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Seminars in
Pediatric
Neurology

The Comorbidity of Migraine and Epilepsy in Children and Adolescents

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Migraine and epilepsy share a number of clinical attributes, including pathophysiology and clinical expression. Both are paroxysmal in nature and thus constitute episodic disorders, yet either may be chronic and/or recurrent. Epileptic seizures and migraine headaches may be mistaken one for the other and may even overlap. In particular, occipital lobe seizures may be misdiagnosed as migraine auras. In this article, we review the relationship between migraine and epilepsy, including the known genetic contributions to both conditions, prodromal, ictal, and postictal headache and shared pathophysiology and treatment options. We describe clinical conditions in which both migraine and epilepsy are prominent features. Lastly, we discuss electronecephaographic abnormalities that have been known to occur in individuals with migraine.
Semin Pediatr Neurol 23:83-91 Published by Elsevier Inc.

Introduction

Headache is a common somatic complaint in children and adolescents.[1] Migraine and epilepsy share common clinical features and are two of the most common conditions seen in pediatric neurology. Both are considered disorders of neuronal hyperexcitability that result in episodic attacks of neurologic dysfunction, partially prevented by antiepileptic drugs. According to the Centers for Disease Control, adults with no history of epilepsy were found to have severe headache or migraine in 16.2%, whereas the presence of active epilepsy increased the prevalence of severe headache or migraine to 35.5%.[2] Migraine and epilepsy both have various amounts of headache, gastrointestinal, autonomic, and psychological features.[3] A large epidemiologic study revealed that adult persons with epilepsy were 2.4 times more likely to develop migraine than their relatives without epilepsy.[4] A survey study of 597 patients from 32 epilepsy clinics, found that the age at the onset of epilepsy was lower in patients with seizure-related headaches than in those without, and the risk of occurrence of seizure-related headaches was significantly greater in patients with longer epilepsy duration. Seizure-related headaches could be classified as a type of migraine in 46.2% of patients with prodromal seizure-related headache and in 36.3% of patients with postictal seizure-related headache.[5] Individuals with migraine and with epilepsy each go through an orderly sequence of events from the interictal state to the preictal (premonitory) and finally the postictal phase and then resolution.[6] In a recent study of 400 children presenting to a pediatric epilepsy center, migraine was found in 25%, greater than that reported for children without epilepsy (3%-23%).[7] Children who were older, as well as children with two epilepsy syndromes (benign rolandic epilepsy and juvenile myoclonic epilepsy) were more likely to have migraines.

Attacks of migraine and of epilepsy are each characterized by abrupt, paroxysmal changes in mood and behavior, sometimes consciousness and may be accompanied by changes in visual, motor, sensory, or speech function. Thus, drawing the distinction between attacks of migraine and epilepsy may be complex. In addition, a number of underlying neurologic conditions may predispose children to both seizures and headache.[8] Acute treatments tend to be condition specific (eg, benzodiazepines for acute seizures vs triptans for acute migraine), whereas, preventive options may overlap the therapy of both migraine and epilepsy. Generally, the preventive treatment of migraine is targeted to treat any comorbid condition as well. Indeed, the only medication Food and Drug Administration-approved for the preventive treatment of migraine in the pediatric age group is an anticonvulsant (Topiramate).

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1071-9091/16/$-see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.spen.2016.01.012

This article reviews current research on the comorbidity of migraine and epilepsy. We discuss the known genetic contributions to migraine and epilepsy, the shared semiology between migraine and epilepsy, common pathophysiological mechanisms involving both conditions, treatment overlap between migraine and epilepsy, clinical conditions in which migraine and epilepsy may be common and electroencephalographic (EEG) abnormalities in individuals with migraine.

Known Genetic Contributions to Migraine and Epilepsy

A relationship between migraine and epilepsy has long been suspected.[9] The association between migraine and epilepsy has been shown to be present across idiopathic, cryptogenic, and symptomatic types of epilepsy.[10] A more recent study indicated a shared genetic susceptibility to migraine with aura in may types of nonacquired focal and generalized epilepsies.[11] In the pediatric neurology literature, before the mid-2000s there was conflicting evidence of a specific association between migraine and benign rolandic epilepsy (benign childhood epilepsy with centrotemporal spikes). In 2006, a gender and age-matched cohort study compared rates of definite, probable and possible migraine, as well as, no migraine. The authors found that those with benign rolandic epilepsy had higher rates of definite, probable, and possible migraine, and of migraine equivalents, excluding motion sickness, than did those without seizures; however, they did not differ significantly from the cryptogenic or symptomatic partial epilepsy cohort. The authors thus concluded that their study confirms the increased prevalence of migraine in children with epilepsy; however, it does not support the concept that those with benign rolandic epilepsy have a substantially higher rate of migraine than do other epilepsy types.[12]

Subsequent studies have shown the prevalence of migraine in benign rolandic epilepsy at 15% vs 7% in nonepilepsy probands and in siblings of benign rolandic epilepsy probands the authors found a prevalence of 14% vs 4% in nonepilepsy siblings.[13] Indeed, a genome-wide linkage analysis of the migraine phenotype in 38 families with rolandic epilepsy found evidence of linkage to migraine at chromosome 17q12-22 and suggestive evidence at 1q23.1-23.2, a known locus associated to familial hemiplegic migraine (FHM), type 2.[14] A case report recently identified a 3-generation family with 5 patients having a novel *ATP1A2* mutation on exon 19 that co-segregated in the 5 living relatives with migraine, 4 of whom had hemiplegic migraine, type 2.[15] In addition, a 4-generation Italian family was described with FHM type 2 and epilepsy due to a novel *ATP1A2* missense mutation.[16] Regarding FHM type 3, a recent report identified the *T1174S SCN1A* (NaV1.1) mutation in a 3-generation family with both epileptic and FHM phenotypes.[17]

Other groups have looked specifically at the comorbidity of migraine with forms of occipital epilepsy. A syndrome of idiopathic occipital epilepsy with visual hallucinations is associated with blindness, which occurs usually from the beginning and postictal headache, often indistinguishable from migraine. However, the elementary visual hallucinations, it was concluded, cannot be anything else but visual seizures. They were found to be entirely different from migraine visual aura in color, shape, size, location, movement, duration, and development. In distinction, the visual aura of migraine with aura and acephalgic migraine was said to start with predominantly flickering black and white, linear, and zigzag patterns in the center of the visual field, gradually expanding over minutes toward the periphery of 1 hemifield and often leaving a scotoma.[18] A later onset benign occipital epilepsy of childhood (BOEC) has been described (often referred to as Gastaut syndrome), with the suggestion that EEG may play a role in select cases to distinguish migraine from epilepsy.[19-22] A cross-sectional study of 75 patients with juvenile myoclonic epilepsy, showed a higher prevalence of migraine with and without aura than in the general population.[23]

Shared Semiology Between Migraine and Epilepsy

There is a tendency for specialists in epilepsy to define an electroclinical event by EEG recordings whereas an approach based upon classification is more commonly used by neurologists who specialize in headache.[24] The International Headache Society recognizes 3 main types of headache related to seizure as follows: migraine aura-triggered seizure (or migralepsy), hemicrania epileptica, and postictal headache. Migralepsy (1.4.4 ICHD-III, beta) is a particularly rare and somewhat controversial condition wherein a seizure occurs during or within one hour after a migraine aura, and it can mime occipital lobe seizures, which might be under recognized without EEG recording.[25,26] Hemicrania epileptica (7.6.1 ICHD-III, beta) is also a rare condition with headache occurring during a partial epileptic seizure, ipsilateral to the epileptic discharge, and remitting immediately or soon after the seizure has ended. Some authors feel that ictal epileptic headaches should be considered a secondary headache disorder, as the condition is primarily an epileptic condition with headache presenting as a manifestation of the seizure.[27] Perhaps the most common in the classification scheme is postictal headache (7.6.2, ICHD-III, beta), or headache caused by and occurring within 3 hours after an epileptic seizure, and remitting spontaneously within 72 hours after seizure stopped.[28] A recent review article pointed out the confusion among the terms listed earlier and called for a revision of terminology and classification.[29,30]

A multicenter Italian study examined periictal and interictal headache in 142 children and adolescents with idiopathic epilepsy. Postictal headaches were most frequent (62%). Preictal headaches were less common (30%). Interictal headaches were described in 57.6%. Clear migrainous features were present in 93% of preictal and 81.4% of postictal headaches. Interictal headaches met criteria for migraines in 87%.[31]