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ORIGINAL PAPER

Peri-ictal and inter-ictal headache in children and adolescents with idiopathic epilepsy: a multicenter cross-sectional study

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Abstract
Purpose Headache in epileptic population ranges from 8% to 15%. The aim of this paper was to study the clinical and temporal characteristics of primary headache comorbidity in idiopathic epileptic children.
Methods From June 2006 to June 2009, a cross-sectional multi-center study involving five Italian Child Neurology University Centers (two in Rome, one in Chieti, one in Naples, and one in L'Aquila) was conducted. Among 1,264 consecutively newly diagnosed, idiopathic, partial, or generalized, epileptic children, according to ILAE diagnostic criteria (aged between 5 and 15 years of age), we selected 142 children (11.2%) (130 of whom completed the study) who showed an associated peri-ictal and/or inter-ictal headache diagnosed according to the International Headache Society Criteria. Rare cases of "ictal epileptic headache", in which headache represents the sole ictal epileptic manifestation, were excluded from this study.
Results and conclusions Post-ictal headaches were most frequent (62%). Pre-ictal headaches were less common (30%). Inter-ictal headaches were described in 57.6%. Clear migrainous features were present in 93% of pre-ictal and 81.4% of post-ictal headaches. Inter-ictal headaches meet criteria for migraines in 87%. The association between partial epilepsy and migraine without aura is most common and reported in 82% of our patients with peri-ictal headache and in 76.5% of patients with post-ictal headache.

Keywords Peri-ictal headache · Pre-ictal headache · Post-ictal headache · Idiopathic epilepsy · Headache · Migraine · Tension-type headache

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Introduction

The comorbidity of headache and epilepsy is well known, and it has been reported with the frequency of migraine in the epileptic population ranging from 8% to 15% [1–5]; however, the influence of headache on seizures-related-headache (SRH) has not been thoroughly investigated. Peri-ictal headache (Peri-ictalHA) has been studied in patients with different seizure patterns and syndromes: they may be pre-ictal (PIHA), ictal (IHA), or post-ictal (PostHA). PIHA is regarded as a headache that had lasted for more than 10 min before the onset of seizures, IHA is a headache that had occurred alone just before or simultaneously with the onset of other ictal signs/symptoms. Recently, Parisi P. [6]

has suggested that IHA can rarely be the sole ictal epileptic manifestation and, in these rare cases, the term "ictal epileptic headache" has been proposed; these rare cases [6–8], which deserve specific neurophysiopathologic considerations, were excluded from this study. PostHA is a headache that had begun immediately after cessation of seizure [9]. Moreover, inter-ictal headache (inter-ictalHA) is a headache not temporally related to a seizure. Migrainous features of peri-ictalHA have been documented but its value is still unclear [2, 10–12]. PostHA is a common symptom after generalized tonic–clonic seizures [2] but also occurs after complex partial seizures originating in the temporal lobe [2, 12–14]. The characteristics of SRH have been reported in many studies [2–5, 10, 11, 13, 15–18]; however, only a few studies have been conducted on large patient populations in pediatric age [4, 13, 17]. The aim of this study is to describe the clinical characteristics of headache in pediatric patients with newly diagnosed idiopathic epilepsy and to explore the temporal associations between peri-ictalHA and clinical ictal features of epilepsy.

Definitions

Seizures and epilepsy syndromes were classified according to guidelines of the International League Against Epilepsy (ILAE) [19]. PIHA was defined as headache occurring during the 30 min or longer prior to a seizure and lasted until the onset of seizure [20]. IHA occurred simultaneously with the other symptoms of a partial seizure, and PostHA occurred immediately after cessation of seizure [10]. Headache experienced by the patient that was not temporally related to a seizure was regarded as inter-ictalHA. Based on the patient's description of the headache, Peri-ictalHA has been classified according to the diagnostic criteria of the International Headache Society [21].

Methods, inclusion/exclusion criteria, and statistical analysis

From June 2006 to June 2009, a multicenter cross-sectional, cohort survey of children with newly diagnosed idiopathic epilepsy was conducted at five Italian Departments of Pediatrics and/or Child Neuropsychiatry (two in Rome, one in Chieti, one in Naples, and one in L'Aquila). Particularly, among 1,264 consecutively newly diagnosed, idiopathic, partial, or generalized epileptic children, according to ILAE diagnostic criteria (aged between 5 and 15 years of age), we enrolled 142 children (11.2%) (130 of whom completed the study) who showed an associated peri-ictal or inter-ictal headache diagnosed according to the International Headache Society Criteria.

Inclusion criteria (a) Age of 5–15 years (old enough to describe headache); (b) headache history onset reported both before or simultaneously with the onset of the first recognized epileptic seizure; (c) normal psychomotor development, accordingly with chronological age, assessed by means of Terman-Merrill (from 5 to 7 years of age) and WISC-III Edition for children (from 8 to 15 years of age); (d) two or more reported idiopathic generalized or partial seizures according to ILAE classification; (e) normal results at magnetic resonance imaging (MRI) investigations (acquired on a 1.5-T scanner with a T1-fast field echo, proton-density, T2-weighted, and fluid-attenuated inversion recovery images); (f) children satisfying the reported inclusion criteria were included whether or not they had already received antiepileptic medications.

Demographic and clinical data were obtained both, at first admission through interviews with patients and their relatives, and at 12 months from the first admission by recalling patients and families at our child neurology outpatient services and by reviewing their hospital charts. In order to "keep a diary" of "co-morbid headache characteristics" and their temporal correlations with seizures occurrence, a "headaches diary" was given at first admission. All children were followed and visited every 3 months at outpatient services and, lastly, headache diagnosis, frequency, and temporal correlations with seizures was performed 12 months after the first admission for epileptic seizures. One hundred thirty out of 142 comorbid enrolled children completed the study till 12 months of follow-up.

Diagnoses of the seizure focus were based on a comprehensive evaluation including seizure history and semiology, neurologic examination, video-EEG telemetry with scalp electrodes. The seizure focus was determined by predominantly ipsilateral inter-ictal epileptic abnormalities and by unequivocal seizure onset.

Statistical analysis was conducted using SPSS version 17.0 (SPSS Inc Chicago, IL, USA). The results were expressed as percentage for categorical variables. The differences in categorical data were compared using chi-square test. Statistical significance was defined as P value<0.05.

Results

Epilepsy syndrome included idiopathic generalized seizures in 61 patients (10 childhood or juvenile absence epilepsy, 45 generalized tonic–clonic seizures alone, and 4 juvenile myoclonic epilepsy, 2 epilepsy not classified), idiopathic partial in 69 (of whom 15 were benign rolandic epilepsies) (see Table 1). Eleven children experienced generalized tonic–clonic seizures. The average seizure duration for this

Table 1 Children with peri-ictal headaches

Epilepsy type	No.	Pre-ictal headache	Post-ictal headache
Generalized epilepsy	61	22	37
Partial epilepsy	69	23	50

seizure type was under 3 min for seven, from 3–5 min for four children. Focal epileptiform discharge was clearly present in 39 children with partial epilepsy: focal discharges were frontal in 12 patients, temporal 5, occipital in 16. Six children demonstrated multifocal discharges. Table 2 shows the distribution of epileptic discharges of EEG recordings in patients who suffered from peri-ictalHA.

All patients showed peri-ictalHA: of those, 39 (30%) had PIHA and 81 (62.3%) had PostHA. Ten (7.7%) patients had both PIHA and PostHA. Inter-ictalHAs were reported in 75 (57.6%) patients. Twenty-five (19.2%) of these 130 patients had tension-type HAs, 97 (74.6%) had migraine-like HAs and 8 (6.1%) had unclassifiable headache.

1. Pre-ictal HA

   Thirty-nine (32.5%) patients had PIHAs. Of these, 33 (86%) had headache migraine without aura, 3 (7%) had migraine with aura and 3 (7%) had tension-type headache. Thirty-five (89.2%) had early PIHA within 30 min to 1 h before seizure onset, and 4 (10.2%) had headache 2 h before seizure onset (i.e., prodromal PIHA). Of children reporting PIHA, 11 (25.6%) stated that headaches were more likely with longer seizures, and 7 children manifest headache of long duration. Thirty-two (82%) children with a PIHA showed partial simple seizures. Twenty-five (64%) PIHA were typically bilateral.
2. Post-ictal HA

   Eighty-one (62.3%) patients had PostHAs. Of these, 61 (75.3%) had migraine without aura features, 5 (6.1%) had migraine with aura features, and 15 (18.5%) had tension-type headache. Duration was from 30 min to 1 h in 39 (48%) patients and >3 h in 42 (52%) patients. In one case, duration was 80 h. Longer seizures were reported to correlate with a greater risk of PostHA by 33%. Of 19 children with generalized seizures reporting PostHA, headache occurred after 2–3 h from the seizures in ten patients (53%). Among the 62 (76.5%) patients with partial complex seizures and PostHA, 25 (40%) reported headache after 2–3 h from seizures. Again, 65 (80%) PostHA were bilateral.
3. Inter-ictal HA

   Seventy-five patients had interHAs. Sixty-one (81%) reported migraine without aura unrelated to seizures. Of the other 14 patients, 4 (6%) had migraine with aura and 10 (13%) had tension-type headache according to IHS criteria. The different characteristics of headache in all patients are reported in Table 3.

Discussion

Previous studies have documented that up to 50% of epilepsy patients have various forms of headache temporally related or unrelated to seizures [1–5]. Moreover, in children the association between headache and epilepsy has been reported, but data are conflicting and studies have been limited by the small numbers of patients and to the lack of clearly stated diagnostic criteria for childhood headaches till 2004, when the latest edition of International Headache Disorders Classification was published. In fact, in the last 20 years, few studies have been performed concerning the comorbidity between headache and epilepsy in epileptic children, and the majority of them are quite difficult to compare due to the different methodologies used [22].

In our study, we have analyzed the prevalence of peri-ictalHA and interHAs types and clinical characteristics and their temporal correlations with seizures onset in a large sample of newly diagnosed idiopathic epileptic children and adolescents, followed at our outpatient service for 12 months after the epilepsy onset. PostHAs were the most frequent types (62%), similar to the proportion in studies of adults with epilepsy [2, 11, 18, 23]. PIHAs were less common, and were reported by 30% of our cohort. InterHAs were described by 57.6% of patients. Most previous studies reported postHAs with a range of incidence from 37% to 51% [2, 13, 17].

Migrainous-type features are common in peri-ictalHAs, and some investigators noted a relationship between migraine and peri-ictalHAs [11, 17]. Ito et al. found that adults with partial epilepsy who had migrainous postHAs were significantly more likely to manifest inter-ictal migraines, and those without postHAs were less likely to manifest inter-ictal migraine [17].

Table 2 Peri-ictal headaches and focal epileptic discharge at EEG recording

Focal epilepsy	PostHA	PIHA
Frontal	9*	3
Temporal	4**	1
Occipital	10	6
Multifocal discharges	6***	0

Related statistical analysis data are also reported

*$P<0.05$

**$P<0.01$

***$P<0.001$

Table 3 Percentage of the different types of headache in our series

Headache	Migraine without aura%	Migraine with aura%	Tension-type headache%
Pre-ictal HA	86*	7	7
Post-ictal HA	75.3**, ***	6.1	18.5
Inter-ictal HA	81****, *****	6	13

Related statistical analysis data are also reported

* $P<0.001$ vs. migraine with aura and tension-type headache

** $P<0.001$ vs. migraine with aura

*** $P<0.01$ vs. tension-type headache

**** $P<0.001$ vs. migraine with aura

***** $P<0.01$ vs. tension-type headache

However, Schon and Blau noted that migrainous features were common in PostHAs, even without a history of inter-ictal migraines [2]. In this study, we found an important correlation between migraine-type headaches both in post-HA and in PIHA; in particular, the most frequent form was migraine without aura (86% in PIHA; 75.3% in postHA).

Although previous adult studies noted that postHA was more commonly associated with generalized seizures than partial seizures [5–11], in our study, the association between partial epilepsy and headache, including migraine without aura is most common and reported in 82% of patients with PIHA and in 76.5% of patients with postHA. On the other hand, it should be taken into account that epidemiological data on the idiopathic partial epilepsy in infancy and childhood are clearly different from the adult age [1–5, 22].

In this respect, we found no significative correlation between EEG-abnormalities localizations (occipital, frontal, parietal, or temporal) and headache attack types. On the other hand, we have previously hypothesized the lack of correlation between cortical localizations of the EEG abnormalities and headache attacks, as also suggested for Panayiotopoulos syndrome [24]. Moreover, in our epileptic children sample, accordingly with our physiopathological considerations (published in the last decade [24]) on the relationship between epilepsy and headache, children with better seizure control seem to show a better headache/migraine control as well, although not showing a statistical significant correlations in the sample here described.

As it regards the prophylactic pharmacological headache treatment, as known, it should be considered when headache frequency exceeds three or four episodes per month and/or the attacks are so severe and prolonged that they interfere with school or normal activities. The goals of prophylactic therapy include: reducing attack frequency, severity, and duration; improving responsiveness to treatment of acute attacks; improving function and quality of life and reducing disability [25]. Thus, in light of the current views of the pathophysiology of migraine with a primary neuronal initiation and propagation through cortical excitation and, later, "spreading depression," anticonvulsants pose an intriguing, though yet incompletely defined role [24]. Accordingly, to date [25], among available anticonvulsant drugs, topiramate, valproate, and levetiracetam seem to show better results as prophylactic treatment.

As it regards, the acute therapy of headache attacks, the aim of treatment should be a rapid response with return to normal activity and without relapse. Ibuprofen and acetaminophen are effective and they should be considered for the acute treatment of migraine in children. The efficacy and safety of other drugs (e.g., acetylsalicylic acid, diclofenac, naproxen, mefenamic acid) in the treatment of migraine in children and adolescents have still not been assessed [25].

Lastly, we also found that the association of peri-ictalHA is most frequent in patients with longer seizures than the others. This aspect is in agreement with the data reported by Shayne at al. [26].

Peri-ictalHAs were often severe, and the duration of headache in our data is often high, especially in postHA. No significant association between inter-ictal migraine and migrainous peri-ictalHA in children was found in previous studies [26] probably because the number of children with inter-ictal migraines was relatively small; conversely, our findings, show high frequency of migraine features (81% migraine without aura, 6% migraine with aura) in inter-ictalHAs .

In conclusion, this study confirms the prevalence of the postHA as headache associated to seizures and the migraine headache as a form of headache mostly represented. Moreover, this study also confirms an association between partial epilepsy and peri-ictalHA. Additionally, we showed that the duration of headache was often elevated especially in postHA, and moreover, we found the prevalence of migraine features in children with inter-ictalHA. There is a paucity of data in relation to the presence of peri-ictalHA in epileptic children and adolescents. Therefore, further and larger studies are

needed. A caring and understanding approach to peri-ictalHA of the epileptic children and adolescents will indeed enable the physicians to manage better the problems related to the coexistence of peri-ictalHA and epilepsy.

Conflict of interest We have no conflict of interest in publishing this article.

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