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COMORBIDITY OF EPILEPSY AND MIGRAINES EPIDEMIOLOGICAL AND CLINICAL ASPECTS

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Summary: In patients with migraines, epilepsy occurs in 5.9% (1–17%) of cases compared to a prevalence of 0.5–1% in the general population. Comorbidity of migraines and epilepsy can be explained by neuronal hyperexcitability, while cortical spreading depression is considered to be a pathophysiological mechanism that lies in the basis of the migraine aura.

The study included 259 patients with epilepsy and 40 patients with both epilepsy and migraines. The aim of the investigation was to determine the prevalence of migraines, the existence of a temporal association between epileptic and migraine attacks, to determine the clinical characteristics of joint epileptic and migraine attacks, the existence of a significant connection between a certain type of epileptic seizure and type of headache, and finally to determine heredity for epilepsy and migraines in patients who have these conditions associated. Patients were diagnosed clinically, neurophysiologically and neuroradiologically. The research results show that the frequency of associated epilepsy and migraines occurred in 15.44%. The results of this investigation point to a significantly higher frequency of epilepsy and migraines in female patients (ratio 5 : 1), which is different from the data we found in existing studies. Temporally connected attacks of epilepsy and migraines were observed in 48% of patients. Preictal headaches appeared in 20% of patients, postictal in 28% of patients. There was no significant association between migraines and the particular type of epileptic attack. Heredity for migraines was present in 35% of patients with both epilepsy and migraines. This

data is significantly lower than the data found in other studies.

Key words: epilepsy, migraine, adults, comorbidity.

INTRODUCTION

Migraines and epilepsy are two chronic disorders characterized by repeated attacks of neurological dysfunction and are variously accompanied by gastrointestinal, autonomic and other pathophysiological disorders. Migraines and epilepsy are linked by their symptom profiles, comorbidity and treatment. A person suffering from one of these diseases is twice as at risk of having the other one, too (1, 2).

The association of epilepsy and migraines indicates comorbidity which does not occur by accident, according to epidemiological studies. The reasons are partly genetic (3, 4), but at the same time both disorders exhibit common pathophysiological and electrophysiological phenomena (5). These two disorders also exhibit comparable clinical phenomena which may lead to confusion.

The prevalence of epilepsy in patients with migraines varies from one author to another and it ranges from 1–17% (mostly reported 5.9%), while in the general population it ranges from 0.5–1% (6). The pathophysiological mechanism of the association between epilepsy and migraines is still unclear. There is an opinion that neuronal hyperexcitability may explain the comorbidity of these two disorders (7, 8). Cortical spreading depression during migraine aura (9, 10) is considered to be a pathophysiological mechanism which lies at the root of epileptic seizures in patients suffering from epilepsy and migraines with aura. The

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association of epilepsy and migraines may be classified as:

1. Association of epilepsy and migraines with independent seizure occurrence
2. Migraine-induced epilepsy
3. An epilepsy-induced headache
4. Epilepsy-migraine syndromes
5. Symptomatic epilepsy-migraine syndromes

Anamnestic data has an important place in differential diagnosis of epilepsy and migraines without aura (11, 12). Many symptoms of migraine and epilepsy overlap and the most useful symptoms in its diagnosis are those that differentiate these two diseases. The differential diagnosis: a) between migraines with aura and epilepsy without tonic-clonic movements, in the case of a b) migraine equivalent (the occurrence of migraine aura without headache), c) basilar migraine, d) confusion migraine and e) migraine associated with occipital epilepsy, may be very difficult.

AIM OF RESEARCH

The goal of this study was to estimate the frequency of migraine occurrence in adult patients with epilepsy, to determine the temporal association of epileptic and migraine attacks, the clinical characteristics of these associated attacks, to explore the possible connection between specific types of epileptic seizure and headache, as well as to determine the heredity of patients suffering from epilepsy and migraines.

METHOD AND PATIENTS

In this study we investigated a group of 259 consecutive outpatients, with a confirmed diagnosis of epilepsy. The group consisted of 115 male and 144 female patients. Patients were treated in the Dispensary for Epilepsy at the Clinical Centre of Montenegro, Podgorica. The investigation lasted for 30 months. Patients were followed up at intervals ranging between 3 and 6 months. Criteria for the diagnosis of epilepsy were based on clinical symptoms and electroencephalographic findings (EEG), neuroradiological methods such as computed tomography (CT) and/or magnetic resonance imaging of the brain (MRI). The study included 86 patients with connected epilepsy and headaches. Out of 259 patients, 40 patients reported the coexistence of epilepsy and migraines. Patients with a progressive disease of the brain or recent brain injury were excluded from the study. Patients included in the study were interviewed using a standardized questionnaire.

The questionnaire contained:

A. *General information:* gender, age.

B. *Information related to epilepsy:* age of onset, duration of epilepsy, data regarding seizure semiology, data regarding the phenomena before and after epileptic seizure, the incidence of attacks, the presence of aura attacks, heredity of epilepsy, heredity of migraine headaches. Types of seizures were determined according to the Classification of the International League Against Epilepsy (ILAE, 1989). According to ILAE criteria epileptic syndromes were classified as partial and generalized seizures.

C. *Issues related to the headache:* does the patient have pain all over the head or on one side of the head, quality of pain (tightness, pulsation, throbbing, pressure-like feeling), the intensity of pain, pain worsened by physical activity, pain followed by associated symptoms, the presence of migraine aura, family history of migraines. According to the ICDH II criteria, headaches were classified as: a) Migraine headaches; or b) Other, non-migraine headaches.

D. *Questions about the temporal association of epilepsy and migraines:* a temporally associated epilepsy and headache is defined as a headache occurring one hour before or after an epileptic attack or both. This criterion has been adopted in a similar survey regarding the association of epilepsy and headaches in a population of patients with epilepsy (Leniger et al, 2001).

The time of headache onset in relation to the epileptic attack was defined as: preictal; ictal; postictal; or interictal.

EEG findings were categorized into 5 categories: normal EEG, focal-specific activity, generalized epileptiform activity, nonspecific focal activity, diffuse nonspecific activity.

CT results were classified into two categories: a) normal; and b) pathological.

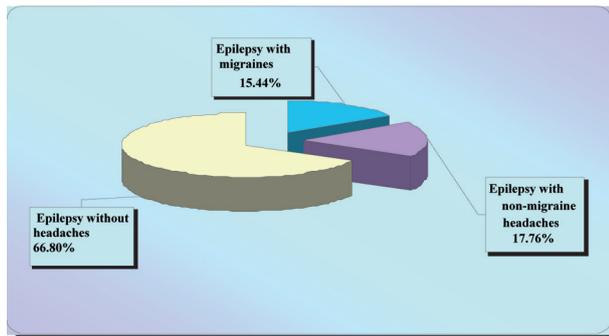
MRI was carried out in all patients with migraines and epilepsy, except for two patients, where MRI was contraindicated. Magnetic resonance angiography (MRA) was performed in 3 patients, who had headaches always on the same side of the head. MRI was performed on a device with a magnetic field strength of 1 Tesla.

The results are classified into two categories: a) normal; and b) pathological.

The control group consisted of: a) Patients with migraine headaches without epilepsy; and b) Patients with epilepsy without headaches.

RESULTS

In a group of patients with epilepsy, migraines and epilepsy were diagnosed in 40 (15.44%) patients, 46 (17.76%) patients had epilepsy and other non-migraine



Graph 1: Incidence of migraine and non-migraine headaches in the population of epilepsy sufferers

headaches, while epilepsy without headaches was found in 173 (66.80%) patients (graph 1). In this research, migraines occurred prior to the onset of epilepsy. Out of the total number of patients suffering from epilepsy and migraines, 85% were females. Out of the total of 40 patients, 32 (80.00%) had a generalized type of seizure (with or without focal onset) and partial seizures were found in 8 (20.00%) patients. Most patients

40 years old or younger had generalized seizures with or without partial onset which was statistically significant in comparison to patients older than 40 years ($p < 0.05$). The association of a specific type of epileptic seizure and migraine headaches was not statistically significant.

Temporal association of epileptic and migraine attacks was found in 19 (47.5%) out of 40 patients with epilepsy and migraines. Eight of them (20%) had preictal migraines while in 11 (28%) patients migraines occurred postictally. The rest of the patients (52%) had interictal migraine headaches. Preictal temporal association of a migraine and epileptic seizure was statistically significantly more common in patients with epilepsy and migraines than in patients with epilepsy and other, non-migraine headaches ($p < 0.05$). Patients with postictal headaches more frequently suffered from non-migraine headaches associated with epileptic seizures (32 or 74.42%) than from migraines (11 or 25.58%).

Tables 1 and 2 show the temporal association of epileptic seizures and migraines, in relation to the presence of migraines with aura.

Patient	Gender/Age	Type of seizure	Therapy	Migraine	EEG	MRI
1	F/21	GTK + PC	CBZ + VPA	MwA	foc. spec. act.	Normal MRI
2	M/51	GTC	CBZ + VPA	MwA	normal	Multi ischaemia
3	M/53	GTC + PC	VPA	MwA	gen. spec. act.	Multi ischaemia
4	F/23	GTC + PC	CBZ + LTG	MwA	normal	normal MRI
5	M/17	GTC	CBZ	MoA	normal	Normal MRI
6	F/30	GTC + PC	CBZ + VPA	MoA	foc. nonsp. act.	Normal MRI
7	F/23	GTC	VPA	Basilar migraine	normal	Normal MRI
8	F/38	GTC + PC	VPA	MoA	foc. spec. act.	Normal MRI

Table 1. Patients with preictal migraine attacks

Patient	Gender/Age	Type of seizure	Therapy	Migraine	EEG	MRI
1	F/26	PC	CBZ + TPM	MoA	gen. spec. act.	Normal
2	F/42	GTC	VAL + TPM	MoA	gen. spec. act.	Normal
3	F/31	GTC	VPA	MoA	gen. spec. act.	Normal
4	F/48	GTC	CBZ + VPA + PB	MoA	gen. spec. act.	Hippocampal sclerosis
5	F/48	PC	CBZ	MoA	foc. nonspec. act.	Hippocampal hypotrophy
6	F/18	GTC + Myoclonic	VPA + LTG	MwA	gen. spec. act.	Normal
7	F/20	GTC	VPA	MoA	normal	Normal
8	F/48	PC	CBZ + PB	MoA	foc. Spec. act.	Normal
9	F/20	GTC	VPA	MoA	normal	Normal
10	F/43	PC	CBZ + LTG	MwA	normal	Normal
11	F/23	GTC	VPA	MoA	normal	Normal

Legend: F — female, M — male, PC — partial complex seizures, GTC — generalized tonic-clonic seizure, CBZ — carbamazepine, TPM — topiramate, VAL — valproate, VPA — valproic acid, PB — phenobarbitone, LTG — lamotrigine, MoA — migraine without aura, MwA — migraine with aura, gen. spec. act. — generalized specific activity, foc. nonspec. act. — focal nonspecific activity.

Table 2. Patients with post-epileptic seizure migraine attack

The temporal association of migraines with aura and epileptic seizures was statistically significantly more frequently found than migraines with aura not temporally associated with epileptic seizures ($p < 0.05$).

A positive family history for migraines was found in 14 (35.0%) patients with epilepsy and migraines, in 27 (67.25%) patients with migraines and in 5 (10.86%) patients with epilepsy and other non-migraine headaches. Heredity of migraines was statistically significantly more common in patients with migraines than in patients with epilepsy and migraines ($p < 0.05$).

In a group of patients suffering from epilepsy and migraines, 25% of patients had migraines with aura while in a group of patients with migraines but without epilepsy this percentage was 47.5%. Migraines with aura were significantly more frequent in patients with migraines but without epilepsy, than in patients suffering from epilepsy and migraines, $p < 0.05$.

DISCUSSION

Our study has demonstrated a connection between epilepsy and migraine headaches in 15.44% (40) of our patients. The prevalence of migraines in the general population is around 11% in contrast with an estimated 15% for patients with epilepsy (13, 14). These figures are consistent with the results of our study. Similar results were obtained in another study where the prevalence of migraines was 14% (15). A slightly higher prevalence of migraines in the epileptic population was found in a study where 42% of patients had headaches associated with their primary condition (16). Among the total number of patients suffering from epilepsy and migraines, 85% were females. This result was statistically significant in comparison to male patients ($p < 0.001$). Such a high frequency of female patients with the female to male ratio 5 : 1 among patients with epilepsy and migraines was not found in the available literature. Studies regarding this problem usually reported the female to male ratio as 3 : 1 (17). A strong association between epilepsy and migraines, irrespective of the type of attack, etiology, sex, age of onset and family history, was reported by the authors Othman and Lipton (18). The authors found a cumulative incidence of migraines in 24% of patients with epilepsy under the age of 40, which is slightly higher than in our study. In our research, out of a total of 40 patients with epilepsy and migraines, 32 (80%) patients had generalized seizures, and 8 (20%) patients had partial seizures. A higher in-

cidence of partial seizures compared to generalized seizures was found in the study of associated epilepsy and migraines in 341 patients with epilepsy. 67.2% (174) of those patients had focal seizures (19).

Of the total 259 patients, 3.08% had preictal migraines, while a lower incidence (1.7% of patients) of preictal migraine headaches was found in the survey by the Turkish authors (14), in contrast to our research.

Ito et al. (20) investigated postictal headaches that occurred immediately after partial seizures, and found that 5.5% of patients had migraine headaches, which is slightly higher than in our study. Overall, both preictal and postictal occurrences of migraine headaches in our study were equally represented. Similar results were found in the research papers of several different authors (21, 22, 23).

In our study, in patients with epilepsy and a family history of migraines, migraines were discovered in 35% of the total number of patients. A similar frequency of positive family history of migraines was found in a related survey (18), where a positive history of migraines was present in 40.6% of patients.

CONCLUSION

In conclusion, the results of this study indicate that the prevalence of headaches associated with epilepsy was 33.20%, while the prevalence of migraines in the same group was 15.44%. Of the total number of patients with epilepsy and migraines, 85% were women.

Among all patients with epilepsy, an association between preictal migraines and epileptic seizures was found in 3.08%, while postictal association was observed in 4.25%. Preictal headaches were reported in 20% of patients, postictal in 28%. Postictal migraine headaches were present more often after generalized seizures compared with partial seizures. Migraines with aura are often preceded by a seizure. Preictal migraine headaches occurred significantly more often than other non-migraine headaches, but postictal migraine headaches occurred significantly less often than other, non-migraine headaches. Some kind of postictal headache was reported in 50% of patients, out of a total of 86, with epilepsy and headaches, while preictal headaches were almost five times less frequent. Among patients with epilepsy and migraines, positive heredity for migraines, on the basis of medical history, was noted in 35% of patients.

Sažetak

KOMORBIDITET EPILEPSIJE I MIGRENE, EPIDEMIOLOŠKI I KLINIČKI ASPEKT

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Epilepsija kod pacijenata sa migrenom javlja se u 5.9% (od 1–17%) slučajeva u poređenju sa prevalencijom od 0,5–1% u opštoj populaciji. Komorbidnost migrene i epilepsije bi se mogla objasniti neuronskom hierektabilnošću, dok se kortikalna šireća depresija smatra patofiziološkim mehanizmom koji je u osnovi migrenske aure.

Studija je obuhvatila 259 pacijenata sa epilepsijom, a u istraživanje je uključeno 40 pacijenata sa udruženom epilepsijom i migrenom. Cilj istraživanja je bio da se utvrdi prevalenca migrene u epileptičnoj populaciji, postojanje vremenske udruženosti između epileptičkih i migrenskih napada, značajna povezanost između tipa epileptičkog napada i tipa glavobolje, da se utvrdi hereditet za epilepsiju i migrenu kod pacijenata kod kojih postoji udruženost ova dva entiteta. Pacijenti su dijagnostikovani klinički, neurofiziološki i neuroradiološki. Rezultati istraživanja su pokazali da prevalenca migrene u epileptičkoj populaciji iznosi 15.44%. Rezultati ovog istraživanja upućuju na značajno veću udruženost epilepsije i migrene kod ženskog pola (5 : 1), što se razlikuje od podataka iz literature. Vremenski udruženi napadi migrene i epilepsije javljali su se u 48% pacijenata. Preiktusne glavobolje javile su se kod 20% a postiktusne kod 28% pacijenata. Nije bilo značajne udruženosti migrene i određenog tipa epileptičnog napada. Hereditet za migrenu prisutan je kod 35% bolesnika sa epilepsijom i migrenom, značajno manje nego u literaturi.

Ključne riječi: epilepsija, migrena, odrasli, komorbiditet.

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