HEADACHE IN CHILDREN WITH EPILEPSY

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ABSTRACT

Headache is a common comorbidity in pediatric epileptic patients. The relationship between headache and epilepsy is considered complex and though there is evidence of association, its mechanisms are not yet completely clear. Numerous studies of comorbidity focus on primary headaches, such as migraine and tension-type headache, describing them as the most prevalent in patients with epilepsy. Some authors, though, report similar prevalence of headache and specifically migraine in epilepsy patients as compared to that of the general population. When describing this comorbidity, it should be noted that secondary headaches can also be frequent in patients with structural epilepsy, e.g. in brain tumors or other space-occupying lesions.

In this paper we summarize literature data on the problem of epilepsy and headache comorbidity, and also present two clinical cases of patients with tension-type and with secondary headache, respectively.

Keywords: *children, comorbidity, epilepsy, headache*

INTRODUCTION

Headache is among the most common neurological symptoms, not only in adults, but also in pediatric patients. It can therefore be expected to appear in subjects with different neurological disorders without being related to them. However, the coexistence of headache and epilepsy is often considered to be more than just a coincidence. It appears to be of complex nature and though evidence of association between the two disorders has been reported, its mechanisms are not yet completely clear.

Both headache and epilepsy are characterized by transient attacks of brain dysfunction. Several decades ago, Sir William Gowers assumed that "migraine borders on epilepsy" and pointed out some possible pathophysiological mechanisms, such as dysfunction of neurotransmitters and ion channels (1). In recent times there have been theories stating that increased neocortical excitability is a common mechanism underlying headache and epilepsy, thus explaining their common features (2). Genetic mutations, such as CACNA1A and ATP1A2, have also been found in families with both migraine and epilepsy, explaining the similar pathophysiologic mechanisms, such as the imbalance between excitatory and inhibitory factors that result in the altered brain function and autonomic symptoms observed during seizures (3).

The attempts to study and classify headache that is somehow related to epilepsy are numerous. Headache attacks in epilepsy have been classified as preictal, ictal, postictal, and interictal (4). Terms such as "hemicrania epileptica" or "migralepsy", "ictal epileptic headache", "autonomic seizure", "migraine aura-triggered seizure", etc. have been introduced in an attempt to describe specific conditions on the borderline between headache and epilepsy. Some of them can be potentially confusing (1), and the diagnostic criteria are not always very clear.

Epidemiological data on epilepsy and headache comorbidity shows differences among studies. According to a cross-sectional study of 142 pediatric patients with epilepsy, performed recently using a structured questionnaire, there was a significant share of patients with headaches (45.7%) compared with the control group (2%). Among the patients with headaches, most had migraine (44.6%), 18.4% had tension-type, and in 36.9% the headache remained unclassified (5). In a study that included 200 patients with juvenile myoclonic epilepsy and 100 healthy controls, headache was present in 56% of

the patients and in 50% of the healthy participants. From the patients, 42.3% had migraine 46.8% had tension type headache 3.6% had both, and 7.2% had other non-primary headaches. Headache frequency was not significantly different in the healthy control group, however, migraine frequency was higher among the patients. The authors therefore suggest a genetic relationship and shared pathophysiological mechanisms between juvenile myoclonic epilepsy and migraine (6). Çilliler et al. (7) also discuss that headaches, particularly migraine, are frequently experienced by patients with epilepsy. The authors found that postictal headaches were the most common, and the frequency of migraine attacks could be linked with seizure frequency and the type of treatment. In another study though, the prevalence of headache and that of migraine, which is considered to be pathogenetically linked to epilepsy, were not different in epilepsy patients as compared to that of the general population (8).

According to Syvertsen et al. (9) seizures may trigger postictal migrainous headaches, while migrainous headaches sometimes proceed into epileptic seizures. The comorbidity of migraine and epilepsy should not be overlooked, as it may influence treatment choice. This would concern not only the antiepileptic drugs, but also the specific treatment, which may be required for the headache.

CLINICAL CASE DESCRIPTION

In this paper we present two clinical cases of patients with different types of epilepsy and headache.

CLINICAL CASE 1

VHH is a 17-year-old Caucasian girl, born from a first, normal pregnancy, by planned Caesarean section, without evidence of asphyxia. She had a proper physical and neuropsychological development. There is no family history of neurological diseases. The girl is currently practicing sports. For the last 4 years she has had complaints of headache with bilateral parietal and frontal localization, described as a feeling of pain, tightness and pressure, without photo- or phonophobia. The frequency of the attacks was 2 to 3 per week. Analgesics were required to alleviate the symptoms. On this background, the patient had an epileptic seizure debuting with upper limb myoclonus and evolving into a bilateral tonic-clonic seizure. No consultation with a neurologist was performed at that time (July 2019). In February 2020, while removing her make-up, she had a second seizure with similar characteristics. For the next 5 months she had had seizures with staring and non-responsiveness. She was then hospitalized. Clinical and neurological examination, complete blood count, biochemistry, and MRI of the brain were all normal. EEG showed generalized discharges of spike-and-wave complexes with a frequency of 3 Hz and a duration of up to 6 seconds (Fig. 1).

Two diagnoses were discussed as coexisting in the patient: juvenile myoclonic epilepsy and tension type headache. Treatment with lamotrigine was initiated. No new epileptic seizures were observed and the attacks of headache were reduced in number and severity.

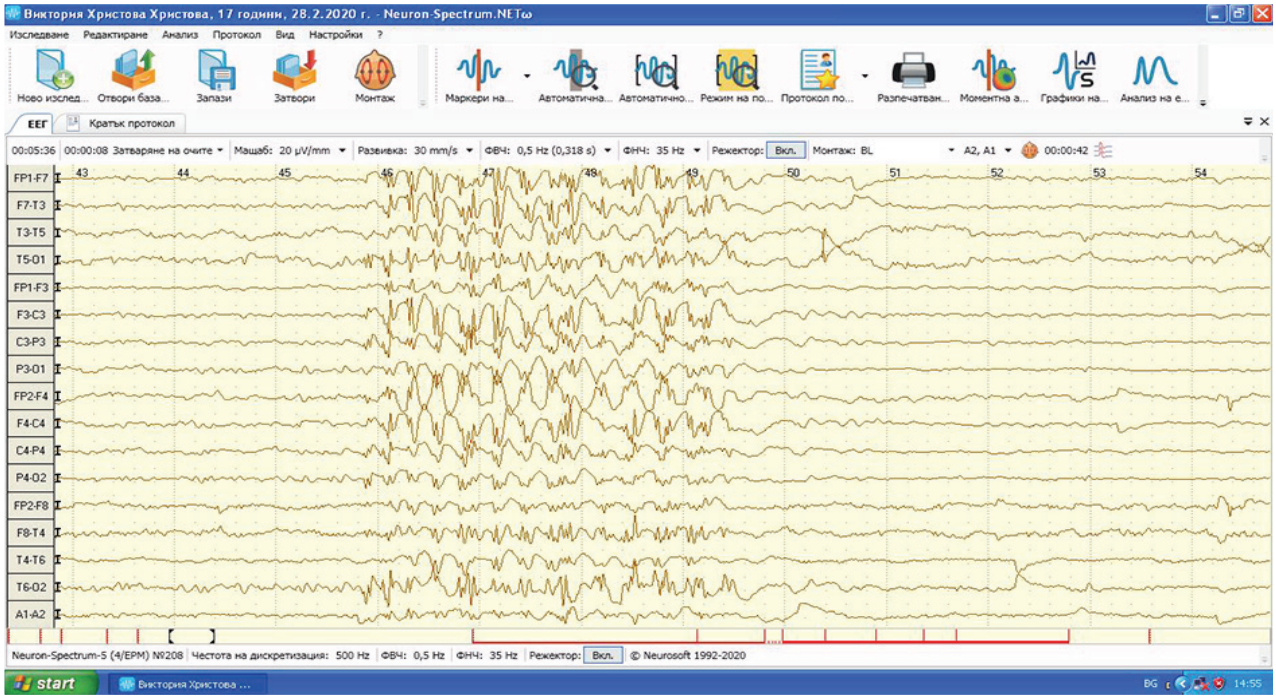

Fig. 1. Generalized discharges of spike-and-wave complexes with a frequency of 3 Hz

CLINICAL CASE 2

FGY is a 17-year-old Caucasian boy, born from a first, normal pregnancy, by vaginal birth, with proper physical and neuropsychological development. In January 2008, at the age of 7, he was diagnosed with disseminated neurofibrosarcoma with a suspected primary localization in the area of the left forearm. Eight courses of chemotherapy with ifosfamide, etoposide and vincristine were conducted. The subcutaneous tumors were reduced in size, the patient was afebrile and was not reporting pain. Another 4 courses of carboplatin-etoposide-vincristine (CEV) treatment were performed. The clinical response was satisfactory and the patient remained asymptomatic for the next 7 years. In May 2017, at the age of 16, he had 3 epileptic seizures in a day. The first one occurred after sleep deprivation and presented with version of the head and the eyes, without complete loss of consciousness. A similar seizure was observed several hours later. In the afternoon the patient had a bilateral tonic-clonic seizure and was hospitalized. MRI of the brain revealed numerous (about 27) bilateral supratentorial lesions at the border between the cortex and the white matter in multiple regions: frontal, parietal and occipital, varying in size from 3.5 to 10 mm (Fig. 2). Some perifocal hyperintensity of the T2 signal was noted, as in gliosis and/or edema. The lesions had hemosiderin and calcium deposits. Some of the lesions showed annular contrast enhancement. They were interpreted as most likely being secondary, probably through hematogenous dissemination. Calcifications were attributed to the effect of chemotherapy.

EEG showed sharp waves in the left frontotemporal area. The diagnosis of symptomatic (structural) epilepsy was accepted and treatment with valproic acid was initiated. Due to weight gain it was replaced with carbamazepine. Later, the patient presented with headache localized in the frontal region, described as compressing the head like a band, and incompletely relieved by analgesics. Restlessness, aggressive behavior and sleep inversion were also observed. The treatment with carbamazepine was discontinued and lamotrigine was introduced. The seizure frequency was reduced, and so were the headache and the behavioral symptoms.

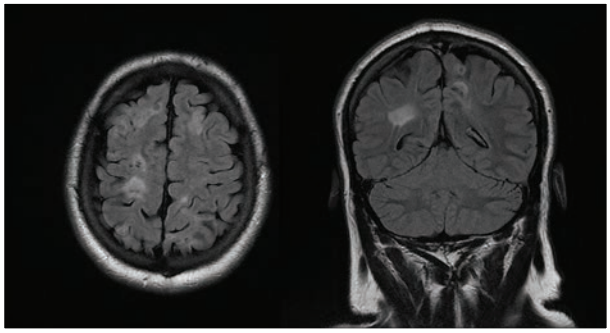

Fig. 2. Brain MRI, coronal and axial. Multiple supratentorial lesions

DISCUSSION

Numerous studies of comorbidity focus on primary headaches, such as migraine, describing them as the most prevalent in patients with epilepsy. Some authors, though, report similar prevalence of headache in epilepsy patients as compared to that of the general population. When describing this comorbidity, it should be noted that secondary headaches can also be frequent in patients with structural epilepsy, e.g. with brain tumors or other space-occupying lesions. Such lesions remain, of course, a reason for epilepsy that should not be overlooked. At the same time they can be detected relatively easily using widely available neuroimaging methods.

EEG is not routinely recommended in children with headache, but it is an assessment that should be performed in patients with prolonged complaints and especially in cases of comorbid headaches and different types of epileptic seizures in the same patient.

The clinical cases described in this paper demonstrate two different scenarios for comorbidity of epilepsy and headache. In the first case there is no evident relationship between the juvenile myoclonic epilepsy and the headache which has tension type characteristics. We accept that the patient had two coexisting and possibly unrelated disorders. As known from the literature, the incidence of headache in children with epilepsy may not be higher than in the general population, especially if it is non-migrainous (6). In the second case, structural lesions were evident on MRI, and combined with focal discharges on EEG, gave us a reason to establish the diagnosis of structural epilepsy. The postictal headache with tension type character in this patient is not an unexpected comorbidity. Though mainly emphasized in idiopathic occipital seizures, and with dominating migrainous features, postictal headache has been reported in patients with symptomatic epilepsy. It is in line with the statement that the onset of epileptic seizures may facilitate the onset of cortical spreading depression, and therefore the onset of headache (10).

Regarding treatment, both our patients received lamotrigine, an antiepileptic drug that acts by blocking voltage-sensitive sodium channels, and suppressing the excessive release of excitatory amino acids such as glutamate. It has been shown to be effective not only in epilepsy, but also in various types of

headache such as migraine (11). After the introduction of lamotrigine both patients improved regarding not only seizure frequency, but also headaches. This could be attributed to the beneficial effect of the drug and would justify its use in similar cases of comorbidity.

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