REVIEW ARTICLE

Migraine and Epilepsy in Children: A Narrative Review of Comorbidity and Similar Treatment Option

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Keywords:

Children

Migraine

Epilepsy

Comorbidity

Received:

05- Jan -2024

Accepted:

13- May -2024

Published:

22- Jun -2024

ABSTRACT

Migraine and epilepsy belong to the category of chronic paroxysmal neurological disorders and share numerous clinical features, as well as potential treatment options. This narrative review emphasizes the similarities between pediatric migraine and epilepsy, exploring epidemiology, pathophysiology, genetics, clinical presentation, and pharmacology. Although various syndromes exhibit symptoms common to both conditions, further research is needed to clarify the underlying pathophysiological and genetic connections contributing to their coexistence. Prophylactic medications used in the management of both migraines and epilepsy exhibit similar pharmacological characteristics. The review assesses treatment strategies for epilepsy and migraines, emphasizing antiseizure medications alongside nonpharmacological interventions like ketogenic diet, supplements, and vagal nerve stimulation. It aims to highlight how these interventions, originally targeted for epilepsy, may also show promise in preventing migraines. The urgent need for further randomized, controlled clinical trials investigating both pharmacological and nonpharmacological interventions for treating both disorders is emphasized, aiming to pave the way for innovative therapeutic strategies.

How to cite this article: Momen AA, Jelodar Gh, Azizimalamiri R. Migraine and Epilepsy in Children: A Narrative Review of Comorbidity and Similar Treatment Options. Iran J Child Neurol. Summer 2024; 18(3): 9-20. https://doi.org/10.22037/ijcn.v18i3.44282

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Introduction

Migraine and epilepsy, the predominant diagnoses within pediatric neurology, fall under the category of chronic neurological disorders characterized by recurrent episodes of nervous system dysfunction (1). Both genetic and environmental factors play crucial roles in the manifestation of these conditions (2). Clinically, migraine and epilepsy share similar sensorimotor and cognitive impairments originating in the cerebral cortex and subject to subcortical modulation (3). Common manifestations include postictal lethargy, consciousness disorders, visual disturbances, dizziness, paresthesia, hemiparesis, and aphasia (4).

Historically, migraine was categorized as a disease on the borderland of epilepsy, differing notably in the duration of visual symptoms and the severity of headaches (5). Importantly, seizures, unlike migraines, can pose life-threatening risks (6). Despite the high prevalence of migraine in the general population, the coexistence of migraine and epilepsy may not be mere coincidence, as statistical evidence suggests a mutual influence between the two (7).

There is a significant overlap in prophylactic pharmacotherapy for both conditions, although the precise mechanism of this comorbidity remains incompletely understood (8). A bidirectional mechanism has been proposed, suggesting that epilepsy may heighten the risk of migraine, and vice versa (9). Cortical hyperexcitability is theorized as a potential underlying pathophysiological mechanism for both conditions (2).

Epidemiology

Epilepsy prevalence among pediatric populations ranges from 0.4% to 1.0%, peaking in children under 3 years of age (10). Certain epileptic syndromes are age-dependent and self-limiting, while others lack age correlation (11). Benign epilepsy with centrotemporal spikes often sees spontaneous remission during the peripubertal period (12). Studies generally indicate no gender-specific differences in epilepsy prevalence, except for childhood absence epilepsy, more frequent in females, and syndromes like Doose and Landau-Kleffner, which are more common in males (13).

Contrastingly, migraine is up to 20 times more common than epilepsy in the pediatric demographic, with an approximately 8% prevalence in children and adolescents, lower under age 14 (14). Unlike epilepsy, migraine exhibits gender specificity, with females more susceptible in the population over 14 years, while gender prevalence is equal in younger ages (15). Migraine without aura is five times more prevalent in children than migraine with aura, a ratio that shifts to 3 to 4 times in adults (16).

Compared to the general population, epilepsy is significantly more frequent in individuals with migraines (17). Studies on pediatric patients with headaches reveal a 3% co-occurrence of epilepsy, mostly associated with childhood migraine. Headaches precede epilepsy in 27% of cases, while both conditions onset simultaneously in 29% (18). Research indicates an elevated risk of unprovoked seizures in children with migraine with aura compared to those without (9). Moreover, individuals with epilepsy have a 2.4 to 4.5 times higher rate of migraine than those without (19). Recent pediatric studies report a 25% migraine prevalence in children with epilepsy, increasing to 32% in adolescents (7).

Pathogenesis

Mutations in specific genes situated on chromosomes 9, 12, and 14 are associated with distinct migraine and epilepsy syndromes (20, 21). The cellular connection between migraine

and epilepsy involves channelopathies (2), disruptions in ion balance within neuronal and glial cells (22), disturbances in GABAergic or glutamatergic systems (1), and disorders in mitochondrial function (23). Familial hemiplegic migraine (FHM) represents a rare, monogenic, autosomal dominant form of migraine, with three known genes—CACNA1A, ATP1A2, and SCN1A—currently identified as involved. Familial hemiplegic migraine subtypes have been extensively studied, with three of them being better characterized. Mutations in CACNA1A are linked with FHM type 1 (FHM1), while mutations in ATP1A2 are associated with FHM type 2 (FHM2), and mutations in SCN1A lead to FHM type 3 (FHM3). Although the correlation with epilepsy is more pronounced in FHM2 (with epilepsy present in 20% of families), epilepsy can also occur in FHM1 and FHM3 (24). Furthermore, these genes, including CACNA1A, ATP1A2, and SCN1A, are implicated in childhood epilepsies such as childhood absence epilepsy and Dravet syndrome (25, 26). Similarly, genes such as SLC1A3, POLG, and C10orF2 are also associated with the interplay between migraine and epilepsy (27).

Recent research indicates a genetic link between various epileptic syndromes and migraines, though the specific genetic locations remain unidentified (1). In benign occipital epilepsy of childhood, postictal headache occurs in 36% of cases, and a heightened risk of migraines is observed in Panayiotopoulos syndrome and benign Rolandic epilepsy (28). Despite not fully understanding the exact mechanisms of migraine and epilepsy, recent studies propose neocortical hyperexcitability as a shared underlying factor (29).

Recent research indicates that neocortical hyperexcitability, stemming from similar molecular and genetic dysfunctions, serves as the primary pathophysiological basis for both conditions. In epilepsy, this hyperexcitability results in abnormal neuronal discharges and paroxysmal depolarizing shifts. Most studies suggest that migraine aura arises from the transition of neocortical hyperexcitability to cortical spreading depression, a phenomenon where depolarization cascades through the cortex, affecting intracellular calcium and neurotransmitter levels, leading to prolonged neural suppression. (29) Despite the associated increase in cerebral blood flow during the depolarization phase, reduced neural activity follows, possibly activating the trigeminal nociceptor system, triggering neuroinflammation and pain during migraine attacks (29). However, recent debate surrounds the role of cortical spreading depression in migraine, with some disputing its significance in migraine aura. Currently, cortical spreading depression is generally viewed as a shared mechanism in both epilepsy and migraine, supported by evidence linking it to neuronal synchronization preceding its onset, possibly mediated by glutamate (30). Occipital cortex sensitivity to cortical spreading depression reinforces the notion of a lower activation threshold in the cortex, possibly contributing to both conditions (29, 31-33).

Ictal headache, rarely the sole manifestation of seizures, may be triggered by epileptic discharges activating the trigeminovascular system (32). Clinical observations, such as the association of postictal headaches with occipital seizures and the prophylactic effects of certain antiepileptic drugs on migraines, provide support for the hyperexcitability hypothesis as a potential common pathophysiological mechanism (34).

Ongoing investigations suggest a potential link between epilepsy and migraines through pituitary adenylate cyclase-activating polypeptide (PACAP) (35). Acute seizures increase PACAP levels, which may induce headache and migraine-like attacks, especially in patients with migraine (36). Therapies targeting PACAP and its receptors could present a promising strategy against migraines, although concerns about potential side effects limit their use in patients with comorbid epilepsy (37).

Classification of Headaches

Categorizing headaches linked to epilepsy involves considering their temporal association with seizures (38). Interictal headaches occur more than 24 hours before or after epileptic seizures, spanning over 72 hours (18). Peri-ictal headaches, like migraines, emerge shortly before, during, or immediately after a seizure, presenting a diagnostic challenge (18). While distinguishing between epilepsy and peri-ictal headaches is typically clear, temporal or symptomatic overlap can occur (18). These temporally classified headache types (pre-ictal, post-ictal, ictal, and interictal) may coexist in the same individual (9, 18).

Accurate classification of epilepsy and headaches is essential for timely and appropriate treatment, requiring a detailed description of symptoms and their temporal relationships (39). Notably, the ILAE seizure classification lacks a specific category for seizures exhibiting overlapping symptoms with headaches (40). In contrast, the ICHD-III includes various categories of seizure-related headaches, such as migraine aura-triggered seizure, ictal epileptic headache, and post-ictal headache (41).

Migraine-Aura Triggered Seizure

In the third edition of the International Classification of Headache Disorders (ICHD-III), this particular condition is classified as a complication arising from migraine (41). It is characterized by an epileptic seizure that is triggered by a migraine attack with aura. The diagnostic criteria specify that the seizure occurs either during or within one hour of a migraine attack with aura. This phenomenon, once referred to as "migralepsy," is an infrequent event observed in individuals with a history of migraine with aura (42). Some scholars contend that the term "migralepsy" is outdated, suggesting that it may represent a phenomenon that likely does not exist and is often the result of a misinterpretation of symptoms (43). Notably, "migralepsy" is not included in the seizure classification provided by the International League Against Epilepsy. Moreover, there may be confusion between occipital epilepsy and seizures triggered by migraine aura (44). Diagnosing occipital lobe epilepsy proves challenging, as visual phenomena and headaches may be the sole symptoms (45). Patients may struggle to differentiate between visual auras and bright lights that induce headaches or photosensitive seizures (46).

Preictal Headache

Pre-seizure headaches, not meeting "migralepsy" criteria, are rare and not categorized in ICHD-III (47). There's a potential for both patients and physicians to overlook these headaches. In a study by Yankovsky et al. with 47 patients having intractable epilepsy and peri-ictal headaches, 23% experienced preictal headaches, mostly localized to the seizure focus (48). The study suggests that increased blood flow to the seizure focus, occurring before symptoms or EEG changes, may cause the headache preceding the seizure, likely through trigeminovascular system activation. Further research is essential to understand the

occurrence and features of preictal headaches.

Ictal Epileptic Headache

The most recent version of ICHD-III has recently included the term "ictal epileptic headache" (49). This refers to a headache triggered by a partial epileptic seizure, appearing as part of the seizure discharge (50). Furthermore, one of the following features is necessary: the headache is on the same side as the ictal discharge, and/or it significantly improves or resolves immediately after the partial seizure ends (18). This condition is thought to be insufficiently recognized and reported. Parisi et al. highlighted the importance of identifying this diagnosis to initiate the appropriate investigation and treatment (32). Nonconvulsive status epilepticus, presenting as a single migraine attack (referred to as status epilepticus migrainosus), has also been documented. Hemicrania epileptica, a rare ictal epileptic headache, likely results from reactive hyperemia (51). EEG evidence demonstrating synchronicity and ipsilaterality of manifestations is necessary to confirm the diagnosis (51).

Postictal Headache

Post-ictal headache, a headache resulting from an epileptic seizure, is characterized by its occurrence within three hours after the seizure event and spontaneous resolution within 72 hours after seizure termination (30). It is noteworthy that this type of peri-ictal headache is observed in less than 45% of individuals with epilepsy, despite being the most prevalent type of peri-ictal headaches (30). About half of those experiencing post-ictal headache report symptoms resembling migraines. According to a 2019 meta-analysis, one-third of individuals with epilepsy have post-ictal headache, with 16% experiencing post-ictal migraine (52). Intriguingly, individuals with occipital epilepsy in focal epilepsy are more prone to post-ictal headache compared to those with epilepsy originating in the frontal or temporal lobes. Additionally, post-ictal headache is more frequently encountered after convulsive seizures than after non-convulsive seizures (53).

Epilepsy Syndromes in Children and Migraine

Self-limited epilepsy with autonomic seizures (SeLEAS), also known as Panayiotopoulos syndrome, typically presents within the age range of 3 to 6 years, characterized by sporadic focal seizures that often endure for extended periods, predominantly occurring during nighttime. These seizures involve a combination of autonomic and behavioral manifestations, accompanied by alterations in consciousness. Headaches may accompany the preictal phase. Notable features include abnormalities in occipital EEG readings and autonomic symptoms such as vomiting, paleness, mydriasis, and sweating. (54, 55).

Childhood occipital visual epilepsy (COVE), previously known as Gastaut syndrome or late onset benign occipital epilepsy, a rare condition, begins between ages 3 and 15, peaking at 8-9 years. It is characterized by brief focal seizures with visual symptoms, followed by postictal headaches, and, in a significant number of cases, nausea and vomiting (55).

Self-limited epilepsy with centrotemporal spikes (SeLECTS), also known as benign Rolandic epilepsy or benign epilepsy with centrotemporal spikes, the predominant form of pediatric idiopathic focal epilepsy, typically initiates between the ages of 7 and 10. Seizures involve unilateral sensorimotor facial manifestations progressing to one arm, along with unilateral paresthesias within the oral cavity and anarthria. These patients also exhibit an increased incidence of episodic abdominal pain and headaches. Research indicates a strong association between

SeLECTS and migraine, challenging previously optimistic prognoses due to subtle neurocognitive challenges observed in affected children (55).

Familial hemiplegic migraine (FHM) is a rare, inherited disorder marked by migraines accompanied by specific symptoms such as motor weakness. FHM has three known subtypes, each caused by distinct genetic mutations and varying likelihoods of epilepsy. (24) The most common subtype, FHM type 1, stems from a mutation in the CACNA1A gene, leading to cortical spreading depression and hyperexcitability, potentially resulting in seizures and ataxia. A severe phenotype of FHM type 1 is associated with the S218L CACNA1A mutation, while the T666M mutation leads to frequent migraines, nystagmus, and severe coma episodes. (56) FHM type 2 results from a mutation in the ATP1A2 gene, with epilepsy being more prevalent compared to other FHM subtypes. Screening for ATP1A2 mutations is advised in families with migraine and epilepsy history. (57) FHM type 3 is linked to a mutation in the SCN1A gene, also associated with various epilepsy syndromes such as Dravet. (58) Additionally, mutations in the PRRT2 gene can cause paroxysmal disorders including hemiplegic migraine and epilepsy. (58)

Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) constitute a genetically diverse mitochondrial ailment characterized by central nervous system manifestations, including seizures, hemiparesis, and headaches (59). Sturge-Weber syndrome, identified by nevus flammeus and ipsilateral leptomeningeal angiomas, correlates with focal seizures and migraine headaches. Neurological symptoms are thought to arise from compression of brain parenchyma by leptomeningeal angiomas, and postictal headaches are believed to result from epileptic hypersynchronization facilitating cortical spreading depression (60).

Electroencephalography (EEG) Application in the Headaches

Individuals experiencing hemiplegic migraine often display abnormalities in their EEG patterns (61). The ictal and postictal EEG findings typically indicate a moderate to severe level of delta activity in regions opposite to the hemiplegia (61). A study involving 126 children diagnosed with epilepsy or migraine highlighted that unilateral occipital EEG spikes, coupled with the epileptiform photoparoxysmal response, suggest epilepsy (62). In contrast, an excessive photic driving response is observed at flash rates exceeding 20 Hz (H-response). Sensitivity ranges from 25% to 100%, and specificity from 80% to 91%. Despite the relatively high sensitivities and specificities of the H-response in discerning migraine patients from controls and tension headache sufferers, it is not deemed more effective than utilizing history and examination for diagnosing headaches, thus not recommended for clinical practice. However, it could prove beneficial for clinical diagnosis in complex headache cases and assist in monitoring therapeutic responses (63). The use of video EEG monitoring proves valuable in discerning between a migraine aura and an epileptic aura (64). In the context of migraine auras, there may be occasional observations of paroxysmal spikes that bear a resemblance to ictal epileptiform EEG patterns. However, a critical distinction exists: EEG readings during migraine aura exhibit alterations in amplitude separated by normal EEG activity, while ictal epileptiform EEG patterns display a higher frequency with lower amplitude, progressing into rhythmic epileptiform discharge of high amplitude (65). This differentiation underscores the significance of meticulous EEG

analysis in distinguishing between migraine and epilepsy, highlighting the potential utility of video EEG monitoring in clinical assessments.

Intersection of Treatment and Prevention

Clinical research has lent support to the utilization of conventional antiepileptic drugs for migraine prevention in adults (66). Valproate (500-1500 mg/d) and topiramate (200 mg/d) present the most compelling evidence for diminishing migraine frequency in adults (66). Conversely, the data supporting gabapentin (900-2400 mg/d) remains insufficient (66). Although topiramate has gained FDA approval for migraine prophylaxis in individuals aged 12 and above, its effectiveness in preventing pediatric migraines remains uncertain, as evidenced by the inconclusive results of the CHAMP trial (67).

In contrast to trials involving adult migraines, where the placebo response rate stands at 35%, pediatric trials with a placebo reveal response rates of 50% or higher, suggesting a potential therapeutic advantage of the placebo effect in pediatric migraine treatment (68). While valproate might prove effective in preventing migraines in adults, there is a lack of evidence supporting its use in pediatric cases (69, 70). Lamotrigine has demonstrated efficacy in addressing Sturge-Weber syndrome characterized by chronic headaches and hemiplegic seizures (71). Furthermore, while Lamotrigine has shown potential effectiveness in treating migraine with aura, its use as a prophylactic medication for migraine without aura is not recommended. This recommendation is grounded in current understanding and clinical evidence, which indicate that other medications may be more suitable for preventing migraines in individuals without aura symptoms. Therefore, Lamotrigine is generally not advised as the first-line prophylactic treatment for migraine without aura, and alternative therapies should be considered in these cases. (72, 73) Additionally, the efficacy of other antiepileptic drugs, such as pregabalin, zonisamide, and levetiracetam, in migraine treatment remains unconfirmed (70).

Prophylactic medications for migraines that are not antiepileptic include tricyclic antidepressants (74), beta-blockers (69), and calcium channel blockers (75). Calcium channel blockers like verapamil, flunarizine, and cinnarizine (76) may prove effective in migraine prevention and are at times employed as supplementary therapy to enhance antiepileptic drug concentrations in the brain. (1)

Nonpharmacological interventions, such as vagal nerve stimulation, have demonstrated effectiveness in addressing both migraines and epilepsy, potentially through mechanisms such as EEG desynchronization, alterations in thalamic blood flow, and changes in neurochemical composition in cerebrospinal fluid (77). Dietary therapy, notably the ketogenic diet, has proven effective in treating epilepsy, with some studies suggesting its potential role in preventing migraines (78). However, the limited sample sizes and compliance challenges in these studies underscore the need for further exploration through larger randomized controlled trials.

In Conclusion

Recent research has solidly established a connection between headaches, particularly migraines, and epilepsy, underscoring the frequent coexistence of these conditions in neurological contexts. It is imperative to raise awareness of this association during both neurological and medical training, as it can significantly enhance the vigilance of neurologists and general physicians regarding the intricate relationship

between headaches and epilepsy. To delve deeper into this association, comprehensive longitudinal studies involving large, multicentric cohorts become essential, providing a more nuanced understanding of the nuanced dynamics at play.

Continued research efforts should place a strong emphasis on uncovering the pathophysiological mechanisms that link headaches to epilepsy, aiming to refine our grasp of these complex conditions. Moreover, there is a critical need to enhance the management strategies for individuals experiencing both headaches and epilepsy. At its core, the manifestation of headaches and epilepsy is indicative of altered excitability within the neuronal network. Thus, exploring the multifaceted causes contributing to various constellations of epilepsy-headache scenarios is crucial for the development of aetiological diagnostic classifications and corresponding therapeutic approaches. This holistic approach is vital for improving the overall care and outcomes for individuals grappling with both conditions.

Acknowledgment

The Research Deputy of Ahvaz Jundishapur University offered spiritual support for this study, without any engagement in the study design, data collection, analysis, interpretation, report writing, or the decision to submit the article for publication.

Authors' Contribution

Ali Akbar Momen, Golamreza Jelodar, and Reza Azizmalamiri have all made substantial contributions to the conception, design, and execution of the work. Each author has been actively involved in drafting and revising the manuscript critically for important intellectual content. Furthermore, all authors have given their final approval of the version to be published and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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