Epilepsy and migraine in children: a focus on clinical syndromes and diagnostic pitfalls

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Abstract

Epilepsy and migraine are quite common neurological disorders, both presenting with episodic, paroxysmal manifestations. A common etiopathogenetical basis has been hypothesized. Peri-ictal headache is present in the majority of the epileptic patients, however, may be neglected by the patients themselves as seizures represent the predominant disabling symptom. Comorbidity between migraine and several types of epilepsies has been increasingly reported in childhood; however, diagnosis of migraine in children is far to be easy and several symptoms need to be interpreted from the child's behavior. Indeed, clinical manifestations of several epileptic syndromes may imitate migraine and, in contrast, non-epileptic syndromes may imitate epilepsy. According to the etiopathogenetical link between migraine and epilepsy, common therapeutic strategies can be tried in both. The main epileptic syndromes of childhood associated with migraine as well as clinical and therapeutic implications of the comorbidity in children will be focused in the present review.

Keywords: Epilepsy, Migraine, Children, Comorbidity

Introduction

Migraine and epilepsy are very common neurological disorders, both presenting with episodic, paroxysmal manifestations. Migraine prevalence is 12% of general adult population and 23% of children and adolescent population, while the prevalence of epilepsy is 0.5-1 (http://www.who.int/topics/epilepsy) of the general population. There is an increasing body of evidence that migraine and epilepsy strongly occur in comorbidity and the prevalence of migraine in patients with epilepsy is 8-24%, 4, 5, 6. Comorbidity between the two disorders has been reported also in children, and prevalence data vary among the different studies. Although migraine is one of the most common neurological disorders affecting 4-10% of school-aged children, it appears to be underestimated. In epileptic patients, migraine is frequently neglected as seizures represent the predominant disabling symptom. Moreover, diagnosis of migraine is often far to be easy in children because they are not properly able to describe their symptoms. The features of the pain as type (in children is rarely throbbing) or duration (migraine attacks tend to be shorter in childhood) or the presence of photosensitivity and phonophobia is often not explicitly referred. Comorbidity between migraine and epilepsy would suggest important insights on the pathophysiological bases of both disorders as well as offer common effective therapies. A state of neuronal hyperexcitability has been hypothesized to explain the high rate of co-occurrence between migraine and epilepsy. However, this relationship is still under debate.

This review will focus on the main clinical and nosological aspects of migraine in children with epilepsy and their implications on diagnostic and therapeutic interventions.

Clinical presentation of migraine in epileptic patients

The main concern about the relationship between migraine and epilepsy is due to the frequent difficulty to identify what is "epilepsy" and what is "migraine" within the same patient. This "nosological impasse" is further felt in children in which migraine is often under-diagnosed. The second edition of the International Classification of Headache Disorders (ICHD-II) provided the diagnostic criteria of migraine in children. Clinical manifestations in terms of duration and localization of pain and associated symptoms of the migraine attacks in children, were detailed. The attacks tend to be short-lasting in children from 1 to 72 hours. The pain is referred to be bilateral and fronto-central. Photophobia and phonophobia are often not referred and need to be interpreted by the child's behavior. Limitation of the child's daily activities is one of the striking features. Both migraine with aura (MA) and migraine without aura (MWA) were reported in association with epilepsy. Although MWA is more frequent, it could be harder to be recognized and diagnosed in epileptic patients.

On the other hand, visual symptoms of migraine aura, together with other somatosensory, motor, and psychiatric manifestations, may be similar to those found in focal epileptic discharges with occipital, temporal or frontal seizures. The first aspect the clinicians has to face up to is the temporal relationship between migraine attacks and epileptic seizures. Peri-ictal headache, occurring before, during or after an epileptic seizure, is very common in patients with epilepsy. Peri-ictal headache is defined as occurring 5 minutes before the onset of the epileptic seizure and it was found in 5 to 15% of the epileptic patients. The ICHD-II included a peculiar form of peri-ictal headache, the migraine-triggered seizures or migraplegy. This was first described in 1960 by Lennox and Lennox, however, its existence is still controversial. Migraplegy was rarely reported in children and many of the cases were mis-diagnosed occipital or temporal lobe epilepsy. Ictal headache occurs when migraine is the sole ictal manifestation. The ICHD-II includes Hemicrania-Epileptica (HE), a newly reported syndrome, in which migraine is the sole ictal symptom and occurs with concomitant EEG epileptiform paroxysmal discharges homolaterally to the pain. Of the five cases in the literature, none met the current ICHD-II criteria for HE. Four patients showed partial status epilepticus in the occipital lobes, one had absence status 17, 18, 19, 9. Post-ictal headache occurs in 10-40% of patients with epilepsy and in particular in patients with occipital lobe epilepsy. It develops within 3 hours following the seizure and resolves within 72 h after the seizure.

Conversely, peri-ictal headache has been considered as part of the seizure itself and not exactly comorbid condition with migraine. Indeed, ictal headache may occur in children with occipital lobe epilepsy in association with visual symptoms and dysautonomic manifestations. As well as peri-ictal headache, migraine attacks may occur separately in-between epileptic seizures (inter-ictal headache) in most patients. Benign Childhood Epileptic Syndromes mainly comorbid with migraine

Benign Occipital Epilepsy of Childhood

Andermann et al reported patients with occipital lobe epilepsy having a high risk to present migraine. Benign Occipital Epilepsy of Childhood (BOEC) is commonly associated to migraine. The Early-Onset BOEC (Panayiotopoulos syndrome) occurs in 2-3/1000 in the general pediatric population and is mainly characterized by ictal autonomic manifestations. The full emetic triad, nausea, retching and vomiting is observed in the majority of patients, and it is often followed by post-ictal headache. Moreover, behavioral changes as restlessness, terror or quietness may appear. Occipital or parietal-temporal spikes are detected at the EEG recording. The late-onset BOEC (Gastaut syndrome) accounts for about 2-7% of benign childhood focal epilepsies and is mainly characterized by visual hallucinations and focal motor seizures, occurring at daytime. Ictal headache often precedes the visual or other occipital symptoms, whereas severe, unilateral and pulsating post-ictal headache, may be indistinguishable from migraine and is present in half of the patients. Despite characteristic clinical and EEG manifestations of the occipital epilepsies, they are often confused with several non-epileptic disorders including migraine. The full EEG testing is crucial to an accurate diagnosis. Italiano and coworkers reported a patient with recurrent occipital seizures presenting status migrainosus as the sole ictal manifestation. Conversely, non-epileptic conditions in children may be misdiagnosed as occipital lobe epilepsy. The Alice in the Wonderland syndrome, is characterized by episodic fits of visual hallucinations as micropsia, macropsia, palinopsia, derealization and depersonalization feelings and impaired sense of passage of time. This bizarre neurological picture may be found in parietal-occipital temporal epilepsy and migraine, too.26. The EEG monitoring during the attacks is of crucial importance for the appropriate diagnosis and treatment choice.
Antiepileptic drugs have been used in such patients 27, 29.

Bening Rolandic Epilepsy

Bening rolandic epilepsy is the most common idiopathic epileptic syndrome in childhood 29.

It is characterized by unilateral facial sensory motor symptoms, dysarthria and hypersalivation, with onset between 7 to 10 years 21.

Comorbidity between rolandic epilepsy and migraine has been robustly reported 29. A linkage analysis in a wide pedigree from Belgium with occipitotemporal lobe epilepsy associated with MA revealed a susceptibility locus on chromosome 9q21-2247.

A mutation of the SLC2A1 gene was identified in two monochorionic twins presenting a constellation of episodic neurological disorders such as paroxysmal exercise-induced epileptic syndromes.

Familial Hemiplegic Migraine type 1, A common genetic background was reported but monogenic defects have been found only in few patients with rare syndromes associated with migraine.

A speculative case presenting this relationship concerned a 14-year-old girl that presented her first generalized tonic–clonic seizure preceded and followed by a 3-day epileptiform status mimoriosus.

The attack resolved only after intravenous diazepam administration and occurred after prolonged television viewing.

Photosensitomaximal response (PRP) was detected after IPS in the EEG testing 17.

Although this case was first labeled as migralepsy, it was subsequently reviewed by Sances and coworkers, and latterly considered as case of occipital lobe epilepsy imitating migraine 15.

JME is a generalized epilepsy syndrome with onset within the first decade whose complete clinical expression (absences, myoclonic jerks and GTCS) appears later-in life in about 37.

The syndrome has a strong genetic background as most of the patients present a positive family history 21.

Dysfunction associated with JME at the level of ion channels subunits, acetylcholine receptors, somatosensory memories, for the regulation of apoptosis 38.

The intelectual EEG typically shows generalised polyspikes and generalised spike and wave discharges 21.

Moreover, JME is a syndrome with a high incidence of clinical or EEG photosensitivity and PRP is typically observed in such patients 39.

Comorbidity between migraine and JME has been retrospectively studied in young adults 39.

Among 75 patients affected from JME, the authors found migraine in 41% of them (RR 4.4).

Both MA (27%) and MwA (15%) were present. A higher risk of MA (7.3) and MwA (3.6) was found in JME compared to the general population.

A close temporal relationship between migraine and epileptic seizures was evidenced in 24% of patients as pre-or post-ictal headache.

Indeed the prevalence of migraine in this group of patients with JME resulted to be higher than other groups of patients with unselected seizures epidemies for MA 39.

A possible genetic and pathophysiological mechanism between the two conditions could be expressed by the presence of photosensitivity in most of the JME patients. A bidirectional link between two disorders mediated by a common neurophysiological dysfunction has been hypothesized 45.

A casual relationship is unlikely as the prevalence of migraine and epilepsy in comorbidity appear to be quite higher than either prevalences per se in the general population.

Neuronal hyperexcitability has been hypothesized to be the pathophysiological basis of migraine.

The pain during the attack is mediated by the activation of the trigeminovascular system 16.

On the other hand, a depolarisation wave across the brain cortex 15.

It was subsequently reviewed by Sances and coworkers, and lastly considered as case of occipital lobe epilepsy imitating migraine 15.

Onset of epilepsy preceded the onset of migraine in all patients 44.

Inter-ictal migraine occurred in all patients, 46% had migraine (43.5%) and the headache usually started in the same year or after the diagnosis of epilepsy 40.

Children with MA resulted to have an increased 4.1-fold risk for epilepsy in a population-based study 41.

The risk was not increased in patients with MA.

Migraine prevalence was 20.2% in cases and 6.9% in controls 41.

Migraine was highly prevalent in a population of children with epilepsy with a different distribution according to the subtypes MA (18.8%) and MwA (45.3%) 42.

A speculative investigation has been performed in a wide population of children with diagnosis of primary headache (1,795 subjects) in which comorbidity with idiopathic cryptogenic epilepsy or unprovoked seizures was found in 56/1, 795 subjects (3.1%) 43.

Migraine was associated to epilepsy in 46/58 patients with no significant differences between MA compared to MwA.

The majority of patients showed focal idiopathic/cryptogenic epilepsy (76.8%) rather than idiopathic generalized epilepsy (17.9%) 43.

Prevalence of migraine was recently investigated in a cohort of 316/693 (46%) of children from Southern Italy by our group.

Migraine was present in 14% of patients with idiopathic/cryptogenic epilepsy compared to 0.97% of controls with 16.50 higher risk than controls.

MwA was found in 24% of patients with partial idiopathic/cryptogenic epilepsy and 6% of patients with generalized seizures 44.

It is notable that patients in all patients, occasionally presenting with epilepsy, among patients primary idiopathic occipital lobe epilepsy, three presented post-ictal headache whereas one had ictal headache.

The epilepsy preceded migraine in 63% of patients, conversely, migraine preceded epilepsy in 37%.

Onset of epilepsy preceded the onset of migraine in all patients 44.

Discussion

Although the association between epilepsy and migraine has been abundantly investigated for the last 20 years, a clear etiopathogenetical basis of their comorbidity has not been demonstrated, yet.

There are currently three main hypotheses to explain the relationship between migraine and epilepsy: a) casual association as they are very common in the general population b) the two conditions may be causally related as migraine can be cause of epilepsy or vice versa c) the existence of a common genetic background4, 45.

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A causally link between rolandic epilepsy and migraine due to mutations of ELP4 gene has not been reported,

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