



Incidence and Characteristics of Headaches in a Retrospective Cohort of Taiwanese Children with Focal Epilepsy

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Abstract

Objective: To study the incidences and characteristics of headaches in children with focal epilepsies.

Methods: We enrolled 476 of 865 patients with childhood epilepsy: 178 with frontal lobe epilepsies (FLEs), 194 with temporal lobe epilepsies (TLEs), 35 with parietal lobe epilepsies (PLEs), and 69 with occipital lobe epilepsies (OLEs). The characteristics of migraines in these different focal epileptic syndromes were analyzed.

Results: Six patients with FLE (3.4%), 13 with TLE (6.7%), 13 with PLE (37%), and 14 with OLE (20%) presented with migraines. The incidences of migraine were significantly higher in the OLE and PLE groups than in the FLE and TLE groups ($p < .001$; odds ratio = 6.51). In children with migraines and PLE or OLE, and with a probable or definite lesional etiology were significantly associated with more-frequent seizures and more antiepileptic drugs (both $p < .05$) than were those without migraines.

Conclusions: The incidence of migraine was significantly higher in children with PLE and OLE than in those with FLE and TLE. Children with migraines and PLE or OLE, and with a probable or definite lesional etiology were significantly associated with more-frequent seizures and more antiepileptic drugs.

Keywords

Migraine, Children, Epilepsy, Focal

Introduction

Migraines are common (prevalence: 4-10% [1,2]), especially in children. Migraines can significantly and adversely affect daily life by, for example, decreasing academic performance and increasing social withdrawal [3,4]. The true prevalence of migraines is unknown, but it appears to be about 10% in children 5-15 years old, and 28% in adolescents 15-19 years old [5]. Migraine and epilepsy share several clinical

attributes, including pathophysiology and clinical expression. Both are paroxysmal and thus constitute episodic disorders, but either might be chronic or recurrent [2].

The debate regarding a possible pathophysiologic association between migraine and epilepsy continues [2,6-8]. Higher incidences of migraines have been reported in patients with photosensitive epilepsy [9] and partial epilepsy [10,11]. Relatives of these patients complain

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more often about headaches than do relatives of patients with other types of epilepsy [12]. Headache is associated with seizure occurrence in 34-58% of epileptic patients, and 60% of these patients have periictal headache. Headaches in these patients are temporally related to seizures [2,13]. Epileptic children have a higher prevalence of headaches than does the general population [14-16]. Partial epilepsy, regardless of etiology, is associated with higher rates of migraine in children [11]. Headache can occur in epileptic children around the time of seizure, or might not be associated with seizure. In specific patients, headache is an ictal sign of epilepsy [17].

The International Headache Society (IHS) [18] lists three possible temporal associations between epileptic seizures and headaches: (1) migraine aura-triggered seizure, (2) familial hemiplegic migraine, and (3) postictal headache, which has led to unclear and controversial terminologies [19]. The classification of the International League Against Epilepsy (ILAE) does not refer to such associations. Most studies that have surveyed the relationship between epilepsy and migraine have primarily focused on adult patients with epilepsy. Thus, whether specific pediatric epileptic syndromes are associated with a higher incidence of migraine requires further investigation [11].

The purpose of this study was to investigate the incidences and characteristics of headaches in children with focal epilepsies.

Patients and Methods

We retrospectively reviewed the records of 865 pediatric patients from the epilepsy databases of the departments of Pediatric Neurology at National Cheng Kung University Hospital and Chung Shan Medical University Hospital. The inclusion criteria were having (1) at least 2 unprovoked seizures, (2) at least 2 electroencephalographic recordings with specific focal epileptic discharges, and (3) at least one of these two conditions: (a) seizure semiologies that matched a specific lobe epilepsy or (b) magnetic resonance or computed tomography images that confirmed specific lobe lesions compatible with clinical seizures. We classified the EEG focus as frontal, temporal, parietal, or occipital. EEGs were recorded using the routine international 10-20 system, and the EEG focus was determined using referential and bipolar recording, which included longitudinal and transverse montages.

The medical records included 178 cases of frontal lobe epilepsy (FLE), 194 cases of temporal lobe epilepsy (TLE), 69 cases of occipital lobe epilepsy (OLE), and 35 cases of parietal lobe epilepsy (PLE). We classified etiologies as: (1) lesional (symptomatic): with a structural-metabolic cause, (2) probable lesional (cryptogenic): probable lesional epilepsy with an unknown cause, and (3) idiopathic: with an unknown cause, all based on the ILAE classification. Each child with a confirmed diagnosis of epilepsy began monotherapy. A second-line antiepileptic drug (AED) was added for compliant patients when seizures were not controlled by first-line drugs already prescribed at their targeted dose. Seizure frequency was defined as how often seizures occurred after adequate treatment with AEDs. We classified seizure frequency as low (1/year), intermediate (1 every 1-6 months), and high (> 1/month).

International classification of headache disorders definition of migraine

The diagnosis of migraine in most children and adolescents can be established through a headache history [20,21]. We classified migraines as definite (meeting International Classification of Headache Disorders, 3rd edition [Beta version] [ICHD-3Beta] [5,18] for children criteria), probable (recurrent headaches with pulsating quality and nausea, vomiting, photophobia, or phonophobia, but not meeting ICHD-3Beta criteria), possible (recurrent headaches with either a pulsating quality or associated with nausea or vomiting), or nonmigraine (recurrent headaches that are not pulsating in character or associated with nausea or vomiting) [11]. Because of the difficulty in understanding headaches in children, we classified definite and probable headaches as migraines. Based on their relationship with epileptic seizures, we classified the headaches as interictal (unrelated to seizures) and periictal (occurring during or after the seizure, or both, and spontaneously remitting within three days) [2,22,23]. Data collected included patient age, sex, age at first seizure, seizure type, neurophysiology, neuroimaging, medical treatment, and outcome.

Ethical approval of the study was provided by Chung Shan Medical University hospital's Institutional Review Board (IRB#: CS13036).

Statistical analysis

Data are presented as mean \pm standard deviation. Significance was set at $p < .05$. The differences in the ratios and distributions of the outcomes

between groups were assessed using a χ^2 test. Fisher's exact test was used when there were <6 cases. Differences between different groups were analyzed using an independent t test (SPSS 18.0; SPSS Institute, Chicago, IL). If the sample distribution was nonparametric, a Mann-Whitney U test was used.

Results

We retrospectively analyzed the medical records of 476 children with a focal epileptic syndrome: 178 cases were FLE, 194 were TLE, 35 were PLE, and 69 were OLE. We compared the incidences of migraines in these groups. There were 46 of 476 (9.7%) cases with migraine: 6 of 178 (3.4%) with FLE, 13 of 194 (6.7%) with TLE, 13 of 35 (37%) with PLE, and 14 of 69 (20%) with OLE. There were significant differences in the incidences of migraine in the PLE ($p<.005$; odds ratio (OR) = 16.94; 99% confidence interval (CI): 4.23-67.88) and OLE ($p<.005$; OR = 7.3; 99% CI: 1.96-27.12) groups when compared with the FLE group (Table 1). All 6 FLE-group cases included migraines and were classified as probable lesional (cryptogenic). The seizure semiology was: 6 (100%) with secondary generalization, 1 with periictal headaches, and 5 with interictal headaches. The etiologies of the 13 TLE-group cases with migraines were: 1 idiopathic, 6 probable lesional, and 6 lesional (symptomatic). Twelve cases included secondary generalization, 4 included periictal headaches (2 included postictal headaches, and 2 included headaches during a seizure), and 9 with interictal headaches. In the 14 OLE-group cases with migraines, etiologies included 11 idiopathic and 3 lesional or probable lesional. Four cases included periictal headaches, and another 10 included interictal headaches. Nine cases included secondary generalization. In the 13 PLE-group cases with migraines, etiologies included 4

idiopathic and 9 lesional or probable lesional. Ten cases included secondary generalization. In addition, 6 cases included periictal headaches and 7 included interictal headaches.

Thirty-three (59%) of the 46 cases with migraine were in the PLE and OLE groups. There were no significant differences in the incidences of migraines between the TLE and FLE groups. However, there were significant differences in the incidences of migraines for FLE plus TLE and PLE plus OLE ($p<.001$; odds ratio=6.51; 99% confidence interval: 2.23-12.63) (Table 1).

More cases with PLE and migraines included lesional and probable lesional etiologies ($p<.05$) than did those with OLE and migraines (Table 2). In the OLE and PLE groups, there were higher incidences of migraines in cases with idiopathic epilepsy. In cases with idiopathic PLE or OLE, 13 (87%) of 15 migraines were classified as interictal. However, in cases with probable lesional or lesional PLE or OLE, 8 (75%) of 12 migraines were classified as periictal (Tables 2 and 3).

In the 44 cases with idiopathic OLE, 11 (25%) included migraines, and in the 25 cases with cryptogenic or symptomatic OLE, 3 (12%) included migraines. In childhood idiopathic PLE and OLE cases, more headaches were classified as interictal, in contrast to probable lesional and lesional PLE and OLE cases, in which most headaches were classified as periictal (Table 3). In FLE and TLE cases, 5 of 19 (26%) migraines were not related to episodes of seizures, and thus were classified as interictal.

We identified 52 cases of probable lesional and lesional PLE and OLE and classified them as with migraine (n=12) and without migraine (n=40) groups. In cases with migraine, significantly more AEDs were required ($p<.05$) and seizures occurred more frequently ($p<.05$) (Table 4).

Table 1: Comparisons of different focal childhood epileptic syndromes.

Lateralization of epileptic syndrome	Number (n)	Age during study	Migraine (%)	No migraine (%)	Odds ratio	99% CI	P value
Frontal lobe epilepsy	178	6.4 (4.1)	6 (3)	172 (97)	1		
Temporal lobe epilepsy	194	5.9 (4.1)	13 (7)	181 (93)	2.06	0.54 to 8.21	
Parietal lobe epilepsy	35	6.3 (3.4)	13 (37)	22 (63)	16.94	4.23 to 67.88	# $p<.005$
Occipital lobe epilepsy	69	6.7 (4.2)	14 (20)	55 (80)	7.3	1.96 to 27.12	# $p<.005$
Frontal lobe epilepsy and temporal lobe epilepsy	372	6.1 (4.1)	19 (5)	353 (95)	1		
Parietal lobe epilepsy and occipital lobe epilepsy	104	6.7 (4.3)	27 (26)	77 (74)	6.51	2.23 to 12.63	* $p<.005$

focal epileptic syndrome compared with frontal lobe epilepsy. * frontal lobe epilepsy and temporal lobe epilepsy compared with parietal lobe epilepsy and occipital lobe epilepsy.

Table 2: Characteristics of headaches in different focal epileptic syndromes.

Focal epilepsy syndrome with migraine	Number with headaches	Male	Female	Seizure with generalization	Drug number	Idiopathic	Lesional/probable lesional	Periictal	Interictal
Frontal lobe epilepsy	6	3	3	6 (100)	1.83 (1.17)	0	6	1	5
Temporal lobe epilepsy	13	3	10	12 (92)	2.15 (1.28)	1	12	4	9
Parietal lobe epilepsy	13	5	8	10 (77)	1.11 (1.24)	4	9*	6	7
Occipital lobe epilepsy	14	7	7	9 (64)	1.50 (0.94)	11	3*	4	10
Total (n)	46	18	28	37(80)		16	31	15	31

*Parietal lobe epilepsy with migraine was associated with more cases of lesional or probable lesional etiology (p<.05; add ratio, 8.3; 95% confidence interval, 0.17 to 0.93) when compared with occipital lobe epilepsy with migraine.

Table 3: Lesional and non-lesional occipital lobe and parietal lobe epilepsy associated with migraine.

	Numbers (n)	Migraine (n, %)	Interictal	Periictal
Occipital lobe epilepsy				
Idiopathic	44	11 (25)	10 [#]	1
Lesional / probable lesional	25	3 (12)	0	3*
Parietal lobe epilepsy				
Idiopathic	8	4 (50)	3 [#]	1
Lesional/ probable lesional	27	9 (33)	4	5*

[#]idiopathic parietal and occipital lobe epilepsy with migraine belonged to interictal (13/15, 87%); * probable lesional or lesional parietal and occipital lobe epilepsy with migraine belonged to periictal (8/12, 75%) (p<.05).

Table 4: Outcomes of antiepileptic drugs and seizure frequencies related to probable lesional or lesional parietal lobe epilepsy and occipital lobe epilepsy with and without migraine.

	N	Age during study	Drug number [#]	Male	Female	Seizure-free ⁺	Low ⁺	Intermediate ⁺	High ⁺
Probable lesional or lesional PLE and OLE without migraine	40	5.7 (3.9)	1.38 +/- 0.95	16	24	7	22	10	1
Probable lesional or lesional PLE and OLE with migraine	12	8.1 (3.8)	2.17 +/- 1.11	6	6	0	7	2	3
Total	52			22	30	7	29	12	4

[#]P<.05 for drug number.

⁺Seizure-free indicates no seizures for one year or more. Low indicates 1 seizure every year; intermediate, 1 seizure every month to 1 seizure every six months; high, more than one seizure every month. P<.05 by Pearson's chi-squared test for seizure frequency.

Discussion

Others [24,25] have reported that most patients with epilepsy have headaches. We found that cases with associated migraines had a predilection for OLE and PLE. Second, the initial incidence of FLE with migraines was not significantly different from the reported incidence of migraines in children without epilepsy, which indicated that FLE headaches are not associated with epilepsy. Third, PLE and OLE groups had higher incidences of migraines. Fourth, children with probable lesional or lesional PLE and OLE with migraines required significantly more AEDs and had more frequent seizures. This probably means that they are more difficult to treat. Headache in posterior lobe epilepsy are associated with ictal or non-ictal events; they require additional clarification. Because migraines might not be associated with seizures, cognitive behavior therapy, an evidence-based

nonpharmacological treatment, might be an alternative [26].

The pathophysiological mechanism of epilepsy and migraine is still unclear. However, focal epileptic discharges (particularly in the posterior lobes) might activate cortical spreading depression (CSD) and the trigeminovascular system [7,8]. The excitability characteristic supports a persistent visual aura in migraine spectrum disorders and suggests a pathophysiological link to sustained excitatory effects, which might be related to reverberating CSD [27]. Others [17,19,28,29] have reported similar findings of visual cortex involvement. This might help us better understand the mechanism of migraines. We found higher incidences of migraines in the OLE and PLE groups, which is consistent with the findings of other studies. Moreover, a myofascial trigger is probably involved in the migraine. Future studies should investigate

trapezius muscle myofascial triggers and migraine in children.

Children with partial epilepsy, regardless of etiology, have higher rates of migraine than do children without seizures [11]. However, there were no significant differences between patients with benign rolandic epilepsy and centrotemporal spikes and patients with cryptogenic or symptomatic focal epileptic syndrome. Twice as many children with benign epilepsy and centrotemporal spikes meet the criteria for migraines than do non-epileptic children [30]. In patients with shared susceptibility to migraines and benign epilepsy and to centrotemporal spikes, there is no direct mediation by epileptic seizures. Susceptibility gene variants for benign epilepsy with centrotemporal spikes might be a risk factor for migraines [30]. We found that more idiopathic PLE and OLE cases with idiopathic etiology included migraines, which indicated that idiopathic epilepsy shares genetic risk factors with migraines. Pediatric cases of lesional PLE and OLE also included migraines, but with different pathogeneses. Lesional PLE and OLE were associated with postictal headaches. However, in idiopathic cases, most migraines were interictal. The mechanism differs from that of benign epilepsy with centrotemporal spikes.

Fifty-two percent of epilepsy patients have headaches [31]: 20% present with interictal migraines and 44% with postictal headaches. Headache lateralization and interictal EEG abnormalities are associated in partial epilepsy, which is consistent with our findings. In a study of 100 patients with partial epilepsy, postictal headache occurred in 51 and most commonly lasted 6-72 hours. Major seizures are more often associated with postictal headache than minor attacks. It is, therefore, probable that seizures provoke headache [31] or that headache is a “subtle” symptom of seizures [8]. This incidence is higher than in our study, possibly because of the differences in epileptic syndromes and the cases studied. We did not include patients with one unprovoked seizure when the risk for

another was known to be high. Children might not be able to express the characteristics of headaches, and a possible recall bias should be considered a limitation of our study. Another limitation is that all patients in our cases were treated with AEDs, which might contribute to underestimating the incidence of epilepsy.

Conclusion

The migraine ratio in the children with focal epilepsy ratio was 9.7%. Children in the PLE and OLE groups had higher incidences of migraines than did those in the FLE and TLE groups, and those with migraines and probable lesional or lesional PLE and OLE required significantly more AEDs and had more frequent seizures. Future studies might want to focus on probable links with the visual cortex, migraine, and PLE, and to investigate probable trapezius muscle myofascial triggers for migraine in children.

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Compliance with Ethical Standards

Conflict of Interest

The authors (ICL and YJC) declare that they have no conflicts of interest related to the authorship or publication of this article.

■ Research involving human participants and animals

Our study did not include any animal experiments. Ethical approval of the study was provided by Chung Shan Medical University Hospital’s IRB (CS13036).

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