

# The comorbidity of headaches in pediatric epilepsy patients: How common and what types?

Hanin Al-Gethami, MD, Muhammad Talal Alrifai, MD, Ahmed AlRumayyan, MD, Waleed AlTuwaijri, MD, Duaa Baarmah, MD.

## ABSTRACT

**الأهداف:** كان هدفنا هو تقدير مدى انتشار الصداع وخصائصه لدى مرضى الصرع عند الأطفال.

**المنهجية:** أجريت هذه الدراسة على مدى 6 أشهر من يناير 2018م إلى يونيو 2018م في مستشفى الملك عبد الله التخصصي للأطفال، مدينة الملك عبد العزيز الطبية، الرياض، باستخدام استبيان منظم.

**النتائج:** كان هناك 142 مريضاً مسجلين (ذكور، 57.7%؛ متوسط العمر،  $10.7 \pm 3.1$  سنة) يعانون من الصرع مجهول السبب (81%،  $n=115$ ) أو الصرع العرضي (19%،  $n=27$ ). بالإضافة إلى مرضى الصرع البؤري (72%،  $n=102$ ) أو الصرع المعمم (40%،  $n=40$ )، ومن بينهم، كان هناك 11 مريضاً مصاباً بنوبات الغيبوبة. كان 65 (45.7%) من المرضى يعانون من الصداع مقارنة مع 3/153 (2%) في مجموعة الشاهد ( $p < 0.0001$ ) و من بين 65 مريضاً، كان هناك 29 (44.6%) مصابين بصداع الشقيقة، و 12 (18.4%) مصابون بنوع التوتر، و 24 (36.9%) يعانون من صداع غير مصنف. لم يكن هناك اختلاف كبير في العمر والجنس ونوع متلازمة الصرع ومضادات الصرع المستخدمة إلا في المرضى الذين يعانون من الصداع النصفي، فقد كان هناك انخفاض في معدل انتشار هذا الصداع في المجموعة الفرعية التي عولجت بحمض الفالبرويك مقارنة مع العلاجات الأخرى.

**الخلاصة:** يعد الصداع و بالأخص صداع الشقيقة، مشكلة شائعة عند مرضى الصرع الأطفال واختيار دواء حمض الفالبرويك عندما يكون ذلك ممكناً يمكن أن يكون مهماً في الوقاية من صداع الشقيقة لدى هؤلاء المرضى.

**Objectives:** To estimate the prevalence and characteristics of headache in pediatric epileptic patients.

**Methods:** This cross-sectional study was performed over 6 months period from January 2018 to June 2018 at King Abdullah Specialist Children Hospital, King Abdulaziz Medical City, Riyadh, Kingdom

of Saudi Arabia using a structured questionnaire in pediatric patients with epilepsy.

**Results:** There were 142 patients enrolled (males, 57.7%; average age,  $10.7 \pm 3.1$  years) with idiopathic epilepsy ( $n=115$ , 81%) or symptomatic epilepsy ( $n=27$ , 19%). Additionally, patients had focal epilepsy ( $n=102$ , 72%) or generalized epilepsy ( $n=40$ , 28%), and among them, 11 had absence epilepsy. Overall, 65 (45.7%) patients had headaches compared with 3/153 (2%) in the control group ( $p < 0.0001$ ). Among the 65 patients with headaches, 29 (44.6%) had migraine-type, 12 (18.4%) had tension-type, and 24 (36.9%) had unclassified headache. There was no significant difference in age, gender, type of epilepsy syndrome, and antiepileptic used except in patients with or without headache. For migraine patients, there was a lower headache prevalence in the subgroup treated with valproic acid compared with other treatments.

**Conclusion:** Headache, predominantly migraine, is a common problem in pediatric epileptic patients and choosing valproic acid when possible can be important in preventing migraine in these patients.

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From Neuro-science Center (Al-Gethami), King Fahd Medical City, and from Pediatric Neurology Division (Alrifai, Al-Rumayyan, Al-Tuwaijri, Ba-armah), Pediatric Department, King Abdullah Children Specialist Hospital, King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Muhammad Talal Alrifai, Pediatric Neurology Consultant, Pediatric Neurology Division, Pediatric Department, King Abdullah Children Specialist Hospital, King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia.  
E-mail: rifaim@ngha.med.sa  
ORCID ID: <https://orcid.org/0000-0002-3939-0793>

Epilepsy and headache are chronic paroxysmal disorders that affect adult and pediatric patients<sup>1</sup> with episodic manifestations. Headache or (cephalgia) is defined as a feeling of pain in the region of the head or neck. Primary headaches include migraines, tension-type headache, and cluster headache. Epileptic seizure is a brief episode of signs or symptoms caused by abnormal excessive synchronized neuronal activity.<sup>2</sup> Epilepsy is defined as a condition where the patient has an enduring tendency to have recurrent unprovoked seizures.<sup>2</sup> These two disorders coexist in some patients.<sup>3</sup> There are few studies on the comorbidity of headaches in children with epilepsy.<sup>4-6</sup> Other studies reported a significant association between migraine and epilepsy.<sup>1,7-9</sup> Additionally, the genetic predisposition for both entities was reported in some forms of channelopathy,<sup>10</sup> and others found more prevalence of migraine headache in specific diseases in pediatric like benign epilepsy with centrotemporal spikes and juvenile myoclonic epilepsy.<sup>11</sup> Seizure-associated headache is common, with an incidence of 42–51% in adult epileptic patients.<sup>12</sup> However, for pediatric patients, it is often neglected by parents and physicians because of other neurological manifestations of the seizure such as loss of consciousness and motor components,<sup>13</sup> and approximately 36% of the parents were reported to be unaware that their children experienced headache.<sup>14</sup> It is our experience that headache is a common problem in up to 50% of epilepsy patients but we do not know exactly the prevalence, in addition to what type of headache is most commonly found in epileptic pediatric patients. Because of few reports on this topic have conflicting results, the objective of this study was to evaluate the prevalence and characteristics of headache in children with epilepsy who were seen at one center in Saudi Arabia.

**Methods.** This cross-sectional study was performed over a 6-month period from January 2018 to June 2018 at King Abdullah Specialist Children Hospital, King Abdulaziz Medical City, Riyadh.

Inclusion criteria were as follows: pediatric epilepsy patients (5–16 years of age) and who were mentally normal and could communicate their symptoms with and without other comorbidities like diabetes,

asthma, or renal disease. Epilepsy syndrome patients were excluded since most of them mentally affected. Patients with intellectual disability and patients with unclear information supplied by the patient or their family were also excluded. We had up to 20 patients / pediatric neurology clinic, and 8 clinic/ week, so 142 patients met our inclusion criteria and more than 20 patients were excluded. Patients' parents/guardians provided informed consent and the study was approved by an ethics board at our hospital. Also, the study was according to principles of Helsinki Declaration.

Patients and their family were interviewed by one of the researchers (H.G.) using a structured questionnaire during their visit to the clinic. The questionnaire was structured to include demographic and clinical information about the symptoms of epilepsy and headache when present. Each patient was asked specifically if had headache, and if yes, the exact age of onset, how many attacks/ month, the relationship to seizure in timing, quality of headache, location, severity, other associated symptoms like nausea, vomiting, photophobia, phono-phobia, facial pain, orbital pain, and eye swelling, if had aura before headache, and frequency of headache. Further data regarding neurological exam, electrophysiological and neuroimaging studies were obtained from the patients' charts.

The control group comprised siblings of the patients with epilepsy who were free from epilepsy and who were 5–16 years of age, otherwise healthy, and could communicate their symptoms.

Headache was diagnosed based on the International Classification of Headache Disorders (ICHD-II) criteria,<sup>15</sup> and epilepsy was diagnosed based on the International League Against Epilepsy (ILAE) criteria.<sup>16</sup> Seizures were considered frequent if they occurred 2 or more times per month; otherwise, they are considered to be infrequent. Seizure-associated headache was defined as a headache starting within 1 hour before or after the seizure. Headache was either classified to be peri-ictal or inter- ictal headache, however, the peri-ictal headache can be classified to pre- ictal, ictal, and post-ictal headache. Pre-ictal headache is a headache that began before the seizure and lasted until its onset. ictal headache defined as epileptic seizures in which headache is one of the constituents of the epileptic seizure, besides other manifestations like sensory-motor, psychiatric or non-autonomic one. A headache that occurred only after the seizure is called a post-ictal headache. This classification is based on the IHS criteria.<sup>17-19</sup> Other headaches are considered inter-ictal.

The data were entered into a database and analyzed using SAS (Statistical Analysis Software). Statistical

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**Table 1** - Demographics and presence of headaches in the patient and control groups.

Demographics	Patients n=142	Control n=153	P-value
Gender (male)	82 (57.7%)	85 (55.5 %)	0.70
Age (years; mean, standard deviation)	10.7 ( $\pm$ 3.1)	10.6 ( $\pm$ 2.9)	0.35
Headache	65 (45.7%)	3 (1.96%)	<0.00001

analysis tests for both continuous and categorical variables were used as appropriate. No other systems were used.

We calculated measures of the association between variables expressed as the *p*-value, and for each test the level of significance was set at 0.05.

**Results.** There were 142 patients with epilepsy who fulfilled the entry criteria for this study. Among these patients, 82 were males (57.7%) and the overall average age for both male and female was 10.7 $\pm$ 3.1 years. Idiopathic epilepsy was present in 115 (81%) patients while symptomatic epilepsy was present in 27 (19%) patients. Focal epilepsy was present in 102 (72%) and generalized epilepsy was present in 40 (28%) patients, 11 of whom had absence epilepsy. Neuroimaging (CT or MRI) was performed in all patients, and 30/142 (21%) of the studies showed abnormal results, such as focal cortical dysplasia and mild ischemic brain insult.

The EEG which is an electrophysiological monitoring method used to record electrical activity of the brain, was also performed for 141 patients, and 59 (41.8%) showed normal results, 73 (51.8%) showed epileptiform activity focal and generalized interictal discharges with majority had generalized discharges, and 9 (6.4%) showed focal or generalized slowing.

Among the 142 patients, 65 (45.7%) had headache compared with 3/153 (2%) of the control group (*p*<0.0001). The 2 groups were matched for age and gender (Table 1).

Among the 65 patients with headache, 29 (44.6%) patients had migraine-type headache, 12 (18.4%) patients had tension-type headache, and 24 (36.9%) patients had headache that was an unclassified type. The headache and epilepsy started at the same year in 28 patients, and headache preceded epilepsy in total of 7 patients, it was 1-year period in 5 patients, 2 years period in 1 patient, and 3 years period in 1 patient.

Epilepsy started 1 year before headache in 10 patients, 2 years before in 3 patients, 3 years before in 6 patients, 4 years before in 5 patients; 5 years before in 2 patients; and 6 years before in 2 patients, 8 years before in one patient, and 11 years before in one patient.

For the timing of headache in relation to seizures, 56 out of 65 (86%) patients had interictal headaches, 5 (7.6%) patients had post-ictal headaches, 17 (26%) patients had preictal headaches, and 3 patients had ictal headache (4.6%). In fact, some patients have mixed

**Table 2** - Comparison of patients with headache to patients without headache.

Characteristics	Patients with headache n=65	Patients without headache n=77	P-value
	n(%)		
Gender (male [%])	35 (53.8)	47 (61)	0.38
Age (years; mean $\pm$ standard deviation)	11( $\pm$ 3.1)	10.6 ( $\pm$ 3.2)	0.22
Type of seizures: Partial (%)	47 (72.3)	55 (71.4)	0.90
Generalized (%)	18 (27.6)	22 (28.5)	
Epilepsy syndrome: Idiopathic	54 (83)	61 (79.2)	0.55
Symptomatic	11 (16.9)	16 (20.7)	
Frequent seizures	24 (36.9)	29 (37.6)	0.92
Lobe type seizure: Occipital lobe seizure	7 (10.7)	9 (11.6)	0.86
Temporal lobe seizure	19 (29.2)	22 (28.5)	0.93
Parietal lobe seizure	3 (4.6)	5 (6.4)	0.68
Frontal lobe seizure	17 (26)	17 (22)	0.57
Drug used: Carbamazepine	25 (38.4)	30 (38.9)	0.95
Levetiracetam	17 (26)	18 (23.3)	0.70
Valproic acid	20 (30.7)	24 (31)	0.95
Topiramate	3 (4.6)	8 (10.3)	0.22
Poly-therapy	14 (21.5)	11 (14.2)	0.25
Others anti-epileptic drugs	13 (20)	7 (9)	0.06

**Table 3** - Comparison of patient subgroups with migraine or non-migraine headaches.

Patient subgroups	Migraine n=29 n (%)	No migraine n=36 n (%)	P-value
Age (years; mean, standard deviation)	10.9 (2.8)	11.1 (3.4)	0.39
Gender: male	16 (55)	19 (52.7)	0.84
female	13 (44.8)	17 (47.2)	0.84
Epilepsy syndrome: Idiopathic	21 (72.4)	22 (61.1)	0.33
Symptomatic	6 (20.6)	5 (13.8)	0.46
Type of seizure: Focal	22 (75.8)	25 (69.4)	0.56
Generalized	7 (24)	11 (30.5)	0.56
Focal seizure: occipital lobe	3 (10.3)	3 (8.3)	0.78
Temporal lobe	8 (27.5)	10 (27.7)	0.98
Parietal lobe	1 (3.4)	2 (5.5)	0.68
Frontal lobe	10 (34.4)	6 (16.6)	0.09
Medication: Carbamazepine	12 (41.3)	13 (36.1)	0.66
Levetiracetam	9 (31)	8 (22.2)	0.42
Valproic acid	5 (17.2)	15 (41.6)	0.03
Topiramate	0	3 (8.3)	0.24
Poly-therapy	4 (13.7)	9 (25)	0.35
Others anti-epileptic drugs	7 (24.1)	6 (16)	0.45

more than one type of headache, like inter-ictal/preictal which was present in 12 patients (18.4%), and one patient (1.5%) had interictal/post-ictal, another one also (1.5%) had interictal/ ictal / post-ictal, and one patient (1.5%) had ictal/pre-ictal headache.

There was no significant difference in age, gender, type of epilepsy syndrome, and the antiepileptic used in patients who had headaches compared to patients without headaches (Table 2).

In a subgroup analysis of patients with migraine compared with non-migraine headaches, there was no significant difference in age, gender, type of epilepsy syndrome, and antiepileptic drug used except for the valproic acid, which showed fewer migraine patients compared with non-migraine patients (Table 3).

**Discussion.** Our study shows that about 46% of patients with epilepsy had headache as a comorbidity compared to 2% in the control group. The link between headache and seizures is controversial, and the literature review on this topic for the pediatric age group is limited.

In a study by Kanemura et al<sup>4</sup> that enrolled 98 pediatric epilepsy patients, 35% of them had headache. Another study conducted by Yamane et al<sup>5</sup> enrolled 50 pediatric epilepsy patients, and headache was reported by 46% of them, while Papavasiliou et al<sup>6</sup> found that 11.4% among 70 pediatric epilepsy patients reported headache. Published studies in adult epileptic

patients up to 2015 showed that the prevalence of migraine headache ranged from 6.6% to 32.9%, and the minimum age included in those studies was 10 years.<sup>7,12,18-32</sup> The most recent studies were published by Wang et al<sup>32</sup> who interviewed 1109 adult patients aged 18 years or older, and they found that headache occurred in 12.5% of the patients. In 2015, Mainieri<sup>33</sup> reported that 53.9% of epilepsy patients had headache.

In cohorts of migraine patients, epilepsy was reported infrequently. In a cohort of 172 headache patients, 1.7% had unprovoked seizures and 3 of 84 (2.3%) had coexisting migraine and epilepsy.<sup>6</sup> In another study that was conducted at a pediatric headache center and that enrolled 1,795 patients, 56 (3.1%) patients also had epilepsy. Among these epileptic patients, 46/56 (82%) had migraine headache.<sup>34</sup>

The pathophysiology behind the relationship between headache and epilepsy was reviewed in 2008, particularly the migraine type.<sup>34</sup> It is postulated that migraine attacks, similar to epileptic seizures, may be triggered by excessive neocortical cellular excitability. In migraine, this leads to cortical spreading depression and aura followed by additional recruitment of the trigeminal nucleus, resulting in central sensitization and pain. However, in epilepsy, neuronal overactivity can cause further neuronal recruitment and lead to firing in a rhythmic manner that constitutes an epileptic seizure. Migraine aura and headache may act as a trigger for epilepsy.<sup>35</sup> Additionally, some forms of

epilepsy and migraine are known to be channelopathies, which result from mutations in the same genes that can cause migraine, epilepsy, or both. This is similar to familial hemiplegic migraine syndromes where different mutations are found and can produce epilepsy, migraine, or both, and this can explain why some antiepileptic drugs, including valproate and topiramate, are effective in both conditions.<sup>34</sup>

For the timing of headache related to seizures, Yamane et al<sup>5</sup> showed that about 60% of headaches were inter-ictal and the rest were pre- or post-ictal. In another group of pediatric and adult patients, 71% had inter-ictal headaches.<sup>36</sup> These findings are similar to our study, where most headaches occurred in the inter-ictal period and affected 84% of our patients. However, Kanemura et al<sup>4</sup> indicated that there was a higher prevalence in the post-ictal period in 28/34 (82%) of their patients, which is not consistent with our, and others', results. In a group of adult patients, post-ictal headache was the most common type, especially in patients taking polytherapy; these patients have a higher seizure frequency, suggesting that a severe epilepsy phenotype and seizures can act as a trigger for headache attacks.<sup>28,32,30</sup>

The migraine type was also the most frequent type of headache seen in 44.6% of our patients, while tension-type headache was present in 18.4% and unclassified headache was present in 36.9% of patients. Similar findings were reported in other studies such as Ottman et al<sup>7</sup> who enrolled 1948 adult patients with epilepsy and demonstrated a two-fold higher risk for migraine in patients with epilepsy compared to their first-degree relatives without epilepsy. They also showed a two-fold higher risk of migraine compared to controls (24% vs. 12%). In Yamane et al<sup>5</sup> migraine was present in 43.5% of the patients and 17.4% had tension-type headache, while in 39.1% of the patients, the type of headache could not be established. Others reported migraine in more specific epileptic syndromes, such as benign rolandic epilepsy and benign occipital epilepsy of childhood,<sup>1,8,9</sup> others found it more common in benign epilepsy with centrotemporal spikes and juvenile myoclonic epilepsy.<sup>11</sup>

In our study, migraine was observed less frequently in patients who took valproate compared to patients who received other treatments, indicating a potential preventative effect for migraine in epilepsy patients who are treated with this drug compared to other drugs. However, further studies are required to confirm this hypothesis. Although valproic acid was shown to be effective in adults,<sup>37</sup> there are few controlled trials in children. A previous placebo-controlled trial showed

the efficacy of topiramate for prevention of migraine in children,<sup>38</sup> but a recent study comparing topiramate, amitriptyline, and placebo found no difference compared to placebo.<sup>39</sup> In our study, topiramate was administered in epileptic patients with or without headache, and there was no statistically significant difference between the groups, which is in agreement with the findings of Powers et al.<sup>39</sup>

We also found that headache and epilepsy started in the same year in 28 patients (43%), but headache preceded epilepsy in 19 patients (29%) and epilepsy started before headache in 17 patients (26%). This indicates that in most patients, the headache started in the same year with epilepsy. Our findings are comparable to the findings of Toldo et al<sup>34</sup> where in 44% of patients, epilepsy started earlier than headache with 28.6% starting in the same year, while headache started before seizures in 27.4% of the patients. Yamane et al. showed that the headache usually starts in the same year or after an epilepsy diagnosis.<sup>5</sup>

The main limitation of our study is the recall bias of our patients and the cross-sectional nature. However, it has a relatively large sample size compared to other, similar studies and it is the only study in Saudi patients. A larger sample size with a prospective cohort study is required to better address the questions related to comorbidity of headache in pediatric epilepsy patients.

In conclusion, headache, predominantly migraine, is a common problem in pediatric epileptic patients, that can be secondary to similarity in their pathophysiology. A careful history related to headaches is recommended in those patients to improve their care and quality of life. Choosing valproic acid when possible can also be of importance in preventing migraine in these patients.

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