Neurologia i Neurochirurgia Polska, 2023, vol. 57, no. 6

NEUROLOGIA I NEUROCHIRURGIA POLSKA

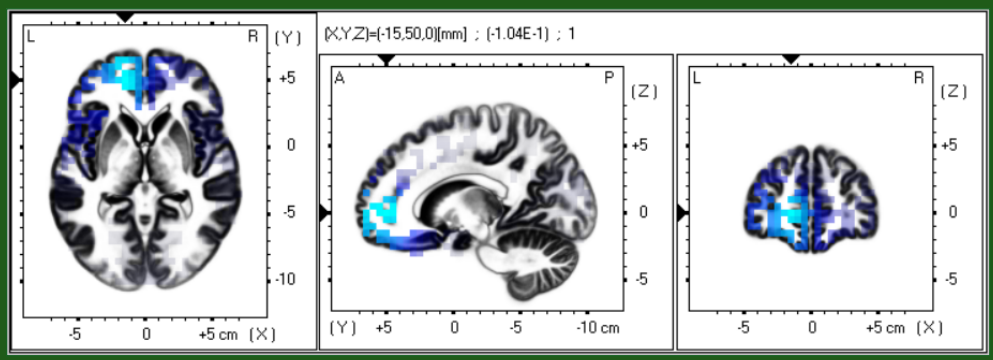
POLISH JOURNAL OF NEUROLOGY AND NEUROSURGERY

The Official Journal of Polish Neurological Society

2023, vol. 57, no. 6

Impact Factor: 2.9

MINISTRY OF EDUCATION AND SCIENCE • POLISH 140



Established: 1938

VIA MEDICA

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

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

Editorial address: VM Media Group sp. z o.o.
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 CrossRef, Chemical Abstracts, DOAJ, EBSCO, EMBASE, Google Scholar, Index Copernicus, MEDLINE/PubMed, OpenMed, Polish Medical Library, Polish Ministry of Education and Science, Polish Scientific Bibliography, Science Citation Index Expanded, Scopus.

Current Impact Factor of Neurologia i Neurochirurgia Polska (2022) is 2.9
Current Index Copernicus score (2022) is 174.23

The Journal has been included in the register of journals and proceedings of international conferences published by Polish Ministry of Education and Science on July 17th, 2023 with 140 points awarded.

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

Cover photo: C.E. Bistriceanu et al. Log of F ratio statistics, for each frequency and each voxel. (see figure on page 481)

22-6129.006.001

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REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 6, pages: 457–464
DOI: 10.5603/pjnns.97307

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

Is there a correlation between migraine and eating disorders? A systematic literature review

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ABSTRACT

Introduction. Migraine is a common primary headache disorder, which affects mainly young females, usually those with some specific personality traits including neuroticism and obsessive-compulsive disorder. Among many factors that may trigger headache are to be found those associated with eating patterns and behaviours.

Eating disorders are psychiatric disorders of abnormal eating or weight-control behaviours. According to the most up-to-date classification, six main types are identified, including anorexia nervosa, bulimia nervosa, and binge eating disorder. Similar to migraine, eating disorders are mainly diagnosed in young adults and, moreover, personality pattern, in at least some of the eating disorders, is also suggested to be consistent.

Material and methods. This systematic review aimed to summarise the available literature related to this topic. We performed an electronic article search through the Embase, PubMed, and Cochrane databases and included 16 articles into analysis in accordance with PRISMA 2020 guidelines.

Results. Most of the studies revealed the presence of a putative correlation between migraine and eating disorders, and these encourage further investigations. Moreover, apart from the clinical aspect, also the pathogenesis underlying both disorders is suggested to be similar. More frequent co-occurrence of other psychiatric disorders in migraineurs, such as depression and anxiety, was reported and should be considered in future research. Furthermore, adverse interactions between pharmacotherapy and symptoms of comorbid conditions underline the importance of this problem.

Conclusions. A correlation between migraine and eating disorders appears highly probable. However, further investigations are required focusing on diverse aspects such as clinical, psychological, and pathogenic.

Keywords: anorexia nervosa, bulimia nervosa, eating disorders, migraine, primary headache disorders

(*Neurol Neurochir Pol 2023; 57 (6): 457–464*)

Introduction

Key information about migraine

According to The International Classification of Headache Disorders, 3rd Edition (ICHD-3), migraine is a common primary headache disorder with two major types: migraine without aura and migraine with aura, plus a third: chronic migraine [1]. Importantly, in the Global Burden of Disease Study 2015 (GBD2015), it was recognised as one of the leading causes of disability among young adults [2]. Migraine prevalence worldwide has been estimated at 15% and it affects over 1,000,000,000 people globally [3].

Migraine is more common in women than men at a rate of 3:1 [4], with the highest prevalence in people aged 18 to 44 [5]. Among the known causes of recurrent, disabling attacks are: stress, fatigue, weather changes, menstrual cycle changes, light, noise, and sleep disturbances [6]. Moreover, diverse dietary factors including fasting and particular foods and drinks such

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Received: 6.09.2023 Accepted: 26.10.2023 Early publication date: 1.12.2023

as chocolate, milk, cheese, nuts, and alcohol (especially red wine), can trigger headache pain [7]. Last but not least, some studies have revealed overeating and obesity to be significantly associated with migraine attacks compared to non-migraine headaches [8, 9].

Background of eating disorders

Eating disorders (ED) are defined as psychiatric disorders characterised either by abnormal eating or weight-control behaviour [10]. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) [11] and the International Classification of Diseases, 11th Revision (ICD--11) [12], six main types of ED are distinguished. Apart from the generally known ED including anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorders, three more have been identified: avoidant-restrictive food intake, pica, and rumination disorder, previously classified as a childhood disorder [13].

An eating disorder not otherwise specified (EDNOS) has been found to be the most common eating disorder, followed by AN, BN, and binge eating disorder. Similarly to migraine, the prevalence of ED is highest among young women, especially adolescents [14]. Importantly, the mortality rate appears to be increased in all types of ED, and quality of life to be reduced compared to the general population [15]. The most striking mortality rate occurs in AN, while statistics for BN and EDNOS are similar [16].

Arguments for a correlation between migraine and eating disorders

Summarising the above information about the prevalence and patient profile in migraine and ED, similarities can be shown between the two groups. Several behaviours specific to ED, such as fasting or overeating, appear to trigger headache pain. Moreover, fatigue, with an underlying cause of weight loss plus a lack of essential nutritional elements, has been shown to lead to migraine attacks.

Some personality traits, especially neuroticism, and symptoms of obsessive-compulsive disorder, or striving for perfection, have been found to be correlated with an elevated risk of both migraines [17, 18] and ED [19], which may suggest an association between both types of disease. However, the data related to this topic is very limited. One of the common monoamines, serotonin (5-HT), is expected to play a role in the aetiology of migraine, as well as of eating disorders. Nevertheless, as yet no particular genetic component has been explicitly stated. This systematic review aimed to summarise the current state of knowledge and analyse a possible correlation between eating disorders and migraine.

Material and methods

Three databases were screened in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020) [20], including the Embase, PubMed, and Cochrane databases. The search terms were: migraine AND (eating disorders OR eating disorder OR anorexia nervosa OR bulimia nervosa) AND (correlation OR association OR relation OR relationship), and they remained the same for all three databases.

Inclusion and exclusion criteria

To maintain consistency, inclusion and exclusion criteria were applied. Primary research articles, including clinical and cohort studies, were allowed. But meta-analyses, systematic reviews, narrative reviews, case reports, letters to the editor, and commentaries were excluded. Because of the limited data, in addition to articles, conference abstracts were also accepted based on generally acknowledged recommendations [21].

Only clinical research studies were found, with no preclinical studies. Involved publications focused on the correlation between migraine and diverse ED in patients without or with other conditions, primarily psychiatric. Studies describing only headaches other than migraine, or psychiatric disorders different to ED, were excluded. Studies written in languages other than English were excluded.

Selection process

After the initial search of three databases based on the aforementioned search strategy, 425 records were identified, of which 79 were duplicates. Out of 346 records assessed by title or type, 257 were excluded. Subsequently, the abstracts' assessment of the 89 remaining research articles identified 27 studies in which complete data was thoroughly analysed. Eventually, the selection process led to the inclusion of 16 studies in our systematic review (Fig. 1).

Results

Putative correlation between migraine and eating disorders in clinical studies

A possible correlation between migraine and ED has been suggested; however, the number of studies related to this topic is small. To perform the most detailed and precise analysis possible, we divided the involved studies into three parts focusing on different theses, i.e. that: (i) migraine and eating disorders are presumably correlated; (ii) that the correlation may be associated with depression and anxiety; and (iii) uncertainties of putative correlation.

Migraine and eating disorders are presumably correlated

Several studies have shown a putative correlation between migraine and diverse ED, including anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorders, the results of which are presented below. Additionally, this association has also been observed in paediatric populations. For instance, an interesting study by de Oliveira-Souza et al. [22] investigated

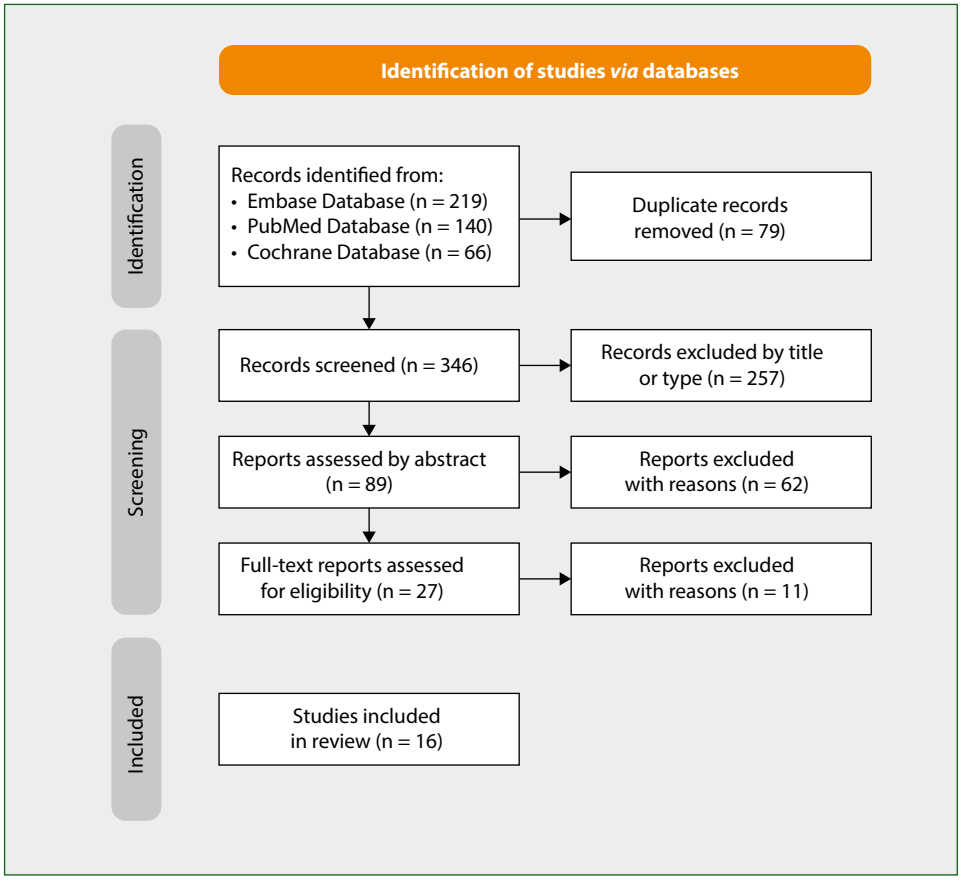

Figure 1. Flowchart of selection process according to guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses [20]

the correlation between migraine and ED in children aged 11 to 18. Both migraine and ED were more common in females than males. Importantly, regardless of sex, BN symptoms were positively correlated with migraine. Moreover, the risk of developing ED was higher in female migraineurs. D'Andrea et al. [23] studied female patients suffering from ED, with a specification into AN or BN. Migraine was present in a significant majority of the study group (74.3%), while other types of headaches (tension-type headaches or non-classifiable headaches) were observed only in 9.2%. Furthermore, no significant differences were shown when comparing patients affected by AN to those suffering from BN.

Another research group [24] conducted a study on a paediatric population and compared migraineurs to children without diagnosed migraine headaches or equivalents for the presence of diverse psychiatric disorders. Although the ED rate was higher in the study group, it was not statistically significant. However, with $p = 0.079$, the result was close to statistical significance, suggesting it deserves further study. Importantly, the first reports regarding a putative correlation began to appear before the end of the 20th century. In a study conducted in 1993, Brewerton et al. [25] investigated female patients suffering from migraine and compared them to healthy controls. Among migraineurs, binge eating disorder was present in 59% and self-induced vomiting in 26%. Moreover, compared to healthy controls, migraine patients presented elevated scores in four out of eight subscales of the Eating Disorders Inventory.

A slightly different approach to the topic was shown by Lebow et al. [26], who carried out a retrospective study on a small group of adolescents treated with topiramate because of migraine or chronic headache. Four of seven patients were diagnosed with unspecified ED, two with AN, and one with BN. Three patients reported no ED history before the topiramate use, and one patient was in remission with recurrence after the start of topiramate intake. Although this research was conducted on a small group of patients, it highlights the importance of ED and migraine comorbidity in terms of pharmacological treatment. Importantly, significant weight loss should be listed among the main adverse effects of topiramate use.

Interesting observations were demonstrated in another article [27] based on the previously described research by D'Andrea et al. Researchers aimed to verify the hypothesis of a similar pathogenesis of ED to migraine, which suggests catecholamine and trace amine dysregulation in both diseases. Since this has been demonstrated to play a role in migraine [28, 29], similar observations in ED would allow better understanding of some consistent mechanisms underlying both disorders. Therefore, plasma levels of dopamine (DA), noradrenaline

(NA), tyrosine (Tyr), and octopamine (Oct) were measured in BN and AN patients, and compared to healthy controls. Interestingly, increases in Tyr and DA levels were shown when comparing patients suffering from ED to the control group. On the other hand, the NA level was significantly lower in the study group. Moreover, differences were observed between AN and BN patients, with higher levels of Oct in the first group and of Tyr in the second.

Correlation may be associated with depression and anxiety

Some included studies have not only investigated a correlation between migraine and ED, but also suggested depression and anxiety as factors that may be associated. Mustelin et al. [30] conducted a study on female patients with ED over a lifetime, including either AN or BN, and compared them to healthy controls. Migraine occurred significantly more frequently in the study group. Importantly, the prevalence of major depressive disorder was assessed in the study and control group, and depression was positively correlated with both migraine and ED. Moreover, migraine levels were the highest in patients presenting ED and major depressive disorder. Therefore, there is a great need for further studies on ED in migraine, including the impact of depression.

Hamamci et al. [31] investigated patients suffering from episodic migraine and compared them to healthy controls. Significantly more patients from the study group presented ED attitudes. Nevertheless, migraineurs with ED statistically more frequently suffered from other disorders, such as depression and anxiety, than those unaffected by ED, which may have influenced the results.

A similar observation has also been made in a pediatric population. Tarantino et al. [32] investigated adolescent girls suffering from migraine with a specification of attack frequency. ED were present in most of the study group. Specifically, AN symptoms were observed in 42.9% of girls, while 28.6% presented with BN behaviour. Furthermore, bulimic symptoms were positively correlated with school anxiety and depression, but only in the high-frequency group.

Inanc et al. [33] studied patients diagnosed with primary headache disorder (migraine or tension-type headache) and compared them to healthy controls. The mean score in the Eating Attitudes Test (EAT) was significantly higher in the study group than in the control group, with the highest points among migraineurs. Additionally, Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) showed increased points for patients suffering from headaches compared to healthy controls.

Similarly, Demirci et al. [34] compared migraine patients to healthy controls in terms of eating disorder attitudes assessed by EAT. It appears that migraineurs presented statistically significant higher EAT points, with a score of 30 or over in 11.9%, compared to 2.1% of healthy controls. Moreover, in the study group, levels of anxiety (BAI) and depression (BDI) were increased. Interestingly, the EAT, BAI, and BDI scores among migraineurs positively correlated with the Migraine Disability Assessment Score (MIDAS). All studies are summarised in Table 1.

Uncertainties of putative correlation

Apart from studies proving the analysed correlation, there have also been some in which results have appeared to be questionable, starting with a study by LeBaron et al. [35] investigating comorbidity of ED and migraine in patients with mood disorders. Although a positive correlation between migraine and ED in general was observed, migraine was shown not to be associated with AN after the specification of ED type. However, a correlation was revealed between migraine and both BN and binge eating disorder in the study group. On the other hand, Roux et al. [36] conducted a follow-up assessment of 97 female patients hospitalised due to AN as adolescents: 6–12 years after hospitalisation, almost a third of the study group had been diagnosed with migraine. Interestingly, the presence of migraine appeared to be negatively correlated with the lifetime occurrence of BN.

Going further, any correlation between migraine and ED was revealed in two included studies. Seidel et al. [37] studied the migraine prevalence in female patients suffering from ED and compared them to their sisters who had no ED history. Among 120 pairs, 80 were concordant (13 were affected by migraine, 67 were unaffected), and 40 were discordant. However, the latter group presented no significant differences between females with and without ED. Among these 40 pairs, migraine co-occurred with ED in 21, while in 19 one sister suffered from ED, and the 40th was a migraineur.

Another research group [38] conducted a large clinical study on adolescent patients, comparing diverse mental disorders to the presence or absence of different headache types. Among mental disorders were included ED. However, it must be emphasised that there was a majority of binge ED over both AN and BN. The results revealed a positive correlation between ED and headaches in general. Nevertheless, ED were demonstrated to be less common in patients with migraine than other types of headache.

Another interesting study was carried out by Wang et al. [39]. Researchers conducted a nationwide cohort study investigating the presence of multiple psychiatric disorders in the offspring of mothers affected or unaffected by migraine. Children born between 1978 and 2012 were assessed with a median follow-up time of 19 years. Interestingly, although multiple significant associations between migraines and psychiatric disorders were demonstrated, no correlation was observed between migraine in mothers and ED in children. All studies are summarised in Table 2.

Table 1. Summary of studies regarding correlation between migraine and ED

Ref.	Year	Population	Comparison	Outcome	ED diagnosis
de Oliveira Souza et al. [22]	2022	607 adolescents (388 females, 219 males)	Males to females MIG pts to non-MIG pts	43.7% risk of BN in MIG females to 34% risk in non-MIG females 29.6% risk of BN in MIG males to 21.8% in non-MIG males	EAT-26, BITE
D'Andrea et al. [23]	2009	109 ED pts (76 AN, 33 BN)		Migraine present in 81 ED pts; no significant differences between AN and BN	Based on DSM-IV criteria
Kandemir et al. [24]	2018	50 MIG paediatric pts	50 HC	↑ ED rate in MIG pts compared to HC (P = 0.079)	K-SADS-PL, EAT
Brewerton et al. [25]	1993	34 female MIG pts	577 HC	Binge eating disorder in 59% of MIG pts BN behaviour in 26% of MIG pts ↑ in 4/8 EDI subscales in MIG pts compared to HC	EDI, DSED
Lebow et al. [26]	2015	7 topiramate-treated paediatric headache pts		ED beginning during topiramate treatment in 3 pts ED beginning before topiramate treatment in 3 pts ED in remission before topiramate treatment in 1 pt	Based on DSM-IV criteria
D'Andrea et al. [27]	2008	125 ED pts (89 AN, 36 BN)	27 HC	↑ DA and Tyr in ED pts compared to HC ↓ NA in ED pts compared to HC ↑ Oct in AN pts compared to BN pts ↑ Tyr in BN pts compared to AN pts	Based on DSM-IV criteria
Mustelin et al. [30]	2014	55 female AN pts 60 female BN pts	40 non-ED co-twins from FinnTwin16 cohort, 289 non-ED unrelated women	Migraine present in 22% of AN and BN pts, 13% of co-twins, and 12% of unrelated women	Based on DSM-IV criteria
Hamamci et al. [31]	2020	91 MIG pts	87 HC	ED in 23.1% of MIG pts and 9.5% of HC	EAT
Tarantino et al. [32]	2021	35 adolescent MIG pts	High-frequency MIG to low-frequency MIG	AN behaviour in 42.9% and BN behaviour in 28.6% of MIG pts	SAFA test
Inanc et al. [33]	2019	89 MIG pts 87 TTH pts	89 HC	↑ mean EAT points in MIG pts and TTH pts compared to HC	EAT
Demirci et al. [34]	2015	59 MIG pts	HC	EAT ≥ 30 in 11.9% of MIG pts and 2.1% of HC; positive correlation between EAT and MIDAS in MIG pts	EAT

↑ — increased; ↓ — decreased; AN — anorexia nervosa; BITE — Bulimic Investigatory Test, Edinburgh; BN — bulimia nervosa; DA — dopamine; DSED — Diagnostic Survey of Eating Disorders; DSM-IV — Diagnostic and Statistical Manual of Mental Disorders; EAT — Eating Attitudes Test; ED — eating disorders; EDI — Eating Disorders Inventory; HC — healthy controls; K-SADS-PL — Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version; MIDAS — Migraine Disability Assessment Score; MIG — migraine; NA — noradrenaline; Oct — octopamine; pts — patients; Ref. — reference; SAFA — Self Administrated Psychiatric Scales for Children and Adolescents; TTH — tension-type headache; Tyr — tyramine

Table 2. Summary of studies showing uncertainties of correlation between migraine and ED

Ref.	Year	Population	Comparison	Outcome	ED diagnosis
LeBaron et al. [35]	2015	153 mood disorders pts		Positive correlation between mig and ed No correlation between mig and an	Based on DSM-IV criteria
Roux et al. [36]	2013	97 adolescent AN pts	Follow-up after 6–12 years	Migraine in 32% of an pts Negative correlation between mig and lifetime BN	Based on DSM-IV
Seidel et al. [37]	2011	120 female ED pts	120 non-ED pts' sisters	13 MIG pairs 67 non-MIG pairs 40 discordant pairs (in 21 MIG was present in ED pts, in 19 in non-ED pts)	Based on DSM-IV criteria
Hommer et al. [38]	2022	2,711 headache pts (1,245 MIG, 1,466 non-MIG)	7,412 non-headache pts	↑ ED in study group compared to HC ↓ ED in MIG pts compared to non-MIG pts	Based on DSM-IV criteria
Wang et al. [39]	2021	51,717 MIG female pts	1,800,517 non-MIG female pts	No correlation with ED in children of MIG and non-MIG mothers	Based on ICD-8, ICD-10 codes

↑ — increased; ↓ — decreased; AN — anorexia nervosa; BN — bulimia nervosa; DSM-IV — Diagnostic and Statistical Manual of Mental Disorders; ED — eating disorders; ICD — International Classification of Diseases; MIG — migraine; pts — patients; Ref. — reference

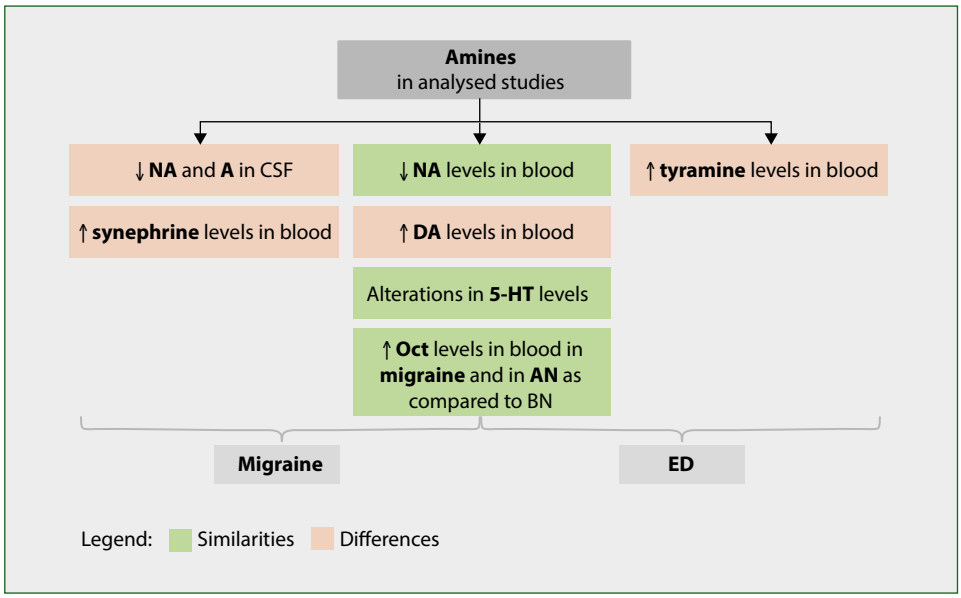

Figure 2. Summary of role of amines in migraine and eating disorders (including similarities and differences) shown in analysed studies. ↑ — increase; ↓ — decrease; 5-HT — serotonin; A — adrenaline; CSF — cerebrospinal fluid; DA — dopamine; ED — eating disorders; NA — noradrenaline; Oct — octopamine

Conclusions

Most studies have revealed that a correlation between migraine and ED is highly probable based on diverse aspects including clinical approach and pathogenesis.

To summarise the aforementioned studies, five main conclusions can be drawn:

1. Patient profiles in migraine and ED are substantially similar; however, studies related to this issue are lacking
2. Migraine and eating disorders may have a similar pathogenesis, which should be investigated
3. Not all studies have revealed a correlation, which remains to be explained
4. Depressive disorder probably influenced the results of several studies, and therefore it must be considered
5. Pharmacotherapy of these diseases may exacerbate the others.
6. All these statements have been expanded below.

Both analysed types of disease are known to appear in similar patient profiles i.e. a young female, usually with several traits of neuroticism or obsessive-compulsive disorder. Despite this, there is a lack of studies focusing on this issue. Analysis of available literature has allowed us to outline the profile of a typical migraineur, which remains consistent with a person suffering from AN. Based on the analysed data, personality traits such as perfectionism, politeness, and diligence may appear significantly more frequently in these patients. However, in the analysed clinical studies, we did not find any that focused on this part of the problem. Therefore, further research is undeniably required.

One group of researchers has suggested that pathogenesis with alterations of amine levels acknowledged for migraine may be similar in ED (Fig. 2). Furthermore, 5-HT has been shown to be involved in mechanisms underlying both diseases.

Alterations of common biochemical compounds in both conditions suggest that some particular genes might be responsible for developing these conditions, making genetic backgrounds similar. Moreover, both diseases are likely to occur more frequently in patients with family predispositions. Although several aspects potentially indicate that the role of genetics is at least partly shared in both conditions, the particular connections have yet to be discovered.

Undoubtedly, the fundamentals must be explored to understand better the correlation between migraine and ED. Therefore, further studies regarding the mechanisms and factors underlying the development of both diseases are urgently needed. A consistent biochemical background could clear up many unanswered questions regarding the existence of a putative correlation.

Although a correlation was observed in most studies, several revealed no association between migraine and ED (Fig. 3). Interestingly, those studies had been conducted on a limited group of patients or with a predominance of specific eating disorders, which may be less associated with migraine than the others. Based on risk factors and triggers of migraine headaches, only part of the ED included in the classifications may be positively correlated with migraine.

Analysing the data summarised in our systematic review, primary attention should be paid to AN and BN due to the specific traits of typical patients, and fasting as the triggering

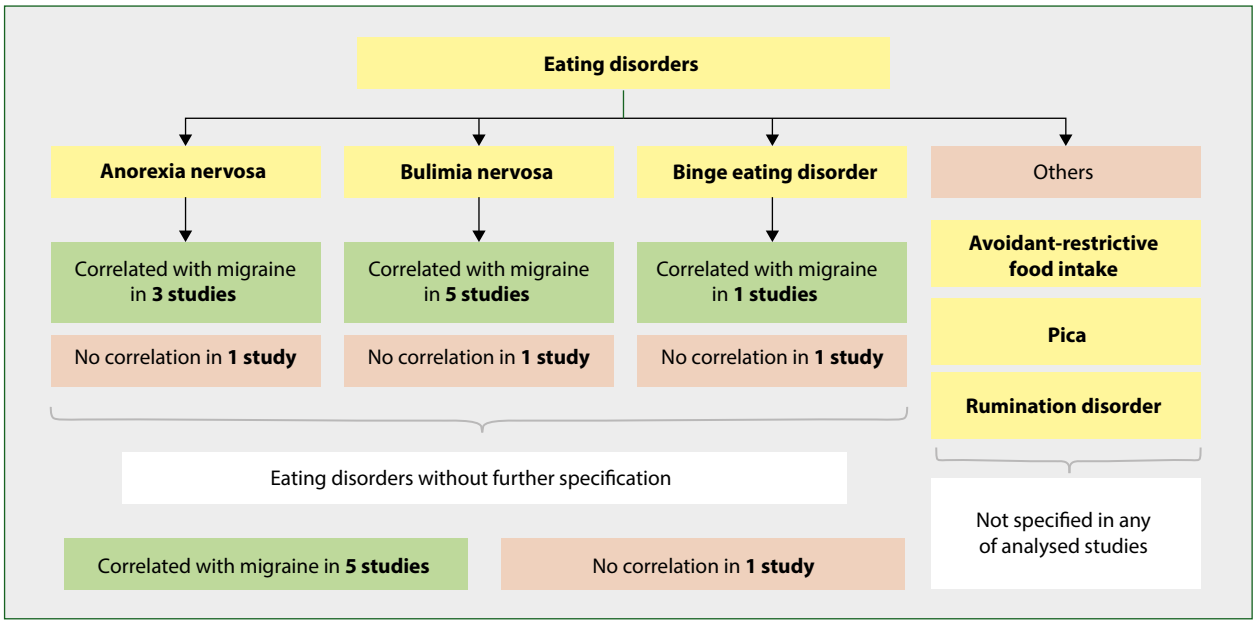

Figure 3. Summary of correlation between particular eating disorders and migraine in analysed studies

factor. Moreover, some studies have revealed that overeating may be associated with migraine headache pain. Therefore, binge eating disorder may increase the risk of developing migraine over the course of a lifetime, as demonstrated in most studies reflecting this specific disorder. Studies on expanded and more diverse groups of patients should be conducted.

Finally, depression and anxiety have been shown many times to correlate with migraine and ED, which may influence the results. Further studies should be conducted after minimising the possible impact of these disorders. It is worth underlining that a pharmacological treatment used in one disease may exacerbate the other as a drug side effect, meaning that it should be carefully analysed before a drug is prescribed.

All of the foregoing proves the importance of this topic, and the need for further studies.

Limitations

Undoubtedly, our results show a high probability of a significant correlation and encourage further investigation. Interestingly, many analysed studies were conducted on very limited groups of patients, usually representing only a few specific EDs or ED in general, with a lack of research on patients suffering from less common EDs. Furthermore, due to a higher prevalence of both migraine and ED in females, there needs to be more research focused on males. Finally, a high coincidence of other psychiatric disorders may influence the results and should be taken into account in future studies.

Additionally, together with psychiatric diseases, other factors related to headaches or abnormal eating behaviours that have not been raised in this systematic review, such as premenstrual syndrome, may interfere with the results.

Article information

Conflict of interest: *None.*
Funding: *Article Processing Charge was covered by the Nicolaus Copernicus University in Toruń.*

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RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 6, pages: 465–476
DOI: 10.5603/pjnns.96469

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

Reversing dabigatran effect with idarucizumab to enable intravenous thrombolysis in patients with acute ischaemic stroke — a single centre experience

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ABSTRACT

Introduction. Our study analysed the safety and effectiveness of idarucizumab in enabling intravenous thrombolysis (IVT) in dabigatran-treated patients with acute ischaemic stroke (AIS).

Clinical rationale for the study. New oral anticoagulants (NOAC), including dabigatran, are the first-choice treatment option for preventing ischaemic stroke in patients with non-valvular atrial fibrillation (AF). However, a significant percentage of AF patients develops AIS despite NOAC treatment. According to current guidelines, treatment with IVT is contraindicated in patients who have received NOAC within the last 48 hours. Idarucizumab is a fragment of a monoclonal antibody that reverses the anticoagulation effect of dabigatran. The latest research shows that it can enable safe and successful IVT in patients with recent dabigatran intake, but more data is needed to confirm the safety and effectiveness of such treatment.

Material and methods. Our study included dabigatran-treated patients who received idarucizumab to allow AIS treatment with IVT in the University Hospital in Kraków (Poland) from December 2018 to June 2023. We gathered data on their past medical history, stroke severity, course of treatment and outcomes as defined by modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS) scores at discharge. A good functional outcome was defined as mRS 0–2 points at discharge.

Results. This observational study included 19 patients (13 male and six female) with a median age of 74 (IQR = 13) years. In all patients (100%), the reason for dabigatran treatment was AF. A good functional outcome after treatment (mRS 0–2) was achieved in 68.4% of patients, but mRS was already ≥ 3 points before stroke onset in three (15.8%) patients. Haemorrhagic transformation of stroke occurred in three (15.8%) patients, including symptomatic intracranial haemorrhage in two (10.5%). The mortality rate was 5.3%.

Conclusions and clinical implications. Our study results are in line with previous research on this topic, showing that IVT after idarucizumab can be successfully administered and is reasonably safe in dabigatran-treated patients with AIS.

Keywords: acute ischaemic stroke, intravenous thrombolysis, idarucizumab, dabigatran, new oral anticoagulants

(*Neurol Neurochir Pol 2023; 57 (6): 465–476*)

Introduction

Acute ischaemic stroke (AIS) is the most common form of stroke, and is an important cause of death and disability worldwide [1]. Early treatment with reperfusion therapies (intravenous thrombolysis, IVT; and/or mechanical thrombectomy, MT) is crucial for improving the prognosis [2].

New oral anticoagulants (NOAC) including dabigatran have been proven to prevent stroke in patients with nonvalvular atrial fibrillation (AF) [3], but a significant percentage of AF patients develop AIS despite NOAC treatment [4]. According to current guidelines, treatment with IVT is contraindicated in patients who have received NOAC within the last 48 hours [5].

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Received: 11.07.2023 Accepted: 26.09.2023 Early publication date: 13.11.2023

Idarucizumab is a fragment of a monoclonal antibody that binds with dabigatran. Its application has been proven to be safe and effective in rapidly reversing dabigatran's anticoagulation effect in patients with uncontrolled bleeding or requiring emergency surgery or urgent procedures [6]. There is growing evidence that idarucizumab can be safely used in patients with AIS to reverse dabigatran's effect for enabling IVT. Current ESO guidelines state that the evidence is so far insufficient to make a recommendation for or against using idarucizumab and IVT in patients with AIS who have taken dabigatran within the last 48 hours, although in the expert consensus statement most group members suggested that this form of treatment should be preferred over no IVT [5].

Clinical rationale for study

More data is needed to establish the safety and effectiveness of idarucizumab in enabling thrombolytic treatment of AIS in dabigatran-treated patients. We here present a single centre report from Poland concerning outcomes of dabigatran-treated AIS patients who received idarucizumab to allow treatment with IVT.

Material and methods

This observational study is a retrospective analysis of medical documentation of patients hospitalised in the University Hospital in Kraków (Poland) from December 2018 to June 2023. Based on the documentation of patients included in studies: *Identification and clinical validation of biomarkers for long-term outcome after cerebral ischaemia* (Jagiellonian University Bioethics Committee approval number KBET/1072.6120.118.2020) and *Molecular genetics of age-related diseases of the nervous system - a bank of genetic material and clinical data* (Jagiellonian University Bioethics Committee approval number KBET/54/B/2007), we identified patients treated with idarucizumab to enable thrombolytic treatment of AIS over this period. The abovementioned studies include all AIS patients hospitalised in our centre, and the study group represents all AIS patients who have received idarucizumab for enabling IVT in our clinic to date. We did not include patients who had received idarucizumab and IVT in another centre, before being transferred to our hospital. The decision regarding idarucizumab administration was made individually for each patient according to his or her clinical situation and the current guidelines and expert consensuses as updated during the analysed time (2018–2023).

From the documentation of this selected group of patients, we gathered data concerning their age, biological sex, and relevant comorbidities: 1. arterial hypertension (diagnosed in previous medical history and/or antihypertensive treatment prior to stroke onset and/or aystolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg at least in two different measurements after the first three days of hospitalisation); 2. atrial fibrillation (diagnosed in previous medical history or during hospitalisation based on electrocardiograms); 3. coronary artery disease (based on medical documentation, available electrocardiograms and/or laboratory data); 4. carotid artery atherosclerosis (intima-media complex thickening or presence of atherosclerotic plaques, with stenoses > 50% considered haemodynamically significant); 5. stroke or transient ischaemic attack (TIA) in previous medical history; 5. diabetes or prediabetes (diagnosed according to ESC criteria [7]); 6. dyslipidaemia (defined as a cholesterol level > 5.2 mmol/L or use of cholesterol–lowering treatment); 7. peripheral artery disease (presence of atherosclerotic plaques in arteries other than coronary and cerebral confirmed by ultrasound during hospitalisation or in previous medical history); 8. history of smoking during the last 15 years; and 9. obesity (BMI > 30 kg/m^2).

We noted functional disability before stroke onset (assessed using modified Rankin Scale, mRS) and neurological deficit at admission (assessed using National Institutes of Health Stroke Scale, NIHSS). We noted the reason for dabigatran treatment, which dose was used, when the last dose was taken, and what was the patient's compliance to treatment (as non-compliant we classified patients who had missed any dabigatran dose within the week preceding the stroke). We analysed time from stroke onset to hospital admission (time to admission, TTA) as well as time from admission to the start of intravenous thrombolysis (door-to-needle time, DTN). Ischaemic lesion size was estimated using perfusion computed tomography (CT) analysis with iRAPID software [8]. We noted whether or not thrombolytic treatment was followed by mechanical thrombectomy (MT), and if so, what was the radiological effect of the reperfusion (assessed with modified thrombolysis in cerebral infarction scale, mTICI). If present, we classified haemorrhagic transformation of the stroke using the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) definitions [9]. Symptomatic intracranial haemorrhage was defined as haemorrhagic transformation of stroke causing a worsening of neurological condition > 4 points in NIHSS score or resulting in mortality within 22–36 hours post-treatment. We gathered data concerning in-hospital mortality and the percentage of patients needing transfer to the intensive care unit (ICU). Short term outcome was measured by mRS and NIHSS score at discharge. A good functional outcome was defined as mRS 0–2 points at discharge.

Statistical analysis of the gathered data was performed using Imago Pro 8.0. We presented categorical data as counts and percentages, and continuous data as median and interquartile range (IQR).

Results

This study included 19 patients who developed AIS while being treated with dabigatran and who received idarucizumab to enable intravenous thrombolysis. The individual patient characteristics are set out in Table 1.

Table 1. Individual characteristics of included patients

	Age, sex	Comorbidities	mRs before stroke onset	Reason for dabigatran treatment	Dabigatran dose	Last dabigatran dose before admission	Compliance	Stroke localisation	Time from stroke onset to arrival (min)	Time from stroke onset to IVT (min)	NIHSS at arrival (pts)	Stroke volume	Mechanical thrombectomy (mTICI effect)	Outcome at discharge
1.	77, F	Atrial fibrillation Arterial hypertension History of stroke Atherosclerosis of carotid arteries	1	Atrial fibrillation	2 × 150 mg	0–12 h	Non compliance	Left cerebral hemisphere	68	135	22	CBF < 30% = 0 mL Tmax > 6 s = 81 mL Mismatch volume = 81 mL	1 (TICI = 3)	NIHSS = 2 mRS = 1
2.	68, F	Atrial fibrillation Arterial hypertension Coronary artery disease Atherosclerosis of carotid arteries Smoking	0	Atrial fibrillation	2 × 150 mg	12–24 h	No information	Right cerebral hemisphere	110	155	17	CBF < 30% = 25 mL Tmax > 6 s = 124 mL Mismatch volume = 99 mL	1 (TICI = 3)	NIHSS = 2 mRS = 1
3.	63, M	Atrial fibrillation Arterial hypertension Diabetes mellitus Atherosclerosis of carotid arteries Obesity	0	Atrial fibrillation	2 × 150 mg	0–12 h	Non compliance	Right cerebral hemisphere	108	155	6	CBF < 30% = 0 mL Tmax > 6 s = 33 mL Mismatch volume = 33 mL	0	NIHSS = 1 mRS = 1
4.	83, M	Atrial fibrillation Arterial hypertension Atherosclerosis of carotid arteries Coronary artery disease	0	Atrial fibrillation	2 × 150 mg	12–24 h	Non compliance	Right cerebral hemisphere	169	255	7	CBF < 30% = 0 mL Tmax > 6 s = 95 mL Mismatch volume = 95 mL	0	NIHSS = 3 mRS = 1
5.	79, F	Atrial fibrillation Arterial hypertension Diabetes mellitus Atherosclerosis of carotid arteries Peripheral atherosclerosis Coronary artery disease History of stroke Smoking	1	Atrial fibrillation	2 × 110 mg	12–24 h	Non compliance	Left cerebral hemisphere	94	188	9	CBF < 30% = 9 mL Tmax > 6 s = 44 mL Mismatch volume = 35 mL	0	NIHSS = 2 mRS = 1

Table 1. Individual characteristics of included patients (cont.)

	Age, sex	Comorbidities	mRs before stroke onset	Reason for dabigatran treatment	Dabigatran dose	Last dabigatran dose before admission	Compliance	Stroke localisation	Time from stroke onset to arrival (min)	Time from stroke onset to IVT (min)	NIHSS at arrival (pts)	Stroke volume	Mechanical thrombectomy (mTICI effect)	Outcome at discharge
6.	38, M	Atrial fibrillation Arterial hypertension Smoking	0	Atrial fibrillation	2 × 150 mg	0–12 h	Non compliance	Left cerebral hemisphere	46	100	6	CBF < 30% = 13 mL Tmax > 6 s = 57 mL Mismatch volume = = 44 mL	1 (TICI = 3)	NIHSS = 0 mRS = 0
7.	79, M	Atrial fibrillation Arterial hypertension Atherosclerosis of carotid arteries Peripheral atherosclerosis Coronary artery disease History of stroke	0	Atrial fibrillation	2 × 110 mg	0–12 h	Full compliance	Right cerebral hemisphere	192	255	20	CBF < 30% = 0 mL Tmax > 6 s = 83mL Mismatch volume = = 83 mL	0	NIHSS = 1 mRS = 0
8.	70, M	Atrial fibrillation Arterial hypertension Dyslipidemia Atherosclerosis of carotid arteries Coronary artery disease History of stroke	1	Atrial fibrillation	2 × 150 mg	0–12 h	Non compliance	Left cerebral hemisphere	102	155	5	CBF < 30% = 0 mL Tmax > 6 s = 79 mL Mismatch volume = = 79 mL	0	NIHSS = 2 mRS = 1
9.	84, M	Atrial fibrillation Arterial hypertension Atherosclerosis of carotid arteries Peripheral atherosclerosis	3	Atrial fibrillation	2 × 110 mg	0–12 h	Full compliance	Right cerebral hemisphere	143	225	9	CBF < 30% = 0 mL Tmax > 6 s = 15 mL Mismatch volume = = 15 mL	0	NIHSS = 3 mRS = 3
10.	72, M	Atrial fibrillation Arterial hypertension Diabetes mellitus Dyslipidemia Atherosclerosis of carotid arteries Coronary artery disease Smoking	0	Atrial fibrillation	2 × 150 mg	0–12 h	Full compliance	Left cerebral hemisphere	53	112	4	CBF < 30% = 0 mL Tmax > 6 s = 53 mL Mismatch volume = = 53 mL	0	NIHSS = 0 mRS = 0

Table 1. Individual characteristics of included patients (cont.)

	Age, sex	Comorbidities	mRs before stroke onset	Reason for dabigatran treatment	Dabigatran dose	Last dabigatran dose before admission	Compliance	Stroke localisation	Time from stroke onset to arrival (min)	Time from stroke onset to IVT (min)	NIHSS at arrival (pts)	Stroke volume	Mechanical thrombectomy (mTICI effect)	Outcome at discharge
11.	61, M	Atrial fibrillation Arterial hypertension Diabetes mellitus Dyslipidemia Atherosclerosis of carotid arteries Coronary artery disease History of stroke Smoking	0	Atrial fibrillation	2 × 150 mg	0–12 h	Full compliance	Right cerebral hemisphere	166	260	11	CBF < 30% = 0 mL Tmax > 6 s = 50 mL Mismatch volume = = 50 mL	0	NIHSS = 0 mRS = 0
12.	81, F	Atrial fibrillation Arterial hypertension Diabetes mellitus Dyslipidemia Atherosclerosis of carotid arteries Peripheral atherosclerosis Coronary artery disease	1	Atrial fibrillation	2 × 110 mg	0–12 h	Full compliance	Right cerebral hemisphere	81	160	7	CBF < 30% = 0 mL Tmax > 6 s = 0 mL Mismatch volume = = 0 mL	0	Deceased
13.	69, M	Atrial fibrillation Arterial hypertension Diabetes mellitus Dyslipidemia Atherosclerosis of carotid arteries Peripheral atherosclerosis Coronary artery disease History of stroke	0	Atrial fibrillation	2 × 150 mg	24–48 h	Non compliance	Brainstem stroke	85	130	12	CBF < 30% = 0 mL Tmax > 6 s = 0 mL Mismatch volume = = 0 mL	0	NIHSS = 10 mRS = 4

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Table 1. Individual characteristics of included patients (cont.)

	Age, sex	Comorbidities	mRs before stroke onset	Reason for dabigatran treatment	Dabigatran dose	Last dabigatran dose before admission	Compliance	Stroke localisation	Time from stroke onset to arrival (min)	Time from stroke onset to IVT (min)	NIHSS at arrival (pts)	Stroke volume	Mechanical thrombectomy (mTICI effect)	Outcome at discharge
14.	80, M	Atrial fibrillation Arterial hypertension Dyslipidemia Atherosclerosis of carotid arteries Peripheral atherosclerosis Smoking Obesity	0	Atrial fibrillation	2 × 110 mg	0–12 h	Full compliance	Right cerebral hemisphere	36	142	20	CBF < 30% = 0 mL Tmax > 6 s = 93 mL Mismatch volume = = 93 mL	0	NIHSS = 4 mRS = 1
15.	74, M	Atrial fibrillation Arterial hypertension Diabetes mellitus Dyslipidemia Atherosclerosis of carotid arteries Peripheral atherosclerosis Coronary artery disease	0	Atrial fibrillation	2 × 150 mg	0–12 h	No information	Right cerebral hemisphere	68	160	8	CBF < 30% = 0 mL Tmax > 6 s = 0 mL Mismatch volume = = 0 mL	0	NIHSS = 6 mRS = 2
16.	83, M	Atrial fibrillation Arterial hypertension Atherosclerosis of carotid arteries History of stroke	0	Atrial fibrillation	2 × 110 mg	0–12 h	No information	Left cerebral hemisphere	178	238	7	CBF < 30% = 0 mL Tmax > 6 s = 68 mL Mismatch volume = 68 mL	1 (TICI = 3)	NIHSS = 2 mRS = 1
17.	86, F	Atrial fibrillation Arterial hypertension Diabetes mellitus Atherosclerosis of carotid arteries History of stroke Obesity	3	Atrial fibrillation	2 × 110 mg	12–24 h	Non compliance	Brainstem stroke	95	135	7	CBF < 30% = 0 mL Tmax > 6 s = 18 mL Mismatch volume = = 18 mL	0	NIHSS = 1 mRS = 4

Table 1. Individual characteristics of included patients (cont.)

	Age, sex	Comorbidities	mRs before stroke onset	Reason for dabigatran treatment	Dabigatran dose	Last dabigatran dose before admission	Compliance	Stroke localisation	Time from stroke onset to arrival (min)	Time from stroke onset to IVT (min)	NIHSS at arrival (pts)	Stroke volume	Mechanical thrombectomy (mTICI effect)	Outcome at discharge
18.	63, F	Atrial fibrillation Arterial hypertension Dyslipidemia Atherosclerosis of carotid arteries Coronary artery disease History of stroke	3	Atrial fibrillation	2 × 150 mg	12–24 h	No information	Right cerebral hemisphere	65	143	10	CBF < 30% = 0 mL Tmax > 6 s = 0 mL Mismatch volume = = 0 mL	0	NIHSS = 0 mRS = 3
19.	70, M	Atrial fibrillation Arterial hypertension Atherosclerosis of carotid arteries	0	Atrial fibrillation	2 × 150 mg	0–12 h	No information	Right cerebral hemisphere	154	180	1	CBF < 30% = 4 mL Tmax > 6 s = 71 mL Mismatch volume = = 67 mL	1 (TICI = 3)	NIHSS = 27 mRS = 5

CBF — cerebral blood flow; IVT — intravenous thrombolysis; mRS — modified Rankin scale; NIHSS — National Institutes of Health Stroke Scale; Tmax — time to maximum

The patients were aged between 38 and 86 with a median age of 74 (IQR 68–81) years. Thirteen (68.4%) were male. The most common cardiovascular risk factors were atrial fibrillation (AF) and arterial hypertension (AH), present in all patients (n = 19; 100%). Eighteen (94.7%) patients had concomitant internal carotid artery atherosclerosis (intima-media complex thickening or presence of atherosclerotic plaques) with haemodynamically significant stenosis (> 50%) present in four (21.1%) patients. Coronary artery disease was present in 11 (57.9%), previous stroke or transient ischaemic attack (TIA) in nine (47.4%), diabetes or prediabetes in eight (42.1%), dyslipidaemia in eight (42.1%), peripheral artery disease in seven (36.8%), history of smoking in six (31.6%), and overweight or obesity in three (15.8%) patients. The dependence level assessed with mRS before stroke onset was 0 in 12 (63.2%), 1 in 4 (21.1%), and 3 in 3 (15.8%) patients.

In all patients (n = 19; 100%), the reason for dabigatran treatment was AF. Dabigatran dose was 2 × 150 mg in 12 (63.2%) and 2 × 110 mg in seven (36.8%) patients. Thirteen (68.4%) patients took the last dose of dabigatran within 0–12 hours, 5 (26.3%) patients within 12–24 hours and one (5.3%) patient within 24–48 hours before admission. Six (31.6%) patients took dabigatran on a regular basis, eight (42.1%) were noncompliant, and in five (26.3%) the compliance was unknown. APTT result before idarucizumab administration was available in 14 patients. It ranged from 22.4 to 48.7 seconds (median = 35.1, IQR 29.2–40.8), with the upper normal limit for our hospital laboratory diagnostics department being 36 seconds.

In six (31.6%) patients, the ischaemic lesion was located in the left cerebral hemisphere, in 11 (57.9%) in the right cerebral hemisphere, and in two (10.5%) in posterior circulation territory. The neurological deficit at admission assessed with NIHSS ranged from 1 to 22 points (median 8, IQR 6–12). Median of ischaemia volume assessed with perfusion CT analysis using iRAPID software was 53 ml (IQR 15–81 mL), with median of irreversible ischaemic changes volume being 0 ml (IQR 0–0) and median of penumbra volume being 50 mL (IQR 15–81).

TTA ranged from 36 to 192 minutes (median = 95, IQR 68–154). DTN ranged from 26 to 106 minutes (median = 63, IQR = 47–86). Five (26.3%) patients were additionally treated with MT, and in all of them full reperfusion was achieved (mTICI = 3).

Haemorrhagic transformation of stroke occurred in three (15.8%) patients, with sICH occurring in two (10.6%) patients. Using definitions from SITS-MOST, in one patient the haemorrhage was classified as HI1 (small petechiae along the margins of the infarct), in one as PH2 (local or intra-ischemic confluent hematoma > 30% of the infarcted area with a substantial space-occupying effect), and in one as PHr2 (large confluent haematoma located remotely from the actual infarct(s), with substantial space-occupying effect). One patient (PHr2) was treated with only IVT, and two others (HI1 and PH2) with both IVT and MT.

Table 2. Summary of results

Personal information	
Age [median (IQR)]	74 (IQR 68–81)
Male sex [n (%)]	13 (68.4%)
mRS before stroke onset [n (%)]	
— 0 points	12 (63.2%)
— 1 points	4 (21.1%)
— 3 points	3 (15.8%)
Cardiovascular risk factors	
Arterial hypertension [n (%)]	19 (100%)
Atrial fibrillation [n (%)]	19 (100%)
Carotid artery atherosclerosis [n (%)]	18 (94.7%)
— significant stenosis [n (%)]	4 (21.1%)
Coronary artery disease [n (%)]	11 (57.9%)
Previous stroke/TIA [n (%)]	9 (47.4%)
Diabetes/prediabetes [n (%)]	8 (42.1%)
Dyslipidaemia [n (%)]	8 (42.1%)
Peripheral artery disease [n (%)]	7 (36.8%)
History of smoking [n (%)]	6 (31.6%)
Overweight/obesity [n (%)]	3 (15.8%)
Dabigatran treatment	
Reason for dabigatran treatment	
AF [n (%)]	19 (100%)
Dabigatran dose [n (%)]	
2 × 150 mg	12 (63.2%)
2 × 110 mg	7 (36.8%)
Last dose of dabigatran before admission [n (%)]	
< 12 hours	13 (68.4%)
12–24 hours	5 (26.3%)
24–48 hours	1 (5.3%)
Compliance [n (%)]	
Full compliance	6 (31.6%)
Non-compliance	8 (42.1%)
Unknown	5 (26.3%)
Stroke localisation	
Left cerebral hemisphere [n (%)]	6 (31.6%)
Right cerebral hemisphere [n (%)]	11 (57.9%)
Posterior circulation territory [n (%)]	2 (10.5%)
Stroke severity	
NIHSS [median (IQR)]	8 (IQR 6–12)
Total ischaemia volume [median (IQR)]	53 (IQR 15–81) mL
Infarct volume [median (IQR)]	0 (IQR 0–0) mL
Penumbra volume [median (IQR)]	50 (IQR 15–81) mL
Disease course	
TTA [median (IQR)]	95 (IQR 68–154) minutes
DTN [median (IQR)]	63 (IQR 47–86) minutes
MT [n (%)]	4 (21.1%)
Full reperfusion (mTICI = 3)	4 (100%)
Complications	
Haemorrhagic transformation	
Total [n (%)]	3 (15.8%)
sICH	2 (10.5%)
HI1	1 (5.3%)
PH2	1 (5.3%)
PHr2	1 (5.3%)
Transfer to ICU [n (%)]	1 (5.3%)
Death [n (%)]	1 (5.3%)
Functional outcome	
NIHSS [median (IQR)]	2 (IQR 0.75–3.25)
mRS at discharge [median (IQR)]	1 (IQR 1–3)
mRS 0 [n (%)]	4 (21.1%)
mRS 1 [n (%)]	8 (42.1%)
mRS 2 [n (%)]	1 (5.3%)
mRS 3 [n (%)]	2 (10.5%)
mRS 4 [n (%)]	2 (10.5%)
mRS 5 [n (%)]	1 (5.3%)
mRS 6 [n (%)]	1 (5.3%)

AF — atrial fibrillation; DTN — door-to-needle time; ICU — intensive care unit; IVT —intravenous thrombolysis; mRS — modified Rankin scale; NIHSS — National Institutes of Health Stroke Scale; TIA — transient ischaemic attack; TTA — time to admission

One patient (5.3%), with PHr2 haemorrhage, died during hospitalisation. In the remaining 18 patients, the NIHSS score at discharge ranged from 0 to 27 (median = 2 points, IQR 0.75–3.25), and median mRS score at discharge was 1 point (IQR 1–3). A good functional outcome (mRS 0–2) was achieved in 13 (68.4%) patients, but it is worth noting that among the remainder mRS was already 3 points before stroke onset in three patients. One patient (5.3%), with PH2 haemorrhage, needed temporary transfer to the ICU. In 12 (63.2%) patients, dabigatran was continued in the secondary prophylaxis of stroke. Four patients (21.1%) were given a different NOAC instead, and two (10.5%) were discharged with deferred anticoagulation due to persistence of intracranial haemorrhage.

Results are summarised in Table 2.

Discussion

NOACs (including dabigatran) are the first-choice treatment option for preventing ischaemic stroke in patients with non-valvular AF [10]. However, despite being treated, each year 1–2% of patients with AF receiving NOAC will develop AIS [11]. According to different studies, 20–36% of AIS in patients with AF occur despite anticoagulation therapy with

NOAC or vitamin K antagonists. This may result from other comorbidities (aetiology of stroke other than cardioembolic), non-compliance, inappropriate dosage or, in the most challenging situation, even despite sufficient anticoagulation and with no other cause [4].

As the number of patients with AF receiving NOACs is increasing, the number of AIS patients with preceding NOAC treatment is also growing [12]. Current European Stroke Organisation (ESO) guidelines recommend that IVT should not be used in patients who have received NOAC within the last 48 hours (or more, if their renal function is impaired) [5]. With early reperfusion therapy being the key factor for improving prognosis of patients with AIS [2], a need for antidotes reversing NOAC effect to enable IVT treatment has emerged.

Idarucizumab is a fragment of a humanised monoclonal antibody that binds with dabigatran and then quickly (within minutes) reverses its anticoagulation effect [13]. A dose of 2×2.5 g (5 g in total) administered intravenously was approved for dabigatran reversal in 2015 [14]. Currently, the use of idarucizumab for enabling IVT in dabigatran-treated patients with AIS is allowed based on expert consensuses included, among others, in ESO guidelines [5] and Polish Neurological Society guidelines [15].

So far, many case reports [16–44] and some case series including 2–80 dabigatran-treated AIS patients who have received idarucizumab for enabling IVT [45–56] have been published, with their results pointing towards the safety and effectiveness of such a procedure.

There have been descriptions of idarucizumab application before IVT treatment of stroke due to rare aetiologies, such as antiphospholipid antibody syndrome in the course of systemic lupus erythematosus [57]. A case series from Australia showed successful implementation of idarucizumab treatment before IVT in a prehospital setting in a mobile stroke unit [58]. A case series from Australia and New Zealand showed the safety of idarucizumab for allowing IVT not only with alteplase, but also tenecteplase [59]. Although bad outcomes have also been reported [60–62], current data shows that enabling IVT in dabigatran-treated AIS patients seems to be generally safe and efficient.

A systematic review by Frol et al. including 251 AIS patients who received idarucizumab to enable IVT showed the rates of haemorrhagic transformation, symptomatic intracranial haemorrhage, and mortality to be 7.6%, 3.6%, and 8.4% respectively, which was similar to previous studies concerning IVT-treated AIS patients without preceding anticoagulation [63]. Mortality rate was higher than haemorrhagic transformation of stroke. Other causes of death included malignant media infarct and pulmonary embolism [46].

A multicentre study with systematic review and meta-analysis by Romoli et al. showed that 39 IVT-treated patients after dabigatran reversal with idarucizumab had an insignificantly higher risk of symptomatic intracerebral haemorrhage and death, but their functional outcome was comparable to IVT-treated AIS patients without preceding use of anticoagulants. The rates of haemorrhagic transformation, sICH and mortality in the idarucizumab-treated group were 23.1%, 10.3% and 17.9% respectively. Good functional outcome (mRS 0–2) was reached in 64.1% of patients [64].

Another study comparing idarucizumab-treated AIS patients who subsequently received IVT to patients treated with IVT with no prior anticoagulation showed better improvement (measured using NIHSS) and better functional outcome (measured using mRS) in the idarucizumab-treated group, with a similar frequency of complications [65]. The incidence of thromboembolic events after idarucizumab uptake also seems to be low — a recent systematic review with meta-analysis including 3,602 patients found it to be 2% [66].

The findings of our study accord with the results of previous research on this topic. The incidence of haemorrhagic transformation was 15.8% with symptomatic intracranial haemorrhage in two (10.5%) patients. The mortality rate was 5.3% and, in our study group, associated only with secondary haemorrhagic transformation of stroke. A good functional outcome was achieved in the majority of patients (68.4%), but, as mentioned before, within the remainder mRS was already ≥ 3 points before stroke onset in three (15.8%) patients.

Our study has some limitations, the most important being its retrospective character and the lack of a control group. We did not gather data on patients with AIS on dabigatran who were not treated with idarucizumab and IVT.

Clinical implications/future directions

The results of our study align with previous research on the safety and effectiveness of idarucizumab in enabling IVT in patients with AIS receiving dabigatran. They also provide reassurance that IVT after idarucizumab is a reasonable option for patients with AIS receiving dabigatran who are not eligible to MT.

More multicentre, prospective, cohort studies are required. Future research should also focus on the reasons why patients treated with NOAC go on to develop AIS, with the aim of more successful prevention of thromboembolic events in this group.

Article information

Data availability statement: *Our data can be shared with other scientists, if needed.*

Ethics statement: *Jagiellonian University Bioethics Committee approval numbers for the study are KBET/54/B/2007 and 1072.6120.118.2020.*

Authors' contributions: *E.W., K.S. — data aquisition, statistical analysis, draft writing and revision; P.W. — data acquisition; A.S. — conceptualisation, data aquisition, draft revision, supervision.*

Funding: *This study was supported by the iBioStroke grant (Identification and clinical validation of biomarkers*

for long-term outcome after cerebral ischaemia, ERA-NET-NEURON/21/2020, K/NCB/00057).

Acknowledgements: *The authors would like to thank the staff of the Stroke Unit of the University Hospital in Kraków for contributing to this article: Szymon Andrasik, Mateusz Czyżycki, Justyna Derbisz, Mateusz Dwojak, Agnieszka Fryźlewicz, Elżbieta Gradek-Kwinta, Jeremiasz Jagiełła, Mariana Kalyniak, Dominik Karch, Alicja Kępińska-Wnuk, Tomasz Kęsek, Bartosz Kołodziejczyk, Jadwiga Kosowska, Wojciech Koźmiński, Jeremiasz Kubisiowski, Monika Marona, Iwona Mazurkiewicz, Maciej Motyl, Małgorzata Napierała, Klaudia Nowak, Michał Paykart, Roman Pułyk, Agnieszka Rzemińska, Kamil Wężyk, Magdalena Witkowska, Małgorzata Włodarczyk, and Katarzyna Wójcik.*

Conflicts of interest: *None.*

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RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 6, pages: 477–483
DOI: 10.5603/pjnns.97039

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

Default mode function in patients with generalised epilepsy syndromes: from generalised to focal findings

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ABSTRACT

Introduction. Many recent studies have suggested that generalised epilepsy is associated with cortical epileptogenic focus, and therefore distinguishing between focal and generalised often becomes difficult.

Aim of study. We aimed to detect differences between default mode function in patients with idiopathic generalised epilepsy who have discharges on EEG, and healthy persons.

Material and methods. This was a case-control study; we performed EEG analysis with LORETA in 17 patients with a type of generalised epilepsy and a control group represented by 17 healthy age-matched persons. We performed statistical non-parametric tests for current density electrical distribution for our two groups ('t-statistic on Log transformed data') and we defined regions of interest (ROIs) from the default mode network. In the second part, we compared the average activation for each ROI for each timeframe in the epoch for the group with epilepsy, and for controls (we performed a Wilcoxon rank-sum test for two means).

Results. In the first part, we obtained that in the medial frontal gyrus (BA 9) delta oscillations significantly differed in patients with epilepsy who had electrical discharges on EEG in resting state conditions compared to healthy controls (medial frontal gyrus in this group had a greater number of synchronously oscillating neurons than did the controls). In the second part, we ran statistics on our localised activity from the default mode network (defined ROIs) and we obtained statistically significant differences in the left medial frontal gyrus (the values were higher for the group with epilepsy, p-value = 0.0066).

Conclusions and clinical implications. It may be possible to move from a 'generalised theory' about epilepsy to a 'focused theory' by understanding how various areas of interest are activated within default mode networks. Insights into the pathophysiology of generalised epilepsy may lead to new treatment options.

Keywords: idiopathic generalised epilepsy, resting state electroencephalography (EEG), low-resolution brain electromagnetic source tomography (LORETA)

(*Neurol Neurochir Pol 2023; 57 (6): 477–483*)

Introduction

The idiopathic generalised epilepsy group includes childhood absence epilepsy (CAE), juvenile myoclonic epilepsy (JME), juvenile absence epilepsy (JAE), and epilepsy with generalised tonic-clonic seizures alone (EGTCS) [1].

Regardless of the idiopathic generalised epilepsy subtype, evidence has been provided that functional connectivity is reduced. In all subtypes, the default mode network is most affected [2].

Functional resting-state MRI has demonstrated that default mode network activity in EGTCS patients differs from

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Received: 20.08.2023 Accepted: 21.09.2023 Early publication date: 13.11.2023

normal controls at rest. Results suggest that EGTCS patients have reduced functional integrations of the default mode network, which might provide insight into the neural correlations of impaired consciousness in these patients [3].

In other studies, a decrease in functional connectivity has been found in the self-referential, somatosensory, visual, and auditory networks, as well as increases and decreases in functional connectivity in the default-mode and dorsal attention networks in EGTCS patients compared to healthy subjects [4].

Other studies that have used dynamic methods in functional connectivity have detected specific disruptions in patients with generalised tonic-clonic seizures, with many functional abnormalities in the default mode network. The authors concluded that dynamic functional network connectivity could distinguish patients with generalised tonic-clonic seizures (idiopathic generalised epilepsy) from controls (defined in the study as age-, gender-, and handedness-matched healthy controls) with an accuracy of 77.91% ($p < 0.001$). Functional connectivity between resting state networks may aid in understanding the pathological aspects of idiopathic generalised epilepsy [5].

Electrical source localisation uses temporal and spatial information derived from an EEG to find the source of potentials recorded on the scalp. These techniques, including LORETA (low resolution electromagnetic tomography), have been validated for ictal and interictal studies [6].

Studies that have used routine EEG examination and imaging methods have concluded that epilepsy is a network disease, with cortical and subcortical disturbance; identifying epileptic networks may provide new insights into a better characterisation of epileptic syndromes and individualised treatment [7, 8].

The idea that the pathological basis of idiopathic generalised epilepsy involves the entire cortex has evolved over time, and many ictal and interictal studies have found abnormalities in frontal lobes in these patients. These studies concluded that there are frontal areas that play an important role in generating generalised seizures [9].

Studies during interictal EEG epochs in focal epilepsies have revealed alterations in global brain functional connectivity and in specific resting-state networks. This can provide a chronic effect on pathological mechanisms involving these structures, and could increase the sensitivity of scalp EEG in detecting abnormalities in the absence of interictal discharges [10].

Compared to other functional imaging methods, investigating functional connectivity via EEG has many advantages i.e. a higher temporal resolution, lower cost, ease of obtaining EEG data in epileptic patients, and being part of a routine investigation [11].

Exact low resolution brain electromagnetic tomography (eLORETA) can be used to compute the cortical distribution of current density [12].

In LORETA, there are measures applied to pairs of EEG signals between time series that correspond to different spatial locations. In other words, at each voxel in the cortical grey matter, a vector time with three components is computed, and this corresponds to a density vector with dipoles moments along the X, Y, and Z axes. This method is linear; it has zero localisation error and low spatial resolution [13].

There is comprehensive literature data available based on different algorithms that solve the electromagnetic inverse problem for LORETA. This is a noninvasive method that can determine the distribution of active neurons in time, and it can help to study the dynamics of neural networks in the brain [14].

Material and methods

Subjects

We selected 17 consecutive right-handed patients diagnosed with a type of generalised epilepsy syndrome (JME, JAE, EGTCS) who had undergone an EEG in our unit within the last three years, and 17 age-matched healthy subjects.

The characteristics of the patient group are set out in Table 1. The control group was composed of healthy age-matched subjects. There were no statistical differences in the mean ages or gender balance of the two groups, obtaining a p-value of 0.55 in the Chi square test.

This study was in accordance with the tenets of the Helsinki Declaration and received institutional and ethical consent.

EEG scalp recording

The EEG was performed in an isolated room using 19 scalp electrodes (Cadwell, Kennewick, WA, USA), placed according to 10–20 international montages, with a sampling rate frequency of 256 Hz. The impedances were kept below 5kΩ.

We included only patients who had typical interictal/ictal discharges on EEG, i.e. generalised spike-wave discharges (GSW), multispike-wave/multispike discharges, ictal 3Hz GSW discharges, or generalised spikes/sharp waves. The EEG selection criteria were the following: a) presence of posterior alpha rhythm; b) absence of drowsiness/sleep; c) absence of winking or other artifacts; and d) absence of epileptic discharges, with a mean distance of at least five seconds from them. A certified EEG neurologist selected the EEG data during wakefulness between discharges according to selection criteria.

Processing signals

The selected EEG data was imported in MATLAB R2022b (MathWorks, Natick, MA, USA) toolbox EEGLAB v2020, and the following steps were followed: high- and low-pass filtered at 0.5 and 40 Hz; other types of artifacts removed; re-referenced to average reference. From the EEG data, 60 epochs (each 2 s, a total of 120 s) were selected for each patient. These pre-processing steps were carefully followed by decomposition of the signals with independent component analysis (ICA) and the removal of data that did not contain brain activity. The ICA components with artifacts were manually removed. The obtained data was exported in LORETA (Low Resolution

Table 1. Characteristics of patients

Patient	Age (years)	Epilepsy type	EEG duration (min)	Discharges type (IED/ID)	Medication
1	21	EGTCS	90.5	GSW	Lamotrigin 100 mg/day
2	22	EGTCS	24	GSW	Lamotrigin 400 mg/day
3	22	EGTCS	158	GSW/Sharp waves	Levetiracetam 1,500 mg/day
4	21	JME	636	Multispike-wave discharges	Levetiracetam 1,000 mg/day
5	45	JAE	152	3–3.5 Hz ictal GSW discharges	Sodium valproate 1,500 mg/day
6	18	EGTCS	59	GSW	Levetiracetam 1,000 mg/day
7	24	JME	598	Multispike-wave discharges	Levetiracetam 1,000 mg/day
8	28	EGTCS	40	GSW	Sodium valproate 900 mg/day
9	34	JME	35	GSW/multispike-wave discharges	Levetiracetam 2,000 mg/day Lamotrigin 100 mg/day
10	23	JME	180	Multispikes/multispike-wave discharges	Levetiracetam 1,000 mg/day
11	23	EGTCS	150	GSW	Topiramate 150 mg/day Levetiracetam 500 mg/day
12	26	JAE	66	3 Hz ictal GSW discharges	No medication
13	24	EGTCS	160	Generalised spikes/sharp waves	No medication
14	21	EGTCS	149	Pseudofocal frontal discharges	Levetiracetam 1,000 mg/day
15	42	EGTCS	180	Bilateral frontal spike wave discharges	No medication
16	47	EGTCS	26	GSW	Sodium valproate 1,000 mg/day
17	19	EGTCS	30	GSW	Levetiracetam 1,000 mg/day

EGTCS — epilepsy with generalised tonic-clonic seizures only; IED — interictal discharges; ID — ictal discharge; GSW — generalised spike-wave; JAE — juvenile absence epilepsy; JME — juvenile myoclonic epilepsy

Electromagnetic Tomography). This is one of the many methods of electrical source localisation that computes the 3D cortical distribution of current density.

LORETA

eLORETA (exact low resolution brain electromagnetic tomography) represents an improvement over previously developed LORETA tomographies and the standard version of LORETA (sLORETA) [14, 17]. eLORETA is a real inverse solution (not simply a linear imaging method) with zero error localisation in the presence of measurement and structured biological noise [15].

In eLORETA, we compared the cortical distribution of electric activity from the two groups to see the default mode function in patients with epilepsy who had discharges on EEG and control subjects. Practically, the oscillatory activity in eight EEG frequency bands was analysed: delta (0.5–4 Hz), theta (4–8 Hz), alpha 1 (8–10 Hz), alpha 2 (10–12 Hz), beta 1 (12–16 Hz), beta 2 (16–20 Hz), beta 3 (20–24 Hz) and gamma (32–80 Hz) [16].

The head model used in LORETA is the MNI152 template, with a three-dimensional solution space restricted to cortical grey matter. A total of 6,239 voxels at 5 mm spatial resolution represents the intracerebral volume [12, 17].

We defined five ROIs (regions of interest) to estimate the electrical activity from defined regions from the default mode network. The regions selected from the default mode network using MNI (Montreal Neurological Institute) space are described in Table 2. These regions of interest were selected for both hemispheres, and every ROI contained Talairach coordinates for these regions from the default mode network (the selection can be adjusted if a small number of voxels are defined).

We created ROIs in eLORETA from the following five brain regions belonging to the default mode network: posterior cingulate cortex from BA31 (PCC), medial prefrontal cortex from BA9 (MPFC), parahippocampal gyrus from BA36 (HF), inferior parietal cortex from BA40 (IPC), and middle temporal gyrus from BA39 (MTL). All voxels belonging to the same ROI were averaged in the transformation matrix.

Table 2. Regions of interest selected for default mode network

Lobe	Structure	Brodmann area	X-MNI	Y-MNI	Z-MNI
Limbic lobe	Parahippocampal gyrus	36	25	–35	–20
Limbic lobe	Parahippocampal gyrus	36	25	–30	–20
Temporal lobe	Middle temporal gyrus	39	–60	–60	10
Temporal lobe	Middle temporal gyrus	39	–55	–75	10
Limbic lobe	Posterior cingulate	31	–20	–65	15
Limbic lobe	Posterior cingulate	31	–10	–70	15
Parietal lobe	Inferior parietal lobule	40	–65	–40	25
Parietal lobe	Inferior parietal lobule	40	–65	–35	25
Frontal lobe	Medial frontal gyrus	9	–10	35	35
Frontal lobe	Medial frontal gyrus	9	–10	45	35

Table 3. Log of F ratio of spectral densities; LnF: Log of F ratio of spectral densities with 'Cohen's d' effect size: low = 0.2; med = 0.5; hi = 0.8

	LnF (0.01)	LnF (0.05)	LnF (0.10)	Extreme P
One-tailed (A > B):	0.786	**0.726**	0.696	0.01040
One-tailed (A < B):	–0.793	–0.731	–0.691	0.65700
Two-tailed (A < > B):	0.810	0.760	0.729	0.02360

The average activation for each region of interest for each timeframe in the epoch was computed. We obtained a matrix with five columns and 256 rows for each group.

We performed a statistical test known as a 't-statistic on Log transformed data' test in LORETA for independent groups A = B for all timeframes (frequencies). We conducted a voxel-by-voxel analysis of the current density distribution between the two groups with the help of statistical nonparametric mapping. We applied a log of F-ratio statistics for independent groups, a variance smoothing parameter of 0, and 5,000 randomisations for multi-comparison correction.

In these tests, threshold values were calculated ('log F-ratio') and a file was generated with extremes of probability (ExtremePs), the corresponding maximal thresholds, and thresholds at values of $p < 0.01$, $p < 0.05$ and $p < 0.10$ with $p < 0.05$ for statistical significance.

These statistical analyses are included in the sLORETA/eLORETA software package. The methodology, which is non-parametric, is based on estimating, via randomisation, the empirical probability distribution for the max-statistic (e.g. the maximum of a *t* or an *F* statistic), under the null hypothesis. There are also corrections for multiple testing [18].

Results

We obtained differences in our groups applying voxel-by-voxel F-ratio tests (Log of ratio of averages current densities in each frequency band). We obtained a value of 0.726 for LnF (0.05) corresponding to a p-value of 0.01040 (statistical significance for $p < 0.05$) one-tailed threshold, and a value of 0.760 for LnF (0.05) corresponding to a p-value of 0.02360 ($p < 0.05$) two-tailed threshold result (Tab. 3).

In LORETA, this value corresponded to the medial frontal gyrus (BA 9), meaning that generators of delta oscillations (low frequency band) are significantly different in epileptic patients who have electrical discharges in resting state conditions compared to healthy controls. This means that neurons from the medial frontal gyrus in epileptic patients oscillate more strongly than controls (Fig. 1).

In the second part, we obtained in LORETA a matrix for each group, with a column corresponding to each ROI defined and a line for each timeframe. The Wilcoxon rank-sum test for equality of medians (this test is a non-parametric version of the t-test for independent samples) was applied for all five features of interest (5 ROIs = 5 columns).

The null hypothesis (H0) was that the group with epilepsy (Epi) and the control group (C) had equal means, and the alternative hypothesis (H1) was that Epi features had different medians (two-tailed test), H1 Right was that Epi features had higher medians (one-tailed test), while H1 Left was that Epi had lower medians (one-tailed test). We obtained statistically significant values ($p = 0.0066$) for ROI 5, the one that corresponded to the left medial frontal gyrus (Fig. 2).

Discussion

We statistically compared the default mode function between patients with generalised epilepsy and healthy age-matched persons. We found differences in the middle frontal gyrus in the delta band for epileptic patients compared to controls, meaning that epileptic patients had a larger number of synchronous neurons in this region for delta oscillations than controls (with statistics for each frequency, for each voxel). For regions of interest defined from the default mode

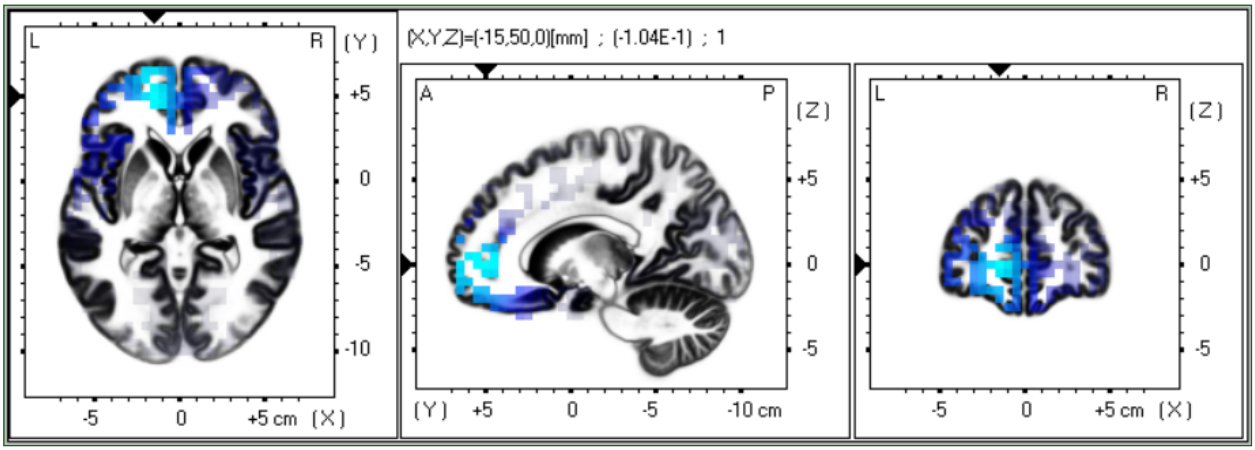

Figure 1. Log of F ratio statistics, for each frequency and each voxel. Electric neuronal activity corresponds to a colour scale

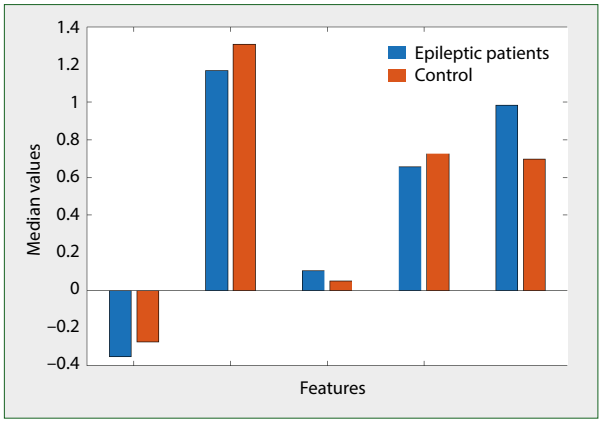

Figure 2. Results from Wilcoxon rank-sum test for two means after comparison of every matrix obtained (for epileptic group and control group) that contained values at specified ROIs; a significant difference (p = 0.0066) between ROI 5 corresponded to left medial frontal gyrus

network, we found statistically significant values for the left medial frontal gyrus.

As a result of these findings, we may be able to hypothesise a common mechanism underlying generalised epilepsy syndromes, but we can also speculate about the particularities of each type.

It has been demonstrated that regions from the default mode network (medial prefrontal cortex) are involved in focal activation of generalised spike-wave discharges in juvenile absence epilepsy. Using magnetoencephalography (MEG), these studies have pointed out that absences do not involve generalised cortical networks, but instead involve selected regions such as the orbital frontal and medial frontal regions [19].

Some data suggests that ictal discharges propagate through selective cortical networks, including orbital frontal and mesial frontal regions, rather than being truly 'generalised' in primary generalised epilepsy with absences. It has been clear since the early neurophysiological studies of fronto-thalamic enhancing responses that orbital and frontopolar control the thalamic regulatory mechanisms [20, 21].

Other MEG studies that use graph theory and coherence have compared focal and generalised epilepsies in a resting state. They have demonstrated increased network connectivity in bilateral mesial-frontal and motor regions in patients with idiopathic generalised epilepsy [22, 23].

Another fMRI-EEG study on 12 patients with genetic generalised epilepsy that used dynamic causal modelling found that DMN can be considered a gateway to generalised spike-wave discharges. The authors analysed the interactions between DMN, dorsal attention network, salience network and thalamus to see what role they played in down-regulation of consciousness. It was concluded that DMN had a driving role in this mechanism, although there were many differences between patients and there was heterogeneity in the results [24].

Other EEG-fMRI studies in IGE have revealed BOLD changes in posterior cingulate, lateral parietal and frontal cortices a few seconds before the onset of generalised spike-wave discharges. This suggests an essential role of DMN in GSWDs mechanism [25].

Network studies such as integrated value of influence have found an important role played by nodes such as the insular gyrus and left inferior parietal gyrus at 3-4 Hz during spike-wave activity in patients with generalised tonic-clonic seizure alone, suggesting that some nodes of a particular network may play a crucial role in generating GSWDs [26].

Some EEG-fMRI studies have attempted to find specific brain regions activated prior to generalised discharges; they found inconsistently activated regions prior to generalised spike-waves such as the precuneus, prefrontal and parietal cortical regions [27–29]. A high sensorimotor synchrony and a low posterior network synchrony before generalised spike-wave discharge has been shown; this is speculated to be a predisposing state for discharges [30].

According to some authors, network analysis might be a way to predict seizures. Clinical application of functional connectivity analysis could impact upon epilepsy diagnosis and treatment, but validated results are required [31]. Some researchers even believe that network analysis could be superior to conventional EEG in the diagnosis of epilepsy [32, 33].

Many recent studies have suggested that generalised epilepsy causes increased focal epileptogenic hubs that trigger generalised epileptic discharges. 'Cortical focus theory' describes an epileptogenic focus that entails generalised discharges through corticothalamic and corticocortical networks. These findings may have an impact on physiopathology and treatment options [23].

One of the brain regions particularly related to cognition and execution is the medial frontal gyrus, a part of the prefrontal cortex [34]. It has been found that patients with idiopathic generalised epilepsy have increased grey matter abnormalities in their medial fontal gyrus, and that the thalamo-frontal network has abnormalities in generalised epilepsy subtypes [35]. These particularities may be useful in patients resistant to antiepileptic drugs.

For the most part, generalised epilepsies respond well to treatment, but remission probability decreases as more antiepileptic drugs are used [36]. Increasing understanding of pathophysiology and connectivity may lead to new approaches in such cases.

Neuromodulation is an alternative treatment for patients with drug-resistant genetic generalised epilepsy after the failure of multiple anti-seizure medications. Various factors influence the outcome of neurostimulators (mainly DBS) including electrode placement, stimulation parameters, the subtype of epilepsy, and the individual cortical-subcortical connectivity profile [36, 37].

Numerous advanced noninvasive studies have supported this view by highlighting the importance of early cortical involvement, particularly in the frontal and the parietal cortex [23].

Limitations

Several limitations should be considered with regard to the current study. Firstly, we included a small number of patients limited to specific non-parametrical statistical tests. Secondly, it is difficult to divide patients into groups with specific generalised epileptic syndrome. Thirdly, larger studies may compare these parameters found in default mode network with other networks such as the dorsal attention network, and salience network. To confirm the present findings, future studies should include more patients and healthy subjects.

Our study was also limited by the small number of electrodes used for electrical source imaging, especially in the temporal region. The influence of gender on the default mode network was not described, and this represents another limitation of the study.

Conclusions

Our study supports the idea of a move away from a generalised theory to a more focused one in generalised epilepsies. We found that the left medial frontal gyrus synchronises more easily, and we hypothesise that this could be more than a co-activation during generalised epileptic activity.

Searching for subtle interictal epileptiform discharges that are not recognised by visual inspection on EEG might be an interesting research area in defining focal abnormalities in generalised epileptic syndromes. New insights into physiopathology will continue to improve treatment options regarding generalised epilepsy.

Article information

Data availability statement: *Datasets analysed in this study are available from the corresponding author upon reasonable request.*
Ethics statement: *Due to the retrospective nature of this study, institutional consent was obtained prior to the study.*
Authors' contributions: *CEB and DIC designed study; CEB collected and analysed data; IS compiled statistics; CEB wrote manuscript. All authors approved final manuscript.*
Funding: *None.*
Conflicts of interest: *None.*

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RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 6, pages: 484–491
DOI: 10.5603/pjnns.97534

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

Sense of happiness in Polish patients with multiple sclerosis

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ABSTRACT

Introduction. Happiness is crucial to patient well-being and their acceptance of their disease. The aim of this study was to assess the sense of happiness in persons with multiple sclerosis (PwMS), compare it to the level of happiness in patients with other neurological conditions, and determine which factors affect the sense of happiness in PwMS.

Material and methods. Five hundred and eighty-nine PwMS and 145 control subjects (post-stroke patients with chronic pain syndromes and neuropathies) were included in the study. Due to the differences between the groups in terms of demographic variables, an adjusted group of PwMS (n = 145) was selected from the entire group of PwMS. All patients were assessed using the Oxford Happiness Questionnaire (OHQ), the Satisfaction with Life Scale (SLS), and the Family APGAR Questionnaire. Based on regression analysis, the study examined which variables affected the level of happiness in the groups.

Results. Analysis of the OHQ scores showed that PwMS had a lower sense of happiness compared to the control group in the overall score [113.21 (25–42) *vs.* 119.88 (25–49), respectively; p = 0.031] and the subscales (OHQ subscale 1 — 54.52 *vs.* 57.84, respectively; p = 0.027; subscale 2 — 35.61 *vs.* 37.67; respectively; p = 0.044). Based on linear regression analysis, life satisfaction (β = 0.40; p < 0.001), positive orientation (β = 0.32; p < 0.001), and primary education (β = 0.08; p = 0.009) were the most significant predictors of a higher level of happiness in PwMS. Similar results were found in the control group.

Conclusions. The sense of happiness in PwMS was lower than in patients with other conditions. The most important factors influencing happiness included life satisfaction and positive orientation. Influencing these predictors should be the aim of psychological interventions, especially in patients with a reduced sense of happiness.

Keywords: multiple sclerosis, happiness, well-being, positive psychology, psychosocial interventions

(*Neurol Neurochir Pol 2023; 57 (6): 484–491*)

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Received: 21.09.2023 Accepted: 31.10.2023 Early publication date: 27.11.2023

Introduction

Multiple sclerosis (MS) significantly affects all aspects of a patient's life and is the cause of many years of struggle with disability [1]. Given usual disease onset at a young age, and therefore little life experience, it can be assumed that persons with MS (PwMS) may be less happy compared to healthy individuals or to patients with other conditions. On the other hand, patients with sudden onset stroke or chronic pain may also have a reduced sense of happiness. PwMS struggle with psychosocial consequences, the necessity to reevaluate their life goals, work, personal life, leisure activities, and daily living. In MS, psychological consequences are significantly more frequent and severe compared to healthy individuals and those affected by other chronic diseases. Various psychological consequences, especially depression, anxiety, decreased well-being, quality of life and problems associated with social roles and relationships, have been analysed in many studies [2–8]. However, the sense of happiness in PwMS has been assessed much less frequently [9, 10]. In chronic diseases such as MS, positive mood and the sense of happiness can significantly influence attitudes toward care and treatment. Therefore, learning how it is formed in PwMS may have practical significance, particularly for developing psychological interventions.

There are various definitions of happiness in the literature. Tatarkiewicz defines happiness as "permanent, complete and justified satisfaction with life as a whole" [11], while for Kraut it is "the belief that one is getting the important things one wants, as well as certain pleasant effects that normally go along with this belief" [12]. According to Diener, happiness is "a preponderance of positive affect over negative affect with a distinct focus on the affective evaluation of one's life situation" [13]. Happiness is also conceptualised as a "positive inner experience, the highest good, and the ultimate motivator for all human behaviours" [14, 15], and as "the degree to which an individual judges the overall quality of his or her life as a whole favourably" [16]. Happiness includes emotional and cognitive elements and consists of three main elements: positive affect or joy; a high level of satisfaction; and the absence of negative feelings (depression and anxiety) [18].

Studies on happiness have approached the question from different perspectives. Personality models consider happiness to be a fixed trait, largely dependent on personality traits [19], which determines how a person responds to events rather than situations they encounter or seek out. From this perspective, there is a tendency to experience things positively, and a person enjoys pleasure because of being happy [13]. Based on life-event models, it is assumed that the level of happiness can change over time, and therefore both positive and negative events result in changes in happiness [20]. From this perspective, happiness is the sum of many small pleasures [13].

Many theories have tried to determine the causes of happiness. It can be achieved when some state, goal, or need is fulfilled [13], or through social interactions, leisure, or other activities. Happiness is also brought about by comparing some standard with the actual situation (the happier a person is, the closer the standard is to the actual status).

There are three basic views on happiness [21]. The first approach (hedonism) posits happiness as an individual balance between pleasure and dissatisfaction (wherein experiencing more pleasure means being happy). The second, known as the life-satisfaction view, identifies happiness as an attitude regarding one's own life (wherein a favourable attitude towards life means being happy). Thirdly, in the context of affective state theory, happiness is identified with an overall positive emotional state.

Research into happiness has mainly focused on identifying the mechanisms that lead to the sense of happiness and determining which personality traits they may be associated with [22]. Psychological mechanisms are important in experiencing happiness. These mechanisms include attitudes, perspectives, beliefs, self-esteem, optimism and future time perspectives [23]. When personality has been analysed, it has been determined that traits such as extraversion, being agreeable, and openness to new experiences are particularly associated with happiness [22].

The aim of our study was to assess the sense of happiness in PwMS and compare it to the levels of happiness in patients with other neurological conditions, as well as to identify factors affecting happiness in MS patients.

Material and methods

Study population and design

Five hundred and eighty-nine PwMS from nine Polish centres providing the diagnosis and treatment of MS (Białystok, Końskie, Międzylesie, Rzeszów, Sandomierz, Szczecin, Zabrze and two in Warsaw) were enrolled in this cross-sectional study. The clinical characteristics of the entire group of PwMS are set out in Table 1.

The inclusion criteria were: age 17–70 and clinically confirmed MS according to the 2010 or 2017 McDonald criteria [24]. The exclusion criteria were: an advanced medical condition preventing study participation such as cognitive or speech impairment, the coexistence of neoplastic diseases, and the ingestion of psychotropic drugs, including antidepressants, mood stabilisers, anxiolytics, or antipsychotics. The presence of comorbidities was verified based on the medical records. Patients with a history of psychiatric illness, or severe cardiovascular, pulmonary, haematological, or endocrine disorders were excluded from the study.

The control group comprised 145 patients (aged 18 to 70) with diseases other than MS. They were being treated in the centres participating in the study. The study subjects had a history of stroke, chronic root pain syndromes and

Table 1. Clinical characteristics of PwMS group

Variable	Patients with MS (n = 589)
Male, n (%)	157 (26.7)
Female, n (%)	432 (73.3)
Age, years, mean ± SD	
Age at survey completion	43.9 (12.83)
Age at disease onset	29.8 (8.6)
Disease duration (years, mean ± SD)	8.62 (6.69)
EDSS score	3.2 (2.1)
Disease course subtypes, n (%)	
Relapsing remitting	437 (74.2)
Secondary progressive	127 (21.6)
Primary progressive	25 (4.2)
Treatment, n (%)[a]	
Interferon beta	202 (34.3)
Glatiramer acetate	43 (7.3)
Dimethyl fumarate	226 (38.4)
Teriflunomide	52 (8.8)
Natalizumab	26 (4.4)
Fingolimod	22 (3.7)
Other (ocrelizumab, alemtuzumab, mitoxantrone)	18 (3.1)

[a]Treatment data at 31 December 2020; PwMS — persons with MS; SD — standard deviation

neuropathies. Patients with dementia, comorbid depression, anxiety or a speech disorder that impaired communication were excluded from the study.

The sociodemographic and clinical data of the study subjects was collected at the beginning of the questionnaire. Demographic covariates included age, gender, education, marital status, place of residence, and financial status. All participants provided written informed consent prior to the study.

Measurements

All participants completed the following questionnaires:

1. The **Oxford Happiness Questionnaire (OHQ)** is widely used for assessing personal happiness. The OHQ was developed in 2002 by scientific research psychologists [25]. It measures the complex construct of happiness, which is composed of satisfaction with one's own life and self-assurance and personal resources conditioning it. The questionnaire has 29 self-report statements for responses on a 6-point Likert scale (the highest possible average is 6, while the lowest possible is 1). The Polish version of the OHQ consists of two subscales: general satisfaction with life, and control of life [26]. The measure has high parameters of reliability, as well as construct and criterion validity. A slightly shortened, 26-item, version of the tool is recommended for use.
2. The **Satisfaction with Life Scale (SLS)** was developed and validated by Diener et al. [27]. It is a short (5-item) instrument designed to measure global cognitive judgements of satisfaction with one's life. The scale usually requires only about one minute of a respondent's time, where respondents provide answers on a Likert scale. The questions are open to interpretation, making the scale suitable for adults with a range of backgrounds. It shows favourable psychometric properties, including high internal consistency, and is most appropriate for non-clinical populations.
3. The **Family APGAR Questionnaire** has frequently been used to assess family function [28]. Developed in 1978, it is another 5-item questionnaire (each item being rated on a 3-point scale) measuring the following five constructs: *Adaptability*, *Partnership*, *Growth*, *Affection* and *Resolve*. Because the questionnaire consists of only five questions, it is relatively quick to administer. This has made it the preferred choice for assessing family function and health problems in primary care and general practitioner settings.

Statistical analysis

PwMS and controls were compared in terms of demographic, clinical and outcome variables.

Data was analysed using the independent-samples approach. The two-tailed t-test was applied to examine the differences between quantitative parameters. Examination of differences between the categorical parameters was based on Pearson and Fisher's exact tests.

The test of univariate association of independent variables was performed.

All tests were two-tailed, and p-value ≤ 0.05 was considered statistically significant.

Due to the differences in terms of demographic variables (Tab. 2) between the entire group of PwMS (n = 589) and the control group (n = 145), the adjusted group of PwMS (n = 145) was matched to controls based on age, gender and education, using the Hungarian optimisation algorithm implemented in MATLAB (Mathworks. Natick, MA, USA) [29].

At the beginning of the data analysis, the reliability of the OHQ was examined by determining the Cronbach's alpha coefficient for the groups. According to the questionnaire adaptation study [30], two factors in the Polish population could be extracted from the questionnaire items (i.e. life satisfaction and the sense of power [subscale 1] and the sense of meaning and control [subscale 2]). Cronbach's alpha was also calculated for these subscales.

The normality of distribution was checked for the variables. The results showed slight deviations from normality. Therefore, the level of happiness and the OHQ subscales were compared using the Student's t-test for independent variables. Using regression analysis, we checked which variables in the entire patient group affected the level of happiness. The same analysis was repeated for the subgroups of controls and the adjusted group of PwMS.

Table 2. Demographic characteristics of patients

Variables / Group		Patients			Statistics	
		Entire group of PwMS (n = 589)	Adjusted group of PwMS (n = 145)	Controls (n = 145)	Entire group of PwMS *vs.* controls	Adjusted group of PwMS *vs.* controls
Age (years ± SD)		43.90 (12.83)	42.63 (12.68)	42.71 (11.93)	**Z = –6.41; p < 0.001**[a]	T(274.26) = 1.52; p = 0.250[b]
Gender, n	Female	432	97	96	$chi^2(1) = 1.10$; p = 0.295[c]	$Chi^2(1) = 3.10$; p = 0.212[c]
	Male	157	48	49		
Education, n	Primary	19	7	12	**chi^2 (3) = 13.91; p = 0.003**[c]	$Chi^2(1) = 5.81$; p = 0.121[c]
	Secondary	214	53	49		
	Higher	270	62	52		
	Vocational	86	23	32		

PwMS — persons with MS; SD — standard deviation; [a]Mann-Whitney U test; [b]Student test; [c]chi-square test; statistically significant differences in bold

Table 3. Results of intergroup comparison for level of happiness

	Adjusted group of PwMS (n = 145)	Controls (n = 145)	Parameters
OHQ subscale 1	54.54 (12)	57.84 (12.59)	T(274) = 2.23; **p = 0.027**
OHQ subscale 2	35.61 (8.77)	37.68 (8.19)	T(274) = 2.03; **p = 0.044**
OHQ overall score	113.21 (25.42)	119.88 (25.49)	T(274) = 2.17; **p = 0.031**

Statistically significant differences in bold

All statistical analyses were performed using SPSS Statistics 27.0 (IBM, Armonk, NY, USA).

Ethics approval

This study was approved by the Bioethics Committee of the Institute of Psychology at the University of Szczecin (KB 13/2021, 20 May, 2021) and was performed in accordance with the Declaration of Helsinki.

Results

The reliability analysis of the OHQ showed that for the entire group of PwMS and the controls, Cronbach's α was 0.96. For individual groups, α values were also high (adjusted group of PwMS, α = 0. 96; control group, α = 0.953). The values for the subscales were as follows: subscale 1 — α = 0.91, subscale 2 — α = 0.90 in the PwMS group and subscale 1 — α = 0.88, subscale 2 — α = 0.09 in controls.

Intergroup comparisons

The Student's t-test for independent samples showed that the groups differed in their levels of happiness in terms of the OHQ overall score and the subscales. The results are set out in Table 3.

Regression analysis

Stepwise regression analysis was performed for the entire group of PwMS (n = 589) in which the predictors included age, gender, education, Family APGAR score, positive orientation score, life satisfaction, marital status, mobility, and work status. Based on regression coefficients, life satisfaction (β = 0.40; p < 0.001), positive orientation (β = 0.32; p < 0.001), and primary education (β = 0.08; p = 0.009) were found to be significant predictors of the level of happiness (Tab. 4). Standardised β coefficients showed that the higher the level of life satisfaction and positive orientation a patient had, the higher the level of happiness. Primary education also contributed to a higher sense of happiness. The proposed model was a good fit to the data F (3.644) = 179.48 (p < 0.001) and explained 43% of the variance of the dependent variable (R^2 = 0.43).

Stepwise regression analysis was performed for the adjusted group of PwMS (n = 145) in which age, gender, education, Family APGAR score, positive orientation score, life satisfaction score, marital status, mobility and work status were also predictors. Based on the regression coefficients, life satisfaction (β = 0.37; p < 0.001), positive orientation (β = 0.27; p = 0.006), primary education (β = 0.16; p = 0.016), secondary education (β = 0.22; p = 0.002), and marital status (β = 0.18; p = 0.01) were found to be significant predictors of the level of happiness (Tab. 5). Primary and secondary education, and having a partner, also gave patients higher levels of happiness. The model was also a good fit to the data F (5.120) = 20.58 (p < 0.001) and explained 44% of the variance of the dependent variable (R^2 = 0.44).

When similar predictors were assessed, stepwise regression analysis was also performed for the control group (n = 145). Based on the regression coefficients, life satisfaction (β = 0.37; p < 0.001), positive orientation (β = 0.27; p = 0.006) and primary education (β = 0.16; p = 0.016) were found to be significant predictors of higher levels of happiness (Tab. 6). The model

Table 4. Stepwise linear regression results for level of happiness for entire group

Variables	B	β	p	95% CI
Life satisfaction	0.172	0.398	**< 0.001**	1.32–1.99
Positive orientation	0.209	0.325	**< 0.001**	1.24–2.06
Education (primary)	3.673	0.076	**0.009**	2.36–16.78
Constant	4.399		**< 0.001**	25.51–42.79

B — non-standardised coefficient Beta; β — standardised coefficient Beta; CI — confidence interval. Statistically significant differences in bold

Table 5. Stepwise linear regression results for level of happiness for adjusted group of PwMS

Variables	B	β	p	95% CI
Life satisfaction	1.656	0.373	**< 0.001**	0.81–2.51
Positive orientation	1.536	0.269	**0.006**	0.44–2.63
Education (primary)	21.766	0.166	**0.016**	4.14–39.39
Education (secondary)	11.718	0.22	**0.002**	4.53–18.9
Marital status	9.476	0.175	**0.011**	2.26–16.7
Constant	23.7		**< 0.001**	–0.07 to 47.47

B — non-standardised coefficient Beta; β — standardised coefficient Beta; CI — confidence interval. Statistically significant differences in bold

was also a good fit to the data F (3.118) = 42.64 ($p < 0.001$) and explained 51% of the variance of the dependent variable ($R^2 = 0.51$).

Discussion

Happiness is a positive concept that is crucial for maintaining health. To date, there have been only a few studies on happiness in PwMS. Information about the sense of happiness in any disease can be used in clinical practice to develop psychological support strategies to help patients become happier and think more positively about their health.

A significant percentage of PwMS develop depressive disorders that may also be related to the disease process itself [31]. The sense of happiness may decrease either as a psychological reaction to a severe disease, such as MS, or due to neuronal damage.

The level of happiness and well-being in PwMS used to be seen as unimportant in terms of PwMS quality of life. However, papers in the field of positive psychology in recent years have drawn attention to the significance of the problem and the relevance of these aspects of patient care [10, 32, 33]. Studies have found that strong predictors of happiness include social competence, self-esteem, satisfaction with relationships with close loved ones, and support providers. Additionally, research has shown that many of these relationships are significantly impaired in MS [34].

Barack and Achiron [10] found that happiness as a trait (assessed by the OHQ), life satisfaction (according to the SLS), and personal growth (based on the Personal Growth Initiative Scale) were all relatively well preserved. These studies highlighted a very important point, namely that MS did not necessarily negatively affect levels of happiness, positive thinking, or personal development. Previously, it was thought that healthy individuals considered MS to be a 'tragic change', while PwMS had a completely different view of their life with the disease [35].

Both happiness and personal development are not significantly different in patients and healthy individuals. The willingness and ability to experience positive emotions during the disease process have also been reported in other chronic diseases [36]. From a psychological perspective, chronic patients or those with disability describe themselves as people who, despite their illness, cope well under extraordinary circumstances and calmly accept biological impairment and material, social and institutional obstacles [37]. Despite various limitations, mobilisation of personal, relational and environmental resources allows patients to attain high levels of mental health [36, 38, 39]. In turn, life satisfaction in MS decreases due to the real impact of the disease burden.

Our study showed that some subgroups of PwMS had a reduced sense of happiness compared to patients with other diseases, particularly those with low satisfaction and negative attitudes toward life. We demonstrated that significant predictors of the levels of happiness included life satisfaction, positive orientation and primary education. Since the study group was not very large, results related to primary education should be approached with caution.

The sense of happiness in PwMS may also be influenced by cultural or religious differences. The relationship between love of life and happiness was assessed in an Iranian PwMS population [39]. This was a descriptive cross-sectional study and the instruments included the Love of Life Scale and the self-rating scale of happiness. That study showed that love of life significantly positively correlated with happiness ($p < 0.01$). Despite the cultural differences between Polish and Iranian

PwMS, we are of the same opinion as the authors of the above study that positive excitement, life satisfaction and a lack of negative emotions such as depression and anxiety, all have a positive impact on happiness [39].

The feeling of happiness was also assessed in Bulgarian PwMS with and without comorbidities [40]. Eighty PwMS were evaluated, of whom 40 patients presented with MS alone, and 40 with MS and comorbidities. Health-related quality of life was assessed using the Short Form-36 questionnaire and the Multiple Sclerosis Quality of Life Questionnaire with 54 items. Statistically significant negative correlations were found between depression and the feeling of happiness ($R = -0.591$; $p < 0.01$). Additionally, a statistically significant difference related to the feeling of happiness was reported between the patients with MS only and those with MS and comorbidities ($p < 0.001$) [40]. That study found that MS with comorbidities had an unfavourable influence on an individual patient's feeling of happiness, which is in line with our findings.

The methodology for conducting research on happiness varies. In our study, we preferred face-to-face patient-doctor contact. Eijkholt and Sparling assessed the feeling of happiness in PwMS using online social networks and explored the differential impact of online versus face-to-face interaction on happiness [41]. By definition, such a method could help to increase social participation in PwMS by circumventing potential physical, emotional and cognitive barriers. The study focused on the analysis of responses obtained from 440 patients and assessed the relationship between honesty, anonymity and happiness in PwMS who reported using online social networks. They reported that they could be more honest in face-to-face interactions compared to online contacts, irrespective of whether they were anonymous or identifiable. Happiness was associated with honesty and authenticity in personal interactions. Eijkholt and Sparling concluded that anonymity might not improve the happiness of PwMS [41].

Our results also suggest that positive psychological interventions should be incorporated in PwMS, especially in the subgroups of patients with a reduced sense of happiness. To date, several interventions increasing happiness have been indicated [43–45].

A limitation of our study on happiness in PwMS is related to the possible influence of depressive disorders on happiness. Although our patients declared that they had not been previously treated, and did not have a depressed mood, the data, according to which 42-54% of patients develop depression in the course of MS, could suggest a possible influence of depression on study findings [46]. A similarly confounding factor may be the presence of euphoria, the prevalence of which is estimated to range widely from zero to 63% in MS patients [46]. Concerns about the impact of the above confounding factors on the results have also been expressed by other authors who have analysed the sense of happiness in MS because patients with euphoria, hypomania and dissatisfied patients may have described themselves as being in a normal mood [10].

Clinical implications/future directions

Multiple sclerosis begins at a young age and is a severe, debilitating and life-long disease that rapidly leads to significant disability. Our study found that the sense of happiness in such patients was often lower than in patients with other conditions.

However, MS does not always need to have a negative impact on the level of happiness. The most significant predictors of happiness were life satisfaction and positive orientation. Influencing these predictors should be a target for psychological interventions, particularly in patients with a reduced sense of happiness.

Article information

Data availability statement: *The data that supports the findings of this study is available from the corresponding author, W.B., upon reasonable request.*

Ethics statement: *This study was conducted according to the guidelines of the Declaration of Helsinki. This project research was authorised by the Bioethics Committee of the Institute of Psychology at the University of Szczecin (KB 13/2021, 20 May, 2021). Informed consent was obtained from all subjects involved in the study.*

Authors' contributions: *Conceptualisation: A.P. (Andrzej Potemkowski), W.B.; methodology: A.P. (Andrzej Potemkowski), W.B.; acquisition of data: W.B., M.Ż., P.S., M.S., R.R.S., Z.K., K.K-T., A.C., J.T., B.Z-P., K.K-B., N.M., A.S., J.Z., H.B-P., B.L., A.P. (Adam Perenc), M.P., A.R., M.R.; formal analysis: A.P. (Andrzej Potemkowski), W.B.; project administration: W.B., M. W. (Maciej Wilski), M. W. (Marcin Wnuk); supervision: W.B., A.K., H.B-P., M.A-S.; writing — original draft preparation: A.P. (Andrzej Potemkowski), W.B.; writing — review & editing:* A.P. (Andrzej Potemkowski), *W.B., Z.K. All authors have read and agreed to the published version of the manuscript.*

Funding: *Project financed under the programme of the Ministry of Education and Science called 'Regional Initiative of Excellence' in the years 2019–2023, project no. 024/RID/2018/19, amount of financing PLN 11,999,000,00.*

Acknowledgements: *The authors wish to thank all patients, collaborators and institutions that helped make this study possible.*

Conflicts of interest: *W.B. — received advisory board and speaker honoraria from Biogen, Roche, Novartis, Merck* and *BMS; M.S. — declares no conflict of interest; M.W. (Maciej Wilski) — declares no conflict of interest; M.Ż. — declares no conflict of interest; P.S. — served as a lecturer for Boehringer-Ingelheim, Ever Pharma, and travel expenses to scientific conferences covered by Ipsen and Ever Pharma; M.W. (Marcin Wnuk) — declares no conflict of interest; R.R.S. — declares no conflict of interest; K.K-T. — received support for congress participation from Biogen, Genzyme, Roche; A.C. — received support for congress participation from Novartis, Biogen, Roche; J.T. — declares no conflict of interest; A.K. — received compensation for*

speaking and consulting services from Biogen, Bayer, Novartis, Roche, Merck, Teva, and Sanofi-Genzyme; B.Z-P. — received compensation for speaking and consulting services from Biogen, Novartis, Roche, and Merck; K.K-B. — declares no conflict of interest; N.M. — declares no conflict of interest; M.A.-S. — received compensation for speaking and consulting services from Biogen, Bayer, Novartis, Roche, Merck, Teva, Sanofi-Genzyme and BMS; A.S. — served as a lecturer and an expert at advisory boards for Allergan, Amgen, Bayer, Novartis, Biogen, Merck, Polpharma, Roche, Teva, and Eli Lilly; J.Z. — declares no conflict of interest; H.B-P. — received advisory board and speaker honoraria from Biogen, BMS, Novartis, Merck, Roche and Teva and support for congress participation from Roche and Biogen; B.L. — declares no conflict of interest; A.P. — declares no conflict of interest; M.P. — declares no conflict of interest; A.R. — declares no conflict of interest; M.R. — declares no conflict of interest; Z.K. — declares no conflict of interest; A.P. (Andrzej Potemkowski) — received support for congress participation from Biogen Poland, Novartis Poland, Roche and Merck.

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RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 6, pages: 492–496
DOI: 10.5603/pjnns.97121

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

Long-term cenobamate retention, efficacy, and safety: outcomes from Expanded Access Programme

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ABSTRACT

Aim of the study. To evaluate the long-term retention rate, efficacy, and tolerability of adjunctive cenobamate (CNB) in patients with drug-resistant epilepsy within the Polish Expanded Access Programme (EAP).

Clinical rationale for the study. Long-term retention rate is a useful measure of effectiveness including efficacy, safety, and tolerability of antiseizure medications.

Material and methods. We conducted a multicentre retrospective analysis of consecutive patients with focal epilepsy treated with CNB in the EAP between January 2020 and May 2023. All patients who completed the open-label extension phases of the YKP3089C013 and YKP3089C017 trials were offered the opportunity to continue CNB treatment within the EAP. We analysed cenobamate retention, seizure outcomes, and adverse events.

Results. 38 patients (18 females; 47.3%) continued CNB treatment within the Expanded Access Programme for 41 months. The mean baseline age of patients was 39.3 years (range: 18–57). All patients were on polytherapy, with the most commonly used antiseizure medications being valproate, levetiracetam, and carbamazepine. Adjunctive CNB treatment resulted in a reduced mean seizure frequency from 8.1 seizures (range: 4–20) per month to 3 seizures (range: 0–8) per month. At the final follow-up, the median CNB dose was 200 mg/day (range: 50–350). Among the patients, 24 (63.1%) achieved ≥ 50% seizure reduction, and eight (21%) remained seizure-free for at least 12 months. One in three patients experienced adverse events, which resolved in half of the subjects. The most frequent adverse events were dizziness, somnolence, and headache. The retention rate after completing the open-label extension phase was 100%.

Conclusions and clinical implications. Long-term effectiveness, including ≥ 50% seizure reduction and a 100% retention rate, was sustained over 41 months of CNB treatment within the Expanded Access Programme. No new safety issues were identified. These results provide support for the potential long-term clinical benefits of cenobamate.

Keywords: cenobamate, retention rate, efficacy, safety, adverse events

(*Neurol Neurochir Pol 2023; 57 (6): 492–496*)

Introduction

Epilepsy is one of the most prevalent and serious neurological conditions, afflicting 70 million people worldwide [1]. While antiseizure medications (ASMs) serve as the primary therapeutic area for most patients with epilepsy (PWE), a smaller fraction of patients benefit from alternative approaches such as epilepsy surgery, brain stimulation, and ketogenic diets.

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Received: 26.08.2023 Accepted: 05.11.2023 Early publication date: 19.12.2023

Despite the introduction of c.20 new antiseizure medications with varying mechanisms of action over the last three decades, a significant proportion — about 1/3 — of PWE do not achieve seizure freedom [2–5]. The challenges of drug-resistant epilepsy extend beyond seizures, encompassing somatic and psychiatric comorbidities, an elevated risk of injuries and premature mortality, impaired psychosocial functioning, and a diminished quality of life. Effective seizure management not only mitigates morbidity and mortality within the PWE community, but also holds the potential to improve overall quality of life.

Cenobamate (CNB) is a novel antiseizure medication that gained approval from the US FDA in 2019 and from the EMA in 2021 for adjunctive treatment of focal onset seizures in adults. CNB is an oral tetrazole alkyl mono-carbamate exhibiting a dual mechanism of action: preferential blockade of persistent sodium currents, and positive allosteric modulation of the GABA-A receptor [6]. In randomised clinical trials, CNB demonstrated remarkable efficacy, with a responder rate (≥ 50% seizure reduction) reaching as high as 64%. Furthermore, one in five patients achieved complete seizure freedom with the highest dose [7, 8]. Indirect comparisons between CNB and several second- and third-generation ASMs (brivaracetam, eslicarbazepine acetate, lacosamide, perampanel, lamotrigine, levetiracetam, and topiramate) have indicated that adjunctive CNB yielded a higher responder rate and a greater likelihood of achieving seizure freedom compared to all comparators [9, 10]. Although open-label studies have confirmed its long-term effectiveness and safety [11, 12], real-world experience with CNB remains limited [13, 14]. Cenobamate received approval for reimbursement by the Polish public health system on 1 March, 2023. Prior to this date, patients participating in open-label extension studies of the C013 and C017 trials were provided with the opportunity to access cenobamate through Angelini Pharma's Early Access Programme (EAP).

Clinical rationale for the study

The primary objective of this study was to outline the extended clinical experience with cenobamate among patients with epilepsy who were treated within the Expanded Access Programme in the Silesian Voivodeship of Poland.

Material and methods

This study followed a multicentre, retrospective, observational design, encompassing patients who chose to continue treatment after completing an open-label extension (OLE) of two separate randomised, double-blind, placebo-controlled trials: a 12-week study (YKP3089C013) and an 18-week study (YKP3089C017) [5, 6].

The investigation involved patients who had taken part in the aforementioned trials at all four study sites within the Silesian Voivodeship of Poland. All patients were provided cenobamate through Angelini Pharma's Early Access Programme (EAP), which was initiated in Poland in January 2020.

Upon completing the open-label extension (OLE) phase, every patient was given the opportunity to extend their treatment with CNB through the Early Access Programme (EAP). The decision regarding any subsequent dose adjustment was made by the attending neurologist on a case-by-case basis, taking into account the treatment's effectiveness and tolerability. The maximum allowed daily dose was 400 mg. Data was retrieved from patients' medical records and kept according to usual clinical practice at each centre by participating physicians. All enrolled patients had a history of drug-resistant focal epilepsy. The recorded demographic and epilepsy-related data encompassed age, gender, epilepsy duration, epilepsy treatment type (monotherapy or polytherapy, specific antiseizure medications used, and CNB dosage), monthly seizure frequency before initiating CNB and during the most recent follow-up, duration of CNB exposure, and any encountered adverse events. For the purposes of this analysis, data was collected until the cutoff date of 31 May, 2023.

This study was a retrospective analysis of existing clinical data, so ethics committee review and patient consent were not required.

Results

Patients

Initially, 45 adult patients with epilepsy were enrolled in the open-label extension (OLE) phase. Over the course of the study, three patients were lost to follow-up. Additionally, four patients had to be withdrawn from the OLE for the following reasons: lack of efficacy in one patient (at a CNB dose of 400 mg), psychomotor agitation in another patient (at 50 mg, which resolved after discontinuation of CNB), and dizziness in two patients (at 50 mg and 100 mg doses).

Finally, a total of 38 patients progressed to the Expanded Access Programme. The average baseline age of patients was 39.3 years, and 18 (47.3%) were females. All patients were on polytherapy, with the most frequently employed antiseizure medications being valproate (19/38; 50%), levetiracetam (15/38; 39.5%), and carbamazepine (12/38; 31.6%). The median count of previously unsuccessful antiseizure medication treatments was five (range 2–9). A summary of demographic, clinical, and therapeutic data is set out in Table 1.

Cenobamate treatment outcome

As of May 2023, the median duration of CNB exposure, encompassing both the Open-Label Extension (OLE) and Early Access Programme (EAP), was 96 months (range: 70–132). Within the EAP, the median CNB exposure duration was 41 months. The median dose of cenobamate during the last follow-up was 200 mg/day (with an interquartile range [IQR] of 100 mg, ranging from 50 to 350 mg/day). During the final visit, 34.2% of patients were receiving less than 200 mg of CNB per day.

The addition of cenobamate as an adjunctive treatment led to a significant reduction in mean seizure frequency from

Table 1. Demographics and clinical characteristics of patients treated with cenobamate within Poland's Expanded Access Programme

Variable	n = 38
Age; [years], mean (range)	39.3 (18–57)
Sex (female)	18 (47.3%)
Duration of epilepsy [years] median (range)	15.0 (4–33)
Daily dose of cenobamate [mg]; range	201.3 (50–350)
Number of concomitant ASMs — median	2
1	9 (23.7%)
2	18 (47.4%)
3	11 (28.9%)
Number of ASMs previously tried — median (range)	5 (2–9)
2	2 (5.1%)
3	8 (21%)
4	6 (15.8%)
5	5 (13.6%)
6	4 (10.5%)
7	5 (13.6%)
8	5 (13.6%)
9	3 (7.8%)

ASMs — antiseizure medications

Table 2. Adverse events in patients treated with cenobamate

Adverse event	n (%)
Somnolence	6 (15.8)
Dizziness	4 (10.5)
Elevation of liver enzymes	2 (5.2)
Headache	1 (2.6)
Nausea	1 (2.6)
Nystagmus	1 (2.6)
Balance disorder	1 (2.6)

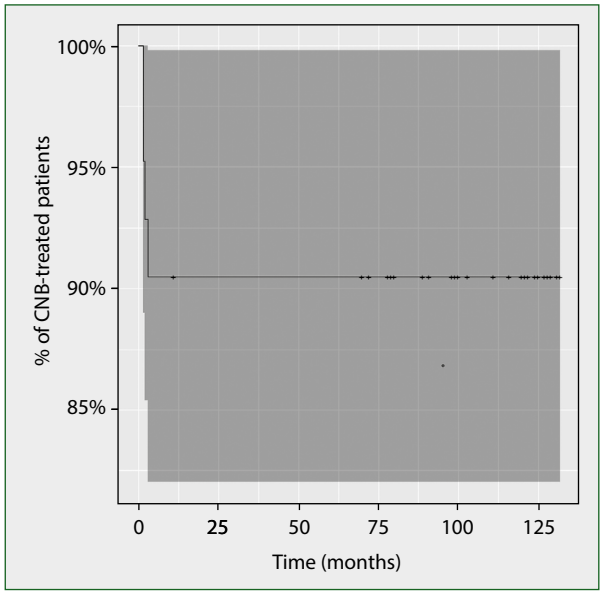

Figure 1. Kaplan–Meier plot presenting treatment retention in RCT and OLE phases. CNB — cenobamate; RCT — randomized controlled trial; OLE — Open-Label Extension

8.1 seizures per month (range: 4–20) to 3 per month (range: 0-8). By the end of the observation period, 24 (63.1%) patients achieved ≥ 50% seizure reduction, while 15 (39.5%) achieved ≥ 75% reduction. Eight (21%) patients experienced complete seizure freedom for at least 12 months. The median cenobamate dose associated with achieving seizure freedom was 200 mg (range: 100–300), while the same dose of 200 mg (range: 100–300) was linked to ≥ 50% seizure reduction.

One-third of patients (31.6%) reported experiencing at least one adverse event during their participation in the EAP. These events included drowsiness in six patients, dizziness in four, non-clinically significant elevation of liver enzymes in two, and nausea, headaches, balance disorder, and nystagmus in one patient each.

Drowsiness and dizziness occurred at CNB dose > 150 mg/day. Among patients encountering adverse events, an equal proportion (50%) were taking three concurrent antiseizure medications, while the remaining 50% were on two concomitant medications. In contrast, among the group without reported adverse events, 19.2% (5/28) were on three medications, 42.8% (12/28) on two, and 39.2% were being prescribed only one concurrent antiseizure medication. Adverse events were resolved during the study for half of the patients who experienced them. Side effects and their frequency are set out in Table 2.

All patients who successfully completed the Open-Label Extension (OLE) phase and transitioned to the EAP continued to receive CNB treatment until 31 May, 2023, resulting in a retention rate of 100%. Figure 1 shows a Kaplan–Meier plot illustrating the treatment retention in randomized controlled trial (RCT) and OLE phases.

Discussion

For the successful treatment of epilepsy, it is critical to find the right balance between obtaining adequate seizure control and avoiding adverse events. Randomised clinical trials are indispensable for assessing the safety and efficacy of new drugs. However, they have important limitations such as the short duration of intervention. Long-term retention rate is a useful measure of effectiveness including efficacy, safety, and tolerability.

In this retrospective study, we describe extensive long-term clinical experience with cenobamate among individuals with epilepsy who were treated under Poland's Expanded Access Programme (EAP). One key strength of our study is the exceptionally long observation period. The duration of cenobamate exposure was 3.5 years within the EAP and 4.5 years within the

Open-Label Extension (OLE), effectively resulting in patients receiving CNB treatment for an average of c.8 years (range: 70 to 132 months), all under the care of the same physician. In this analysis, the use of CNB was consistently linked to remarkable retention rates, ranging from 84.4% (38/45) in the OLE phase to an impressive 100% (38/38) in the EAP, serving as an additional indicator of its sustained long-term effectiveness. It is worth underlining that the retention rate observed in the Polish EAP remained steady across the span of 4.5 years of treatment, surpassing the rates reported in similar Spanish (87%) and Irish (89.5%) studies [11, 12]. It is important to note that both the Spanish and the Irish studies encompassed patients dealing with highly active and ultra-refractory epilepsy, a population more prone to discontinuing a medication due to lack of efficacy and adverse events.

The efficacy of cenobamate, as indicated by the achievement of ≥ 50% seizure reduction (63.1%) and seizure freedom (21%), closely paralleled the outcomes observed in randomised controlled trials. And this efficacy consistently endured over the 3.5-year observation period within the EAP [5, 6]. It is worth noting that the median cenobamate dose for both groups of patients was 200 mg, suggesting that further dose escalation could potentially lead to even higher reduction rates. Similar to other studies, adverse events such as dizziness, somnolence, and headache were observed; notably, these events were more frequent among patients taking a greater number of concurrent antiseizure medications [5, 6, 11, 12]. Encouragingly, in half of the patients experiencing adverse events, they resolved during the course of the study. Furthermore, the study's clinical observation did not identify any serious adverse events. Notably, our extensive long-term follow-up did not uncover any new safety concerns linked to the use of cenobamate.

One notable limitation of our study is the relatively small sample size. Additionally, due to its retrospective design, there was no available data on alterations in concomitant antiseizure medication (ASM) therapy.

Nevertheless, it is noteworthy that this study presents the most extensive follow-up of patients treated with cenobamate published to date. This extended observation period provides valuable insights for physicians regarding the enduring long-term efficacy and safety/tolerability profile of cenobamate.

Clinical implications/future directions

These findings from a long-term observation demonstrate the sustained efficacy and safety/tolerability of cenobamate in adult patients with uncontrolled focal epilepsy.

Article information

Authors' contributions: *ALB: conception and design of study, analysis and interpretation of data, critical revision of article, final approval of version to be published; BK, TZ, AKK, JK, BŻM, KM, KM, AWK: acquisition of data for work, final approval of version to be published; MB: conception and design of study, analysis and interpretation of data, drafting article, critical revision, final approval of version to be published.*

Acknowledgements: *All patients were provided cenobamate through Angelini Pharma's Early Access Programme*

Conflicts of interest: *MB has received honoraria for publications from Sanofi and Zentiva; honoraria for lectures, travel expenses and conference fees from Sanofi, Adamed, Angelini Pharma and UCB Pharma; and honoraria for participation in advisory boards from Sanofi and UCB Pharma ALB, BK, TZ, AKK, JK, BŻM, KM, MM, AWK have nothing to declare*

Funding: *This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.*

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Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 6, pages: 497–498
DOI: 10.5603/pjnns.98603

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

Reperfusion therapy of ischaemic strokes in oral anticoagulated patients: an expanding field in clinical practice

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To the Editors

The optimum treatment for acute ischaemic stroke in patients receiving active anticoagulation, i.e. with effective levels of anticoagulant activity, which most commonly represent the anti-Xa activity of rivaroxaban, apixaban or edoxaban administration or anti-IIa activity after the administration of dabigatran, is unresolved due to relatively poor empirical data.

This is an increasing problem in clinical practice because of the growing use of oral anticoagulants and the associated occurrences of intracranial haemorrhages (ICH) and ischaemic strokes, occurring despite the desirable anticoagulant blood concentrations achieved [1–5].

Current empirical and observational data shows that in patients with acute ischaemic stroke who receive dabigatran, the administration of idarucizumab, a monoclinal antibody that reverses anti-IIa activity, followed by recombinant tissue plasminogen activator (rtPT), is reasonably safe. However, the clinical efficacy of this treatment regimen remains unproven in terms of Evidence-Based Medicine. The low level of evidence (LOE) for clinical outcomes is the result of various factors, including a lack of randomised trials, diverse inclusion criteria in the available observational studies, and the relatively low number of patients in these studies [6–15]. Therefore, information on a new series of patients from different populations might be valuable in establishing management standards [16].

Nevertheless, at the moment, a combination of pharmaceutical and observational data has resulted in positive narrative recommendations from most European experts regarding the use of idarucizumab followed by rtPA for non-large vessel occlusion (non-LVO) stroke in patients with high anti-IIa activity or expected anti-IIa activity [17–19]; the administration of idarucizumab to a patient with no or little anti-IIa activity should not generate any major side effects or complications other than those associated with the administration of any monoclinal antibody [20].

The effectiveness of andexanet alpha, an analogue of endogenous FXa that reverses the effect of all direct and some indirect Xa factor inhibitors (e.g. unfractionated heparin, low-molecular weight heparin and fondaparinux), is more debatable than the use of idarucizumab, even considering the intracranial haemorrhage, especially in view of the recently released results of the ANNEXA-I study at the World Stroke Conference [21], even though it has real promise for some ICH patient subgroups. The use of andexanet alpha in combination with thrombolytics in acute cerebral ischaemia on anti-Xa anticoagulation has been reported in only two cases [19, 22]. The pharmacodynamics and pharmacokinetics of this agent are more complex than those of idarucizumab, it requires a different administration regime (i.e. an intravenous bolus followed by infusion), and its application in ICH patients has been associated with more prothrombotic complications, including ischaemic strokes and myocardial infarctions [21, 23].

Thus far, STROACT (STROke on AntiCoagulants for Thrombolysis), ongoing in selected Polish centres, is the only large-scale study to have evaluated the efficacy and safety of reperfusion thrombolytic therapy with intravenous rtPA for ischaemic stroke in patients receiving non-vitamin K antagonist oral anticoagulants after reversing anticoagulant activity with a specific antidote (https://www.frontiersin.org/articles/10.3389/fneur.2023.1269651/full#supplementary-material). Its 'anti-IIa' substudy is confirmatory to previous reports [7–11, 20] and aims to upgrade the level of evidence for the clinical efficiency of this therapeutic protocol, whereas the substantial 'anti-Xa' substudy tests a novel, four-step, 3-hour therapeutic protocol developed and used for the first time by ourselves [19].

However, before the time of its completion, or indeed that of any potential new study, andexanet alpha should not be administered in ischaemic stroke in any combinations with thrombolytics. This is for multiple reasons, but primarily because of its prothrombotic action that is seen both in specific

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Received: 06.11.2023 Accepted: 13.11.2023 Early publication date: 19.12.2023

laboratory data and in clinical observations in patients with ICH, although this complication has not been found in healthy volunteers.

Article information

Conflicts of interest: *The author has been a member of AstraZeneca and Boehringer Ingelheim advisory boards in regard to stroke treatments.*

Funding: *The STROACT study was funded by the Medical Research Agency, 1A Stanisława Moniuszki St., 00–014 Warsaw, Poland (Grant number: 2019/ABM/01/00084).*

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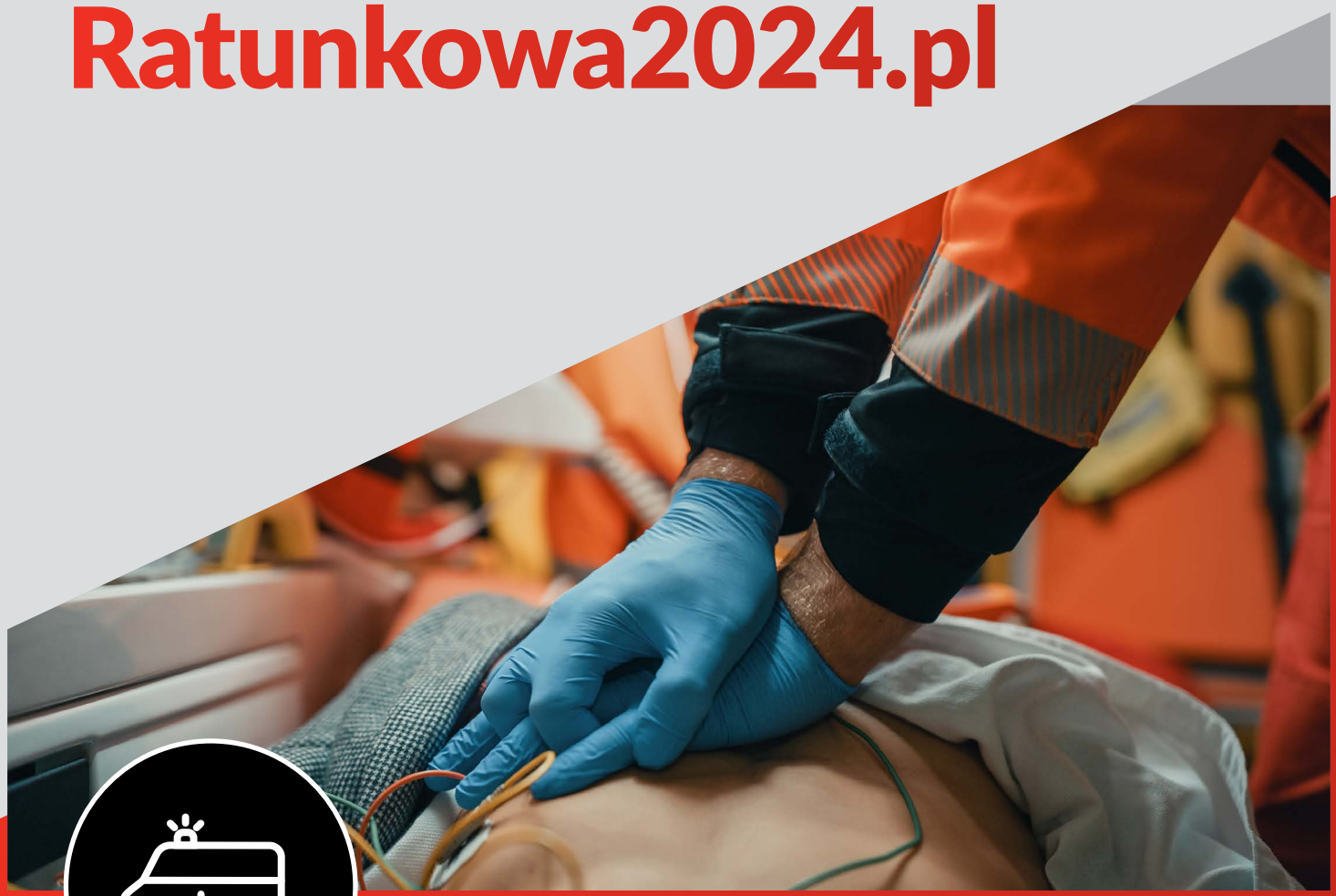

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