a biomarker of neurodegeneration in a memory clinic population. Aging (Albany NY. 2019; 11(22): 10581–10596.
55. Kim JM. The prevalence of cerebral microbleeds in patients with Parkinson's disease and multiple system atrophy [abstract]. Mov Disord. 2017;32(Suppl 2). https://www.mdsabstracts.org/abstract/the-prevalence-of-cerebral-microbleeds-in-patients-with-parkinsons-disease-and-multiple-system-atrophy/ (15.01.2021).
56. Kim SH, Shin DW, Yun JM, et al. Correction: Kidney dysfunction and cerebral microbleeds in neurologically healthy adults. PLoS One. 2017; 12(4): e0176901, doi: 10.1371/journal.pone.0176901, indexed in Pubmed: 28448573.
57. Naganuma T, Takemoto Y, Shoji T, et al. Cerebral microbleeds predict intracerebral hemorrhage in hemodialysis patients. Stroke. 2015; 46(8): 2107–2112, doi: 10.1161/STROKEAHA.115.009324, indexed in Pubmed: 26089331.
58. Qian Y, Zheng Ke, Wang H, et al. Cerebral microbleeds and their influence on cognitive impairment in Dialysis patients. Brain Imaging Behav. 2021; 15(1): 85–95, doi: 10.1007/s11682-019-00235-z, indexed in Pubmed: 31898093.
59. Sakuta K, Yaguchi H, Sato T, et al. The impact of cerebral microbleeds presence on outcome following minor stroke treated with antiplatelet therapy. Front Neurol. 2020; 11: 522, doi: 10.3389/fneur.2020.00522, indexed in Pubmed: 32612570.
60. Romero JR, Preis SR, Beiser A, et al. Cerebral microbleeds as predictors of mortality: The framingham heart study. Stroke. 2017; 48(3): 781–783, doi: 10.1161/STROKEAHA.116.015354, indexed in Pubmed: 28143923.
61. Akoudad S, Ikram MA, Koudstaal PJ, et al. Cerebral microbleeds and the risk of mortality in the general population. Eur J Epidemiol. 2013; 28(10): 815–821, doi: 10.1007/s10654-013-9854-3, indexed in Pubmed: 24072508.
62. Altmann-Schneider I, Trompet S, de Craen AJM, et al. Cerebral microbleeds are predictive of mortality in the elderly. Stroke. 2011; 42(3): 638–644, doi: 10.1161/STROKEAHA.110.595611, indexed in Pubmed: 21233474.
63. Arca KN, Demaerschalk BM, Almader-Douglas D, et al. Does high cerebral microbleed burden increase the risk of intracerebral hemorrhage after intravenous tissue plasminogen activator for acute ischemic stroke? Neurologist. 2019; 24(1): 40–43, doi: 10.1097/NRL.0000000000000228, indexed in Pubmed: 30586035.
64. Schlemm L, Endres M, Werring DJ, et al. Benefit of intravenous thrombolysis in acute ischemic stroke patients with high cerebral microbleed burden. Stroke. 2020; 51(1): 232–239, doi: 10.1161/STROKEAHA.119.027633, indexed in Pubmed: 31739772.
65. Wang S, Lv Y, Zheng X, et al. The impact of cerebral microbleeds on intracerebral hemorrhage and poor functional outcome of acute ischemic stroke patients treated with intravenous thrombolysis: a systematic review and meta-analysis. J Neurol. 2017; 264(7): 1309–1319, doi: 10.1007/s00415-016-8339-1, indexed in Pubmed: 27885484.
66. Dannenberg S, Scheitz JF, Rozanski M, et al. Number of cerebral microbleeds and risk of intracerebral hemorrhage after intravenous thrombolysis. Stroke. 2014; 45(10): 2900–2905, doi: 10.1161/STROKEAHA.114.006448, indexed in Pubmed: 25116882.
67. Turc G, Sallem A, Moulin S, et al. Microbleed status and 3-month outcome after intravenous thrombolysis in 717 patients with acute ischemic stroke. Stroke. 2015; 46(9): 2458–2463, doi: 10.1161/STROKEAHA.115.009290, indexed in Pubmed: 26230857.
68. Yan S, Jin X, Zhang X, et al. Extensive cerebral microbleeds predict parenchymal haemorrhage and poor outcome after intravenous thrombolysis. J Neurol Neurosurg Psychiatry. 2015; 86(11): 1267–1272, doi: 10.1136/jnnp-2014-309857, indexed in Pubmed: 25632155.
69. Werring DJ, Charidimou A, Charidimou A, et al. authors. Microbleeds, cerebral hemorrhage, and functional outcome after stroke thrombolysis. Stroke. 2017; 48(8): 2084–2090, doi: 10.1161/STROKEAHA.116.012992, indexed in Pubmed: 28720659.
70. Shoamanesh A, Kwok CS, Lim PA, et al. Postthrombolysis intracranial hemorrhage risk of cerebral microbleeds in acute stroke patients: a systematic review and meta-analysis. Int J Stroke. 2013; 8(5): 348–356, doi: 10.1111/j.1747-4949.2012.00869.x, indexed in Pubmed: 22973896.
71. Kakuda W, Thijs VN, Lansberg MG, et al. DEFUSE Investigators. R Bammer, L Wechsler, S Kemp, Difuse Investigator. Clinical importance of microbleeds in patients receiving IV thrombolysis. Neurology. 2005; 65(98): 1175–1178, doi: 10.1212/01.wnl.0000180519.27680.0f, indexed in Pubmed: 16247042.
72. Zand R, Tsivgoulis G, Singh M, et al. Safety of intravenous thrombolysis among stroke patients taking new oral anticoagulants--case series and systematic review of reported cases. J Stroke Cerebrovasc Dis. 2015; 24(12): 2685–2693, doi: 10.1016/j.jstrokecerebrovasdis.2015.07.021, indexed in Pubmed: 26542821.
73. Tsivgoulis G, Zand R, Katsanos AH, et al. Risk of symptomatic intracerebral hemorrhage after intravenous thrombolysis in patients with acute ischemic stroke and high cerebral microbleed burden: A meta-analysis. JAMA Neurol. 2016; 73(6): 675–683, doi: 10.1001/jamaneurol.2016.0292, indexed in Pubmed: 27088650.
74. Yan J, Qiu J, Wu X, et al. Pretreatment cerebral microbleeds and symptomatic intracerebral hemorrhage post-thrombolysis: a systematic review and meta-analysis. J Neurol. 2020; 267(2): 301–307, doi: 10.1007/s00415-018-9156-5, indexed in Pubmed: 30542950.
75. Choi KH, Kim JH, Kang KW, et al. Impact of microbleeds on outcome following recanalization in patients with acute ischemic stroke. Stroke. 2018 [Epub ahead of print]: STROKEAHA118023084, doi: 10.1161/STROKEAHA.118.023084, indexed in Pubmed: 30580721.
76. Shi ZS, Duckwiler GR, Jahan R, et al. Mechanical thrombectomy for acute ischemic stroke with cerebral microbleeds. J Neurointerv Surg. 2016; 8(6): 563–567, doi: 10.1136/neurintsurg-2015-011765, indexed in Pubmed: 25994939.
77. Wu X, Yan J, Ye H, et al. Pre-treatment cerebral microbleeds and intracranial hemorrhage in patients with ischemic stroke receiving endovascular therapy: a systematic review and meta-analysis. J Neurol. 2020; 267(5): 1227–1232, doi: 10.1007/s00415-019-09210-6, indexed in Pubmed: 30689017.
78. Kakumoto K, Matsumoto S, Nakahara I, et al. Rapid formation of cerebral microbleeds after carotid artery stenting. Cerebrovasc Dis Extra. 2012; 2(1): 9–16, doi: 10.1159/000337143, indexed in Pubmed: 22566991.

79. Ito AO, Shindo A, Ii Y, et al. Microbleeds after carotid artery stenting: small embolism may induce cerebral microbleeds. Cerebrovasc Dis Extra. 2019; 9(2): 57–65, doi: 10.1159/000500112, indexed in Pubmed: 31203282.
80. Müller MD, Jongen LM, Altinbas A, et al. ICSS-MRI Study Investigators. Silent intracerebral hemorrhage in patients randomized to stenting or endarterectomy for symptomatic carotid stenosis. J Stroke. 2019; 21(1): 116–119, doi: 10.5853/jos.2018.02838, indexed in Pubmed: 30732448.
81. Liu S, Li C. Antiplatelet drug use and cerebral microbleeds: A meta-analysis of published studies. J Stroke Cerebrovasc Dis. 2015; 24(10): 2236–2244, doi: 10.1016/j.jstrokecerebrovasdis.2015.05.022, indexed in Pubmed: 26272868.
82. Lovelock CE, Cordonnier C, Naka H, et al. Edinburgh Study Group. Antithrombotic drug use, cerebral microbleeds, and intracerebral hemorrhage: a systematic review of published and unpublished studies. Stroke. 2010; 41(6): 1222–1228, doi: 10.1161/STROKEAHA.109.572594, indexed in Pubmed: 20431083.
83. Wang DN, Hou XW, Yang BW, et al. Quantity of cerebral microbleeds, antiplatelet therapy, and intracerebral hemorrhage outcomes: A systematic review and meta-analysis. J Stroke Cerebrovasc Dis. 2015; 24(12): 2728–2737, doi: 10.1016/j.jstrokecerebrovasdis.2015.08.003, indexed in Pubmed: 26342996.
84. Qiu J, Ye H, Wang J, et al. Antiplatelet therapy, cerebral microbleeds, and intracerebral hemorrhage: A meta-analysis. Stroke. 2018; 49(7): 1751–1754, doi: 10.1161/STROKEAHA.118.021789, indexed in Pubmed: 29798835.
85. Ge L, Ouyang X, Ban C, et al. Cerebral microbleeds in patients with ischemic cerebrovascular disease taking aspirin or clopidogrel. Medicine (Baltimore). 2019; 98(9): e14685, doi: 10.1097/MD.0000000000014685, indexed in Pubmed: 30817601.
86. Rockson SG, Albers GW. Comparing the guidelines: anticoagulation therapy to optimize stroke prevention in patients with atrial fibrillation. J Am Coll Cardiol. 2004; 43(6): 929–935, doi: 10.1016/j.jacc.2003.11.028, indexed in Pubmed: 15028346.
87. Lioutas VA, Goyal N, Katsanos AH, et al. Clinical outcomes and neuroimaging profiles in nondisabled patients with anticoagulant-related intracerebral hemorrhage. Stroke. 2018; 49(10): 2309–2316, doi: 10.1161/STROKEAHA.118.021979, indexed in Pubmed: 30355114.
88. Wilson D, Seiffge DJ, Traenka C, et al. And the CROMIS-2 collaborators. Outcome of intracerebral hemorrhage associated with different oral anticoagulants. Neurology. 2017; 88(18): 1693–1700, doi: 10.1212/WNL.0000000000003886, indexed in Pubmed: 28381513.
89. Purrucker JC, Wolf M, Haas K, et al. the RASUNOA Investigators. Microbleeds in ischemic vs hemorrhagic strokes on novel oral anticoagulants. Acta Neurol Scand. 2018; 138(2): 163–169, doi: 10.1111/ane.12934, indexed in Pubmed: 29663313.
90. Lioutas VA, Goyal N, Katsanos AH, et al. Microbleed prevalence and burden in anticoagulant-associated intracerebral bleed. Ann Clin Transl Neurol. 2019; 6(8): 1546–1551, doi: 10.1002/acn3.50834, indexed in Pubmed: 31402613.
91. Wilson D, Ambler G, Shakeshaft C, et al. CROMIS-2 collaborators. Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study [published correction appears in 2018; 1796): 578]. Lancet Neurol. 2018; 17(6): 539–547, doi: 10.1016/S1474-4422(18)30145-5 , indexed in Pubmed: 29778365.
92. Charidimou A, Karayiannis C, Song TJ, et al. International META-MICROBLEEDS Initiative. Brain microbleeds, anticoagulation, and hemorrhage risk: Meta-analysis in stroke patients with AF. Neurology. 2017; 89(23): 2317–2326, doi: 10.1212/WNL.0000000000004704, indexed in Pubmed: 29117953.
93. Haussen DC, Henninger N, Kumar S, et al. Statin use and microbleeds in patients with spontaneous intracerebral hemorrhage. Stroke. 2012; 43(10): 2677–2681, doi: 10.1161/STROKEAHA.112.657486, indexed in Pubmed: 22829545.
94. Ziff OJ, Banerjee G, Ambler G, et al. Statins and the risk of intracerebral haemorrhage in patients with stroke: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2019; 90(1): 75–83, doi: 10.1136/jnnp-2018-318483 , indexed in Pubmed: 30150320.
95. Wieberdink RG, Poels MMF, Vernooij MW, et al. Serum lipid levels and the risk of intracerebral hemorrhage: the Rotterdam Study. Arterioscler Thromb Vasc Biol. 2011; 31(12): 2982–2989, doi: 10.1161/ATVBAHA.111.234948, indexed in Pubmed: 21921260.
96. Katsanos AH, Lioutas VA, Charidimou A, et al. International META-MICROBLEEDS Initiative. Statin treatment and cerebral microbleeds: A systematic review and meta-analysis. J Neurol Sci. 2021; 420: 117224, doi: 10.1016/j.jns.2020.117224, indexed in Pubmed: 33183779.
97. Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. American Heart Association Stroke Council and Council on Epidemiology and Prevention. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2016; 47(2): 581–641, doi: 10.1161/STR.0000000000000086, indexed in Pubmed: 26696642.
98. Smith EE, Saposnik G, Biessels GJ, et al. American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Functional Genomics and Translational Biology; and Council on Hypertension. Prevention of stroke in patients with silent cerebrovascular disease: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2017; 48(2): e44–e71, doi: 10.1161/STR.0000000000000116, indexed in Pubmed: 27980126.
99. Ahmed N, Audebert H, Turc G, et al. Consensus statements and recommendations from the ESO-Karolinska Stroke Update Conference, Stockholm 11-13 November 2018. Eur Stroke J. 2019; 4(4): 307–317, doi: 10.1177/2396987319863606, indexed in Pubmed: 31903429.
100. Canavero I, Micieli G, Paciaroni M. Decision algorithms for direct oral anticoagulant use in patients with nonvalvular atrial fibrillation: A practical guide for neurologists. Clin Appl Thromb Hemost. 2018; 24(3): 396–404, doi: 10.1177/1076029617720068, indexed in Pubmed: 28914077.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 5, pages: 462–468
DOI: 10.5603/PJNNS.a2021.0060

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

Venous return in acute ischaemic stroke patients measured during computed tomography angiography of head and neck

Bartłomiej Łasocha[1], Anna M. Grochowska[2], Paweł Wrona[3], Paweł J. Brzegowy[3], Roman Pułyk[3], Agnieszka Słowik[3], Paweł R. Latacz[3], Tadeusz J. Popiela[2]

[1]Diagnostic Imaging Unit, University Hospital, Krakow, Poland
[2]Chair of Radiology, Jagiellonian University Medical College, Krakow, Poland
[3]Chair of Neurology, Jagiellonian University, Medical College, Krakow, Poland

ABSTRACT

Introduction: The aim of this study was to analyse the general features and usefulness of the time elapsed between the start of contrast agent infusion and its appearance in the aortic arch in acute ischaemic stroke patients subjected to baseline computed tomographic angiography. This is, to the best of our knowledge, the first study of this parameter in a clinical context. We will refer to it hereafter as 'needle-to-aorta delay' (NAD).

Material and methods: The following were recorded: the time it took iodinated contrast media to reach the aorta, the site of occlusion, and automatic perfusion assessments of infarct and salvageable tissue volumes. Demographic data such as age and sex, comorbidities, and clinical factors including heart rate, blood pressure, time elapsed from symptom onset, initial stroke severity, and course of disease, were also assessed.

Results: We analysed 252 cases of stroke. NAD correlated with tissue at risk volume, and was greater for patients with hypertension and atrial fibrillation. The observed time was significantly shorter with less favourable core-to-penumbra ratios. No link was found between NAD and either the rate of infarct progression or the long-term clinical result.

Conclusions: Although no clinical benefit was proven as a result of measuring the time it took contrast media to reach the aorta, our study implies that not only is the brain subject to circulation, but it may also affect its functioning.

Key words: stroke, brain perfusion, penumbra, cardiovascular system

(*Neurol Neurochir Pol 2021; 55 (5): 462–468*)

Introduction

The effectiveness of mechanical thrombectomy in patients suffering from acute ischaemic stroke is limited to a subgroup of patients which, unfortunately, has not yet been defined in detail. Initially the time-to-window approach was adopted [1]; however, this was undermined in later trials [2–4].

Among the multiple aspects that must be taken into consideration, the progression rate of ischaemia is particularly interesting, because it varies considerably between cases, and interacts closely with potential benefits and time constraints [5]. In most patients, imaging is performed only once for reasons of time optimisation. Therefore, we establish the progression rate based on a single time point and the assumption that the formation of inadvertent lesions begins with symptom onset. Since the availability of automatic volumetric measurements of the infarct core is limited to the highest-level stroke centres, patients outside the therapeutic time window still present a medical and organisational challenge. It is likely that deteriorating circulation impairs brain function [6], and that autoregulation of cerebral bloodflow may be compromised by cardiac output [7]. A connection between blood inflow to the heart and the course of brain ischaemia is to be expected; however, preload measurement is not only cumbersome, but is of dubious value [8].

We investigated the delay between contrast medium injection and its appearance in the aortic arch (we called this

Address for correspondence: Bartłomiej Łasocha, Diagnostic Imaging Unit University Hospital Krakow, Mikołaja Kopernika 36 Str., 31-501 Krakow, Poland; e-mail: blasocha@su.krakow.pl

Received: 26.04.2021 Accepted: 22.06.2021 Early publication date: 1.09.2021

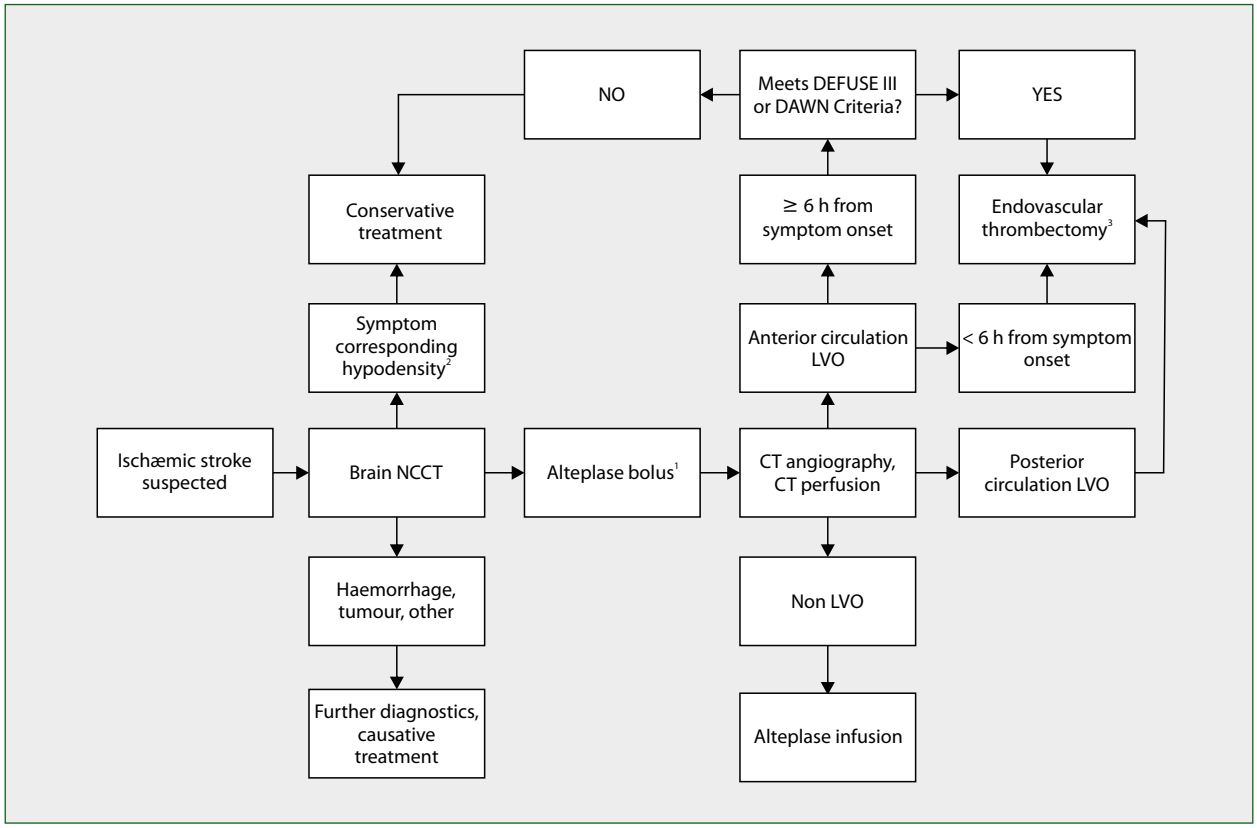


Figure 1. Routine workflow with a patient presenting acute stroke symptoms
[1]Intravenous fibrinolytic treatment was hedged in by multiple contraindications, the most frequent of which was time from symptom onset exceeding 4.5 hours, and anticoagulation with international normalised ratio (INR) above 1.8. Administration was divided into bolus (10% of the dose) injected over one minute, followed by pump infusion of the remainder over one hour; [2]Only regions of hypodensity exceeding one third of middle cerebral artery (MCA) territory, or covering whole area responsible for neurological deficit, were disqualified from causative treatment; [3]In eligible cases, thrombolytic agent infusion was continued until and during endovascular procedure — the so called 'bridging therapy'

needle-to-aorta delay, NAD) as a potential tool for estimating circulatory function in order to find answers concerning the speed of infarction and to help in qualifying patients for reperfusion treatment.

Material and methods

We performed a retrospective observational study of patients diagnosed and treated in a comprehensive stroke centre in 2019. A patient flowchart from the emergency department through the imaging unit and on to the neurointerventional lab and stroke department is set out in Figure 1. Medical records and imaging datasets were reviewed to exclude haemorrhage and stroke mimics, to collect information about comorbidities and the course of disease, and to identify radiological features of strokes. The primary aim was to assess NAD as a predictor of outcome; the secondary aim was to assess its linkage with the speed of conversion from penumbra into irreversible damage.

The patient data we analysed comprised the following: age, sex, presence of hypertension, atrial fibrillation, diabetes, initial National Institute of Health Stroke Scale (NIHSS) severity score, eligibility for fibrinolysis, and mechanical thrombectomy. Admission heart rate, arterial blood pressure, serum creatinine level, weight and height were extracted. Echocardiography performed in order to identify cause of stroke provided ejection fraction values. Additionally, in cases of endovascular treatment, reperfusion results were recorded by means of a modified Thrombolysis in Cerebral Infarction (mTICI) score and 90-day follow-up using a modified Rankin Scale (mRS). mTICI grades of 2b and 3 were adopted as standards for successful recanalisation; a good clinical outcome was assumed at mRS scores of 0 and 1.

Baseline computed tomography (CT) examination consisted of a non-contrast study of brain, head, and neck CT angiography and a brain perfusion CT performed on a 64-slice scanner (Optima CT660, GE Healthcare, Chicago, IL, USA) designated for the use of the emergency department. Intravenous thrombolysis, where applicable, was initiated

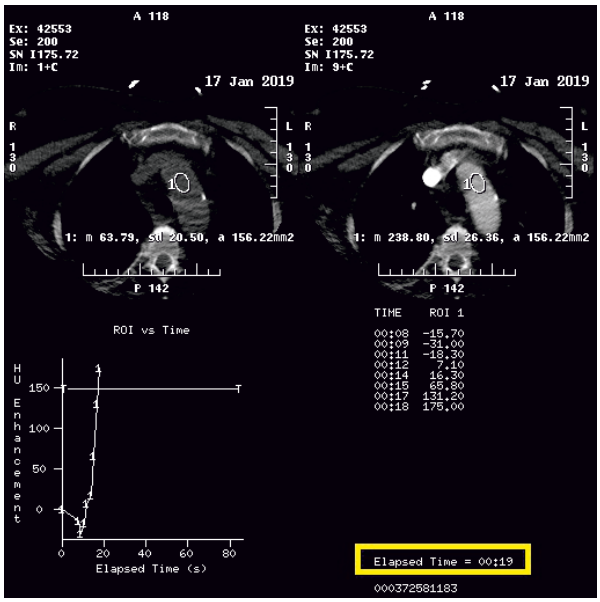


Figure 2. Region of interest (ROI) for bolus triggering, time-enhancement curve, and time delay of scan relative to injection

Table 1. Characteristics of study group

Demographic characteristic	Number or median	Percentage or IQR
Age	70	65–81
Sex (female)	131	52%
Diagnosed arterial hypertension	201	80%
Admission systolic pressure [mmHg]	151	134–170
Admission diastolic pressure [mmHg]	85	75–95
Atrial fibrillation	72	29%
Admission heart rate	80	71.25–90
Ejection fraction	65	60-70
Diabetes	76	30%
Body Mass Index	26.12	24.09–30.42
Admission creatinine	79	69–96
NIHSS	10	4–17
Fibrinolysis	120	48%
Thrombectomy	74	29%

immediately following the non-contrast study. For vascular and perfusion examinations, a contrast agent containing 350 mg/mL of iodine (Iohexol) was administered using a dual-head injector in volumes of 80 and 40 mL, respectively. The line was placed in an antecubital vein; an automated bolus triggering technique (SmartPrep, GE Healthcare) was used to optimise opacification of the vessels. NAD was read directly from the SmartPrep report image automatically appended to the study (Fig. 2). The scans were also evaluated for occlusion site and time elapsed from symptom onset to imaging. Volumes of penumbra and infarct core were calculated automatically using rapid processing of perfusion and diffusion (RAPID, iSchemaView, Menlo Park, CA, USA) software, employing thresholds for time-to-maximum (TMAX) over six seconds to delineate tissue at risk, and cerebral blood flow (CBF) below 30 per cent of contralateral brain tissue to discern irreversible damage [2, 3]. We adopted a mismatch threshold of 1.8 between irreversible damage and tissue-at-risk volumes in order to identify 'penumbral pattern' patients [3, 9]. Infarct progression rate was calculated as core volume divided by the time elapsed from symptom onset to the first image of the perfusion scan. Based on these measurements, biological indices were then computed, using coefficients published previously [10].

R software was used for the statistical workup. For categorical variables, frequencies were presented as percentages. Normal distribution of continuous variables was assessed using the Shapiro-Wilk test. Median and interquartile ranges were given for ordinal and numeric variables which did not follow normal distributions. The connections between ordinal and continuous variables were assessed using a Spearman correlation. The Wilcoxon test was used for assessment of categorical factors influencing bolus arrival delay and ischaemic progression rate.

The Bioethical Committee of the Regional Board of Physicians in Krakow waived the need for approval for this study as it was a retrospective analysis.

Results

The study covered 252 strokes in 247 patients: 131 in females and 121 in males. A summary of patient demographics is set out in Table 1.

The majority of subjects was hypertensive and overweight. One in four of them exhibited obesity and baseline systolic blood pressure exceeding mild hypertension values. Almost half of cases were eligible for intravenous thrombolysis. The data derived from baseline computed tomography is set out in Table 2. No measurement followed a normal distribution.

The delay in contrast medium inflow was prolonged by atrial fibrillation by four seconds on average ($p < 0.001$). Patients diagnosed with arterial hypertension were characterised by NADs prolonged by two seconds ($p = 0.001$), but the measured values of arterial blood pressure did not correlate with NAD. Contrast arrival time exhibited a link with ejection fraction ($p < 0.001$, $R = 0.383$), and heart rate and serum level of creatinine correlated with NAD only when we excluded atrial fibrillation patients.

Also, patients with higher NIHSS scores tended towards longer bolus arrival times ($R = 0.192$, $p = 0.002$). The measurement results did not depend on sex, age, weight, height, BMI or the presence of diabetes. However, in patients with longer times from symptom onset who suffered from M1 and tandem occlusions, NAD was shortened ($R = -0.616$, $p = 0.002$).

Table 2. Imaging findings

Morphological		Number	Percentage
Occlusion site	ICA[1]	23	9
	Tandem[2]	23	9
	M1[3]	55	22
	M2[4]	52	21
	other	99	39
Functional		**Median**	**IQR**
NAD (s)		19	17–24
Time from symptom onset to imaging (min)		172	99.5–268.8
Infarct core [mL]		22.5	10–58.75
Infarct progression rate[5]	Volume [mL/min]	0.131	0.058–0.334
	Neurons [mln/min]	2.761	1.223–7.040
	Synapses [bln/min]	20.163	8.927–51.410
	Fibre length [km/min]	17.34	7.68–44.21

[1]ICA — internal carotid artery; [2]TANDEM — internal carotid artery and middle cerebral artery occlusion in entire segment with or without visible blood flow in between (through ophthalmic artery or anterior cerebral artery); [3]M1 — segment of middle cerebral artery from origin to bifurcation/trifurcation; [4]M2 — segment of middle cerebral artery, also known as insular segment; [5]The rate of infarct progression was calculated only in cases presenting a measurable core (exactly 100 strokes)

Our expected intermediate indicator, i.e. the rate of infarct core growth, remained immutable with regard to age, sex, morphometric parameters, or presence of diabetes, atrial fibrillation, or kidney function impairment. It exhibited a difference of only 0.02 mL/min ($p = 0.049$) between hypertensive (higher) and non-hypertensive patients, and a moderate correlation with measured diastolic blood pressure ($p = 0.009$, $R = -0.164$). Faster progression correlated with higher NIHSS scores ($R = 0.543$, $p < 0.001$).

No connection to long-term clinical results was found for NAD. Good clinical outcomes remained independent of contrast inflow velocity in every subgroup based on occlusion site, reperfusion results, or age.

In cases where successful recanalisation was achieved, the rate of infarct progression was unrelated to good clinical outcomes ($p = 0.088$).

No connection was observed between NAD and the calculated progression rate, either globally or for subgroups limited to anterior circulation strokes or particular occlusion sites ($p > 0.31$).

When analysed in relation to neuroimaging, contrast delay did not correlate with the extent of necrosis either in patients overall or in any of the occlusion site subgroups ($p > 0.508$).

The time that contrast medium took to reach the aortic arch, however, was linked to the volume of tissue at risk ($R = 0.24$, $p < 0.001$, Fig. 3), as well as to the proportion of tissue at risk to irreversible injury volumes ($R = 0.21$, $p < 0.001$). Surprisingly, the longer it took contrast media to reach the aorta, the greater the mismatch. Unfortunately, the area under the ROC curve plotted for 'penumbral pattern' was only 0.579 (Supplementary Fig. 1).

A strong correlation was found between infarction volume and the rate of infarction. The connection between the extent of ischaemic tissue in baseline examinations and the time elapsed from symptom onset was not statistically significant except in the cases of M2 occlusions and core of infarction ($p = 0.50$, $R = 0.237$). In all but ICA occlusions, the rate of infarction was linked to the proportions of core and penumbra ($p < 0.001$).

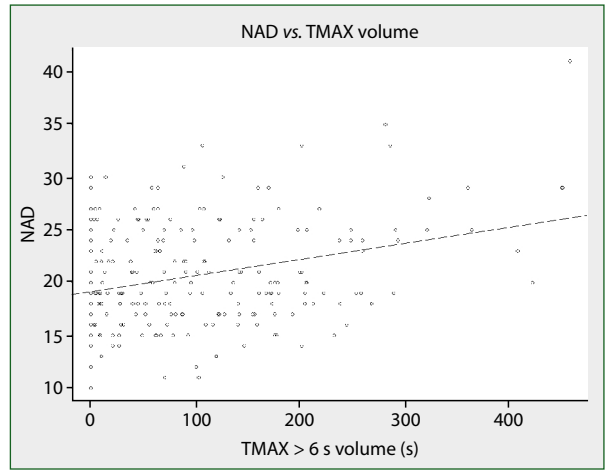


Figure 3. Relationship between needle-to-aorta delay (NAD) and volume of tissue exhibiting time-to-maximum (TMAX) values of 6 seconds or more

Discussion

We expected that slower circulation of blood would promote infarction; however, NAD did not correlate either with the absolute extent of ischaemic lesions nor with their rate of progression. On the other hand, it was closely correlated with the volume of penumbra, something which we had not anticipated. We had presumed the extent of tissue at risk would be determined by the occlusion site, while underestimating global circulatory function. One reason for the above lack of

correlation may be that more than half of the patients had no inadvertent ischaemic lesions, but only tissue at risk. In the remaining half however, it appears that the smaller the amount of salvageable tissue remaining, the greater the acceleration in circulation.

A reverse cause and effect model might explain this last observation: namely, that cardiovascular functions are influenced by the central nervous system, rather than simply that the brain is subject to circulatory variability. There are numerous pathways along which this mechanism might be executed [11], and, although systemic mobilisation is evident, an intracranial obstacle in tandem with local autoregulation failure eventually leads to cell death [12]. A reduction in NAD in patients experiencing a longer period elapsed from symptom onset suggests that the relationship involves slow, maybe humoral-mediated or otherwise complex, processes rather than a neural reflex. Alternatively, the reflex effect may be cumulative.

We are not certain why NAD failed to correlate with either the extent of necrosis or its progression rate, but, in light of the mechanism proposed above, a negative feedback loop may be assumed: initially sluggish circulation accelerates infarction, which in turn hastens bloodflow. Thus, we may see slow bloodstreams in two totally different populations: rapidly progressing patients who have not yet developed a significant proportion of irreversible damage, as well as patients who, thanks to sufficient (i.e. collateral) blood supply, are protected from inadvertent ischaemia and accelerated circulation. At the same time, an accelerated bloodstream may be present in desperate cases due to agitation, as well as in cases where, thanks to very efficient circulation, patients are protected from the conversion of penumbra into infarct core.

This phenomenon may also negate the ability to predict response to treatment, since NAD, the cardiovascular function marker we acquire, is a combination of a true baseline and the result of the influence of brain ischaemia. We are always presented with these coupled components, rather than with a parameter indicating the initial state of the cardiovascular system.

Delay in contrast arrival may remain intact in minor vessel and isolated ICA occlusions due to compensation by collaterals and weaker disturbances of autoregulatory mechanisms.

Another unforeseen phenomenon involves the correlation of NAD and cardiac ejection fraction. Echocardiography requires an experienced, skilled specialist and a cooperative patient, while modern CT is already available in most emergency departments, and will become so in even more over time. Although the link between NAD and ejection fraction appears to be very promising, we need to interpret it cautiously. In our study, cardiac sonography was performed to exclude cardiac origin of embolic material, and optimise secondary prevention. Thus, it was scheduled later during hospital stay: on average on the seventh day after symptom onset. Although mathematically the results are bonded tightly, these patients were already after the stroke acute phase and their circulation had already adapted several times: to bed rest, to the initiation of medication, to undergoing procedures, and to physiotherapy.

Measurements performed simultaneously with NAD, or chronic states, also affected contrast media circulation, necessitating an explanation. If increasing peripheral resistance (an inherent component of hypertension) was to blame for slower bolus arrival — either through pure Poiseuille's law or increased cardiac afterload — a correlation with either systolic or diastolic blood pressure is to be expected. Lacking this correlation, but observing delayed inflow in patients diagnosed with hypertension suggests that impaired autonomous circulatory reflexes might be the cause, either by the disease itself or by the initiation of medication. Atrial fibrillation, on the other hand, disturbs a wider spectrum of parameters, impairing left ventricle filling, cardiac rhythm and cardiac cycle alignment, and each of these might render circulation less efficient. An additional burden is the effect of beta-blockers and calcium channel antagonists used in the treatment of this condition.

We must comment as well on the variability of infarct progression rates in our study population. The relationship between velocity and extent of infarction appears trivial, since this ratio is calculated using the former as the quotient and the latter as the numerator. Infarction extent, according to our understanding of ischaemia [13–15] is, however, also proportional to time, used here as the denominator, and so it should nullify the correlation. It happened that the correlation between core volume and time was apparent for M2 occlusions only. This shows the role of collateral vessels [16, 17] and calls into question the classic viewpoint of anatomically-based classification of occlusions. Since the neurological deficit is caused by hypoperfused, and not necessarily inadvertently injured, tissue, this plays a role in benefit and risk balancing. Not only the branching pattern, but also the criteria according to which the borders between segments are determined, may be involved in explaining why we fail to address the disease appropriately [18].

An optimistic remark is that successful reperfusion can nullify the effect of infarct progression rates on long term clinical results. We colligate it with improvement of fast progressor prognosis [19]. Analysed patients in this group are fortunate in two different ways: firstly, they were diagnosed early enough so as to maximise the amount of salvageable tissue allowed for endovascular treatment; and secondly, the treatment itself was effective.

It must be stressed that more than half of the analysed patients had no infarcted tissue at the time of the CT, which may affect the results. Moreover, unlike anatomically-based cardiovascular measurements [20–23], NAD uses time to assess function. The same time value serves as a basis for the calculation of the perfusion parameters used to delineate penumbra (TMAX) and infarct core (CBF) [15, 24]; thus, they may be not as independent as we assume them to be.

Our study contains other flaws: the number of cases is modest considering the inclusion of posterior and small vessel

strokes. Collected data enabled non-parametric testing only, and clinical follow-up was available only for endovascular cases. However, the parameters and measurements we analysed are either automatic or very well established, rendering them immune to subjectivity and ambiguity.

Conclusions

The most important finding of our study concerns the influence of global circulatory function on tissue at risk. This poses a challenge to anatomically-based occlusion-site grading of the severity of a stroke.

We also observed an inverse relationship between NAD and the progression of ischaemic lesions. This relationship could not be defined to the point where it might serve as a substitute for mismatch ratio; nor can it be used to detect patients benefiting from reperfusion treatment.

Although routine recording of NAD appears to yield no clinical profit, our study suggests that circulatory function has been underestimated both as a cause of, and as an index of, cerebral hypoperfusion.

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

References

1. Berkheimer OA, Fransen PSS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015; 1: 11–20, doi: 10.1056/NEJMoa1411587, indexed in Pubmed: 25517348.
2. Jovin TG, Saver JL, Ribo M, et al. Diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention with Trevo (DAWN) trial methods. Int J Stroke. 2017; 12(6): 641–652, doi: 10.1177/1747493017710341, indexed in Pubmed: 28569123.
3. Albers GW, Lansberg MG, Kemp S, et al. A multicenter randomized controlled trial of endovascular therapy following imaging evaluation for ischemic stroke (DEFUSE 3). Int J Stroke. 2017; 12(8): 896–905, doi: 10.1177/1747493017701147, indexed in Pubmed: 28946832.
4. Thomalla G, Boutitie F, Fiebach JB, et al. WAKE-UP Investigators. Stroke with snknown time of symptom onset: baseline clinical and magnetic resonance imaging data of the first thousand patients in WAKE-UP (Efficacy and safety of MRI-based thrombolysis in wake-up stroke: A randomized, doubleblind, placebo-controlled trial). Stroke. 2017; 48(3): 770–773, doi: 10.1161/STROKEAHA.116.015233, indexed in Pubmed: 28174327.
5. Desai SM, Rocha M, Jovin TG, et al. High variability in neuronal loss. Stroke. 2019; 50(1): 34–37, doi: 10.1161/STROKEAHA.118.023499, indexed in Pubmed: 30566036.
6. Harjola VP, Mullens W, Banaszewski M, et al. Organ dysfunction, injury and failure in acute heart failure: from pathophysiology to diagnosis and management. A review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail. 2017; 19(7): 821–836, doi: 10.1002/ejhf.872, indexed in Pubmed: 28560717.
7. Liu X, Czosnyka M, Donnelly J, et al. Assessment of cerebral autoregulation indices - a modelling perspective. Sci Rep. 2020; 10(1): 9600, doi: 10.1038/s41598-020-66346-6, indexed in Pubmed: 32541858.
8. Lichtwarck-Aschoff M, Beale R, Pfeiffer U. Central venous pressure, pulmonary artery occlusion pressure, intrathoracic blood volume, and right ventricular end-diastolic volume as indicators of cardiac preload. Journal of Critical Care. 1996; 11(4): 180–188, doi: 10.1016/s0883-9441(96)90029-5.
9. Campbell BCv, Parsons MW, Campbell BCV, et al. EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015; 372(11): 1009–1018, doi: 10.1056/NEJMoa1414792, indexed in Pubmed: 25671797.
10. Saver JL. Time is brain--quantified. Stroke. 2006; 37(1): 263–266, doi: 10.1161/01.STR.0000196957.55928.ab, indexed in Pubmed: 16339467.
11. Xiao M, Li Q, Feng H, et al. Neural vascular mechanism for the cerebral blood flow autoregulation after hemorrhagic stroke. Neural Plast. 2017; 2017: 5819514, doi: 10.1155/2017/5819514, indexed in Pubmed: 29104807.
12. Lo EH, Rosenberg GA. The neurovascular unit in health and disease: introduction. Stroke. 2009; 40(3 Suppl): S2–S3, doi: 10.1161/STROKEAHA.108.534404, indexed in Pubmed: 19064779.
13. von Kummer R, Dzialowski I. Imaging of cerebral ischemic edema and neuronal death. Neuroradiology. 2017; 59(6): 545–553, doi: 10.1007/s00234-017-1847-6, indexed in Pubmed: 28540400.
14. Agarwal S, Matys T, Marrapu ST, et al. Is CT-based perfusion and collateral imaging sensitive to time since stroke onset? Front Neurol. 2015; 6: 70, doi: 10.3389/fneur.2015.00070, indexed in Pubmed: 25914673.
15. Wintermark M, Flanders AE, Velthuis B, et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. Stroke. 2006; 37(4): 979–985, doi: 10.1161/01.STR.0000209238.61459.39, indexed in Pubmed: 16514093.
16. Vagal A, Menon BK, Foster LD, et al. Association between CT angiogram collaterals and CT perfusion in the interventional management of stroke III trial. Stroke. 2016; 47(2): 535–538, doi: 10.1161/STROKEAHA.115.011461, indexed in Pubmed: 26658448.
17. Fanou EM, Knight J, Aviv RI, et al. Effect of collaterals on clinical presentation, baseline imaging, complications, and outcome in acute stroke. AJNR Am J Neuroradiol. 2015; 36(12): 2285–2291, doi: 10.3174/ajnr.A4453, indexed in Pubmed: 26471754.
18. Compagne KCJ, van der Sluijs PM, van den Wijngaard IR, et al. MR CLEAN Registry Investigators. Endovascular treatment: The role of dominant caliber M2 segment occlusion in ischemic stroke. Stroke. 2019; 50(2): 419–427, doi: 10.1161/STROKEAHA.118.023117, indexed in Pubmed: 31287757.
19. Rocha M, Jovin TG. Fast versus slow progressors of infarct growth in large vessel occlusion stroke: clinical and research implications. Stroke. 2017; 48(9): 2621–2627, doi: 10.1161/STROKEAHA.117.017673, indexed in Pubmed: 28794271.
20. Chaturvedi A, Oppenheimer D, Rajiah P, et al. Contrast opacification on thoracic CT angiography: challenges and solutions. Insights into Imaging. 2016; 8(1): 127–140, doi: 10.1007/s13244-016-0524-3.

21. Lakoma A, Tuite D, Sheehan J, et al. Measurement of pulmonary circulation parameters using time-resolved MR angiography in patients after Ross procedure. AJR Am J Roentgenol. 2010; 194(4): 912–919, doi: 10.2214/AJR.09.2897, indexed in Pubmed: 20308491.
22. Kathiria NN, Devcic Z, Chen JS, et al. Assessment of left ventricular enlargement at multidetector computed tomography. J Comput Assist Tomogr. 2015; 39(5): 794–796, doi: 10.1097/RCT.0000000000000279, indexed in Pubmed: 26295194.
23. Sohrabi S, Hope M, Saloner D, et al. Left atrial transverse diameter on computed tomography angiography can accurately diagnose left atrial enlargement in patients with atrial fibrillation. J Thorac Imaging. 2015; 30(3): 214–217, doi: 10.1097/RTI.0000000000000132, indexed in Pubmed: 25629578.
24. Heit JJ, Wintermark M. Perfusion computed tomography for the evaluation of acute ischemic stroke: strengths and pitfalls. Stroke. 2016; 47(4): 1153–1158, doi: 10.1161/STROKEAHA.116.011873, indexed in Pubmed: 26965849.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 5, pages: 469–478
DOI: 10.5603/PJNNS.a2021.0075

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

Does granulocyte-colony stimulating factor stimulate peripheral nerve regeneration? An experimental study on traumatic lesion of the sciatic nerve in rats

Doerthe Keiner[1*], Harald von Pein[2*], Jacek Szczygielski[1, 3], Andreas Kramer[4], Axel Heimann[5], Oliver Kempski[5], Clemens Sommer[2], Joachim Oertel[1]

[1]Department of Neurosurgery, Saarland University Medical Centre and Saarland University Faculty of Medicine, Homburg/Saar, Germany
[2]Division of Neuropathology, University Medical Centre of the Johannes-Gutenberg-University, Mainz, Germany
[3]Institute of Medical Sciences, University of Rzeszow, Poland
[4]Department of Neurosurgery, University Medical Centre of the Johannes-Gutenberg-University, Mainz, Germany
[5]Institute of Neurosurgical Pathophysiology, University Medical Centre of the Johannes-Gutenberg-University, Mainz, Germany

ABSTRACT

Aim of the study. To analyse the therapeutic potential of granulocyte-colony stimulating factor (G-CSF) treatment using a rat model of traumatic sciatic nerve lesion.

Clinical rationale for the study. G-CSF has proven strong neurotrophic properties in various models of ischaemic and traumatic brain injury. Fewer studies exist regarding the influence of G-CSF on posttraumatic peripheral nerve regeneration. Currently, the possibilities of pharmacological prevention or treatment of mechanical nerve injury are limited, and there is an urgent need to find new treatment strategies applicable in clinical situations.

Materials and methods. A controlled traumatic right sciatic nerve lesion was set using a waterjet device. Three treatment groups were created. In the first group, G-CSF was administered after sciatic nerve injury. The second group received G-CSF before and after trauma, while the third group was treated with glucose 5%-solution. Sciatic nerve function was assessed clinically and electrophysiologically at day 1, and after weeks 1, 2, 4 and 6. Additionally, α-motoneurons of the spinal cord and sciatic nerve fibres were counted at week 6.

Results. Clinically, rats in both G-CSF groups improved faster compared to the control group. Additionally, animals treated with G-CSF had a significantly better improvement of motor potential amplitude and motor nerve conduction velocity at week 6 ($p < 0.05$). Histologically, G-CSF treatment resulted in a significantly higher number of α-motoneurons and small myelinated nerve fibres compared to placebo treatment ($p < 0.05$).

Conclusions and clinical implications. Under G-CSF treatment, the recovery of motor nerve conduction velocity and amplitude was enhanced. Further, signs of nerve regeneration and preservation of α-motoneurons were observed. These results indicate that G-CSF might accelerate and intensify the recovery of injured nerves. Thus, treatment with G-CSF may be beneficial for patients with peripheral nerve damage, and should be explored in further clinical studies.

Key words: G-CSF, nerve regeneration, peripheral nerve lesion, traumatic nerve injury, waterjet dissection

(*Neurol Neurochir Pol 2021; 55 (5): 469–478*)

Address for correspondence: Joachim Oertel, Department of Neurosurgery, Saarland University Medical Centre, Kirrberger Str. 90.5, 66421 Homburg-Saar, Germany; e-mail: joachim.oertel@uks.eu

Received: 11.11.2020 Accepted: 12.07.2021 Early publication date: 19.10.2021

D. Keiner and H. v. Pein contributed equally to this work

Introduction

Today's neurotrauma research focuses on injury of the central nervous system (CNS). However, one should not forget that peripheral nerve injury as a subject of neurotrauma studies deserves the same attention as do brain or spinal cord trauma, since injury of peripheral or cranial nerves can also result in permanent functional loss of differing degrees of severity, and therefore the potential of neuroprotective treatment should also be explored for the peripheral part of the nervous system. In the past, different agents with possible neurotrophic properties have been investigated in detail. Recently, the use of granulocyte-colony stimulating factor (G-CSF) has been reported as a very promising treatment strategy [1, 2]. This induces proliferation and mobilisation of haematopoietic cells. Further, it regulates maturation and survival of neutrophil granulocyte precursors [1, 2]. The stimulation of neutrophil granulocyte precursors is commonly applied in the management of chemotherapy-associated neutropenia or in stem-cell transplantation [3, 4]. Several studies involving different *in vitro* and *in vivo* experimental stroke models have proven that G-CSF induces neuroprotective and neuroregenerative properties [1, 2, 5–7]. This has also been reported in human subjects with acute stroke [3, 8]. Besides its anti-apoptotic effect, G-CSF enhances angiogenesis after ischaemia and promotes neurogenesis [1, 2]. Furthermore, it has been shown that G-CSF improves the recovery of sensorimotor, as well as cognitive, functions after ischaemia [2].

In the peripheral nervous system (PNS), it has recently been observed that G-CSF protects α-motoneurons of the spinal cord from apoptosis after axotomy of sciatic nerves in chimeric mice [4]. Furthermore, in an experimental mouse model of amyotrophic lateral sclerosis (AML), G-CSF increased the survival of motoneurons *in vivo* and *in vitro* and decreased muscular nerve denervation and atrophy in SOD1 (G93A) transgenic mice [9, 10]. However, the neuroprotective or neuroregenerative properties of G-CSF in traumatic peripheral nerve injury have not been fully evaluated.

The recently developed model of waterjet-induced injury of the sciatic nerve creates a good opportunity to analyse this potential. By adapting a surgical device for waterjet dissection [11–18], one may achieve injury to the nerve wherein the degree of damage can be precisely regulated. Based on these principles, a rat model of waterjet-induced injury to vestibulocochlear and sciatic nerves has been established [19, 20]. According to the previous results, the reliability and replicability of this experimental paradigm is comparable with the canonical model of sciatic nerve crush [4, 21–23]. Moreover, waterjet nerve injury models enable the analysis of functional nerve recovery after a partial lesion with damaged microstructure while maintaining continuity, thus simulating the common clinical situation of iatrogenic nerve injury during a surgical procedure [19, 20].

This current study was prompted by a desire to analyse the impact of G-CSF on peripheral nerve recovery after a moderate trauma (defined as significant and prolonged damage but with recovery capability). We investigated both iatrogenic and incidental injury scenarios, with G-CSF administration before and after trauma, and a waterjet-based model of traumatic nerve injury.

Clinical rationale for the study

There is a growing need to expand the concept of neuroprotective therapies from brain and spinal cord research into the realm of clinical studies on peripheral nerve injury. The main impetus is the growing number of cases resulting from the long list of possible causes of nerve damage. Firstly, accidental injury to the limbs as encountered in road accidents, gunshot wounds or sports injuries may lead to severe nerve damage [24, 25]. Further, a nerve injury can result from surgical procedures. For example, simple manipulation of cranial nerves during surgery at the skull base often causes functional impairment, even in macroscopically intact nerves. Additionally, limb surgery, or even an inappropriate positioning on the surgical table, can lead to nerve compression and subsequently to its functional and structural damage [26, 27]. For surgery-related nerve injury, the timing of a trauma can be predicted. Thus, a potential preventive treatment would be possible.

However, regardless of the cause of nerve injury (accidental or iatrogenic), the grade of the recovery and its duration cannot be prognosticated in every case and there is still a vast population of patients where nerve regeneration is prolonged, arrested, or simply incomplete. Thus, any treatment method able to accelerate or enable recovery in peripheral nerve damage is of paramount importance for clinical practice. Our current study represents an attempt to test one of the promising therapeutic strategies under animal experiment conditions.

Materials and methods

Study design

This study was approved by the local Ethics Committee and by the institutional Animal Welfare Representative. Male adult Sprague-Dawley rats weighting 300–400g were used in this study. Animals were kept under controlled light conditions with a 12h/12h light/dark cycle. Food and water were provided *ad libitum*. The following experimental groups (n = 24 each group) were created: in all groups, traumatic injury to the right sciatic nerve was applied during the surgical procedure, as described below. Twenty-four animals were treated with recombinant human G-CSF (Neupogen®, filgrastim, Amgen GmbH, Munich, Germany) administered intravenously (i.v.) at a dose of 60µg/KGBW on days 1, 3 and 5 after surgery (Group 1). To address the question, if an additional administration of G-CSF prior to a planned surgery with anticipated traumatic impact on a peripheral nerve (i.e. tumour surgery or in severe nerve compression) might result in a better nerve regeneration

compared to G-CSF after surgery, and may become a prophylactic measure in a planned surgical procedure, in 24 animals a G-CSF dose of 60µg/KGBW was given i.v. one day prior to surgery and at days 1, 3 and 5 after surgery (Group 2). In the remaining 24 animals, 5%-glucose (G5%) — solution was administered i.v. as a placebo (Group 3).

Twelve animals in each group were sacrificed for histological evaluation of the sciatic nerve after week 1. The remaining 12 animals were sacrificed after six weeks for histological evaluation of the sciatic nerve and its spinal cord section.

The neurological function was assessed using pace analysis according to the sciatic functional index (SFI) after 24 hrs and after 1, 2, 4 and 6 weeks. Additional instrumental analysis of the motor nerve conduction velocity (NCV) and the motor potential amplitude was performed prior to nerve injury and at the end of the surgery after wound closure, and repeated 24h and 1, 2, 4 and 6 weeks after injury (Nicolet Viking® and Medelec™ Synergy N-EP — EMG/EP monitoring system, Version 12.2, Natus Neurology Inc, Planegg, Germany).

Scoring of neurological deficits

All rats underwent pre- and postoperative walking track analysis in a confined walkway. Hind paw prints were recorded using black ink. The factors for SFI were calculated as described by De Medinaceli et al [28]. Additionally, the number of steps per metre and possible limping following nerve lesion was evaluated as previously described [20]. An SFI of 0 to –5 was considered to be 'intact motor function', an SFI of –6 to –50 was considered to be 'marked neurological deficit', and an SFI of –51 to –100 was considered to be 'severe neurological deficit'.

Surgical and lesion procedure

The rats were anaesthetised with chloralhydrate solution intraperitoneally (i.p.) at a dose of 36 mg/kg body weight (BW) before surgery. Perioperative analgesia was performed with tramadol i.p. at a dose of 50 mg/kg BW. A posterior-laterally skin incision was done parallel to the right femur and the muscle fascia of the gluteus muscles was opened. The sciatic nerve was carefully exposed at midthigh level with the aid of a wound expander. Under microscopic view, the nerve was mobilised from the surrounding muscle fascia until it was exposed from the sciatic notch exit to the division of motor branches. After preparation, the rat was placed on a computer-controlled linear device for dissection of the sciatic nerve (Software Servomanager 6.4.1, Parker Automation; Erbe Elektromedizin Company, Fig. 1). After dissection, the muscle fascia and the skin was closed with 4–0 sutures.

For sciatic nerve dissection, an Erbejet 2 (Erbe Elektromedizin Company, Tuebingen, Germany) was used. A waterjet is generated via a medium converter with an electronically-controlled mechanical system (double piston pump) with a pressure ranging from 1 to 80 bar. The medium converter is connected to a pencil-like handpiece consisting of a narrow

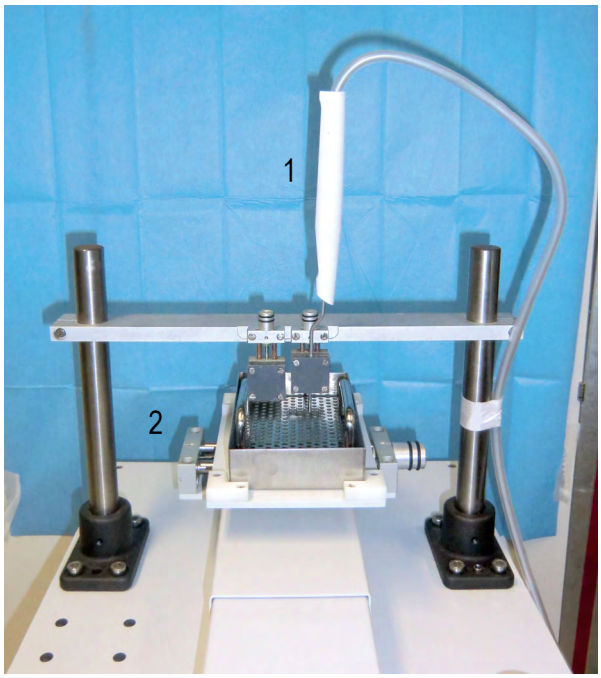


Figure 1. Computer-controlled linear device (Software Servomanager 6.4.1, Parker Automation; Erbe Elektromedizin Company) for application of waterjet dissection. Bayonet-shaped waterjet applicator (1) is placed above platform for animals with movement control (2)

nozzle (diameter of 120 µm), and a surrounding suction tube. The generated water jet is a non-rotatory thin lamina of liquid. Sterile 0.9% isotonic saline is emitted as separating medium with a volume flow of 1–55 mL/min. The pressure can be adjusted. Depending on the surgical procedure, several different settings can be selected. This system has been approved by the regulatory authorities in Germany and the United States of America for surgical use in humans.

To obtain a marked sciatic nerve lesion with retained nerve continuity, the jet intensity was set for 50 bar (Fig. 2A, B). It was applied at a 90-degree angle and with a cutting distance of 2 mm from the nozzle's tip to the nerve surface.

Histological examination

Histological analysis of the sciatic nerves, as well as counting of α-motoneurons, was performed by blinded investigators. The sciatic nerves were fixed in glutaraldehyde (3% glutaraldehyde in 0.1 mol/L sodium cacodylate buffer, cooled to 4°C) and embedded in epon resin. Semi-thin sections of the dissection area were stained with methylene blue and analysed by light microscope (Olympus BH2, Hamburg, Germany) for signs of direct sciatic nerve injury and nerve regeneration. For morphometric analysis of nerve-regeneration, the entire nerve cross-section was photographed. Nerve fibre diameters and nerve fibres/mm^2 were analysed in two representative areas with an edge length of 0.1 mm of each case. Spinal cords were removed *in toto* and fixed in 4%

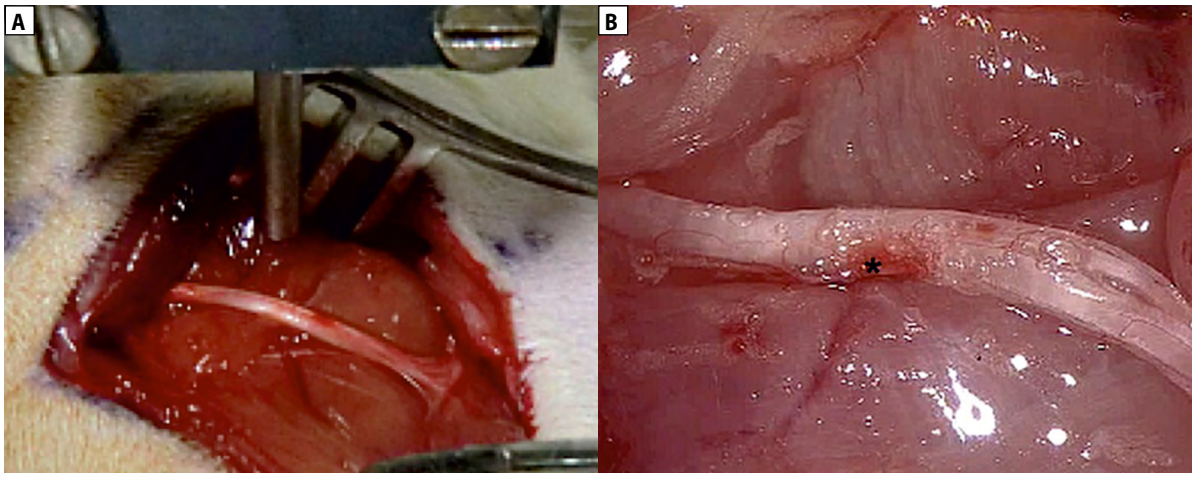


Figure 2. Microscopic view of right sciatic nerve. Setting of 50 bar lesion (**A**) and microscopic view of sciatic nerve directly after applied lesion (**B**)

paraformaldehyde. Thereafter, the relevant lumbar parts of the spinal cord were paraffin-embedded and cut into 10µm thick slices for counting of α-motoneurons. For every spinal cord, 10 slices were analysed. Nissl and haematoxylin and eosin staining were performed. All neurons in laminas 8 and 9 of the ventral horn that were clearly identifiable in the staining and were ≥ 300 µm² in size were counted as α-motoneurons (SIS AnalySIS, Olympus).

Statistics

For statistical evaluation of SFI and electrophysiological examinations, one- and two-way analysis of variance (ANOVA) was calculated with GraphPad Prism. A p value of less than 0.05 was considered statistically significant. For statistical analysis of the SFI, post-injury worsening of the SFI was divided, as described above, into 'intact motor function' = 1 (0 to –5), 'marked neurological deficit' = 2 (–6 to –50), or 'severe neurological deficit' = 3 (–51 to –100).

For statistical evaluation of nerve fibres and α-motoneurons, the total number of the sciatic nerve's fibres per animal, and the number of α-motoneurons counted on 10 slices respectively, was analysed.

Results

Neurological outcome and sciatic functional index (SFI)

All animals were neurologically intact before sciatic nerve lesion. One day after nerve lesion, signs of a severe motor deficit were found in 17/24 (70.8%). Signs of a moderate nerve lesion were found in 7/24 (29.2%) animals in every group. One week after surgery, a marked motor deficit was observed in 14/24 (48.4%) animals in Group 1 and in 13/24 (44.2%) animals in Group 2 compared to 16/24 (66.6%) animals in Group 3. Two weeks after surgery, 9/12 (75%) animals in the control group still had signs of a marked motor deficit. In contrast to these findings, 7/12 (48.4%) rats treated with G-CSF after the lesion procedure, and 6/12 (50%) rats treated with G-CSF both prior to and after surgery, showed a marked motor deficit. At week 6, 4/12 (33.3%) animals in Group 1 as well as Group 3, and 2/12 (16.7%) animals in Group 2, showed a marked motor deficit.

At week 6, 4/12 (33.3%) animals in Group 1 as well as Group 3, and 2/12 (16.7%) animals in Group 2, showed a marked motor deficit (Fig. 3). Nevertheless, measurements of SFI failed to show statistical significance, although in the long term SFI values of both groups treated with G-CSF improved better than did the SFI values of the control group (Fig. 4).

Motor nerve conduction velocity (NCV) and motor potential amplitude

Regarding motor NCV as a marker for a damaged myelin sheath, no disparities were observed between the three groups from day 1 to week 2 after nerve lesion. After 4 weeks, non-significant improvement of the motor NCV was found in both groups treated with G-CSF compared to the animals treated with G5%-solution ($p = 0.1$). At week 6, Groups 1 and 2 had a significantly better improvement in their motor NCV ratio compared to the control group ($p < 0.05$) (Fig. 5). Additionally, the development of motor NCV from week 2 to week 6 according to the initial (pre-lesional) NCV value within one group was analysed. Rats receiving G-CSF both pre- and postoperatively improved significantly better referring to the initial NCV ($p < 0.05$) than did those treated with G5% solution ($p = 0.6$) or with only a preoperative dose of G-CSF ($p = 0.2$).

Besides motor NCV, motor potential amplitude as a marker for loss of sciatic nerve axons was analysed. At week 2, in 6/12 (50%) animals in both G-CSF treatment groups, a recovered motor potential amplitude of > 20 mA was measured. On the contrary, in only 2/12 (16.6%) animals in the control group was the amplitude > 20 mA. At week 4 and at week 6, 6/12 (50%) rats in Group 1 and 8/12 (66.6%) rats in Group 2 had motor potential amplitudes of > 20 mA compared to the control group (3/12; 25%) (Fig. 6).

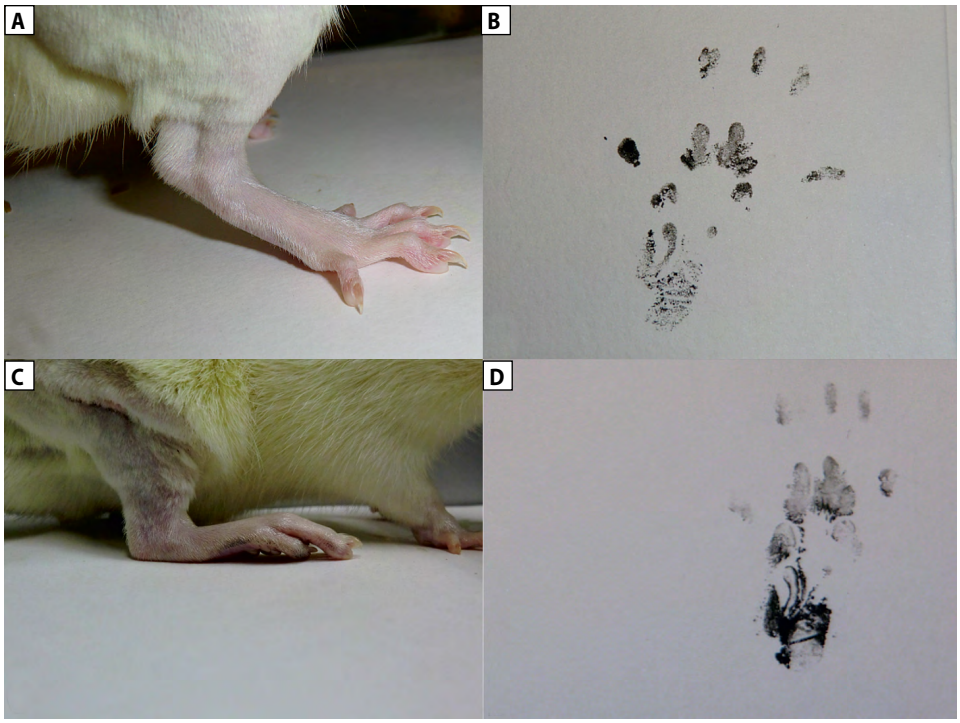


Figure 3. Calculation of sciatic functional index (SFI) was based on a walking track analysis on published values [28]. SFI measurements were performed at weeks 1, 2, 4 and 6. Figures **3A** and **3B** show a 'physiological' footprint with intact motor function. Figures **3C** and **3D** show rat footprint after lesion with marked neurological deficit, and correspondingly longer footprint and reduced toe spread. For statistical evaluation, post-injury worsening of SFI was divided into 'intact motor function' = 1 (SFI 0 to –5), 'marked neurological deficit' = 2 (SFI –6 to –50), and 'severe neurological deficit' = 3 (SFI –51 to –100)

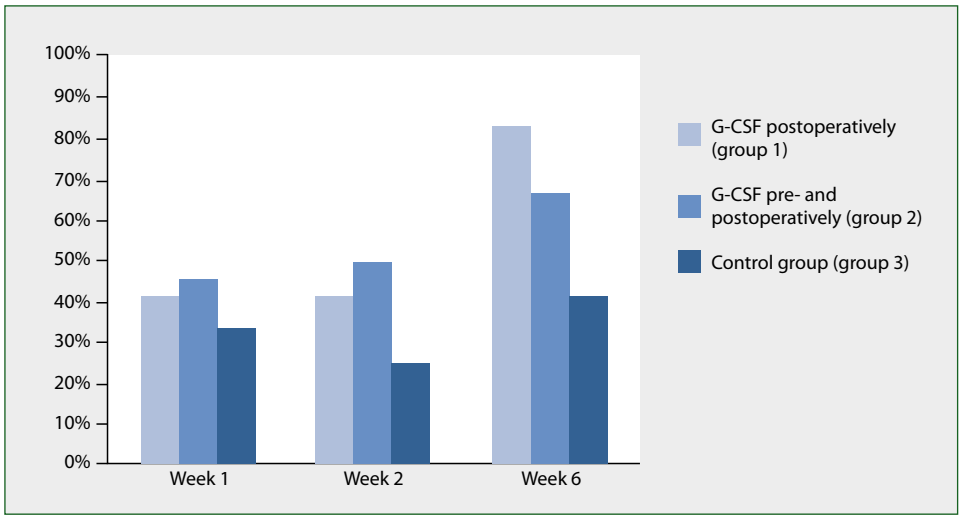


Figure 4. Development of SFI between week 1 and week 6, with proportions of animals without visible motor deficit (SFI 0 to –5) at week 1, week 2 and week 6. Compared to control group, motor deficit had recovered in a larger proportion of animals after G-CSF treatment. Although number of animals with recovered motor function was higher after G-CSF treatment at week 2 and week 6, no statistical difference was observed ($p = 0.3$ at week 2; $p = 0.1$ at week 6)

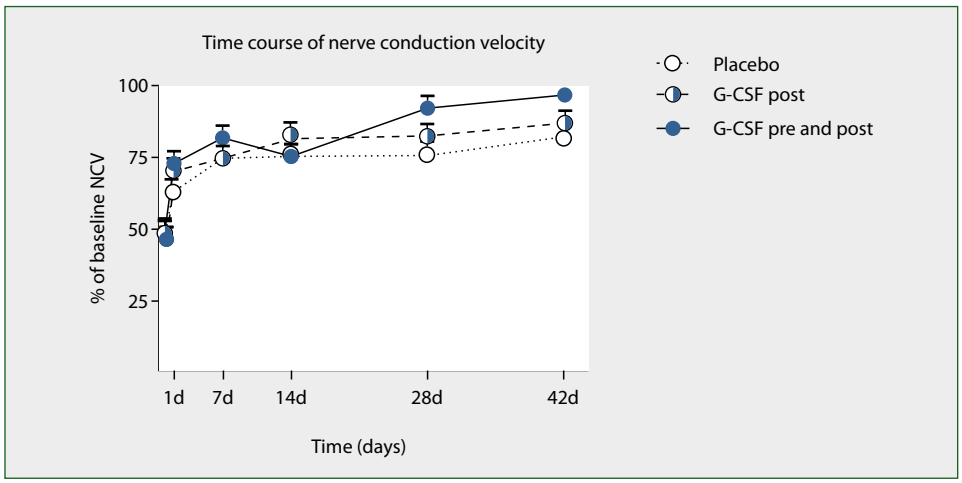


Figure 5. Ratios of preoperative motor NCV directly after lesion procedure, and at day 1, week 1, week 2, week 4, and week 6. Comparison of ratios shows that motor NCV had better improvement in animals receiving G-CSF, but only in long term after 4 and 6 weeks

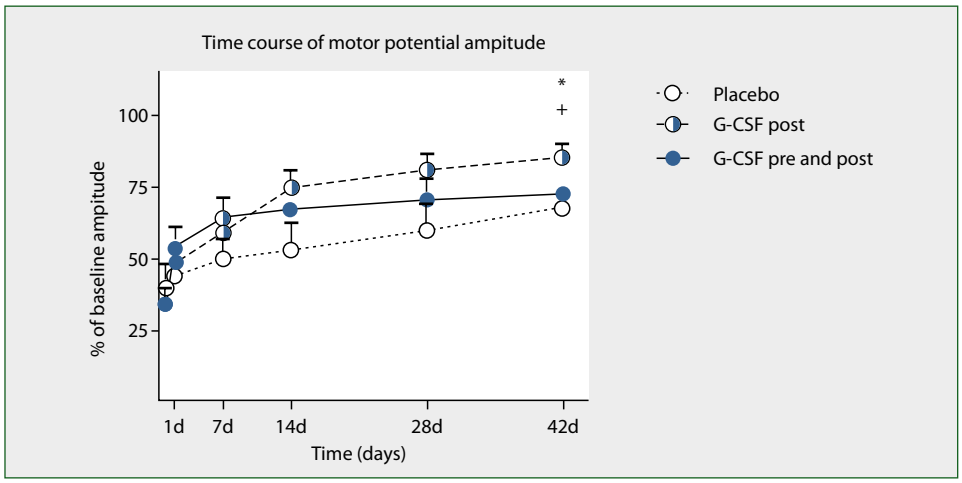


Figure 6. Development of motor potential amplitude after setting of lesion, at day 1, week 1, week 2, week 4 and week 6. Motor potential amplitude improved quickly between first measurement and week 1. In general, motor potential amplitude improved more quickly in animals treated with G-CSF

Analysis of changes in motor potential amplitude compared to the baseline amplitude revealed a faster improvement in animals in both G-CSF groups compared to the control group early on from week 1 to week 6. The recovery of both G-CSF groups was marked at week 1 and week 2 after nerve lesion.

Histological evaluation and morphometric analysis

Myelin debris and regeneration was evident in all specimens after surgical treatment. In rats sacrificed at week 1, the total number of nerve fibres and axonal diameters did not differ significantly. On the contrary, six weeks after the surgical procedure, the fibre density and the number of small regenerated axons were significantly higher in animals treated with G-CSF pre- and postoperatively ($p < 0.05$) (Fig. 7, 8). Due to the considerable increase of small regenerated axons, the fibre density per mm² and the relative number of large myelinated axons was decreased in these animals. Although animals treated with G-CSF postoperatively showed a slight increase of small regenerated fibres as well, no significant difference in regeneration results was evident in these animals compared to controls.

Counting of α-motoneurons (Fig. 9) did reveal a significantly higher number of motoneurons on the lesioned side after G-CSF treatment pre- and postoperatively ($p < 0.05$) (Fig. 10). Comparison between animals treated pre- and postoperatively and animals that were treated with G-CSF only postoperatively did not show a significant difference in the number of motoneurons. Further, counting of

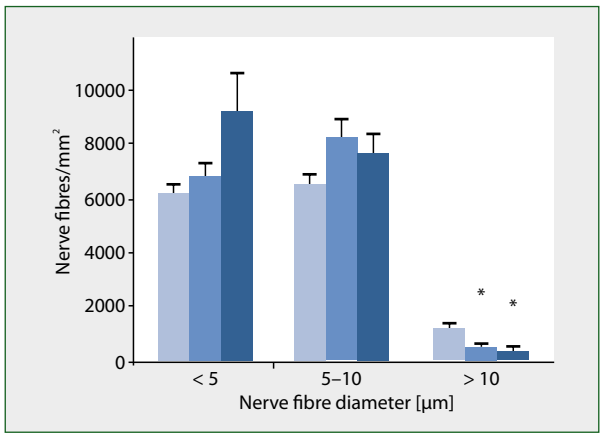


Figure 7. At week 6, fibre density of sciatic nerve was increased in both groups of animals that had received G-CSF. Additionally, in animals treated with G-CSF pre- and postoperatively, number of small, myelinated nerve fibres of < 5 µm in diameter was significantly higher compared to the control group (*; k6 = control group, p6 = G-CSF postoperatively, pp6 = G-CSF pre- and postoperatively)

α-motoneurons of the left (intact) side of the spinal cord sections did not reveal a significantly different number between the groups.

Discussion

Despite numerous research efforts, traumatic or iatrogenic damage to peripheral nerves often results in persistent and/or severe neurological deficits, even where the macro-morphologic nerve structure remains intact. Besides biomechanical or neurophysiological approaches including diverse nerve graft techniques [29–32], several systemic therapeutic agents have been closely investigated, including the administration of neurotrophic factors [33–35]. In recent years, haematopoietic factor G-CSF has been ascribed as having direct protective effects on neurons. The G-CSF receptor and its ligand are expressed in the cortex layers II and V, hippocampus, subventricular zone and in Purkinje-cells [1]. Additionally, G-CSF receptor has been found in deep cerebellar and brain stem nuclei in rodents and humans [8, 36]. Besides its anti-apoptotic and neuroregenerative properties, G-CSF fosters the formation of vessels after brain ischaemia and improves the recovery of sensorimotor and cognitive functions after stroke, in both experimental models and clinical settings [1, 3, 8]. In contrast to stroke models, functional neurological outcome after sciatic nerve lesion and G-CSF therapy has been rarely investigated [4].

In the spinal cord, G-CSF and its receptor have been detected in α-motoneurons of the ventral horn [9, 10]. Henriques et al. observed in an animal model of ALS that G-CSF receptor and its ligand are strongly expressed by α-motoneurons [9]. After axotomy of the sciatic nerves in transgenic

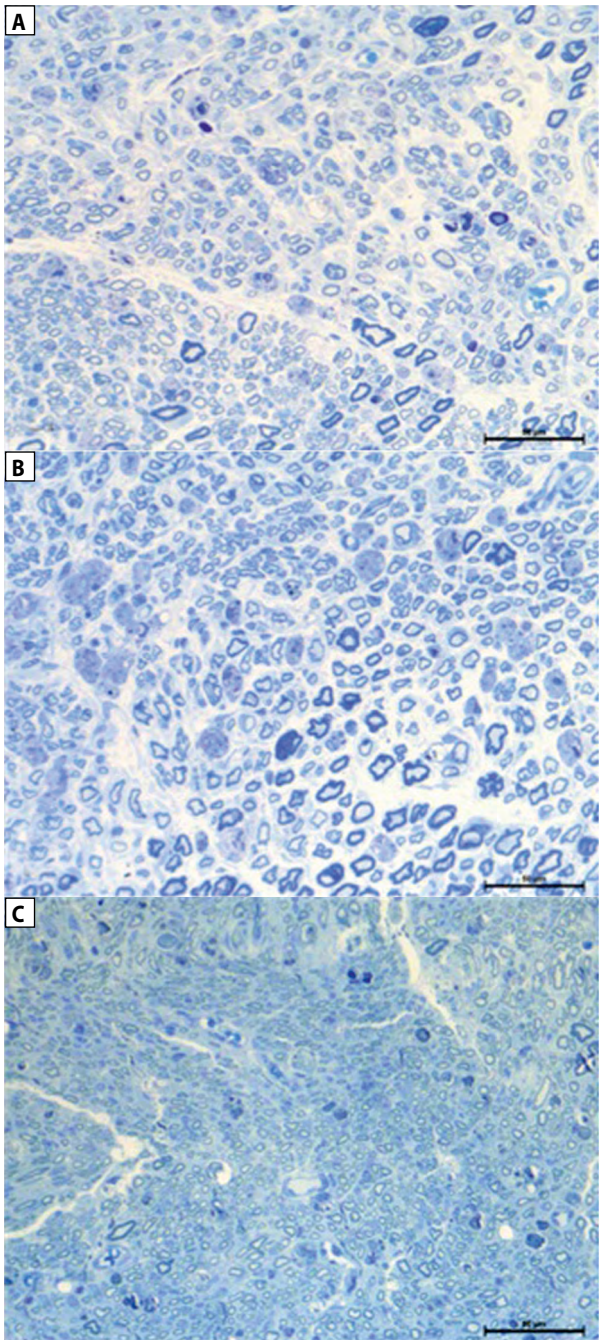


Figure 8. Semi-thin sections of sciatic nerves after 6 weeks of regeneration (methylene blue, scale bars = 50 µm). Control group (Group 3; **A**), animals treated with G-CSF postoperatively (Group 1; **B**), and animals treated with G-CSF pre- and postoperatively (Group 2; **C**). Best regeneration was seen in Group 2, showing a significant increase in number of small, myelinated nerve fibres compared to Group 3

SOD1-mice, a positive influence of G-CSF on motoneuron apoptosis of lumbar α-motoneurons with improvement of neuronal survival has been described. Additionally, G-CSF has been shown to preserve the size of motoneurons after axotomy, with increased expression of G-CSF receptor in

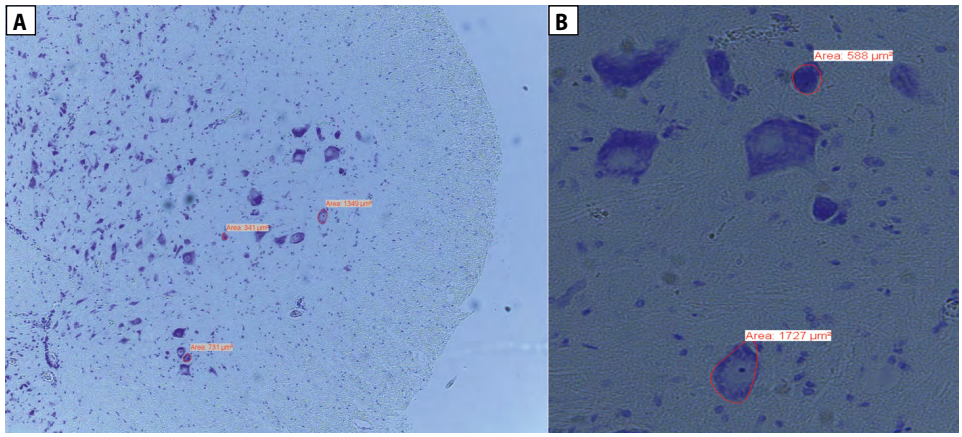


Figure 9. Light microscopic 45-fold enlargement (**A**) and 250-fold enlargement (**B**) of a lumbar cord section (HE-staining; SIS AnalySIS software, Olympus). Prior to microscopic analysis, spinal cord sections were fixed in paraffin and cut into 10-mm thick slices. All α-motoneurons in laminas 8 and 9 of the ventral horn that were clearly identifiable were counted on both sides. α-motoneurons were defined as neurons with a diameter of ≥ 300 µm^2, an intact cell membrane, a clearly definable nuclear membrane with a nucleolus, and clearly definable cytoplasm

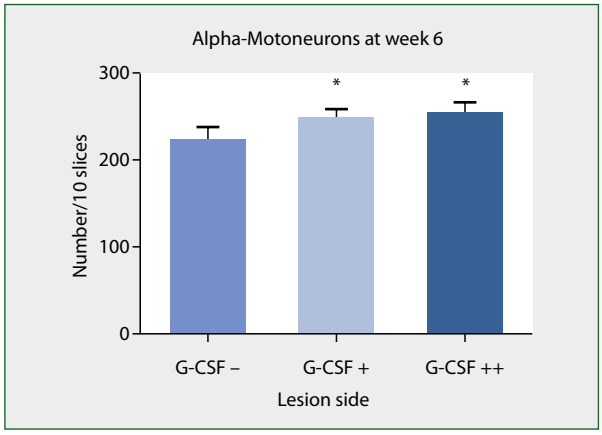


Figure 10. Number of α-motoneurons (mean value of 10 consecutive slices of lumbar spinal cord sections) of lesioned side at week 6. Number of α-motoneurons was significantly higher (*; $p < 0.05$) in animals after G-CSF treatment compared to control group. Comparison between animals that received G-CSF pre- and postoperatively and animals that received G-CSF only postoperatively did not show significant differences

motoneurons at the L4 and L5 levels of the lumbar spine. However, neither the impact of G-CSF on functional impairment nor the number of preserved and regenerated nerve fibres was assessed in that study [9].

In our current study, the potential neuroregenerative effects of G-CSF after reproducible and incomplete peripheral nerve trauma with preserved nerve continuity were investigated. Besides the assessment of histological changes such as the number of α-motoneurons or the number and size of sciatic nerve fibres, the main part of our study included the evaluation of changes in motor function and electrophysiological measurement as carried out in clinical settings.

The improvement of motor deficits in animals treated with G-CSF pre- and postoperatively and with G-CSF postoperatively, seemed superior compared to the control group, contradicting the results of Pan et al. [4] who reported no significance after similar treatment. The explanation may lie in the different experimental design, in particular in the different severity of sciatic nerve lesions.

In stroke models, G-CSF promotes a strong anti-apoptotic effect via activation of the PI3K/Akt pathway and to a lesser extent through activation of the STAT3 and ERK5 pathways [37]. To date, the effect of G-CSF on spinal α-motoneurons after lesion of peripheral nerves has not been systematically investigated. The involvement of several pathways including bcl-proteins, AI, IAPs and caspases has been reported [9, 30, 38]. In general, our findings align with the results of Henriques et al. [9] and with results in the treatment of central lesions. Thus, it appears that neuroregenerative effects mediated by G-CSF after peripheral nerve lesion are possible. Although no statistically significant functional benefit could be shown, long-term beneficial effects regarding peripheral nerve regeneration after (incomplete) traumatic nerve lesion might exist.

Regarding the motor NCV ratio and its improvement in the current study, a strong trend towards faster improvement was observed in the animals treated with G-CSF at week 4 and week 6. After six weeks, motor NCV improved significantly in animals that received G-CSF compared to placebo-treated animals. Additionally, the dynamics of recovery in motor potential amplitude (representing the number of functional axons / number of regenerating motor nerve fibres) was more rapid in G-CSF-treated animals compared to those receiving a placebo. The maximal improvement was seen between week 4 and week 6. This observation aligns with the nerve fibre count surveyed at week 6. Here, we documented a significantly

higher number and density of myelinated fibres in animals who received G-CSF. Previous morphological studies have reported that regenerated nerve fibres are smaller, showing a diameter < 5 µm [32, 39]. Thus, in our experiment, the large number of small myelinated fibres might indicate an improved regeneration. Also the α-motoneurons count was higher in animals treated with G-CSF.

We conclude that anti-apoptotic effects may lead to an increased survival of α-motoneurons and to the initiation/maintenance of regrowth of their axons i.e. motor fibres.

There are some limitations of the present study. Firstly, the translation of data from an experimental setting to bedside has to be done very carefully and requires additional safety analysis in clinical conditions. Secondly, the design of the present study bears the risk of a certain bias due to a larger deviation of results due to between-subject variation in conditions of electrophysiogical assessment. Finally, calculating statistics in a small cohort carries an increased risk of bias.

On the other hand, the multiple strengths of this study rely on prolonged follow-up of electrophysiological and functional nerve recovery, demonstrating a certain similarity to the clinical routine. To the best of our knowledge, this is the first animal study to evaluate the neuroregenerative potential of G-CSF over a period of up to six weeks, using both functional and electroneurophysiological assessments. Furthermore, the waterjet injury technique offers a high reproducibility of nerve damage with I) maintained nerve continuity, II) a rapid form of injury such as is observed in an acute trauma, and III) the possibility of adjusting the injury severity by altering jet pressure level.

Clinical implications and future directions

We believe further investigation of nerve regeneration under G-CSF treatment is worth elucidating in clinical settings. To date, no single efficient pharmacological intervention stimulating a peripheral nerve to recover after mechanical damage has been described.

Even if the role of G-CSF in the regeneration of axons and α-motoneurons after such injury is not completely understood, the results of the present study show a structural improvement of nerve regeneration after the application of G-CSF and acceleration of its functional recovery.

In cases of scheduled neurosurgical procedures on peripheral nerves with an (expected) traumatic impact on the nerve due to prolonged or intense manipulation, G-CSF could be administered prior to surgery. Thus, additional studies investigating the neuroprotective and neuroregenerative mechanisms of G-CSF after peripheral nerve lesions are important. G-CSF has been administered in humans for many years to treat neutropenia, and might be a promising agent after peripheral nerve lesion. However, better understanding of the potential effects of G-CSF in terms of neuroregenerative mechanisms, G-CSF dose, and form of G-CSF administration is of the utmost importance. In the long term, studies investigating G-CSF and its potential to preserve the peripheral nerve or support its regeneration under clinical circumstances may well be worth initiating.

Author disclosure statement: *J. Oertel is consultant to Karl Storz Company. J. Oertel has received grants from Erbe Company. These companies were not involved in the experimental set up, work or analysis of the present study. Other than this, all authors declare that they have no competing financial interest. This study was financially supported by the non-profit foundation Else-Kröner-Fresenius-Stiftung.*

References

1. Schneider A, Krüger C, Steigleder T, et al. The hematopoietic factor G-CSF is a neuronal ligand that counteracts programmed cell death and drives neurogenesis. J Clin Invest. 2005; 115(8): 2083–2098, doi: 10.1172/JCI23559, indexed in Pubmed: 16007267.
2. Strecker JK, Sevimli S, Schilling M, et al. Effects of G-CSF treatment on neutrophil mobilization and neurological outcome after transient focal ischemia. Exp Neurol. 2010; 222(1): 108–113, doi: 10.1016/j.expneurol.2009.12.012, indexed in Pubmed: 20026112.
3. Schäbitz WR, Schneider A. New targets for established proteins: exploring G-CSF for the treatment of stroke. Trends Pharmacol Sci. 2007; 28(4): 157–161, doi: 10.1016/j.tips.2007.02.007, indexed in Pubmed: 17350693.
4. Pan HC, Wu HT, Cheng FC, et al. Potentiation of angiogenesis and regeneration by G-CSF after sciatic nerve crush injury. Biochem Biophys Res Commun. 2009; 382(1): 177–182, doi: 10.1016/j.bbrc.2009.03.003, indexed in Pubmed: 19275877.
5. Diederich K, Quennet V, Bauer H, et al. Successful regeneration after experimental stroke by granulocyte-colony stimulating factor is not further enhanced by constraint-induced movement therapy either in concurrent or in sequential combination therapy. Stroke. 2012; 43(1): 185–192, doi: 10.1161/STROKEAHA.111.622159, indexed in Pubmed: 22020031.
6. Gibson CL, Bath PMW, Murphy SP. G-CSF reduces infarct volume and improves functional outcome after transient focal cerebral ischemia in mice. J Cereb Blood Flow Metab. 2005; 25(4): 431–439, doi: 10.1038/sj.jcbfm.9600033, indexed in Pubmed: 15660101.
7. Lee ST, Chu K, Jung KH, et al. Granulocyte colony-stimulating factor enhances angiogenesis after focal cerebral ischemia. Brain Res. 2005; 1058(1-2): 120–128, doi: 10.1016/j.brainres.2005.07.076, indexed in Pubmed: 16150422.
8. Schäbitz WR, Schneider A. Developing granulocyte-colony stimulating factor for the treatment of stroke: current status of clinical trials. Stroke. 2006; 37(7): 1654; author reply 1655, doi: 10.1161/01.STR.0000227299.62106.0e, indexed in Pubmed: 16728676.
9. Henriques A, Pitzer C, Dupuis L, et al. G-CSF protects motoneurons against axotomy-induced apoptotic death in neonatal mice. BMC Neurosci. 2010; 11: 25, doi: 10.1186/1471-2202-11-25, indexed in Pubmed: 20178614.
10. Pitzer C, Krüger C, Plaas C, et al. Granulocyte-colony stimulating factor improves outcome in a mouse model of amyotrophic lateral sclerosis. Brain. 2008; 131(Pt 12): 3335–3347, doi: 10.1093/brain/awn243, indexed in Pubmed: 18835867.
11. Oertel J, Gaab MR, Knapp A, et al. Water jet dissection in neurosurgery: experimental results in the porcine cadaveric brain. Neurosurgery.

2003; 52(1): 153–9; discussion 159, doi: 10.1097/00006123-200301000-00020, indexed in Pubmed: 12493113.
12. Oertel J, Gaab MR, Piek J. Waterjet resection of brain metastases - first clinical results with 10 patients. Eur J Surg Oncol. 2003; 29(4): 407–414, doi: 10.1053/ejso.2002.1428, indexed in Pubmed: 12711300.
13. Oertel J, Gaab MR, Pillich DT, et al. Comparison of waterjet dissection and ultrasonic aspiration: an in vivo study in the rabbit brain. J Neurosurg. 2004; 100(3): 498–504, doi: 10.3171/jns.2004.100.3.0498, indexed in Pubmed: 15035286.
14. Oertel J, Gaab MR, Runge U, et al. Waterjet dissection versus ultrasonic aspiration in epilepsy surgery. Neurosurgery. 2005; 56(1 Suppl): 142–6; discussion 142, doi: 10.1227/01.neu.0000144316.87764.13, indexed in Pubmed: 15799802.
15. Oertel J, Gaab MR, Warzok R, et al. Waterjet dissection in the brain: review of the experimental and clinical data with special reference to meningioma surgery. Neurosurg Rev. 2003; 26(3): 168–174, doi: 10.1007/s10143-002-0244-7, indexed in Pubmed: 12845544.
16. Piek J, Oertel J, Gaab MR. Waterjet dissection in neurosurgical procedures: clinical results in 35 patients. J Neurosurg. 2002; 96(4): 690–696, doi: 10.3171/jns.2002.96.4.0690, indexed in Pubmed: 11990809.
17. Piek J, Wille C, Warzok R, et al. Waterjet dissection of the brain: experimental and first clinical results. Technical note. J Neurosurg. 1998; 89(5): 861–864, doi: 10.3171/jns.1998.89.5.0861, indexed in Pubmed: 9817429.
18. Keiner D, Gaab MR, Backhaus V, et al. Water jet dissection in neurosurgery: an update after 208 procedures with special reference to surgical technique and complications. Neurosurgery. 2010; 67(2 Suppl Operative): 342–354, doi: 10.1227/NEU.0b013e3181f743bb, indexed in Pubmed: 21099557.
19. Tschan C, Gaab MR, Krauss JK, et al. Waterjet dissection of the vestibulocochlear nerve: an experimental study. J Neurosurg. 2009; 110(4): 656–661, doi: 10.3171/2008.5.17561, indexed in Pubmed: 18834266.
20. Tschan CA, Keiner D, Müller HD, et al. Waterjet dissection of peripheral nerves: an experimental study of the sciatic nerve of rats. Neurosurgery. 2010; 67(2 Suppl Operative): 368–376, doi: 10.1227/NEU.0b013e3181f9b0c8, indexed in Pubmed: 21099560.
21. Dinh P, Hazel A, Palispis W, et al. Functional assessment after sciatic nerve injury in a rat model. Microsurgery. 2009; 29(8): 644–649, doi: 10.1002/micr.20685, indexed in Pubmed: 19653327.
22. Kalender AM, Dogan A, Bakan V, et al. Effect of Zofenopril on regeneration of sciatic nerve crush injury in a rat model. J Brachial Plex Peripher Nerve Inj. 2009; 4: 6, doi: 10.1186/1749-7221-4-6, indexed in Pubmed: 19508704.
23. Yan JG, Matloub HS, Yan Y, et al. The correlation between calcium absorption and electrophysiological recovery in crushed rat peripheral nerves. Microsurgery. 2010; 30(2): 138–145, doi: 10.1002/micr.20709, indexed in Pubmed: 19790186.
24. Kouyoumdjian JA. Peripheral nerve injuries: a retrospective survey of 456 cases. Muscle Nerve. 2006; 34(6): 785–788, doi: 10.1002/mus.20624, indexed in Pubmed: 16881066.
25. Eser F, Aktekin LA, Bodur H, et al. Etiological factors of traumatic peripheral nerve injuries. Neurol India. 2009; 57(4): 434–437, doi: 10.4103/0028-3886.55614, indexed in Pubmed: 19770544.
26. Kretschmer T, Antoniadis G, Braun V, et al. Evaluation of iatrogenic lesions in 722 surgically treated cases of peripheral nerve trauma. J Neurosurg. 2001; 94(6): 905–912, doi: 10.3171/jns.2001.94.6.0905, indexed in Pubmed: 11409518.
27. Wee AS, Truitt NR, Smith LD. Type and frequency of peripheral nerve injuries encountered in a clinical neurophysiology laboratory. Journal of the Mississippi State Medical Association. 2006; 47: 67–71.
28. de Medinaceli L, Freed WJ, Wyatt RJ. An index of the functional condition of rat sciatic nerve based on measurements made from walking tracks. Exp Neurol. 1982; 77(3): 634–643, doi: 10.1016/0014-4886(82)90234-5, indexed in Pubmed: 7117467.
29. McGrath AM, Brohlin M, Kingham PJ, et al. Fibrin conduit supplemented with human mesenchymal stem cells and immunosuppressive treatment enhances regeneration after peripheral nerve injury. Neurosci Lett. 2012; 516(2): 171–176, doi: 10.1016/j.neulet.2012.03.041, indexed in Pubmed: 22465323.
30. Imaizumi K, Benito A, Kiryu-Seo S, et al. Critical role for DP5/Harakiri, a Bcl-2 homology domain 3-only Bcl-2 family member, in axotomy-induced neuronal cell death. J Neurosci. 2004; 24(15): 3721–3725, doi: 10.1523/JNEUROSCI.5101-03.2004, indexed in Pubmed: 15084651.
31. Belkas JS, Munro CA, Shoichet MS, et al. Long-term in vivo biomechanical properties and biocompatibility of poly(2-hydroxyethyl methacrylate-co-methyl methacrylate) nerve conduits. Biomaterials. 2005; 26(14): 1741–1749, doi: 10.1016/j.biomaterials.2004.05.031, indexed in Pubmed: 15576148.
32. Kemp SWP, Webb AA, Dhaliwal S, et al. Dose and duration of nerve growth factor (NGF) administration determine the extent of behavioral recovery following peripheral nerve injury in the rat. Exp Neurol. 2011; 229(2): 460–470, doi: 10.1016/j.expneurol.2011.03.017, indexed in Pubmed: 21458449.
33. Alrashdan MS, Sung MA, Kwon YK, et al. Effects of combining electrical stimulation with BDNF gene transfer on the regeneration of crushed rat sciatic nerve. Acta Neurochir (Wien). 2011; 153(10): 2021–2029, doi: 10.1007/s00701-011-1054-x, indexed in Pubmed: 21656118.
34. Devesa P, Gelabert M, Gonźlez-Mosquera T, et al. Growth hormone treatment enhances the functional recovery of sciatic nerves after transection and repair. Muscle Nerve. 2012; 45(3): 385–392, doi: 10.1002/mus.22303, indexed in Pubmed: 22334173.
35. Haastert-Talini K, Schmitte R, Korte N, et al. Electrical stimulation accelerates axonal and functional peripheral nerve regeneration across long gaps. J Neurotrauma. 2011; 28(4): 661–674, doi: 10.1089/neu.2010.1637, indexed in Pubmed: 21265597.
36. Ridwan S, Bauer H, Frauenknecht K, et al. Distribution of granulocyte-monocyte colony-stimulating factor and its receptor α-subunit in the adult human brain with specific reference to Alzheimer's disease. J Neural Transm (Vienna). 2012; 119(11): 1389–1406, doi: 10.1007/s00702-012-0794-y, indexed in Pubmed: 22430742.
37. Minnerup J, Sevimli S, Schäbitz WR. Granulocyte-colony stimulating factor for stroke treatment: mechanisms of action and efficacy in preclinical studies. Exp Transl Stroke Med. 2009; 1: 2, doi: 10.1186/2040-7378-1-2, indexed in Pubmed: 20142989.
38. Perrelet D, Ferri A, MacKenzie AE, et al. IAP family proteins delay motoneuron cell death in vivo. Eur J Neurosci. 2000; 12(6): 2059–2067, doi: 10.1046/j.1460-9568.2000.00098.x, indexed in Pubmed: 10886345.
39. Lee AC, Yu VM, Lowe JB, et al. Controlled release of nerve growth factor enhances sciatic nerve regeneration. Exp Neurol. 2003; 184(1): 295–303, doi: 10.1016/s0014-4886(03)00258-9, indexed in Pubmed: 14637100.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 5, pages: 479–484
DOI: PJNNS.a2021.0074

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

Spinal muscular atrophy: epidemiology and health burden in children — a Polish national healthcare database perspective before introduction of SMA-specific treatment

Anna Kostera-Pruszczyk[1], Łukasz Napiórkowski[2], Krystyna Szymańska[3], Joanna Jędrzejczak[4], Marcin Roszkowski[5], Jerzy Słowiński[6], Anna Frączek[1], Danuta Ryglewicz[7], Barbara Więckowska[2, 8]

[1]Department of Neurology, Medical University of Warsaw, Warsaw, Poland; ERN EURO-NMD
[2]Department of Analyses and Strategy, Ministry of Healthcare, Warsaw, Poland
[3]Department of Experimental and Clinical Neuropathology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland
[4]Department of Neurology and Epileptology, Centre of Postgraduate Medical Education, Warsaw, Poland
[5]Department of Neurosurgery, The Children's Memorial Health Institute, Warsaw, Poland
[6]Medical University of Silesia, School of Public Health, Katowice, Poland
[7]Military Institute of Aviation Medicine, Warsaw, Poland
[8]Social Insurance Department, Warsaw School of Economics, Warsaw, Poland

ABSTRACT

Introduction: Spinal muscular atrophy (SMA) is one of the most frequent autosomal recessive neuromuscular disorders. It leads to progressive muscle weakness, premature death or permanent ventilation. Significant disability, scoliosis, severe pulmonary infections and other problems require in- and outpatient medical care. Various approaches have been used to evaluate SMA epidemiology, healthcare burden and adherence to standard of care. The recent introduction of pharmacological treatment in a large SMA population will change the course of the disease and the healthcare requirements of patients.

Material and methods: We have used the National Health Fund database to identify children with SMA and the healthcare service they received in the pre-pharmacological treatment era. Pivotal phase II and III medical trials for nusinersen were conducted between 2013 and 2015. The National Treatment Programme of SMA patients with nusinersen in our country was started in January 2019. The year 2014 was used to evaluate incident cases.

Results: 51 new SMA cases (incidence 1:7,356) and 518 SMA patients younger than 18 were identified in 2014. 32 (6.2%) deaths were recorded, half in the first two years of life. 35 (6.8%) patients received palliative and 115 (22.2%) long-term care (including assisted ventilation). A total number of 3,057 days of hospital stay were reported. Only 65/518 (12.6%) patients did not receive publicly-funded healthcare service other than specialist or general practitioner's consultation.

Conclusions: SMA caused significant mortality and morbidity in children. The National Health Fund database can be used to reliably record incident cases and track the care provided to paediatric SMA patients.

Key words: spinal muscular atrophy, epidemiology, healthcare burden, incidence

(*Neurol Neurochir Pol 2021; 55 (5): 479–484*)

Address for correspondence: Anna Kostera-Pruszczyk, Department of Neurology, Medical University of Warsaw, Banacha 1a, 02–097 Warsaw, Poland; e-mail: anna.kostera-pruszczyk@wum.edu.pl

Received: 30.03.2021 Accepted: 6.09.2021 Early publication date: 19.10.2021

Introduction

Spinal muscular atrophy (SMA) is one of the most frequent autosomal recessive neuromuscular disorders. SMA is caused by mutations of the survival motor neuron (*SMN1)* gene located on chromosome 5q [1]. Depending on the severity of symptoms, three SMA forms have been defined by the International SMA Consortium: severe infantile SMA1 — manifested in the first six months of life and diagnosed in children never able to sit unsupported; SMA2 in children who never walk; and SMA3 in those who achieve walking ability. SMA4 is the mildest, and rare, form, and becomes manifest clinically in the second or third decades of life [2]. Overall, almost all patients with SMA are symptomatic and diagnosed in childhood [3]. Access to genetic testing allows precise SMA diagnosis: approximately 97% of patients in our country have exon 7 biallelic deletion of *SMN1* [4]. In the remainder, point mutations in *SMN1* have been identified [5].

SMA is a disease with an incidence of approximately 1:3,900–16,000 live births, as evaluated by direct contact with genetic laboratories across Europe [6]. As a diagnosis of SMA requires genetic confirmation, such a study provides accurate epidemiological data. In the era of emerging SMA therapies, it is important to follow the disease course and the access of patients to healthcare services. One way of doing this is via the use of disease-specific registries, such as the global SMA TREAT NMD registry [7]. Another option is the use of healthcare or insurance databases.

There are several major indicators of the disease course in SMA. SMA1 leads to respiratory insufficiency or death during the first two years of life in the majority of patients. SMA2 and SMA3 can also lead to respiratory compromise later in life and cause significant disability. Scoliosis is seen in most SMA2 and SMA3 patients [3]. Until recently, only symptomatic treatment could be offered [8]. Physiotherapy is indicated in all SMA patients. Scoliosis surgery, respiratory support, gastrostomy (PEG) or gastric fundoplasty are indicated in advanced clinical stages [9, 10]. A recent report on the standard of care received by SMA patients was collected by the TREAT NMD registry [7].

Clinical rationale for study

The aim of our study was to use the national insurance database to estimate disease incidence, identify juvenile SMA patients, and analyse the medical care they received when no treatment for SMA was available worldwide. Pivotal phase II and III medical trials for nusinersen, the first drug registered for SMA treatment, were conducted between 2013 and 2015 [11–13]. The results of these trials led to the approval of the drug in 2016 by the U.S. Food and Drug Administration (FDA) and in 2017 by the European Medicines Agency (EMA). The Polish National Treatment Programme of SMA patients with nusinersen started in January 2019. Nusinersen is currently reimbursed for all patients, regardless of age and SMA type. The next two drugs for SMA treatment registered in the USA or Europe are risdiplam and onasemnogene abeparvovec-xioi [14]. These are currently not reimbursed in Poland. Additionally, a newborn screening programme for SMA was started in April 2021.

Material and methods

We analysed the National Health Fund (NFZ) registry. This national insurance database is principally used for financial settlement of health services by the NFZ, and therefore it contains only healthcare services covered by public funding. Complete data was available for the period 1 January 2009 to 31 December 2015 supplemented with dates of deaths until 21 April 2016. The analyses were conducted for patients treated in 2014, and compared to health services in 2013.

Data was collected on SMA patients younger than 18. ICD10 code G12 was used to identify SMA patients. The code was not restricted to G12.0 (Infantile spinal muscular atrophy, type I [Werdnig-Hoffman]), as the reporting system allows the reporting of a three-character ICD10 code (instead of five-character code) in cases other than inpatient treatment. Only the primary diagnosis code at discharge was taken into account. Age cut-off was used for two reasons: in Poland, all minors are covered by insurance regardless of the employment status of their caregivers, so we assumed that all healthcare services will be recorded. Secondly, all SMA1, SMA2 and most SMA3–4 patients are diagnosed in this age group, allowing us to identify incident cases in 2014.

An SMA patient is defined for the purposes of this study as a person who was recorded at least twice in the NFZ database with an ICD10 G12* code or, for acute cases, only once and who died within two years of their first appearance. The rule was based on the assumptions that SMA patients should regularly visit a physician or attend physiotherapy and that the first outpatient consultation or hospital stay begins the diagnostic process which can confirm the diagnosis of SMA — then more services will be recorded with the same ICD10 code, or, less frequently, an alternative diagnosis can be established (there is only a single public healthcare service with a G12* code).

After an SMA patient was identified, we used her or his unique identifier to follow all healthcare services (the reported ICD10 code was not taken into account), including hospitalisations (ward, length of stay, surgical procedures for scoliosis or gastrostomy tube placement), specialised outpatient consultations, palliative or long-term care, physiotherapy, invasive (IV) or noninvasive (NIV) ventilation, or death. All deaths up to 21 April 2016 were considered in order to measure the death rate in SMA patients.

Results

We identified 51 new SMA cases in 2014. 15 children (29.4%) were diagnosed in the first year of life and 41.2% within the first two years. There were 375,200 live births in

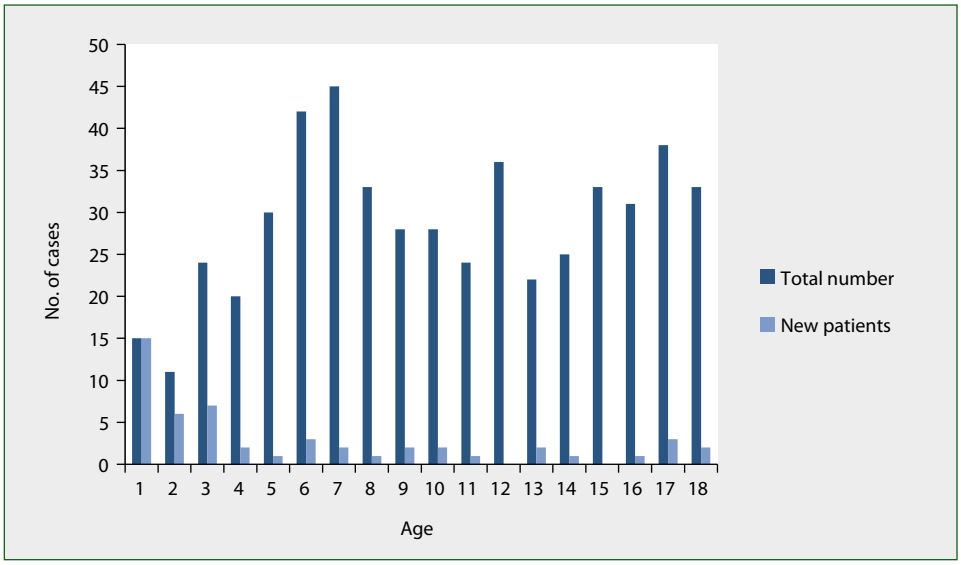


Figure 1. Age distribution at diagnosis date and total number of patients by age in 2014

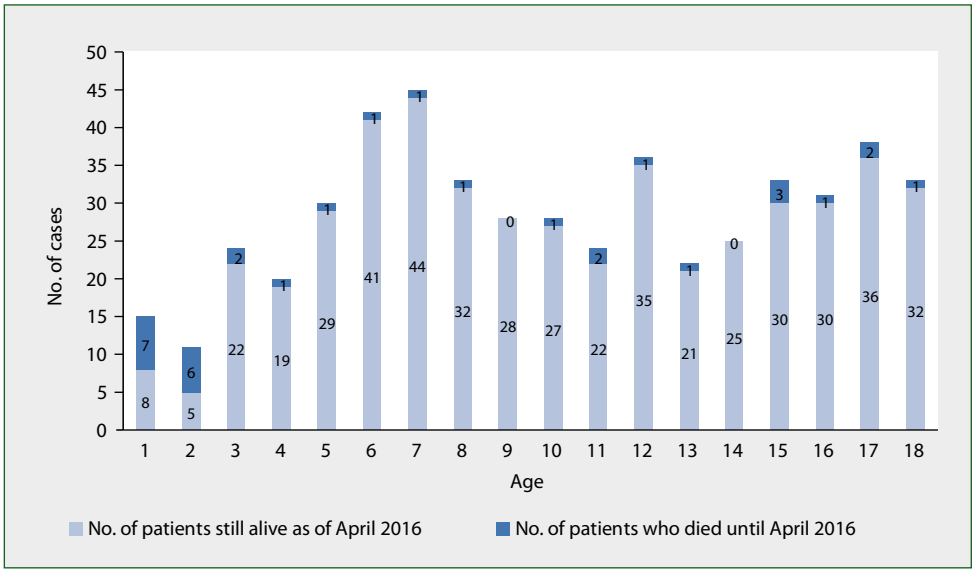


Figure 2. Age distribution and number of deaths per year of age

2014, according to the Central Statistical Office (GUS), yielding an incidence of 1:7,356. The age distribution at diagnosis date and total number of patients by age for 2014 is presented in Figure 1.

There were 518 SMA patients younger than 18; 39.8% were girls. A total of 32 deaths was recorded in 2014 (6.2%). The death rate was highest in the first two years of life, accounting for 50% (13/26 cases) of children in this group (Fig. 2). Age distribution and number of deaths per each year of age is presented in Figure 2.

The results of the analysis indicate that in- or outpatient publicly-funded physiotherapy was provided to 273/518 (52.7%) patients in 2014. Additionally, 35 (6.8%) patients received palliative care (defined by the NFZ as comprehensive care for patients suffering from incurable, progressive and life-limiting illnesses aimed at improving the quality of life, preventing pain and other somatic symptoms) and 115 (22.2%) received long-term care (this includes assisted ventilation and other services for patients with chronic illnesses or disabilities who need constant non-hospital medical care). Overall, 74.3% received physiotherapy, palliative care or long term care.

The method of reporting mechanical ventilation used in 2013 did not allow us to separate NIV from IV. Any kind of ventilation was received by 99 (19.7%) children in 2013. In 2014, ventilation was provided for 112 (21.6%) patients:

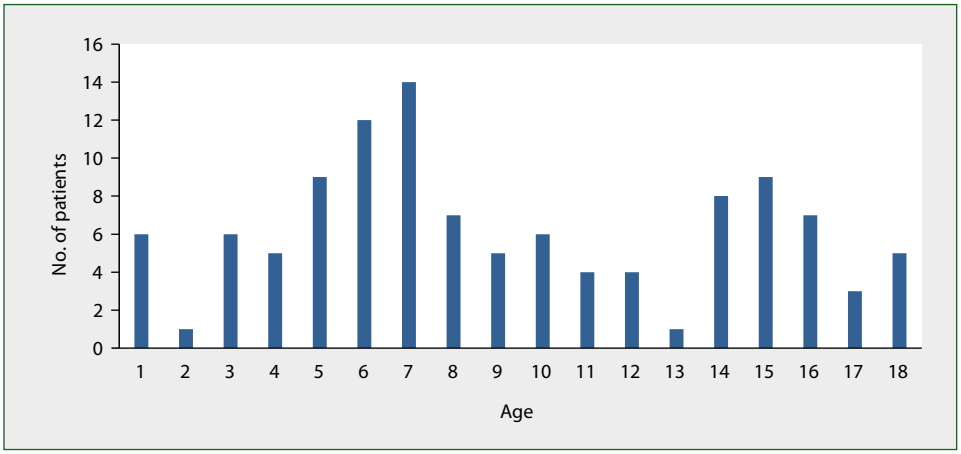


Figure 3. Age distribution of patients receiving mechanical ventilation in 2014

38 (34% of all ventilated) patients received NIV, while IV was reported in 98, indicating that 24 patients were transferred from NIV to IV during that year. NIV was provided to 51 (38%) of 133 receiving ventilator support in 2015.

The age distribution of the patients receiving mechanical ventilation in 2014 is presented in Figure 3.

Hospitalisations

There were 321 hospital stays of SMA paediatric patients in 2013 with a total of 3,057 days of stay, while 313 hospitalisations accounted for 2,883 days of stay in 2014. The average length of stay (ALOS) was similar in both years, and amounted to 9.5 days in 2013 and 9.2 days in 2014. Median length of stay (MLOS) remained unchanged at 4 days.

Most hospital stays in 2013 and 2014 were reported by the paediatric (43.6% and 42.5% respectively), intensive care (11.8% and 12.8%), and paediatric neurology departments (8.4% and 7.3%).

We evaluated two surgical procedures that are related to the progressive course of SMA: gastrostomy and scoliosis surgery. Gastrostomy and scoliosis surgery were reported for four and 11 children in 2013, 10 and 10 children in 2014, and 10 and 13 children in 2015, respectively. Scoliosis surgery was recorded only in children aged six and above.

Specialised outpatient care

There were 1,648 and 1,638 outpatient visits reported in 2013, and 2014, respectively, with 27.3% and 28.4% of visits provided by the paediatric neurology or neurology service. Outpatient geneticists' consultations were received by 48 patients in 2013 and 40 in 2014. The number of specialised outpatient care visits does not include the general paediatric service that is usually provided by primary care physicians. For only 65 (12.6%) patients, no healthcare service other than specialist or general practitioner consultation was recorded.

Discussion

Healthcare databases can be used as surrogate tools in epidemiological studies, if a precise coding method can be applied to a well-defined population [15]. We undertook such an effort for SMA minors in Poland. All of them are covered by health insurance (NFZ) which records all publicly-funded healthcare services. We decided to analyse data from the period when no SMA-specific treatment options had been available. We identified 51 new SMA cases in 2014, corresponding with an incidence of 13.6 per 100,000, or 1 per 7,356 live births. This is in good agreement with a recent SMA epidemiological study conducted by direct contact with genetic laboratories across Europe. With this methodology, SMA incidence in Poland in 2015 was 13.5 per 100,000 (95% CI 10.1–17.6) [6]. In our previous study based on information collected from genetic laboratories, the incidence of all SMA subtypes was 1 per 7,127 in Warsaw and 1 per 9,320 across Poland, suggesting underdiagnosis in some regions of the country [16]. Our current results probably indicate improved SMA diagnosis [6, 16, 17]. A recent literature review estimates that SMA1 patients constitute 50–60% of new cases, with an incidence of 5.5 per 100,000 live births [17]. In the study by Jedrzejowska et al. [16] in 2010, the incidence of SMA1 patients in Poland was 3.2 per 100,000 newborns.

The methodology we currently use does not allow us to verify SMA subtype. 15 patients (only 30%) were diagnosed in the first year of life (incidence of 3.99 per 100,000 live births). This might be explained either by diagnostic delay — with some SMA1 children diagnosed after 12 months of life, or a higher proportion of SMA2–3 patients in our cohort. Genetic testing of *SMN1* gene deletions and point mutations has been available in our country for many years [4, 18]. As SMA1–3 patients are diagnosed during childhood, we assume that the NFZ database identified all, or the vast majority, of SMA1–3 patients.

Most of the information on the medical care in the large SMA patient cohort comes from registries such as the global

TREAT NMD registry [7]. It is estimated that the registry population in the analysed period was at least half that of the true SMA population [6, 19]. Moreover, the most severe SMA1 patients were possibly underrepresented in the registries, as the disease rapidly progresses and many patients die or become ventilator-dependent in the first years of life [7, 20].

In our cohort, 15 (30%) of the patients were diagnosed in the first year of life and 21 (41%) within the first two years. We assume that most of the children diagnosed in the first two years of life represent acute SMA, as seven (33%) of them received ventilatory support and 50% of all recorded deaths occurred in children younger than two, reflecting the natural course of SMA1 [21, 22]. In the study by Farrar et al., survival for SMA1 children at 1, 2, 4 and 10 years was 40%, 25%, 6% and 0%, respectively [20]. The survival probabilities of SMA2 patients at 1, 2, 4, 10, and 20 years are 100%, 100%, 100%, 92%, and 92%, while SMA3 patients generally have normal life expectancy [23]. Overall mortality before the 18th birthday in our study was 6.2%. Although proactive care and NIV or IV ventilation increase survival in SMA1, mortality in this age group can be attributed to SMA1 or SMA2 [2, 3, 20, 24].

SMA patients require multidisciplinary care. Standard of care (SoC) was first published in 2007, and updated in 2016 [8, 25]. Adherence to the current standard of care is a goal for all SMA patients. The TREAT NMD registry study analysed implementation of the 2007 SoC and demonstrated significant variability in participating countries, especially with regard to the preferred method of ventilatory support (NIV vs. IV) [7]. NIV is advocated for patients with neuromuscular diseases [26]. In SMA1 children, it not only improves survival but facilitates development of speech as well [24]. In our cohort, 30.5% of children received ventilatory support. The choice of IV vs. NIV depends on many variables, including the approach to end of life decisions by the patient's parents, the organisation of healthcare systems, and also the physician's personal preferences. Although IV was reported in the majority of cases, there was a trend towards more frequent use of NIV between 2014 and 2015.

Our analysis revealed that approximately 10 children per year had scoliosis surgery between 2013 and 2015. This is a similar proportion to scoliosis surgery performed per year in SMA patients reported in a study from the paediatric USA KID Healthcare Cost and Utilisation Project covering administrative data from over 3,500 US hospitals in 36 states [27]. The number of scoliosis surgeries registered by the NFZ database was higher than the total number reported by patients recruited from our country to the TREAT NMD database at the time of previous analysis [7].

We conclude that the National Health Fund database can be used as a tool to monitor incident cases in children with SMA and the healthcare services they receive. The structure of the database will allow us to follow newly identified patients from the health service perspective.

Our data shows that in 2014 not all SMA children had access to care coordinated by a neurologist or paediatric neurologist, and a substantial number of patients did not receive state-funded physiotherapy. The proportion of patients treated with NIV was still much lower than IV.

Clinical and implications and future directions

Our analysis can serve as a reference for the change in the clinical course and healthcare requirements of patients with this devastating disease brought about by disease-modifying therapy and the implementation of newborn screening for SMA.

Limitations of study

We evaluated only paediatric SMA patients, as in this age group 100% of patients are covered by insurance in our country and there is a very low risk that the G12* code will be related to other than an SMA diagnosis (e.g. ALS). We had no opportunity to verify diagnostic delay or SMA subtype. Although currently all palliative care, long term care and hospitalisations are publicly-funded, some outpatient healthcare services are available in the private sector as well (specialist consultations or physiotherapy). These are not reported to the NFZ database, and could not be included in the analysis.

Acknowledgments: *This study was supported by a project 'Healthcare maps — System Analyses and Implementation Database', implemented by the Department of Analyses and Strategy of the Ministry of Health, co-financed from European Union funds under the European Social Fund. Its purpose is to provide evidence-informed healthcare policy in Poland [28].*
Conflict of interest: *None.*

References

1. Lefebvre S, Bürglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell. 1995; 80(1): 155–165, doi: 10.1016/0092-8674(95)90460-3, indexed in Pubmed: 7813012.
2. Zerres K, Davies KE. 59th ENMC International Workshop: Spinal Muscular Atrophies: recent progress and revised diagnostic criteria 17-19 April 1998, Soestduinen, the Netherlands. Neuromuscul Disord. 1999; 9(4): 272–278, doi: 10.1016/s0960-8966(99)00016-4, indexed in Pubmed: 10399757.
3. Zerres K, Rudnik-Schöneborn S, Forrest E, et al. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. J Neurol Sci. 1997; 146(1): 67–72, doi: 10.1016/s0022-510x(96)00284-5.
4. Jedrzejowska M, Wiszniewski W, Zimowski J, et al. Application of a rapid non-invasive technique in the molecular diagnosis of spinal muscular atrophy (SMA). Neurol Neurochir Pol. 2005; 39(2): 89–94, indexed in Pubmed: 15871052.
5. Wirth B, Herz M, Wetter A, et al. Quantitative analysis of survival motor neuron copies: identification of subtle SMN1 mutations in patients with spinal muscular atrophy, genotype-phenotype correlation, and

implications for genetic counseling. Am J Hum Genet. 1999; 64(5): 1340–1356, doi: 10.1086/302369, indexed in Pubmed: 10205265.
6. Verhaart IEC, Robertson A, Leary R, et al. A multi-source approach to determine SMA incidence and research ready population. J Neurol. 2017; 264(7): 1465–1473, doi: 10.1007/s00415-017-8549-1, indexed in Pubmed: 28634652.
7. Bladen CL, Thompson R, Jackson JM, et al. Mapping the differences in care for 5,000 spinal muscular atrophy patients, a survey of 24 national registries in North America, Australasia and Europe. J Neurol. 2014; 261(1): 152–163, doi: 10.1007/s00415-013-7154-1, indexed in Pubmed: 24162038.
8. Wang CH, Finkel RS, Bertini ES, et al. Participants of the International Conference on SMA Standard of Care. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol. 2007; 22(8): 1027–1049, doi: 10.1177/0883073807305788, indexed in Pubmed: 17761659.
9. Finkel RS, Mercuri E, Meyer OH, et al. SMA Care group. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018; 28(3): 197–207, doi: 10.1016/j.nmd.2017.11.004, indexed in Pubmed: 29305137.
10. Mercuri E, Finkel RS, Muntoni F, et al. SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018; 28(2): 103–115, doi: 10.1016/j.nmd.2017.11.005, indexed in Pubmed: 29290580.
11. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet. 2016; 388(10063): 3017–3026, doi: 10.1016/S0140-6736(16)31408-8, indexed in Pubmed: 27939059.
12. Darras BT, Farrar MA, Mercuri E, et al. An integrated safety analysis of infants and children with symptomatic spinal muscular atrophy (SMA) treated with nusinersen in seven clinical trials. CNS Drugs. 2019; 33(9): 919–932, doi: 10.1007/s40263-019-00656-w, indexed in Pubmed: 31420846.
13. Mercuri E, Darras BT, Chiriboga CA, et al. CHERISH Study Group. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med. 2018; 378(7): 625–635, doi: 10.1056/NEJMoa1710504, indexed in Pubmed: 29443664.
14. Jędrzejowska M, Kostera-Pruszczyk A. Spinal muscular atrophy — new therapies, new challenges. Neurol Neurochir Pol. 2020; 54(1): 8–13, doi: 10.5603/PJNNS.a2019.0068, indexed in Pubmed: 31922583.
15. Andersen JB, Engeland A, Owe JF, et al. Myasthenia gravis requiring pyridostigmine treatment in a national population cohort. Eur J Neurol. 2010; 17(12): 1445–1450, doi: 10.1111/j.1468-1331.2010.03089.x, indexed in Pubmed: 20491896.
16. Jedrzejowska M, Milewski M, Zimowski J, et al. Incidence of spinal muscular atrophy in Poland — more frequent than predicted? Neuroepidemiology. 2010; 34(3): 152–157, doi: 10.1159/000275492, indexed in Pubmed: 20090376.
17. Verhaart IEC, Robertson A, Wilson IJ, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy — a literature review. Orphanet J Rare Dis. 2017; 12(1): 124, doi: 10.1186/s13023-017-0671-8, indexed in Pubmed: 28676062.
18. Jędrzejowska M, Gos M, Zimowski JG, et al. Novel point mutations in survival motor neuron 1 gene expand the spectrum of phenotypes observed in spinal muscular atrophy patients. Neuromuscul Disord. 2014; 24(7): 617–623, doi: 10.1016/j.nmd.2014.04.003, indexed in Pubmed: 24844453.
19. Norwood FLM, Harling C, Chinnery PF, et al. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain. 2009; 132(Pt 11): 3175–3186, doi: 10.1093/brain/awp236, indexed in Pubmed: 19767415.
20. Farrar MA, Vucic S, Johnston HM, et al. Pathophysiological insights derived by natural history and motor function of spinal muscular atrophy. J Pediatr. 2013; 162(1): 155–159, doi: 10.1016/j.jpeds.2012.05.067, indexed in Pubmed: 22809660.
21. Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014; 83(9): 810–817, doi: 10.1212/WNL.0000000000000741, indexed in Pubmed: 25080519.
22. Cobben JM, Lemmink HH, Snoeck I, et al. Survival in SMA type I: a prospective analysis of 34 consecutive cases. Neuromuscul Disord. 2008; 18(7): 541–544, doi: 10.1016/j.nmd.2008.05.008, indexed in Pubmed: 18579378.
23. Chung BHY, Wong VCN, Ip P. Spinal muscular atrophy: survival pattern and functional status. Pediatrics. 2004; 114(5): e548–e553, doi: 10.1542/peds.2004-0668, indexed in Pubmed: 15492357.
24. Bach JR, Saltstein K, Sinquee D, et al. Long-term survival in Werdnig-Hoffmann disease. Am J Phys Med Rehabil. 2007; 86(5): 339–348, doi: 10.1097/PHM.0b013e31804a8505, indexed in Pubmed: 17449977.
25. Finkel RS, Sejersen T, Mercuri E, et al. ENMC SMA Workshop Study Group. 218th ENMC International Workshop: revisiting the consensus on standards of care in SMA Naarden, The Netherlands, 19-21 February 2016. Neuromuscul Disord. 2017; 27(6): 596–605, doi: 10.1016/j.nmd.2017.02.014, indexed in Pubmed: 28392274.
26. Bach JR, Gonçalves MR, Hon A, et al. Changing trends in the management of end-stage neuromuscular respiratory muscle failure: recommendations of an international consensus. Am J Phys Med Rehabil. 2013; 92(3): 267–277, doi: 10.1097/PHM.0b013e31826edcf1, indexed in Pubmed: 23051760.
27. Barsdorf AI, Sproule DM, Kaufmann P. Scoliosis surgery in children with neuromuscular disease: findings from the US National Inpatient Sample, 1997 to 2003. Arch Neurol. 2010; 67(2): 231–235, doi: 10.1001/archneurol.2009.296, indexed in Pubmed: 20142532.
28. Więckowska B. Healthcare Needs Maps — Evidence Informed Healthcare Policy. Journal of Health Policy and Outcomes Research. 2017; 1(1): 14–20, doi: 10.7365/JHPOR.2017.1.2.

RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 5, pages: 485–493
DOI: 10.5603/PJNNS.a2021.0073

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

YouTube as a source of patient information on brain aneurysms: a content-quality and audience engagement analysis

Tomasz Szmuda[1], Shan Ali[2], Alexandra Kamieniecki[2], Daniel Ręcławowicz[1], Hanna Karin Louise Olofsson[2], Paweł Słoniewski[1]

[1]Neurosurgery Department, Medical University of Gdansk, Poland
[2]Scientific Circle of Neurology and Neurosurgery, Neurosurgery Department, Medical University of Gdansk, Poland

ABSTRACT

Introduction: The internet allows patients to access a vast amount of health information. We aimed to evaluate the credibility of YouTube videos that members of the public are accessing on brain aneurysms, and to evaluate what characteristics drive audience engagement.

Material and methods: The first 50 videos for each of the following search terms were taken for analysis: 'brain aneurysm', 'cerebral aneurysm' and 'intracranial aneurysm'. The quality of each video was evaluated by two neurosurgeons and two medical students independently using the Journal of the American Medical Association (JAMA) and the DISCERN instruments. Qualitative and quantitative video data was analysed for quality and audience engagement. Inter-rater agreement was ascertained.

Results: Out of a total of 150 videos, 70 met the inclusion criteria. The mean total DISCERN score was 36.5 ± 8.4 (out of 75 points), indicating that the videos were of poor quality. The mean JAMA score was 2.7 ± 0.7 (out of 4 points). Inter-rater agreement between the four raters was excellent (intraclass correlation coefficient 0.90 for DISCERN and 0.93 for JAMA). Most videos were uploaded by hospitals (50%) or educational health channels (30%). Videos had a higher number of average daily views when they included animation (P = 0.0093) and diagrams (P = 0.0422).

Conclusions: YouTube is a poor source of patient information on brain aneurysms. Our quality and audience engagement analysis may help content creators (i.e. hospital staff and physicians) to create more holistic, educational and engaging medical videos concerning brain aneurysms. Physicians could usefully refer their patients to the highest quality videos that we have found.

Key words: aneurysm, brain aneurysm, cerebral aneurysm, intracranial aneurysm, YouTube, internet, quality

(*Neurol Neurochir Pol 2021; 55 (5): 485–493*)

Introduction

With an estimated 58% of the world having access to the internet, patients often use online sources to acquire health information on various conditions, possible future medical procedures, and therapeutic options [1, 2]. YouTube is the world's second most popular website, and is a popular source of healthcare information for patients [3–5]. However, the quality of YouTube information is highly variable since there is no quality control [5]. Therefore, we thought it imperative to assess the information that is available as it often affects a patient's decision to accept or reject a particular treatment [6–8].

The quality and reliability of YouTube videos have been previously evaluated for hydrocephalus, lumbar disc herniation, stereotactic radiosurgery, and several other conditions [9–17], but analysis has not yet been carried out for intracranial aneurysms.

Address for correspondence: Shan Ali, Scientific Circle of Neurology and Neurosurgery, Neurosurgery Department, Medical University of Gdansk, Marii Skłodowskiej-Curie 3a, 80-210 Gdansk, Poland; e-mail: shanali@gumed.edu.pl

Received: 9.07.2021 Accepted: 24.09.2021 Early publication date: 15.10.2021

Intracranial aneurysms are a type of cerebrovascular disease and may carry high morbidity and mortality due to haemorrhage [18]. It is estimated that between 1 in 20 and 1 in 30 adults will experience an unruptured intracranial aneurysm [19]. Sufficient patient knowledge of cerebral aneurysms is critical because aneurysm rupture can sometimes be predicted, and patients can undergo treatment before aneurysm rupture [20].

Clinical rationale for study

YouTube videos have been shown to influence patient decision-making both positively and negatively [6–8]. Positively, by helping them come to a more informed decision, and negatively by damaging the patient-doctor relationship and providing biased views of certain diseases and treatments. Thus, in the case of intracranial aneurysms, YouTube videos may influence a patient's choice between endovascular coiling, surgical clipping, or conservative treatment.

We aimed to evaluate the credibility of YouTube videos that the public is accessing on intracranial aneurysms. We also sought to assess what visual and educational features drive the greatest audience engagement (i.e. understanding symptoms of a ruptured aneurysm) so that YouTube content creators can create more engaging content in the future.

Material and methods

Search strategy and data collection

The phrases 'brain aneurysm', 'cerebral aneurysm' and 'intracranial aneurysm' were typewritten into YouTube's search bar, and the first 50 videos for each search term were recorded, giving a total of 150 videos. More videos for each search term were not collected since 90% of YouTube users do not look after the 30th video [21]. All searches were done with default 'relevance' sorting on 24 February, 2019. Google Chrome incognito mode was used to collect the videos so that no personal recommendations influenced the results. The videos were evaluated independently by two final-year medical students (S.A. and A.K.) and two neurosurgeons (T.Z. and D.R.). All four raters had more than five years of experience of using the DISCERN and JAMA criteria. Both neurosurgeons had more than 14 years of neurosurgical experience treating cerebral aneurysms at a university hospital.

Inclusion and exclusion criteria

We included the first 50 videos under each search term. We excluded 1) duplicate videos, 2) videos in languages other than English, 3) completely unrelated videos (e.g. music videos), and 4) advertisements (that YouTube explicitly highlighted as an AD on the top of the search page).

Variables extracted

Quantitative data was extracted using the extension 'vidIQ Vision for YouTube' for Google Chrome (browser version 72.0.3626 for Windows, Google Inc.). This plugin extracted the following: the number of comments, view count, likes, dislikes, words spoken per minute, duration, upload date, video referrers, video description word count, video description link count, channel mean daily views, channel mean daily subscribers, and channel subscribers.

Qualitative content extracted included: symptoms of a ruptured aneurysm, symptoms of an unruptured aneurysm, treatments for a ruptured aneurysm, treatments for an unruptured aneurysm, risk factors of aneurysm formation, prognosis, animation, radiological images, diagrams, vessel anatomy, a doctor narrator, and a patient's experience.

Each video was also categorised as deriving from one of the following six sources: a hospital, an educational channel, a physician, a patient, a news channel, or a miscellaneous source (when the uploader could not be determined).

Scoring systems

Two validated instruments were used for video evaluation: the DISCERN score and the Journal of the American Medical Association (JAMA) benchmarks [22–24]. The DISCERN instrument, set out in Table 1, is a 16-item questionnaire with each question allocated a score of 1 to 5 [23, 24]. Question 16 of DISCERN is unique in that it asks the user to rate the overall quality of the publication. Interpretation of the total DISCERN score has been established in previous literature as excellent (63–75 points), good (51–62 points), fair (39–50 points), poor (27–38 points), or very poor (16–26) [25]. Only the video itself was taken into account for the assessment, and the video description was omitted unless the video referenced the information in the video description. Each YouTube video was publicly stamped with an upload date. However, the date on which content is produced and the date on which a video is uploaded may differ. Thus, we interpreted question 7 of DISCERN (which asks when the information was produced and reported) accordingly.

The JAMA benchmark, set out in Table 2, is a four-point scoring system that allocates one point for the inclusion of each of four criteria: authorship, attribution, disclosure, and currency [22]. When analysing the total JAMA score, zero points is the minimum/worst score and four points the maximum/best. Inter-observer agreement between the JAMA and DISCERN scores was statistically analysed to ensure the evaluation of videos was reliable and consistent between raters.

Audience engagement analysis

A like ratio [(likes/likes +dislikes)*100], Video Power Index (VPI) [(like*100/(like + dislike))*(views/day)/100], and average daily views [total views/days since upload] were calculated for each video to measure relative audience approval and engagement for each one. Next, the qualitative video content (e.g. if the video contained information about prognosis) was analysed against the quantitative video characteristics (i.e. the like ratio, average daily views, VPI, and the

Table 1. 16-question DISCERN instrument to evaluate health information

Number	Question	Score				
1	Are the aims clear?	1	2	3	4	5
2	Does it achieve its aims?	1	2	3	4	5
3	Is it relevant?	1	2	3	4	5
4	Is it clear what sources of information were used to compile the publication (other than the author or producer)?	1	2	3	4	5
5	Is it clear when the information used or reported in the publication was produced?	1	2	3	4	5
6	Is it balanced and unbiased?	1	2	3	4	5
7	Does it provide details of additional sources of support and information?	1	2	3	4	5
8	Does it refer to areas of uncertainty?	1	2	3	4	5
9	Does it describe how each treatment works?	1	2	3	4	5
10	Does it describe the benefits of each treatment?	1	2	3	4	5
11	Does it describe the risks of each treatment?	1	2	3	4	5
12	Does it describe what would happen if no treatment is used?	1	2	3	4	5
13	Does it describe how the treatment choices affect overall quality of life?	1	2	3	4	5
14	Is it clear that there may be more than one possible treatment choice?	1	2	3	4	5
15	Does it provide support for shared decision making?	1	2	3	4	5
16	Based on the answers to all of these questions, rate the overall quality of the publication as a source of information about treatment choices	1	2	3	4	5

Table 2. Journal of the American Medical Association scoring benchmarks to evaluate credibility of a source of information

Criterion	Description	Score
Authorship	Authors and contributors, their affiliations, and relevant credentials should be provided	0–1
Attribution	References and sources for all content should be listed clearly, and all relevant copyright information should be noted	0–1
Disclosure	Website 'ownership' should be prominently and fully disclosed, as should any sponsorship, advertising, underwriting, commercial funding arrangements or support, or potential conflicts of interest	0–1
Currency	Dates when content was posted and updated should be listed	0–1

number of comments). In this way, the inclusion of certain health information could be correlated with a higher or lower audience engagement.

The like ratio, average daily views, VPI, and the number of comments were correlated with the DISCERN and JAMA scores to see whether a higher quality video resulted in greater audience engagement.

Statistical methods

The mean, range and standard deviation in our paper are presented as mean ± standard deviation (range). The Kolmogorov-Smirnov test tested for normality, the Mann-Whitney U test found differences between categorical variables, the intraclass correlation coefficient ascertained inter-rater agreement with JAMA and DISCERN, and the Pearson correlation coefficient measured linear bivariate correlations. $P < 0.05$ was deemed significant. Google Sheets (Google LLC) was used for illustrations. MedCalc version 9.1.3 (MedCalc Software, Acacialaan 22, 8400 Ostend, Belgium) and Past (Hammer and Harper, Øyvind Hammer, Natural History Museum, University of Oslo, Norway) were used for statistical analysis. We have provided an electronic supplementary document online with all the raw data [26].

Results

Video contents

Of the 150 videos included, 70 met our inclusion criteria. Figure 1 shows that two thirds of videos, 46 (65%), featured a doctor speaking, and more than half, 40 (57%), discussed treatments for an unruptured aneurysm. Only 10 videos (14%) discussed symptoms of unruptured aneurysms, and only six (9%) explained vessel anatomy.

Video upload source

Figure 2 shows the sources of the videos uploaded. Most were uploaded by hospitals (50%) and educational channels (30%). Only a small minority of videos were uploaded by a physician (8.6%), a news channel (5.7%), or a patient (4.3%).

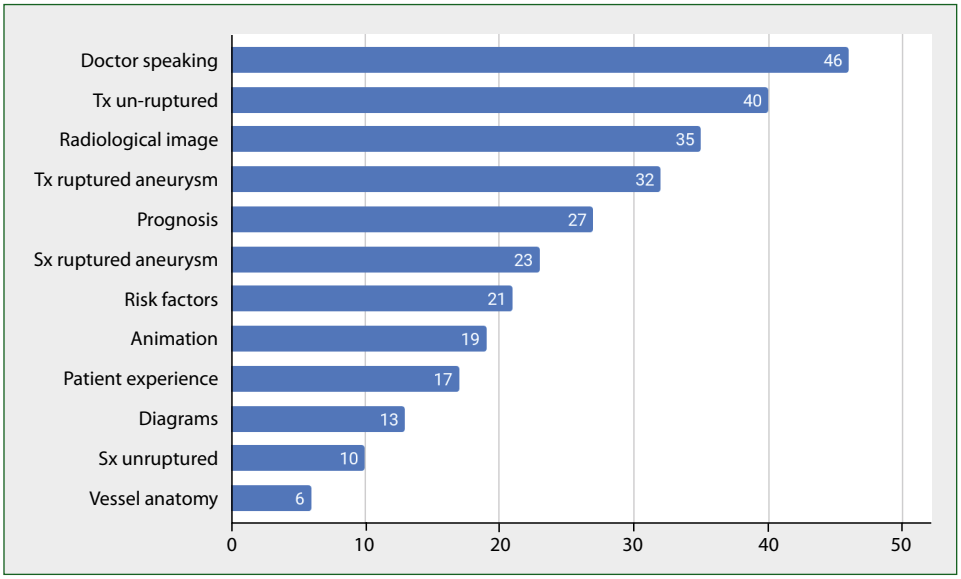


Figure 1. Brain aneurysm video contents on YouTube. Sx — symptoms; Tx — treatment

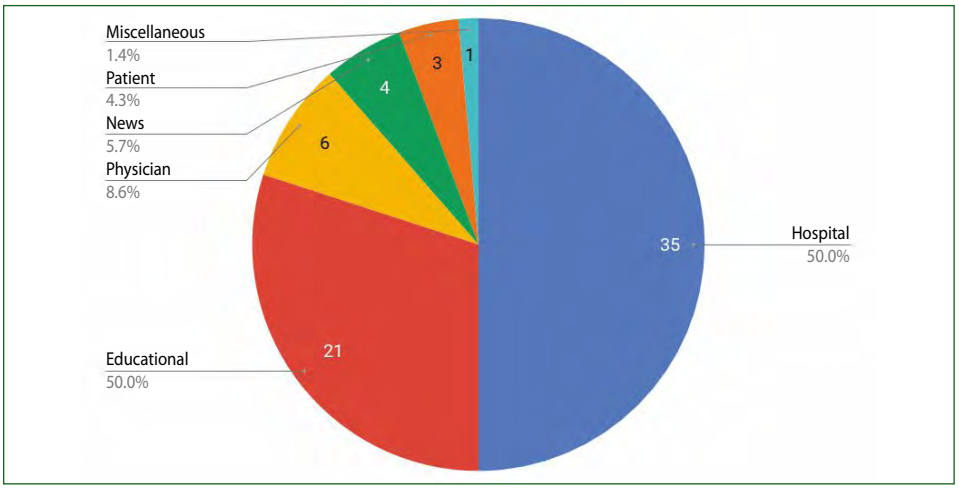


Figure 2. Sources of YouTube video uploads on brain aneurysms

Video statistics

The following are the mean and range for all the quantitative metrics measured: view count 64,443 (32–1,518,180), number of comments 29 (0–428), number of likes 381 (0–8,798) number of dislikes 16 (0–340), average daily views 41 (0–630), like ratio 93.9 (50–100), video referrers 24 (0–182), duration 268.4 (22–1,369) seconds, video description word count 89 (0–460), video description link count 1 (0–17), words spoken per minute 111 (0–184), and days since upload 1,903 (30–4,330).

The following metrics quantify the mean channel popularity of the videos: subscribers 155,519 (32–3,000,000), daily views 92,209 (16–2,100,00) and daily subscribers 5,894 (0–178,700).

DISCERN and JAMA evaluation

The overall DISCERN score between the four raters for the first 15 questions was 36.5 ± 8.4 (18–65); this is regarded as a poor score (the 'poor' scoring range being from 27 to 38). The first neurosurgeon rater, second neurosurgeon rater, first student rater, and second student rater had DISCERN scores of 39.9 ± 9.99 (19–69), 38.4 ± 8.19 (26–62), 39.3 ± 9.33 (21–66) and 39.2 ± 9.18 (22–68) respectively.

The overall score between the four raters for question 16 of DISCERN (which requires a global evaluation of the entire video) was 2.73 ± 1.0 (1–5). Raters had mean scores of 2.7 (1–5), 2.9 (1–5), 2.6 (1–5), and 2.7 (1–5) respectively.

Figure 3 illustrates the mean DISCERN score for each of the 16 questions. Questions 1 to 3 had the highest scores (above 3). These questions relate to the aims and relevance of the information. Questions 4 to 16, however, all had much lower scores (below 3). Questions 4, 7, 10, 11, 12 and 13 had particularly low scores (below 2). These questions ask about references to the sources of information used, additional

sources for supporting patients, benefits of treatment, risks of each treatment, the possibility of no treatment, and how treatment would affect quality of life.

The total mean JAMA score between the four raters was 2.7 ± 0.9 (1–4). Raters had JAMA scores of 2.7 ± 0.9 (1–4), 2.6 ± 0.9 (1–4), 2.7 ± 0.9 (1–4) and 2.7 ± 0.9 (1–4) respectively. Figure 4 shows that while most videos included currency, authorship and disclosure information, they rarely included attribution information.

As shown in Table 3, the intraclass correlation coefficient for absolute agreement was 0.90 for DISCERN and 0.93 for the JAMA score between all four raters; this is regarded as 'excellent' reliability by Koo et al. [27]. This indicates that the scores of the neurosurgeons and of the medical student raters were consistent and reliable with one another.

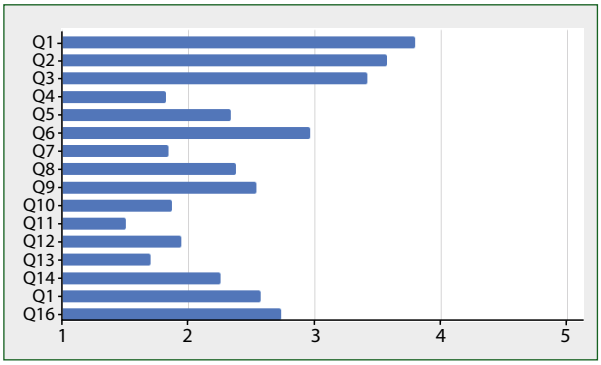


Figure 3. Mean DISCERN scores for each of 16 parts of evaluation

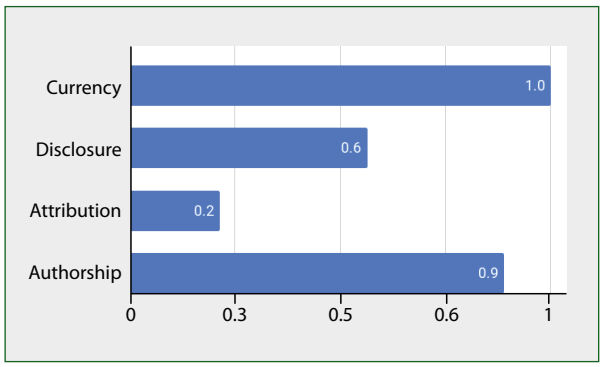


Figure 4. Mean JAMA scores of currency, disclosure, attribution and authorship for YouTube videos on brain aneurysms

Video quality correlations

We observed that videos all had a significantly higher DISCERN score when they included the following qualitative information: symptoms of a ruptured aneurysm (P = 0.0039); risk factors for aneurysm formation (P = 0.0055); treatments for a ruptured aneurysm (P = 0.0007); prognosis (P = 0.0120); diagrams (P = 0.0013); vessel anatomy (P = 0.0156); and a doctor speaking (P < 0.0001). Notably, educational channels had a significantly lower DISCERN score (P = 0.0180). Hospital channels did not obtain a significantly higher or lower DISCERN score. All other qualitative information analysed resulted in no significant results (P > 0.05).

Audience engagement analysis

Videos had a higher number of average daily views when they included animation (P = 0.0093) and diagrams (P = 0.0422). Videos had a higher like ratio when they included the risk factors of aneurysm formation (P = 0.0139) and prognosis (P = 0.0014). Videos had a higher VPI when they included animation (P = 0.0106) or vessel anatomy (P = 0.0216). Videos had a higher number of comments when they included the symptoms of a ruptured aneurysm (P = 0.0162). Videos that had a doctor speaking had a lower number of average daily views (P = 0.0092), a lower number of comments (P = 0.0202), and a lower VPI (P = 0.0085). All other differences between the video groups were not statistically significant (P > 0.05). The like ratio, average daily views, VPI, and the number of comments did not strongly correlate with the DISCERN or the JAMA score (Pearson correlation coefficient < 0.7 or > –70).

Top quality videos

Table 4 sets out the top five highest quality brain aneurysm videos, based on the DISCERN criteria. However, even these videos are only of good quality (51 to 62 DISCERN points) and not of excellent quality (63–75 DISCERN points). It is noteworthy that all these videos are either from hospitals or neurosurgeons.

Table 3. Intraclass correlation coefficient

DISCERN score	Intraclass correlation*	95% Confidence interval
Single measures†	0.9015	0.8618 to 0.9329
Average measures‡	0.9734	0.9615 to 0.9823
JAMA score		
Single measures†	0.9329	0.9035 to 0.9550
Average measures‡	0.9823	0.9740 to 0.9884

*Degree of absolute agreement among measurements; †Estimated reliability of single ratings; ‡Estimated reliability of averages of DISCERN and JAMA ratings; JAMA — Journal of the American Medical Association

Table 4. Top five highest quality brain aneurysm videos based on DISCERN criteria

DISCERN	JAMA	Title	Uploader	YouTube ID
60.3	3.8	#MayoClinicNeuroChat about Brain Aneurysms	Mayo Clinic	8VwV8qmed5s
59.5	4.0	Treatment Options for Unruptured Brain Aneurysms	Mayfield Brain & Spine	L7oXjpL1QVc
55.0	3.0	CEREBRAL ANEURYSMS: Complete Overview	David W Newell MD	kXE3zdXrKTw
54.8	4.0	Brain Aneurysms: FAQs with Rafael Tamargo	Johns Hopkins Medicine	5ZCGwuaapgs
49.5	4.0	Flow Diversion for Cerebral Aneurysms: A Discussion of Controversies	Aaron Cohen-Gadol, M.D.	LrpkJEvSBig

To watch video, simply paste YouTube ID after this address: www.youtube.com/watch?v=

Discussion

Quality analysis

We found the quality and reliability of YouTube videos on cerebral aneurysms to be poor, with a mean DISCERN score of 36.5 (out of 75). This indicates that patients using YouTube for health information concerning brain aneurysms are obtaining incomplete and unreliable information. Thus, most health information from YouTube should not be regarded as credible or reliable. These findings are novel, as our paper is the first to analyse the quality and reliability of YouTube videos on intracranial aneurysms.

According to U.S. News & World Report, Mayo Clinic, Cleveland Clinic, and Johns Hopkins Medicine were the top three hospitals in the world in 2018-2019. All three of these hospitals uploaded educational videos on intracranial aneurysms. Our data shows that even these hospital YouTube channels have room for improvement when it comes to disseminating information. The quality of these videos is of the utmost importance as these channels have millions of subscribers and social media followers, and therefore have a considerable impact in terms of shaping the understanding of some diseases by the public. At the time of data collection, Mayo Clinic had 100,000 YouTube subscribers, 1.1 million Facebook followers, and 1.9 million Twitter followers. Cleveland Clinic and Johns Hopkins Medicine also had considerable YouTube and social media followings.

Suggestions for quality improvement

Most videos scored a low DISCERN score due to not providing enough information about the various treatment options. The JAMA benchmark revealed that YouTube videos frequently displayed when the video had been posted and the author(s) of the work. However, they did not disclose the ownership of the material, and rarely included references to information presented.

Thus, future videos should properly credit their videos and the various treatment options available. Figures 3 and 4 summarise the information lacking from most videos, allowing future medical video creators to use it as a guide to improve quality. Moreover, we suggest that video creators use the DICSERN criteria as a checklist before posting a video. We hope that this study may help hospitals, educational channels and physicians to create more robust content in the future.

Audience engagement analysis

Including animation led to a higher number of average daily views and VPI scores. This shows that the audience appreciates when medical information is simplified into easy-to-understand graphics. Moreover, including vessel anatomy led to a higher like ratio and VPI. Perhaps this is because video viewers felt empowered knowing the basic anatomical basis of aneurysm formation. A study on YouTube found that the most informative medical videos had lower audience engagement compared to lower quality videos [28]. This shows that the best quality videos are often not the most watched.

However, in our study, including diagrams, risk factors of aneurysm formation, and the symptoms of aneurysm rupture all led to a higher audience engagement (whether this was represented by average daily views, like ratio, or comments). These statistically significant findings regarding the most attractive and friendly way in which to present medical information on brain aneurysms may serve as a valuable guide for hospitals, educational health channels and physicians when uploading their videos.

Having a doctor narrate a video led to a lower average number of daily views, fewer comments, and a lower VPI score. We hypothesise that physicians present information in too technical a manner, and often use medical terminology that the average YouTube viewer is unfamiliar with. This may have led to low audience engagement.

No correlations were found with any of the audience engagement metrics analysed and the JAMA score or DISCERN score; this suggests that viewers may not care about the proper attribution of sources or the ownership of data that has been presented.

Context

The quality of YouTube videos on other neurological topics such as hydrocephalus, lumbar disc herniation, glioblastoma treatment, and stereotactic radiosurgery has been found to be poor and incomplete [10, 14, 15, 29].

Even though YouTube is one of the most popular sources for medical information, patients still use other sources such as Google or online health forums to develop understanding of their disease. However, a 2019 readability analysis of online health material on several cardiovascular diseases (including aneurysms) found that 99% of articles had a reading level too difficult for the average patient [30]. This problem can be exacerbated when educational content is mixed with promotional material. Moreover, patients with a new diagnosis of an unruptured intracranial aneurysm often discuss their medical concerns on online forums [12]. A study found that these patients often faced uncertainty, frustration and apprehension when choosing the optimal treatment [12]. Decision-making for patients is multifaceted, as it involves discussing statistical outcomes and financial costs while weighing risks against benefits and personal attitudes. This lack of easily-understood information in popular health articles, health forums and YouTube may make it difficult for patients to become better informed about their condition. Moreover, misinformation can actually lead to worse health outcomes, as several studies have shown [31–37].

A 2015 systematic review of healthcare information found that users often found misleading medical information on YouTube, even though credible sources did exist that provided high-quality information [5]. In our study, however, not one video, even from the world's most respected hospitals, provided an 'excellent' quality of information according to DISCERN.

Most YouTube users look at videos on treatment procedures (e.g. surgery) when searching for brain aneurysm videos [11, 38]. Intracranial aneurysms require a procedure-based treatment (i.e. aneurysm clipping or endovascular coiling) so YouTube would probably be a platform that patients would visit in this case.

Our analysis found that the information concerning treatment was especially poor. This could potentially influence a patient's decision to undergo endovascular coiling or aneurysm clipping without understanding the full implications of each treatment. One of the main advantages of endovascular procedures is that they are minimally invasive. Therefore, patients may prefer this treatment over surgical clipping. We have had good patient outcomes with both procedures at our hospital, and we leave the decision to our patients after fully informing them of both options. Or in some cases, we may recommend one procedure over the other, e.g. surgical clipping for a complex aneurysm.

A previous study by Alotaibi et al. found that social media communications (e.g. YouTube, Facebook, Twitter) can be a platform for social and psychological support for patients with a brain aneurysm [11]. Patients and caregivers use online social platforms for inspiration, to share information, and to seek emotional support. Their analysis concluded that Facebook was the most common platform on which this occurred. While our study focused on YouTube as a source of patient education, we want to stress that the psychosocial needs of patients may also be reflected online.

Several YouTube quality evaluation studies have included physicians scoring the videos [9, 11, 15, 39, 40]. However, physicians are not necessarily required to use the DISCERN instrument as it was designed to be "not dependent on specialist knowledge of a health condition or treatment" [23]. Therefore, both medical students and physicians scored the videos in our study, in order to prove that specialist knowledge was not required to evaluate the quality of the videos.

Limitations

The DISCERN and JAMA tools do not take into account every quality or attribution criterion. However, these are validated instruments and have been used by several other YouTube quality evaluation studies and are regarded as reliable [9, 10, 14, 15, 29, 41, 42]. In our study, the interclass correlation between the four raters was excellent, indicating that our results were robust.

It might be argued that the three search terms in our paper ('brain aneurysm', 'cerebral aneurysm' and 'intracranial aneurysm') do not fully encompass the topic of brain aneurysms, as patients may use other terminology to describe the disease. However, an online study showed that the terms 'brain aneurysm' and 'cerebral aneurysm' were the most common online search terms used by people when referring to brain aneurysms and subarachnoid haemorrhages [43].

Our audience engagement analysis is limited by a selection bias, since not every viewer who likes/dislikes a video clicks the 'like' or 'dislike' button. However, this limitation is inherent to any YouTube evaluation study, and is not specific to ours.

Future directions

This study might be repeated in a few years to analyse whether the quality of YouTube videos has changed. Additionally, we suggest that hospitals use the quality and audience engagement analysis in our paper to prepare better educational content for YouTube. YouTube's potential value as a tool for enhancing telemedicine could also be analysed [44].

Even as relatively long ago as 2015, 65% of American adults were using social networking sites such as Facebook, Twitter, and LinkedIn [45]. Thus, social media platforms may be evaluated for the type, reliability and frequency of health information spread by users.

Clinical implications

YouTube has the potential to influence a patient's medical decisions [6–8]. Thus, we urge health professionals to be aware of the inadequate quality and credibility of most information found on YouTube concerning brain aneurysms. In the words of Ullrich et al., "information is a form of therapy", since a solid foundation of relevant medical knowledge is critical for ensuring patient compliance, establishing realistic treatment expectations, and facilitating follow-up visits [46].

We recommend that hospitals provide in-hospital brochures after patient visits, as this has been proven to improve

patient understanding, satisfaction and relationships with their healthcare provider [47].

Conclusions

YouTube is a poor source of patient information regarding intracranial aneurysms. In our paper, we have listed the most reliable YouTube videos so that physicians can recommend them to their patients.

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

References

1. Diaz JA, Griffith RA, Ng JJ, et al. Patients' use of the Internet for medical information. J Gen Intern Med. 2002; 17(3): 180–185, doi: 10.1046/j.1525-1497.2002.10603.x, indexed in Pubmed: 11929503.
2. World Internet Users Statistics and 2020 World Population Stats n.d. https://www.internetworldstats.com/stats.htm (March 4, 2020).
3. Website Ranking: Top Websites Rank In The World - SimilarWeb n.d. https://www.similarweb.com/top-websites (March 4, 2020).
4. Garcia M, Daugherty C, Ben Khallouq B, et al. Critical assessment of pediatric neurosurgery patient/parent educational information obtained via the Internet. J Neurosurg Pediatr. 2018; 21(5): 535–541, doi: 10.3171/2017.10.PEDS17177, indexed in Pubmed: 29451451.
5. Madathil KC, Rivera-Rodriguez AJ, Greenstein JS, et al. Healthcare information on YouTube: A systematic review. Health Informatics J. 2015; 21(3): 173–194, doi: 10.1177/1460458213512220, indexed in Pubmed: 24670899.
6. Smailhodzic E, Hooijsma W, Boonstra A, et al. Social media use in healthcare: A systematic review of effects on patients and on their relationship with healthcare professionals. BMC Health Serv Res. 2016; 16: 442, doi: 10.1186/s12913-016-1691-0, indexed in Pubmed: 27562728.
7. De Martino I, D'Apolito R, McLawhorn AS, et al. Social media for patients: benefits and drawbacks. Curr Rev Musculoskelet Med. 2017; 10(1): 141–145, doi: 10.1007/s12178-017-9394-7, indexed in Pubmed: 28110391.
8. Ventola LC. Social media and health care professionals: benefits, risks, and best practices. P T. 2014; 39(7): 491–520, indexed in Pubmed: 25083128.
9. Ward M, Ward B, Abraham M, et al. The educational quality of neurosurgical resources on YouTube. World Neurosurg. 2019; 130: e660–e665, doi: 10.1016/j.wneu.2019.06.184, indexed in Pubmed: 31276855.
10. ReFaey K, Tripathi S, Bohnen AM, et al. The reliability of YouTube videos describing stereotactic radiosurgery: A call for action. World Neurosurg. 2019; 125: e398–e402, doi: 10.1016/j.wneu.2019.01.086, indexed in Pubmed: 30703604.
11. Alotaibi NM, Samuel N, Wang J, et al. The use of social media communications in brain aneurysms and subarachnoid hemorrhage: A mixed-method analysis. World Neurosurg. 2017; 98: 456–462, doi: 10.1016/j.wneu.2016.11.085, indexed in Pubmed: 27890750.
12. Feler J, Tan A, Sammann A, et al. Decision making among patients with unruptured aneurysms: a qualitative analysis of online patient forum discussions. World Neurosurg. 2019; 131: e371–e378, doi: 10.1016/j.wneu.2019.07.161, indexed in Pubmed: 31362103.
13. Szmuda T, Ali S, Słoniewski P. Letter to the Editor regarding "A quality analysis of disk herniation videos on YouTube". World Neurosurg. 2019; 130: 570–572, doi: 10.1016/j.wneu.2019.05.171, indexed in Pubmed: 31581395.
14. Szmuda T, Rosvall P, Hetzger TV, et al. YouTube as a source of patient information for hydrocephalus: A content-quality and optimization analysis. World Neurosurg. 2020; 138: e469–e477, doi: 10.1016/j.wneu.2020.02.149, indexed in Pubmed: 32147561.
15. Gokcen HB, Gumussuyu G. A Quality Analysis of disc herniation videos on YouTube. World Neurosurg. 2019 [Epub ahead of print], doi: 10.1016/j.wneu.2019.01.146, indexed in Pubmed: 30721774.
16. Szmuda T, Özdemir C, Fedorow K, et al. YouTube as a source of information for narcolepsy: A content-quality and optimization analysis. J Sleep Res. 2021; 30(2): e13053, doi: 10.1111/jsr.13053, indexed in Pubmed: 32315117.
17. Szmuda T, Syed MT, Singh A, et al. YouTube as a source of patient information for Coronavirus Disease (COVID-19): A content-quality and audience engagement analysis. Rev Med Virol. 2020; 30(5): e2132, doi: 10.1002/rmv.2132, indexed in Pubmed: 32537771.
18. King JT, Horowitz MB, Kassam AB, et al. The short form-12 and the measurement of health status in patients with cerebral aneurysms: performance, validity, and reliability. J Neurosurg. 2005; 102(3): 489–494, doi: 10.3171/jns.2005.102.3.0489, indexed in Pubmed: 15796384.
19. Korja M, Kaprio J. Controversies in epidemiology of intracranial aneurysms and SAH. Nat Rev Neurol. 2016; 12(1): 50–55, doi: 10.1038/nrneurol.2015.228, indexed in Pubmed: 26670298.
20. Prestigiacomo CJ, He W, Catrambone J, et al. Predicting aneurysm rupture probabilities through the application of a computed tomography angiography-derived binary logistic regression model. J Neurosurg. 2009; 110(1): 1–6, doi: 10.3171/2008.5.17558, indexed in Pubmed: 18928360.
21. iProspect Search Engine User Behaviour Study. 2006.
22. Silberg WM, Lundberg GD, Musacchio RA. Assessing, controlling, and assuring the quality of medical information on the Internet: Caveant lector et viewor–Let the reader and viewer beware. JAMA. 1997; 277(15): 1244–1245, indexed in Pubmed: 9103351.
23. Charnock D, Shepperd S, Needham G, et al. DISCERN: an instrument for judging the quality of written consumer health information on treatment choices. J Epidemiol Community Health. 1999; 53(2): 105–111, doi: 10.1136/jech.53.2.105, indexed in Pubmed: 10396471.
24. Rees CE, Ford JE, Sheard CE. Evaluating the reliability of DISCERN: a tool for assessing the quality of written patient information on treatment choices. Patient Educ Couns. 2002; 47(3): 273–275, doi: 10.1016/s0738-3991(01)00225-7, indexed in Pubmed: 12088606.
25. Cassidy JT, Baker JF. Orthopaedic patient information on the World Wide Web: an essential review. J Bone Joint Surg Am. 2016; 98(4): 325–338, doi: 10.2106/JBJS.N.01189, indexed in Pubmed: 26888683.
26. Data for: YouTube as a Source of Patient Information for Brain Aneurysms: A Content-Quality an Auience Engagement Analysis.
27. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chiropr Med. 2016; 15(2): 155–163, doi: 10.1016/j.jcm.2016.02.012, indexed in Pubmed: 27330520.
28. Desai T, Shariff A, Dhingra V, et al. Is content really king? An objective analysis of the public's response to medical videos on YouTube. PLoS

One. 2013; 8(12): e82469, doi: 10.1371/journal.pone.0082469, indexed in Pubmed: 24367517.
29. ReFaey K, Tripathi S, Yoon JW, et al. The reliability of YouTube videos in patients education for Glioblastoma Treatment. J Clin Neurosci. 2018; 55: 1–4, doi: 10.1016/j.jocn.2018.07.001, indexed in Pubmed: 30075980.
30. Ayyaswami V, Padmanabhan D, Patel M, et al. A readability analysis of online cardiovascular disease-related health education materials. Health Lit Res Pract. 2019; 3(2): e74–e80, doi: 10.3928/24748307-20190306-03, indexed in Pubmed: 31049489.
31. Ren SY, Gao RD, Chen YL. Fear can be more harmful than the severe acute respiratory syndrome coronavirus 2 in controlling the corona virus disease 2019 epidemic. World J Clin Cases. 2020; 8(4): 652–657, doi: 10.12998/wjcc.v8.i4.652, indexed in Pubmed: 32149049.
32. Pluviano S, Watt C, Della Sala S. Misinformation lingers in memory: Failure of three pro-vaccination strategies. PLoS One. 2017; 12(7): e0181640, doi: 10.1371/journal.pone.0181640, indexed in Pubmed: 28749996.
33. Ernst E. How the public is being misled about complementary/alternative medicine. J R Soc Med. 2008; 101(11): 528–530, doi: 10.1258/jrsm.2008.080233, indexed in Pubmed: 19029352.
34. Merckelbach H, Jelicic M, Pieters M. Misinformation increases symptom reporting: a test - retest study. JRSM Short Rep. 2011; 2(10): 75, doi: 10.1258/shorts.2011.011062, indexed in Pubmed: 22046494.
35. De Freitas J, Falls BA, Haque OS, et al. Vulnerabilities to misinformation in online pharmaceutical marketing. J R Soc Med. 2013; 106(5): 184–189, doi: 10.1177/0141076813476679, indexed in Pubmed: 23761527.
36. Wang Y, McKee M, Torbica A, et al. Systematic literature review on the spread of health-related misinformation on social media. Soc Sci Med. 2019; 240: 112552, doi: 10.1016/j.socscimed.2019.112552, indexed in Pubmed: 31561111.
37. Szmuda T, Özdemir C, Ali S, et al. Readability of online patient education material for the novel coronavirus disease (COVID-19): a cross-sectional health literacy study. Public Health. 2020; 185: 21–25, doi: 10.1016/j.puhe.2020.05.041, indexed in Pubmed: 32516624.
38. Benetoli A, Chen TF, Aslani P. Consumer health-related activities on social media: exploratory study. J Med Internet Res. 2017; 19(10): e352, doi: 10.2196/jmir.7656, indexed in Pubmed: 29030326.
39. Fat MJ, Doja A, Barrowman N, et al. YouTube videos as a teaching tool and patient resource for infantile spasms. J Child Neurol. 2011; 26(7): 804–809, doi: 10.1177/0883073811402345, indexed in Pubmed: 21551373.
40. Erdem MN, Karaca S. Evaluating the accuracy and quality of the information in kyphosis videos shared on YouTube. Spine (Phila Pa 1976). 2018; 43(22): E1334–E1339, doi: 10.1097/BRS.0000000000002691, indexed in Pubmed: 29664816.
41. Radonjic A, Fat Hing NNg, Harlock J, et al. YouTube as a source of patient information for abdominal aortic aneurysms. J Vasc Surg. 2020; 71(2): 637–644, doi: 10.1016/j.jvs.2019.08.230, indexed in Pubmed: 31611104.
42. Drozd B, Couvillon E, Suarez A. Medical YouTube Videos and methods of evaluation: literature review. JMIR Med Educ. 2018; 4(1): e3, doi: 10.2196/mededu.8527, indexed in Pubmed: 29434018.
43. Ku JC, Alotaibi NM, Wang J, et al. Internet search volumes in brain aneurysms and subarachnoid hemorrhage: Is there evidence of seasonality? Clin Neurol Neurosurg. 2017; 158: 1–4, doi: 10.1016/j.clineuro.2017.04.008, indexed in Pubmed: 28412503.
44. Szmuda T, Ali S, Słoniewski P, et al. Telemedicine in neurosurgery during the novel coronavirus (COVID-19) pandemic. Neurol Neurochir Pol. 2020; 54(2): 207–208, doi: 10.5603/PJNNS.a2020.0038, indexed in Pubmed: 32319670.
45. Perrin A. Social Networking Usage: 2005-2015. 2015.
46. Ullrich PF, Vaccaro AR. Patient education on the internet: opportunities and pitfalls. Spine (Phila Pa 1976). 2002; 27(7): E185–E188, doi: 10.1097/00007632-200204010-00019, indexed in Pubmed: 11923675.
47. Tang PC, Newcomb C. Informing patients: a guide for providing patient health information. J Am Med Inform Assoc. 1998; 5(6): 563–570, doi: 10.1136/jamia.1998.0050563, indexed in Pubmed: 9824803.

SHORT COMMUNICATION

This Short Communication is accompanied by Invited Editorial, see page 416

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 5, pages: 494–498
DOI: 10.5603/PJNNS.a2021.0050

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

Direct admission *versus* secondary transfer for mechanical thrombectomy: long-term clinical outcomes from a single Polish Comprehensive Stroke Centre

Piotr Luchowski[1], Joanna Wojczal[1], Katarzyna Prus[1], Maciej Szmygin[2], Michał Sojka[2], Elżbieta Luchowska[3], Konrad Rejdak[1]

[1]Department of Neurology, Medical University of Lublin, Poland
[2]Department of Interventional Radiology and Neuroradiology, Medical University of Lublin, Poland
[3]Department of Laboratory Diagnostics Medical University of Lublin, Poland

ABSTRACT

Introduction. We aimed to compare 3-month clinical outcomes after mechanical thrombectomy (MT) in patients transferred directly to a comprehensive stroke centre ('mothership', MS) to the outcomes of patients transferred secondarily from primary stroke centres ('drip-and-ship', DAS) in Lubelskie province, the third largest province in Poland.

Material and methods. In a prospective stroke registry, all patients with large vessel occlusion in anterior circulation admitted within six hours of onset and treated with MT between 2017 and 2020 were retrospectively analysed.

Results. A total of 400 patients was evaluated: 267 treated with the MS approach and 133 with the DAS approach. Time from stroke onset to groin puncture was shorter in the MS group. There was a significant difference in 3-month excellent clinical outcomes (mRS 0–1) between these two groups (32.9% of MS patients *vs.* 22.5% of DAS patients, $p < 0.05$), but there was no difference if the 3-month endpoint was expressed as mRS ≤ 2 (42.3% of MS *vs.* 34.5% of DAS patients, $p = 0.13$). The rate of symptomatic intracranial haemorrhage and mortality was comparable in both groups.

Conclusions. Our study shows that direct admission to a comprehensive stroke centre resulted in more patients achieving excellent treatment outcomes (mRS 0–1). At the same time, the superiority of the MT model over the DAS model in obtaining mRS 0–2 was not unequivocally demonstrated. Further studies are needed to determine the best stroke model for patients potentially eligible for MT.

Key words: mothership, drip and ship, acute ischaemic stroke, mechanical thrombectomy, regional stroke care

(*Neurol Neurochir Pol 2021; 55 (5): 494–498*)

Introduction

Different prehospital referral systems have been proposed for patients with acute ischaemic stroke (AIS) who are potential candidates for mechanical thrombectomy (MT). The two most widely known are the drip-and-ship (DAS) and the mothership (MS) models [1].

The DAS model consists of transferring the patient to the nearest primary stroke centre (PSC), where thrombolysis therapy (IVT) is initiated, followed by a transfer of patients who are candidates for MT to a comprehensive stroke centre (CSC). The MS paradigm is direct transfer to a CSC, bypassing the nearest PSC. Both systems have been evaluated in a few observational studies, but as yet the results of only one randomised trial are available [2]. Recently published meta-analysis showed that patients with AIS eligible for reperfusion strategies might benefit more from the MS model than from the DAS model [3]. Furthermore, one recent study has demonstrated lower disability and mortality among patients with large vessel occlusion [LVO] who were directly transported to the CSC if the additional delay was < 30 minutes and < 50 minutes in urban and rural areas, respectively [4].

Address for correspondence: Piotr Luchowski, Medical University of Lublin, Kazimierza Jaczewskiego Str. 8, 20–954 Lublin, Poland; e-mail: piotr.luchowski@umlub.pl

Received: 5.04.2021 Accepted: 2.07.2021 Early publication date: 23.07.2021

On the other hand, the only completed randomised controlled trial (the RACECAT trial) does not support the hypothesis that direct triage of patients with symptoms of ischaemic stroke due to LVO to CSC leads to improved outcomes compared to the current practice of transferring all patients to the PSC [2].

This explains why the debate as to the best stroke strategy is ongoing, and why there are no clear recommendations in the current stroke guidelines.

The CSC located in the Public Clinic Hospital no. 4 (SPSK4) in Lublin, Poland forms a stroke network with 12 PSCs where only IVT is available. This study aimed to compare the onset-to-groin time, reperfusion rate, symptomatic intracranial haemorrhage (sICH) and mortality rate, as well as clinical outcome at 3 months after MT, in direct CSC admission AIS patients *vs.* secondarily transferred AIS patients.

Material and methods

In this single-centre study, we performed a retrospective analysis of prospectively collected data of 400 consecutive patients admitted with acute ischaemic stroke due to LVO of anterior circulation who underwent endovascular thrombectomy between January 2017 and November 2020. The first group included patients directly arriving at CSC at SPSK4 in Lublin (we called this the mothership model, MS), and the second group consisted of patients admitted to one of the above-mentioned hospitals with secondary transfer to the CSC (we called this the drip-and-ship model, DAS). Average distance from PSCs to CSC is 50 km.

The following inclusion criteria were applied: 1) LVO of anterior circulation confirmed by imaging examination (non-contrast CT and CT-angio and/or MRI) and treated with MT; 2) time from symptoms onset to reperfusion of no more than 6 h; 3) National Institute of Health Stroke Scale (NIHSS) score ≥ 6; 4) no prestroke dependency expressed as modified Rankin Scale (mRS) score 0–2.

Clinical data including age, sex, stroke risk factors, baseline medication, initial laboratory results, stroke severity as expressed by the NIHSS score, and time metrics were collected and evaluated. In accordance with the current Guidelines of the Polish Neurological Society for the Management of Patients with Ischaemic Stroke, intravenous thrombolysis (rt-PA) was administered if patients arrived in a window time < 4.5 h and where there was no contraindication [5]. An institutional review committee approved this study (approval number KE-0254/285/2019.). This study was conducted in accordance with the Declaration of Helsinki.

Endovascular thrombectomy

All procedures were performed under biplane angiography unit with 3D rotational angiography and with patients under conscious sedation or general anaesthesia. Mechanical thrombectomy was carried out with aspiration (ACE, Penumbra, Alameda), stent retriever (Solitaire, EV3, Irvine, CA, USA) or a combination of both (the Solumbra technique). Final recanalisation was assessed according to the Thrombolysis in Cerebral Infarction (TICI) classification. Good recanalisation was defined as TICI 2b and TICI 3. Complications related to the procedure were noted.

Follow-up

Routine non-contrast brain CT was performed 24 h after the procedure to evaluate brain infarction and assess the occurrence of intracranial haemorrhage (ICH) if available. ICH was classified as symptomatic according to the classification of the European-Australasian Acute Stroke Study (ECASS II) [6]. Clinical outcome was assessed based on the mRS score 90 days after the procedure. An excellent and a favourable result were defined as mRS 0–1 and mRS ≤ 2, respectively. Mortality rate was calculated.

Statistical analysis

Statistical analysis was conducted using a StatSoft Statistica 13.1PL package. The patients were classified into two groups (MS patients *vs.* DAS patients) and comparisons were made in terms of demographic data, initial NIHSS, risk factors, use of IVT, procedural details, and outcomes. Student's t-test, Mann-Whitney test and Chi-squared Pearson tests were used when appropriate. Statistical significance was defined as $p \leq 0.05$.

Results

During the study period (January 2017–November 2020), 400 AIS patients (267 MS patients and 133 DAS patients) with LVO in the anterior circulation were treated with MT. There was no significant difference between the groups with regards to baseline clinical characteristics or initial neurological deficit. Furthermore, IVT rate was comparable in both groups (74.5% in MS *vs.* 81.9% in DAS; $p = 0.09$). Time from picture-to-puncture and onset-to-groin puncture was significantly shorter in the MS group (61.5 ± 26.5 min for MS and 145.8 ± 67.0 min for DAS patients, $p < 0.001$ and 178.7 ± 64.5 min in MS patients *vs.* 263.7 ± 58.4 min in DAS patients, $p < 0.001$, respectively), whereas door-to-groin puncture time was shorter in the DAS group (median 35.4 ± 25.2 min *vs.* 85.9 ± 44.2 min, $p < 0.001$).

The rate of successful recanalisation (TICI 2b-3) as well as failed recanalisation (TICI 0) at the end of the procedure was similar in both groups (69.6% for MS patients *vs.* 68.4% for DAS patients; $p = 0.799$ for TICI 2b-3 and 10.4% for MS patients *vs.* 9.8% for DAS patients; $p = 0.825$ for TICI 0). The clinical and procedural details are set out in Table 1.

There was a significant difference in the 3-month excellent clinical outcomes expressed as mRS 0–1 between these two groups (32.9% of MS patients *vs.* 22.5% of DAS patients, $p < 0.05$). Similarly, a greater number of patients achieved mRS 0–2 in the MS model compared to the DAS model, although statistical significance was not reached (42.3% MS *vs.* 34.5%

Table 1. Baseline and treatment characteristics. Statistical significance marked in bold

Characteristic	MS group (n = 267)	DAS group (n = 133)	P-value
Baseline			
Males (n, %)	114 (42.7%)	66 (49.6%)	0.18
Age, y (mean)	73.7 ± 11.9	72.3 ± 12.5	0.16
mRS score = 0–1	211 (79.0%)	113 (85.0%)	0.15
mRS score = 2	56 (21.0%)	20 (15.0%)	015
Hypertension (n, %)	137 (51.3%)	59 (44.4%)	0.19
Diabetes (n, %)	75 (28.1)	41 (30.8%)	0.57
Atrial fibrillation (n, %)	56 (21.0)	30 (22.6)	0.72
Baseline NIHSS	18.2 ± 5.4	20.1 ± 4.1	0.11
IV-thrombolysis (n, %)	199 (74.5%)	109 (81.9%)	0.09
Time in min (mean ± SD)			
Picture-to-puncture	61.5 ± 26.5	145.8 ± 67.0	< 0.001
Onset-to-puncture	178.7 ± 64.5	263.7 ± 58.4	< 0.001
Door-to-puncture	85.9 ± 44.2	35.4 ± 25.2	< 0.001
Procedural results (n, %)			
Recanalisation (TICI 2b-3)	186 (69.6%)	91 (68.4%)	0.79
No recanalisation (TICI 0)	28 (10.4%)	13 (9.8%)	0.83
sICH	23 (8.5%)	11 (7.9%)	0.10
Clinical outcome (n, %)			
NIHSS at discharge	7.51	8.47	0.21
3-months mRS score = 0–1	88 (32.9%)	30 (22.5%)	< 0.05
3-months mRS score ≤ 2	113 (42.3%)	46 (34.5%)	0.13
3-months mortality rate	57 (21.4%)	31 (23.1%)	0.44

Used tests: Student's t-test, Mann-Whitney test, Chi-squared Pearson test

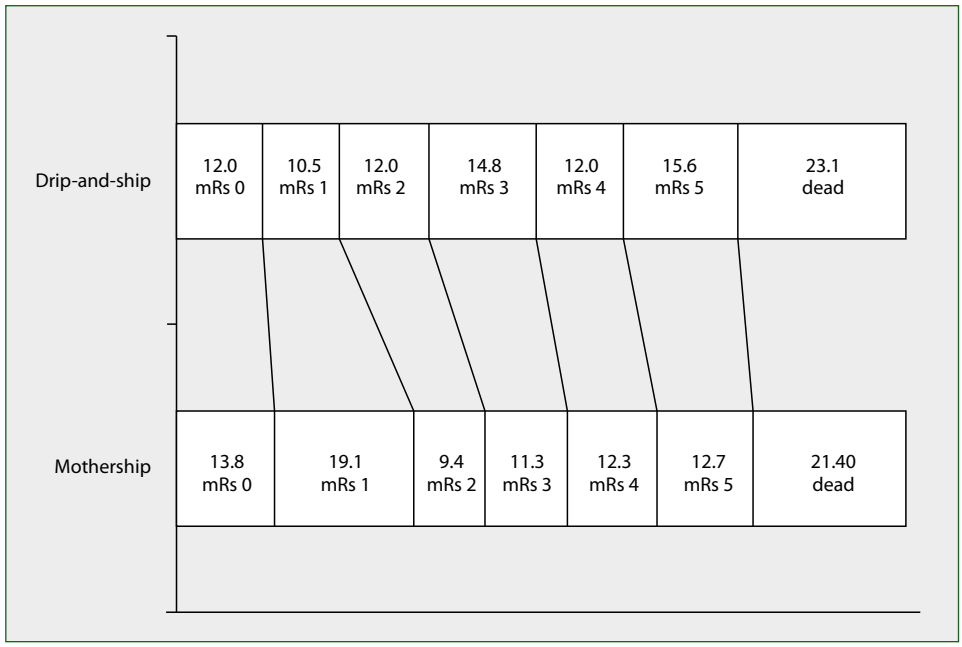


Figure 1. Percentage distribution of patients' modified Rankin scale scores at 3-month follow-up in compared groups

DAS, p = 0.136, Fig. 1). The rate of symptomatic intracranial haemorrhage and mortality was similar in both groups (8.5% in MS *vs.* 7.9% in DAS group, p = 0.101 and 21.4% in MS *vs.* 23.1% in DAS group, p = 0.44, respectively).

Discussion

The aim of this study was to evaluate whether the 'mothership' paradigm featuring direct admission of a stroke patient to the CSC without prior administration of IV thrombolysis in PSC results in a higher rate of favourable clinical outcomes, as it potentially shortens the time from onset to groin puncture and may result in earlier recanalisation. Several clinical trials focusing on endovascular therapy of ischaemic stroke have highlighted the importance of rapid treatment [7, 8]. Ota et al. [9] confirmed that onset-to-puncture time has an independent effect on functional outcomes after MT, and concluded that reducing this time metric is a key factor in successful endovascular therapy. In addition to this, the benefit of bridging IVT prior to MT is currently under discussion, and some studies have reported comparable thrombectomy outcomes with and without thrombolysis [10, 11].

The available studies comparing the results of MT in patients treated in the MS and DAS models do not clearly indicate an advantage for either of them. According to Garchenfeld et al., who compared both paradigms, there was no statistically significant difference either in terms of successful recanalisation or in long-term clinical outcome [14]. Similarly, the results of the RACECAT trial did not support the hypothesis that direct transfer of LVO suspected patients to CSC leads to improved outcomes [2].

On the other hand, Rinaldo et al., who reported clinical outcomes of 8,500 patients with LVO, showed that patients transferred from PSC have an increased risk of mortality compared to patients treated in CSC [12]. Recently published insights from the Ischaemic Stroke Registry in France showed that significantly more functional independence was achieved among MS patients compared to DAS patients [13].

This aligns with our findings. We observed a significant difference in 3-month excellent clinical outcomes expressed as mRS 0–1 between MS patients (32.9%) and DAS patients (22.5%). We also noticed that a greater number of patients achieved mRS 0–2 in the MS model (42.3%) compared to the DAS model (34.5%), although statistical significance was not reached. This result is most likely due to the significant onset-to-puncture time difference between the two groups (–85 min in MS patients *vs.* DAS patients), and was not abolished by significantly longer door-to-puncture time in the MS model compared to the DAS model.

We can assume that further acceleration of acute stroke patient management in CSCs and a 24-hour on-site angio suite team would significantly reduce the door-to-puncture time, resulting in even better treatment outcomes in the MS model. However, we should be aware that one limitation of the MS model is the possibility of overloading CSCs with stroke patients who will not be candidates for MT.

Our study has several limitations: a) the limited number of evaluated patients which limits the generalisability of our findings; b) the retrospective design of the study; c) the data collected in the tertiary hospital in the Lublin operational area and our findings may not be relevant to other regions; and d) our study does not take into account stroke-suspected patients transferred directly to CSC but who are eventually not eligible for MT.

Conclusions

Our study shows that patients with LVO transferred directly to a CSC (the MS model) achieved a better rate of excellent 3-month functional independence expressed as mRS 0–1 compared to the DAS paradigm. However, if the favourable clinical outcome is defined as mRS 0–2, the benefit of the MS approach was still not clearly demonstrated.

Clinical implications

The question of the overall best treatment paradigm for stroke patients remains unanswered. An effective and reliable pre-hospital assessment for LVO may condition the direct transport of the patient to the CSC, resulting in better clinical outcomes after MT. The use of the MS model or the DAS model should be flexible and based on the regional stroke service.

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

References

1. Ismail M, Armoiry X, Tau N, et al. Mothership versus drip and ship for thrombectomy in patients who had an acute stroke: a systematic review and meta-analysis. J Neurointerv Surg. 2019; 11(1): 14–19, doi: 10.1136/neurintsurg-2018-014249, indexed in Pubmed: 30297541.
2. Ribo M (2020) RACECAT results presented at ESO-WSO 2020. https://eso-wso-conference.org/wp-content/uploads/sites/42/2020/11/News-from-ESO-WSO-2020-Conference-PR1_Eng.pdf (April 3 2021).
3. Romoli M, Paciaroni M, Tsivgoulis G, et al. Mothership versus drip-and-ship model for mechanical thrombectomy in acute stroke: A systematic review and meta-analysis for clinical and radiological outcomes. J Stroke. 2020; 22(3): 317–323, doi: 10.5853/jos.2020.01767, indexed in Pubmed: 33053947.
4. Schlemm L, Endres M, Nolte CH. Bypassing the closest stroke center for thrombectomy candidates: what additional delay to thrombolysis is acceptable? Stroke. 2020; 51(3): 867–875, doi: 10.1161/STROKEAHA.119.027512, indexed in Pubmed: 31964288.
5. Błażejewska-Hyżorek B, Czernuszenko A, Członkowska A, et al. Ischemic stroke guidelines. Polski Przegląd Neurologiczny. 2019; 15: 53–55.
6. Larrue V, von Kummer R R, Müller A, et al. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). Stroke.

2001; 32(2): 438–441, doi: 10.1161/01.str.32.2.438, indexed in Pubmed: 11157179.
7. Khatri P, Yeatts SD, Mazighi M, et al. IMS III Trialists. Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: an analysis of data from the Interventional Management of Stroke (IMS III) phase 3 trial. Lancet Neurol. 2014; 13(6): 567–574, doi: 10.1016/S1474-4422(14)70066-3, indexed in Pubmed: 24784550.
8. Fransen PSS, Berkhemer OA, Lingsma HF, et al. Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands Investigators. Time to reperfusion and treatment effect for acute ischemic stroke: A randomized clinical trial. JAMA Neurol. 2016; 73(2): 190–196, doi: 10.1001/jamaneurol.2015.3886, indexed in Pubmed: 26716735.
9. Ota T, Nishiyama Y, Koizumi S, et al. Impact of onset-to-groin puncture time within three hours on functional outcomes in mechanical thrombectomy for acute large-vessel occlusion. Interv Neuroradiol. 2018; 24(2): 162–167, doi: 10.1177/1591019917747247, indexed in Pubmed: 29237321.
10. Coutinho JM, Liebeskind DS, Slater LA, et al. Combined intravenous thrombolysis and thrombectomy vs thrombectomy alone for acute ischemic stroke: A pooled analysis of the SWIFT and STAR studies. JAMA Neurol. 2017; 74(3): 268–274, doi: 10.1001/jamaneurol.2016.5374, indexed in Pubmed: 28097310.
11. Fischer U, Kaesmacher J, Mendes Pereira V, et al. Direct mechanical thrombectomy versus combined intravenous and mechanical thrombectomy in large-artery anterior circulation stroke: A topical review. Stroke. 2017; 48(10): 2912–2918, doi: 10.1161/STROKEAHA.117.017208, indexed in Pubmed: 28887391.
12. Rinaldo L, Brinjikji W, McCutcheon BA, et al. Hospital transfer associated with increased mortality after endovascular revascularization for acute ischemic stroke. J Neurointerv Surg. 2017; 9(12): 1166–1172, doi: 10.1136/neurintsurg-2016-012824, indexed in Pubmed: 27986846.
13. Weisenburger-Lile D, Blanc R, Kyheng M, et al. on behalf of the Endovascular Treatment in Ischemic Stroke Investigators. Direct admission versus secondary transfer for acute stroke patients treated with intravenous thrombolysis and thrombectomy: insights from the endovascular treatment in ischemic stroke registry. Cerebrovasc Dis. 2019; 47(3-4): 112–120, doi: 10.1159/000499112, indexed in Pubmed: 31063998.
14. Gerschenfeld G, Muresan IP, Blanc R, et al. Two paradigms for endovascular thrombectomy after intravenous thrombolysis for acute ischemic stroke. JAMA Neurol. 2017; 74(5): 549–556, doi: 10.1001/jamaneurol.2016.5823, indexed in Pubmed: 28319240.

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2021, Volume 55, no. 5, pages: 499–501
DOI: 10.5603/PJNNS.a2021.0049

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

Unexpected infiltration of meninges by generalised diffuse large B-cell lymphoma manifesting as multiple cranial neuropathies in a patient with history of breast carcinoma

Eva Malá[1], Kateřina Matějová[1], Tomáš Olejár[2], Radoslav Matěj[2, 3], Adam Pavličko[4], Ondřej Sobek[5], Robert Rusina[1]

[1]Department of Neurology, Third Faculty of Medicine, Charles University and Thomayer University Hospital, Prague, Czech Republic
[2]Department of Pathology and Molecular Medicine, Third Faculty of Medicine, Charles University and Thomayer University Hospital, Prague, Czech Republic
[3]Department of Pathology, First Faculty of Medicine, Charles University, and General University Hospital, Prague, Czech Republic
[4]Department of Radiology, Thomayer University Hospital, Prague, Czech Republic
[5]Laboratory for CSF, Neuroimmunology, Pathology and Special Diagnostics, Topelex, Prague, Czech Republic

Key words: meningeal carcinomatosis, subdural haematoma, B-cell lymphoma, cranial neuropathy

(*Neurol Neurochir Pol 2021; 55 (5): 499–501*)

To the Editors

Leptomeningeal spread of malignant tumorous cells occurs more commonly in haematological malignancies (incidence of 10–15%) and less often with solid tumours such as breast cancer, lung cancer, and melanoma (incidence of 1–5%) [1]. Diagnostic methods mainly include clinical assessment, cerebrospinal fluid cytological examinations [2], and magnetic resonance imaging (MRI) to distinguish brain metastases from other brain tumours [3]. We present a case of leptomeningeal malignant infiltration in a patient with known breast carcinoma, that initially presented as multiple cranial neuropathies. Surprisingly, but consistent with previous cerebrospinal fluid (CSF) examinations, the autopsy excluded meningeal carcinomatosis by breast cancer malignant cells, and confirmed generalised B-cell lymphoma, including leptomeningeal infiltration.

An 84-year-old female with a history of diabetes, arterial hypertension, and breast cancer diagnosed three years previously and treated by mastectomy and tamoxifen, presented with multiple cranial nerve palsies. Two months before, she had been hospitalised for acute bleeding into a chronic subdural haematoma, which was treated conservatively (Fig. 1A). Clinical examination revealed an incomplete right oculomotor nerve palsy, peripheral left facial nerve palsy, and left leg instability. Laboratory analysis showed only hyperglycaemia. MRI showed haematoma regression and contrast enhancement of the leptomeninges around the right hemisphere (Fig. 1B).

CSF analysis found elevated cell counts and high total protein levels and increased lactate and glucose levels. Empirical antimicrobial therapy with ceftriaxone was initiated, but discontinued soon after due to CSF cultivation; both it and borreliosis serology were negative. Cytomorphological CSF analysis identified atypical cells and another lumbar puncture was performed for a detailed cytological investigation: the cell count was 240 elements per microlitre with enlarged basophilic cells displaying cytoplasmic and nuclear abnormalities, frequent mitosis, and local cohesive tendencies.

The patient was clinically deteriorating, progressing toward somnolence, with progressive right upper and left lower limb weakness, and renal failure. Chronic neuroinfection, however, was still considered the most probable differential diagnosis; ceftriaxone with ampicillin was started, and a third lumbar puncture was performed.

Address for correspondence: Robert Rusina, Department of Neurology, Thomayer University Hospital, Vídeňská 800 Str., 140 59 Prague 4, Czech Republic; e-mail: robert.rusina@lf3.cuni.cz

Received: 24.04.2021 Accepted: 8.05.2021 Early publication date: 2.07.2021

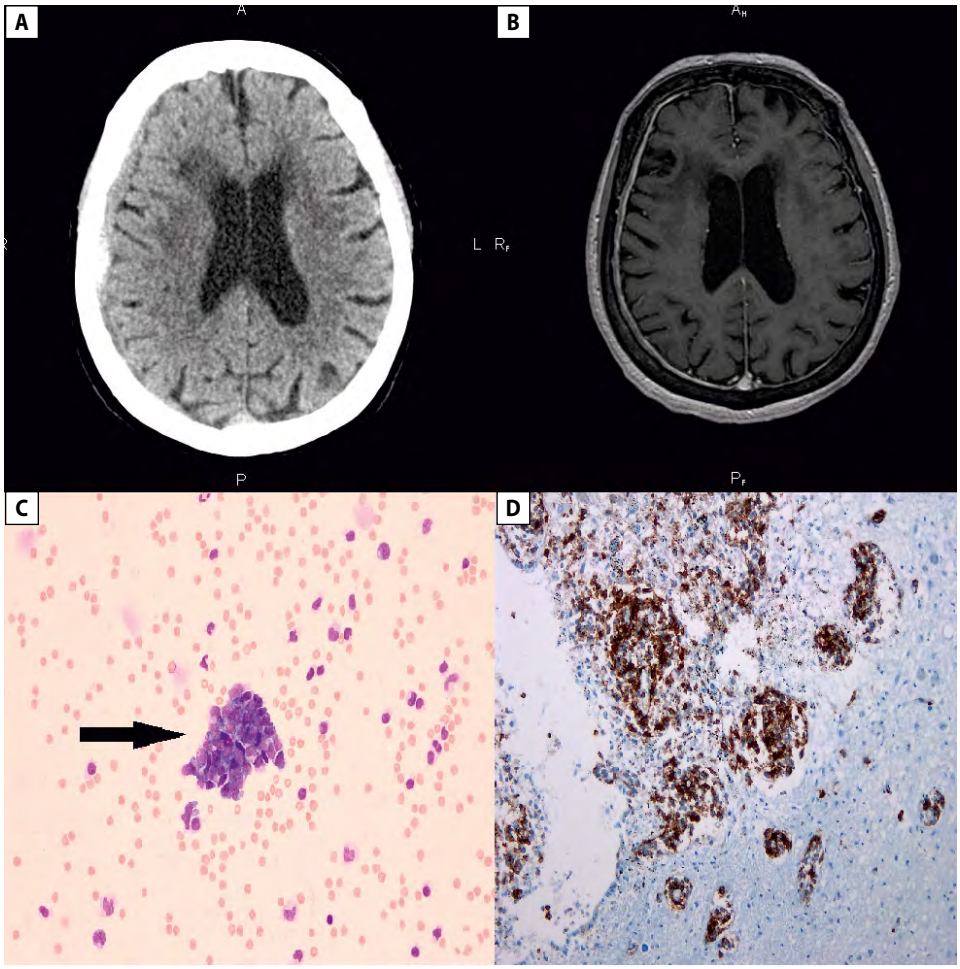


Figure 1. A. Axial non-contrast CT image (two months before disease onset) shows heterogenous subdural effusion above right cerebral convexity, indicating acute bleeding into chronic subdural haematoma; **B.** Axial T1 contrast-enhanced image shows regression of subdural haematoma with asymmetric enhancement of right-sided dura; **C.** CSF cytology — a cluster of lymphoma cells (marked by arrow). May-Grunwald Giemsa stain, 40×; **D.** Neuropathology — diffuse infiltration of meninges at base of mesencephalon by CD20 positive malignant B-cell lymphoma cells. Immunohistochemical staining using an anti-CD20 antibody, 40×

PCR investigation excluded the most likely pathogens. Immunocytochemical typing of cytologically suspected cells (Fig. 1C) surprisingly identified CD45 and PAX5, both hallmarks of B-cell lymphoma.

The patient's condition continued to deteriorate, and she died 11 days after admission. Autopsy confirmed a massive pulmonary embolism as the cause of death. The major finding concerning the aetiology of meningeal involvement (including the spread to cranial nerves at brain stem level) (Fig. 1D) was a generalised tumour affecting several organs (the lungs, stomach, and lymphatic nodes). A detailed histopathological investigation definitively excluded breast cancer extension, and finally confirmed generalisation of high-grade diffuse large B-cell lymphoma as the source of the leptomeninges infiltration.

Establishing the final diagnosis was a difficult task given the concurrence of the unrelated subdural haematoma and a past history of breast cancer. MRI leptomeningeal enhancement was ascribed initially to the subdural haematoma rather than meningeal infiltration. Moreover, the immunocytochemical investigations of potentially malignant cells in CSF were primarily focused on breast carcinoma.

There have been several published cases with a history of malignancy presenting as a spontaneous nontraumatic subdural haematoma that ultimately turned out to be leptomeningeal tumour infiltration [4–7]. However, in our case the regression of the haematoma (Fig. 1B) confirmed the coincidence of a subdural haematoma and tumour, and not subdural haematoma mimicking [8].

This case report offers guidance regarding patients with a known medical history of malignancy. It is always necessary to consider tumour duplicity and be open to a disorder caused by an entirely new type of tumour (in this case, breast cancer and B–cell lymphoma) [9]. This case clearly demonstrates the

importance of close cooperation between clinicians, radiologists, and laboratory specialists in establishing the proper diagnosis.

Acknowledgments: *The authors wish to thank Tom Secrest for revisions to the English version of this article.*

Funding: *This work was supported by the Ministry of Health, Czech Republic (Conceptual Development of Research Organisation VFN64165, General University Hospital in Prague and Thomayer University Hospital in Prague, TN64190), by the Grant Agency of the Ministry of Health (NV19-04-00090), and by Charles University (Project Progress Q27/LF1 and Q35/LF3).*

Conflict of interest: *None.*

References

1. Carroll RD, Leigh EC, Curtis Z, et al. A case of leptomeningeal carcinomatosis from aggressive metastatic prostate cancer. Case Rep Oncol. 2019; 12(1): 311–316, doi: 10.1159/000499761, indexed in Pubmed: 31123457.
2. Ma C, Lv Y, Jiang R, et al. Novel method for the detection and quantification of malignant cells in the CSF of patients with leptomeningeal metastasis of lung cancer. Oncol Lett. 2016; 11(1): 619–623, doi: 10.3892/ol.2015.3971, indexed in Pubmed: 26870256.
3. Aslan K, Gunbey HP, Tomak L, et al. Multiparametric MRI in differentiating solitary brain metastasis from high-grade glioma: diagnostic value of the combined use of diffusion-weighted imaging, dynamic susceptibility contrast imaging, and magnetic resonance spectroscopy parameters. Neurol Neurochir Pol. 2019; 53(3): 227–237, doi: 10.5603/PJNNS.a2019.0024, indexed in Pubmed: 31180131.
4. Boukas A, Sunderland GJ, Ross N. Prostate dural metastasis presenting as chronic subdural hematoma. A case report and review of the literature. Surg Neurol Int. 2015; 6: 30, doi: 10.4103/2152-7806.151713, indexed in Pubmed: 25737800.
5. Reyes MG, Homsi MF, Mangkornkanong M, et al. Malignant lymphoma presenting as a chronic subdural hematoma. Surg Neurol. 1990; 33(1): 35–36, doi: 10.1016/0090-3019(90)90222-b, indexed in Pubmed: 2300875.
6. Ramnarayan R, Anilkumar TV, Nayar R. An unusual extra-axial hypodense lesion mimicking a chronic subdural haematoma. J Neurosci Rural Pract. 2013; 4(2): 216–219, doi: 10.4103/0976-3147.112774, indexed in Pubmed: 23914111.
7. Neeley OJ, Al-Hreish KM, Aoun SG, et al. Tumoral mimics of subdural hematomas: case report and review of diagnostic and management strategies in primary B-cell lymphoma of the subdural space. World Neurosurg. 2020; 133: 49–54, doi: 10.1016/j.wneu.2019.09.091, indexed in Pubmed: 31562973.
8. Catana D, Koziarz A, Cenic A, et al. Subdural hematoma mimickers: a systematic review. World Neurosurg. 2016; 93: 73–80, doi: 10.1016/j.wneu.2016.05.084, indexed in Pubmed: 27268313.
9. Dušková J, Sobek O. Assisting the neurologist in diagnosis of CNS malignancies — current possibilities and limits of cerebrospinal fluid cytology and immunocytochemistry. Brain Behav. 2017; 7(10): e00805, doi: 10.1002/brb3.805, indexed in Pubmed: 29075565.