Seizure 22 (2013) 253–258

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

What have we learned about ictal epileptic headache? A review of well-documented cases

Pasquale Parisi [a,*], Pasquale Striano [b], Alberto Verrotti [c], Maria Pia Villa [a], Vincenzo Belcastro [d]

[a] Child Neurology, Headache Paediatric Center, Paediatric Sleep Disorders, Chair of Paediatrics, NESMOS Department, Faculty of Medicine and Psychology, Sapienza University, c/o Sant'Andrea Hospital, Rome, Italy
[b] Pediatric Neurology and Muscular Diseases Unit-DINOGMI Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, G. Gaslini Institute, Genoa, Italy
[c] Child Neurology, Department of Pediatrics, University of Chieti, Chieti, Italy
[d] Department of Neuroscience, Neurology Clinic, Sant'Anna Hospital, Como, Italy

ARTICLE INFO

Article history:
Received 10 December 2012
Received in revised form 22 January 2013
Accepted 23 January 2013

Keywords:
Migraine
Headache
Epilepsy
Ictal epileptic headache
New classification criteria
Ictal epileptic semiology
Autonomic seizures
Clinical-EEG criteria
Epidemiology
Headache and epilepsy comorbidity

ABSTRACT

Purpose: The case report published in this issue by Wang et al. offers us an opportunity to review previously published "ictal epileptic headache" cases and draw attention to the criteria that have recently been published for this condition, taking into consideration not only the clinical-EEG and physiopathogenetic investigations required to diagnose this condition, but also the therapeutic aspects of the issue.
Methods: To this aim we reviewed all well-documented cases that have been reported in the literature.
Results: The relationship between headache and seizures is somewhat complicated. Although the nature of this association is not yet fully clear, several plausible explanations have been proposed. Further experimental and clinical investigations are, however, warranted to gain a better understanding of this relationship. Epilepsy and idiopathic headache/migraine share several pathophysiological mechanisms; a better understanding of these mechanisms will allow us to more accurately to assess the "real burden" and prevalence of the "ictal epileptic headache" phenomenon and its therapeutic implications.
Conclusions: The development of animal models and molecular studies and, above all, multicenter clinical studies conducted according to the proposed IEH criteria represent the starting point for a definitive international consensus on this intriguing topic. In addition, to improve the recognition of ictal epileptic headache, we should encourage the use of EEG recording in the emergency setting.

1. Introduction

The classification criteria for "ictal epileptic headache" (IEH), a new entity recently proposed by our group,[1] was based on twelve well-documented cases that have been published in the literature (Table 1).

These criteria[1,2] stress that markedly different types of EEG anomalies, i.e. lateralized or generalized, ipsilateral or contralateral, focal theta activity or generalized spike-waves (criteria B and C), as well as brief or longer-lasting episodes (criterion A), may be consistent with a diagnosis of IEH; moreover, it should be borne in mind that a specific headache pattern is not essential, as patients may present with migraine or tension-type headache, and that both idiopathic and symptomatic cases have been described. It thus becomes clear that criterion D ("headache and EEG anomalies resolve within minutes of i.v. antiepileptic medication administration") represents the key to diagnosing IEH. Consequently, in order to improve the recognition of IEH, we should encourage the use of EEG recording in the emergency setting.

Two other important aspects of this topic are the "autonomic" nature of headache (cephalic pain) and the ability of the epileptic cortical focus (originating seizures) and of cortical spreading depression (originating headaches) to trigger each other (though not to the same extent).

This new classification proposal (headache as an isolated ictal autonomic manifestation in IEH) has very different prognostic implications because the outcome in people with long-lasting autonomic status epilepticus[3] is very different (i.e. benign) from that of people with additional ictal motor-sensitive semiology.[2,4–8] We have stressed this important aspect once again more recently.[2]

* Corresponding author at: Child Neurology, Headache Paediatric Center, Paediatric Sleep Disorders, Chair of Paediatrics, NESMOS Department, Faculty of Medicine & Psychology, Sapienza University, c/o Sant'Andrea Hospital, Via di Grottarossa, 1035-1039, 00189 Rome, Italy. Tel.: +39 6 33775971; fax: +39 6 33775941.
E-mail addresses: pasquale.parisi@uniroma1.it, parpas@iol.it (P. Parisi).

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http://dx.doi.org/10.1016/j.seizure.2013.01.013

Headache and epilepsy classifications have always ignored each other.[2,9] In the International League Against Epilepsy (ILAE) classification, headache is included exclusively as a possible semiological ictal phenomenon among the "non-motor" (point 2.0) features. In particular, headache is described as a "cephalic" sensation (sub-classified at sub-point 2.2.1.7) and is not considered as the sole ictal expression of an epileptic seizure. Moreover, headache is not classified as a "pain" (among the "somatosensory" features at 2.2.1.1) or "autonomic" sensation (2.2.1.8), whereas signs of involvement of the autonomic nervous system, including cardiovascular, gastrointestinal, vasomotor and thermoregulatory functions, are classified as "autonomic" features. Whilst still controversial issue, it is now generally accepted that headache pain may actually originate in the terminal nervous fibers ("vasomotor") of cerebral blood vessels; consequently, headache should be classified as an "autonomic" sensation in the ILAE Glossary and Terminology.[10]

In addition, the acceptance of headache as an autonomic phenomenon is crucial when we attempt to understand why headache may be the sole ictal epileptic manifestation[11–13]: the reasons have been thoroughly explained in the Panayiotopoulos Syndrome, while the threshold required to trigger an ictal autonomic phenomenon is believed to be lower than that required to trigger sensitive-sensorial or motor ictal semiology.[14]

An additional argument used against the existence of IEH and, more generally, epilepsy-headache co-morbidity, is the existence of "apparently discordant" epidemiological data in the literature; in this regard, the epidemiological data available for childhood are in sharp contrast to the data available for this comorbidity in adulthood, with data obtained from adults probably being "overshadowed" by the other symptoms and signs during the seizure.[15] The prevalence of this phenomenon in children is also in keeping with a higher incidence of autonomic (even isolated) manifestations in childhood than in adulthood.

Finally, we wish to review all the well-documented (potential or established, according to the proposed criteria) IEH cases previously reported in the literature and explain why the case described in this issue by Wang et al. should not, according to our criteria,[1] be classified as a case of IEH.

2. Review of well-documented IEH cases

Twelve patients presenting **with** headache as a sole ictal epileptic manifestation have been published. Below we review them (Table 1) systematically to ascertain the diagnostic plausibility of each of these cases according to the published IEH criteria.[1] In Table 1 we have summarized the IEH patients' familial, clinical-EEG and neuroimaging characteristics as well as their response to therapy.

According to our criteria,[1] twelve (potential or established) IEH cases have been reported since 1971 (Table 1).[16–28] In addition, we have recently published a further 16 "potential" IEH cases retrospectively isolated from a large (4600 epileptic children) multicentre neuropaediatric sample.[6] All 16 patients displayed focal or generalized ictal EEG abnormalities during migraine attacks. The spike or spike-and-wave pattern, which was the most commonly observed EEG pattern, was associated with both migraine with aura (MA) and migraine without aura (MO), whereas EEG theta activity was surprisingly associated exclusively with MA or a "double migraine pattern," in which MA and MO coexisted. Fourteen of the 16 children displayed interictal EEG abnormalities[6]; unfortunately, we do not have any data regarding a possible therapeutic response to intravenous anticonvulsant administration in these 16 "potential retrospective" IEH cases, nor can we confirm the IEH diagnosis.

Going back to the twelve IEH patients listed in Table 1, the ictal migraine/headache lasted from "seconds/minutes" to hours or even days, and was the sole manifestation of a non-convulsive status epilepticus (NCSE); in this regard, as mentioned above, we have suggested including long-lasting (more than 30 min) IEH episodes among the autonomic status epilepticus (ASE) events, because of their clearly different outcome.[3]

These published IEH cases (Table 1) unequivocally show that criterion D ("headache and EEG anomalies resolve within minutes of i.v. antiepileptic medication administration") represents the key to diagnosing IEH. Indeed, not only is there no specific EEG picture or specific headache-pattern (tension-type headache, migraine as well as other non-typical headache patterns have been reported), but neuroradiological investigations (brain CT and MRI) can be either normal or reveal a range of structural or "transient" abnormalities. Varying associated EEG-patterns have also been recorded. Indeed, high-voltage, rhythmic, 11–12 Hz activity with intermingled spikes over the right temporo-occipital regions,[22,24,25] high voltage theta activity intermingled with sharp waves over the occipital region,[20–22] bilateral continuous spike-and slow wave discharges,[18,19,21] 10–15 Hz paroxysmal fast activity followed by diffusely expressed slow waves[28] and almost continuous ictal beta fast activity alternating with rhythmic theta discharges over the right frontotemporal regions[26] have all been described; photoparoxysmal responses (PPR) associated with complaints of a light pulsating headache during intermittent photic stimulation have also been reported.[20,22]

We would like to underline that the patient described by Fusco et al.,[26] showed the same migraine symptoms with both frontal and occipital ictal discharges, implying that the localization of the epileptogenic area was not an essential requirement for the genesis of the attack, as previously reported in ictal autonomic manifestations related to Panayiotopoulos Syndrome.[14] This finding (the same migraine symptoms associated with different epileptogenic areas) has also been confirmed in the recent, above cited,[6] multicentre neuropaediatric retrospective study. It is also important to stress that there have even been cases of an isolated epileptic headache without scalp EEG abnormalities; in rare cases such as these,[17,26] the ictal origin of the headache has been demonstrated by deep electrode studies, as has occurred by chance in patients studied for pre-surgical investigations.[17,26] In other words, while unequivocal epileptiform abnormalities usually point to a diagnosis of epilepsy, the lack of clear epileptic spike-and-wave activity is not so rare in IEH patients. It is for these reasons that IEH events will inevitably be underestimated.[2]In most of the afore-mentioned patients, complete remission of both the headache and the epileptic abnormalities was achieved not by means of specific antimigraine drugs whereas intravenous administration of anticonvulsant drugs (benzodiazepines or phenytoin) was generally effective.[22,24–27]

3. Discussion

Epilepsy and headache share several pathophysiological mechanisms,[29] related above all to neurotransmitters and ion channel dysfunctions. A better understanding of these mechanisms will shed light on the real burden and prevalence of the "ictal epileptic headache" phenomenon and its therapeutic implications.[2]

As recently pointed out,[2] there have been reports by German,[30] English[31] and Italian[32,33] researchers since the 1950s suggesting that headache can be either simply an epileptic headache or may even be the only clinical manifestation of idiopathic epilepsy.[32] Indeed, the overlap between migraine and epilepsy may be partial or complete, not necessarily synchronous (migraine mainly being a peri-ictal phenomenon), and in some cases (whose number is