


The complex interrelations between two paroxysmal disorders: headache and epilepsy

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Abstract The interrelations between headache/migraine and epileptic seizures are an interesting topic, still lacking a systematization, which is the objective of the present revision. We organize the general setting on: (a) a distinction between pre-ictal, ictal, post-ictal and inter-ictal headaches, assuming “ictal” as epileptic seizure, and (b) the kind of headache, if it is of migraine type or not. Concerning pre-ictal migraine/headache, the necessity of its differentiation from an epileptic headache presenting as an aura of a seizure is stressed; this is connected with the indefiniteness of the term “migralepsy”. The term “migraine aura-triggered seizure” should be used only in front of a proven triggering effect of migraine. Epileptic headache (called also “ictal epileptic headache”) is a well-characterized entity, in which different types of head pain may occur and an ictal EEG is necessary for the diagnosis. It may present as an isolated event (“isolated epileptic headache”), requiring a differential diagnosis from other kinds of headache, or it may be uninterruptedly followed by other epileptic manifestations being in this case easily identifiable as an epileptic aura. Hemiplegia epileptica is a very rare variant of epileptic headache, characterized by the ipsilaterality of head pain and EEG

paroxysms. Ictal non-epileptic headache needs to be differentiated from epileptic headache. Post-ictal headaches are a frequent association of headache with seizures, particularly in patients suffering also from inter-ictal headache-migraine. The reported systematization of the topic led us to suggest a classification which is shown in Appendix.

Keywords Headache · Migraine · Epilepsy · Epileptic headache · Ictal epileptic headache · Hemiplegia epileptica · Migralepsy

Introduction

Headache and epilepsy are both paroxysmal clinical disorders not infrequently occurring together in the same patient, with different interrelations. The common aspects and modalities of these interactions have been the subject of recent reports [1–3] and an attempt of a systematization of the topic is in progress. The International Classification of Headache Disorders, in its 3rd β -version (ICHD-3 β) [4], is at the moment the only available proposal of definition of the headache and epilepsy relationships. ICHD-3 β [4] treats the topic in two different sub-chapters: 1.4.4 (“Migraine aura-triggered seizure”) and 7.6 (“Headache attributed to epileptic seizure”). The 1.4.4 refers to a seizure occurring during or shortly after an attack of migraine with aura. In 7.6, two different forms are included: 7.6.1 “Hemiplegia epileptica” and 7.6.2 “Post-ictal headache”, although it is also made a brief mention of pre-ictal headache.

More recent data from the literature suggest different views of the topic, here we examine for an up-to-date that could lead to suggestions for a classification.

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Methodology

The literature on the topics has been followed for years by the authors. However, for this paper we conducted a systematic review in PubMed searching all the articles with the words epileptic headache, headache and epilepsy, migraine and epilepsy, ictal epileptic headache, hemispheric epileptics, migralepsy, migraine-triggered seizures and ictal headache, for which PubMed gives also pre-, post- and inter-ictal headache. A screening of the pertinent articles led to some more than the ones mentioned in this paper. In fact, for a reason of brevity and practicability, we did not cite some articles or because they do not add new patients or new data or because they are just comments or discussions on the matter resulting repetitive or overtaken by subsequent studies.

Results

The first and most simple organization of the topic, also in the view of a systemic classification, is to consider four possible temporal combinations of headache in relation to the occurring of an epileptic seizure: (1) pre-ictal, (2) ictal, (3) post-ictal and (4) inter-ictal, where ‘ictal’ indicates the epileptic seizure (the term “peri-ictal” refers to conditions 1–3). Moreover, in the setting of these combinations, a distinction needs to be made between migraine and other types of headache.

We will, therefore, deal with the topic according to the four possible temporal relationships of the two clinical entities.

Pre-ictal headache

The definition refers to a headache preceding an epileptic seizure. This can occur with or without an interval between the headache and the epileptic seizures. If the interval exceeds 1 h, conventionally (ICHD-3 β [4], section 1.4.4) the definition is “inter-ictal headache” (see “[Inter-ictal headache](#)”).

A headache followed by an epileptic seizure without interval could be an “epileptic headache followed by other epileptic manifestations” (see “[Ictal headache](#)”). The presence of a time interval between the headache and the seizure suggests a true pre-ictal headache. If there is no interval, the differentiating criterion from an epileptic headache should be the presence or absence of epilepsy-compatible EEG discharges beginning with the onset of headache and continuing during the following seizure. However, the absence is not an absolute criterion, since not always epileptiform discharges are detectable at the scalp EEG during an epileptic aura. Therefore, this differentiation may be not always feasible.

The pre-ictal headache can be differentiated in relation to the type of headache and diagnosed according to ICHD-3 β criteria.

Pre-ictal migraine with visual aura

Cases of migrainous attack with visual aura followed in short time by a seizure have been described [15–20].

This condition needs to be differentiated from an epileptic seizure of occipital origin beginning with visual symptoms and migraine-like headache [5–9], as may occur in childhood benign forms [10] (although this is a rare occurrence, since in most cases the epileptic visual aura alone, without migraine pain, opens the seizure [11–14]). As said above, a time interval between the migrainous attack and the seizure is the main differentiating criterion in favor of a true migraine attack. However, when there is no interval, another discriminating element could be the duration and the characteristics of the visual aura that when of epileptic nature is shorter and consists of colored circular elements [8].

Pre-ictal migraine without aura

Besides migraine with aura, several cases are reported of migraine without aura followed in a short time by an epileptic seizure [19–25] (although the ICHD-3 β , section 1.4.4, states that “Evidence for association of epilepsy with *1.1 Migraine without aura* is still lacking”).

Pre-ictal non-migrainous headache

Other types of headache may be followed by an epileptic seizure, and “*pre-ictal non-migraine-like*” headache has been reported to occur with a frequency lower than 10% in epidemiological studies of seizure-associated headache (all studies having collected the data through interviews) [26–32].

A discussion arose on the possible role of a pre-ictal migraine-with-aura in triggering an epileptic seizure. In the ICHD-3 β , the term “*Migraine aura-triggered seizure*” is proposed for a condition in which an epileptic seizure occurs “during, or within 1 h after, an attack of migraine with aura” in a patient suffering from migraine with aura. However, it should be proven that the seizure is really “triggered” by migraine. In fact, the association may be due to the activation of putatively similar mechanism, or simply be a chance association. Surely cases are not rare where occipital epilepsy is associated with history of migraine with aura [8, 10], suggesting that the modification of excitability of the occipital cortex can foster both. On the other hand, if the association occurs in patients not having history of epilepsy, the triggering mechanism

appears more plausible. Repeated, recurrent association could be another element suggesting a “triggering” mechanism. Then, the term “migraine aura-triggered seizure” should be appropriately used in the infrequent conditions in which the triggering mechanism can be really demonstrated; otherwise, the term “pre-ictal migraine-like headache” is more appropriate.

The possibility that also an epileptic activity, without occurrence of a seizure, can trigger migraine has been suggested [33].

A further discussion point concerns “*migralsepsy*”, a term frequently used in the literature and reported by ICHD-3 β as equivalent to “migraine aura-triggered seizure”. Lennox and Lennox [34] called “*migralsepsy*” an “ophthalmic migraine...followed by symptoms characteristic of epilepsy”. They reported three cases, of which two were clearly occipital lobe epilepsy with seizures beginning with visual colored auras, and sometimes migraine. The definition by Lennox and Lennox [34] may apply to both (a) an occipital epileptic seizure with migrainous aura and (b) the sequence of a true migraine followed by a seizure.

Several cases have been presented with the diagnosis of *migralsepsy* or possible *migralsepsy* [18–20, 35–37]. Some appears to be occipital seizures with migrainous aura but without headache [37], some possible epileptic migraine-like manifestation followed by a generalized tonic–clonic seizure [35], and some migraine with or without aura followed by seizure [19]; finally, the several cases reported by [20] represent different situations.

Sances et al. [38] reviewed 50 cases reported in the literature as “*migralsepsy*” or “potential *migralsepsy*” (43 of which suffering from migraine attacks with aura and 7 without aura). They used the term as meaning “true migraine followed by a seizure”. In their opinion, only 2 of the 50 cases presented features supporting the diagnosis. Noteworthy, in none of the 50 cases an ictal EEG record including the beginning of the seizure was available.

In general, it should be stressed that the term “*migralsepsy*” does not clearly indicate to which kind of association of the two manifestation it refers: epileptic seizure opening with migrainous aura, or true migraine followed (and/or possibly triggering) by a seizure. Therefore, we think better not to use it, at least until a consensus statement will define its meaning.

Ictal headache

Epileptic headache (EH) or ictal epileptic headache (IEH)

This term refers to a headache that is the manifestation of an epileptic seizure. As such, it is an epileptic “aura”. An “aura” may precede without discontinuity other more typical epileptic manifestations, e.g., motor ones, or it may

occur alone, isolated. It is important to differentiate between the cases in which the epileptic headache continues with other epileptic manifestations, and the cases in which headache remains an isolated manifestation, therefore, a “Pure” or “Isolated epileptic headache” [39].

The first condition (“EH followed by other epileptic manifestations”) is easily identifiable as an epileptic seizure beginning with headache as an epileptic “aura”.

The second condition (“Isolated epileptic headache”) is more relevant, because the headache is the only symptom (although sometimes accompanied by other minor symptoms, usually vegetative), and it has no specific features. Therefore, the head pain is not indicative of a possible epileptic nature, representing a diagnostic difficulty: only an EEG during the headache allows the correct diagnosis.

Although not frequent, but probably under-diagnosed and insufficiently known [40, 41], epileptic headache is now a well-characterized phenomenon. A review of 2013 [40] analyzed the features of 15 cases of epileptic headache [39, 42–51] presenting as isolated (although in some cases occasionally followed by motor manifestations). There are, however, older reports [52, 53], but in the past the term was also improperly used in reference to headaches in subjects with EEG epileptiform abnormalities and improvement of headache with antiepileptic therapy [54].

Other cases have been reported after 2013 [55–58] (the last [58] appearing in the evolution of the patient reported in [51]), including two with the features of “*hemicrania epileptica* [59, 60] (see later).

Epileptic headache represents a type of painful epileptic seizure (“cephalic pain”), and under this term several cases have been published [61–64], in all of which EH was followed by other epileptic manifestations. In the study by Kim et al. [65] on headache as an aura of epilepsy, EH followed by behavioral arrest and/or automatisms and/or motor seizure has been reported in five cases, while in a 6th patient it appears as isolated EH.

An epileptic headache with the features of migraine preceded by visual aura may be precipitated by intermittent photic stimulation or other highly contrasted visual stimuli, like in some video games [66–68].

Of two cases [39, 59], a video-EEG sequence documenting the attacks has been published.

Diagnosis The requisite for the diagnosis of EH is that the headache has onset, and cessation if isolated, coinciding with an EEG pattern of epileptic seizure [40] (in two reports, EEG alterations have been only be detectable using deep electrodes [42, 49]).

Headache phase may last several hours until 3 days, configuring a headache epileptic status [45–48]. The clinical characteristics of pain and accompanying symptoms in EH are rather variable; there is no peculiar feature. For this reason, diagnosis is difficult and requires an ictal EEG. The

reported cases show that the focus causing the EH may be localized in different brain lobes (occipital, temporal, parietal, frontal) and the etiology is in several cases due to neoplasms or dysplasias: then, an early diagnosis is recommended.

EH, although not rarely accompanied by autonomic symptoms, is not a type of “autonomic” seizure, but it belongs to the group of sensory seizures, subgroup of painful seizures [69].

Variant Surprisingly, the epileptic headache is not mentioned in the ICHD-3 β [4] that only reports the term “*Hemicrania epileptica*” (7.6.1). This condition was named by Isler et al. [43], who described in five patients the occurrence of unilateral migraine-like attacks coinciding with EEG (scalp and/or deep) epileptic activity localized ipsilaterally to the hemicranial pain.

No similar cases are available in the literature until the ones reported in 2014 [59] and 2015 [60], although also the case by Lindner et al. [70] and that by Belcastro et al. [48] have the features of hemicrania epileptica, and the latter [48] more exactly of an “hemicranial status epilepticus”, with headache and the occipital focus localized ipsilaterally at right side. The peculiar characteristic of ipsilaterality between the epileptic focus and hemicranial pain location (also reported by others, although referring only to inter-ictal EEG [23, 24]), rises the interesting problem of the mechanism involved. Anyway, cases of hemicrania epileptica clearly appear to be only an unusual expression of an epileptic headache. Therefore, if in future similar cases will be found, they should be classified as epileptic headache, with a specification of ipsilaterality of the ictal focus and head pain.

Terminology The denomination of “Ictal Epileptic Headache (IEH)” has been proposed [56, 71]. We prefer the more simple terminology of “Epileptic Headache”: indeed an epileptic headache is necessarily ictal, and the term “ictal” is not necessary to differentiate it from “non-ictal”, since “non-ictal” is not an epileptic seizure.

Diagnostic criteria Diagnostic criteria for epileptic headache have been proposed by Parisi et al. [56, 71]. The authors consider mandatory four criteria, including “B. Headache that is ipsilateral or contralateral to lateralized ictal epileptiform EEG discharges (if EEG discharges are lateralized)” and “D. Headache resolves immediately (within few minutes) after i.v. antiepileptic drugs”.

Although agreeing with the general validity of the proposed criteria, we observe [72] that criterion B is not necessary, due to the largely variable characteristics of headache, and it does not take into account the fact that not infrequently the headache is bilateral. Moreover, the criterion D is an useful support for the diagnosis, but cannot be a mandatory criterion, since any epileptic seizure may not respond to a therapy, this not meaning it is not epileptic. It is the pathological mechanism that characterizes a disorder,

and not the sensibility to a treatment, although some disorder can only respond to a specific treatment.

Ictal non-epileptic headache

Several epidemiologic studies report occurrence of “ictal headaches”, in different percentages (percentages calculated in relation of the total number of epilepsy-headache associations) largely due to different criteria used: 0.5% [30], 0.8% [73], 1.3% [27], 1.5% [29], 2.2% [74], 5.5% [75]. Since these studies are based on interviews or questionnaires, the term refers generically to a headache occurring during an epileptic seizure (necessarily with preservation of consciousness), without an ictal EEG in all cases. In three cases [27], “ictal” headache was the continuation of a pre-ictal one, outlasting as post-ictal. In the three other cases [73], one had head-pressure during myoclonic jerks, one had headache starting during the seizure and often continuing after, and one had headache preceding the seizure a few seconds.

In the absence of an EEG control, the exclusion of an epileptic headache relies on the fact that headache both precedes (pre-ictal) and/or continues after (post-ictal) the seizure (the term peri-ictal headache could be used in these cases). For the headache during myoclonic jerks [73], it is not reported if the EEG showed only the electrographical correspondences of myoclonias, or if continuous epileptic abnormalities were present.

Post-ictal headache

This is the most frequent association between headache and epilepsy. A review [76] on publications including a total of 3261 people with epilepsy reports that the presence of post-ictal headache ranges between 12 and 52%.

In a study on 597 epileptic patients from Korea [29], 146 (24.5%) had post-ictal headache, of which 53 (36.3%) consistent with migraine type. On 1109 epileptic patients from China [30], 34.1% had post-ictal headache, slightly higher (38.4%) in those with partial epilepsy [77]. Post-ictal headache is more frequent after generalized tonic-clonic seizures [78], particularly when prolonged and repetitive [76], moreover, in temporal and occipital lobe epilepsy [77, 79], including the occipital idiopathic childhood forms [8], and in those suffering from inter-ictal headache [76].

Inter-ictal headache

Patients suffering from epilepsy may also suffer from any type of headache, having its occurrence independent of the epileptic seizures, although occasionally near it. This is a comorbid condition, to be kept separate from the above-

reported peri-ictal and ictal headaches. Inter-ictal headache, and particularly migraine, in patients with epilepsy, compared to the general population, appears to be more frequent until the fourth decade, but not in older ages, according to [32]. Some epileptic syndromes of childhood and adolescence (“rolandic” and juvenile myoclonic epilepsy) have higher comorbidity with headache, and those suffering from inter-ictal migraine are more likely to have pre- and post-ictal headache of migraine type [26, 27, 79].

Conclusion

This commented review of the literature gives elements for the proposal of a classification; the main lines of it are shown in “Appendix”. The classification at point 1 is correlated with a “comment” giving support to it and explaining the points when necessary.

We hope this review, like other documented contributions in different areas of the world headache [80], help a correct updating of the future final version of ICHD-3.

For an adequate vision of the topic, we think that some major points need to be saved, particularly the epileptic headache with its peculiar characteristic and different expressions, and an adequate illustration of the pre-ictal headaches, including migraine without aura.

Compliance with ethical standards

Conflict of interest None of the authors has any conflict of interest to disclose.

Appendix

Suggestions for a classification of the possible relationships between headache/migraine and epilepsy.

Headache and epileptic seizures

Headache may precede, be contextual, or follow an epileptic seizure, or may occur independent from it. Moreover, headache may be the expression of an epileptic seizure.

Headache preceding an epileptic seizure (pre-ictal headache)

Description An attack of headache or of migraine, with or without aura, during which, or in short time following which (conventionally within 1 h), an epileptic seizure occurs.

Diagnostic criteria Presence of all A, B, C

- (A) a headache attack of undetermined type, or a migraine attack with or without aura diagnosed according to ICHD-3β criteria.
- (B) a seizure, fulfilling diagnostic criteria for any type of epileptic attack, occurring during, or within (conventionally) 1 h after cessation of, the headache attack.
- (C) headache as an epileptic manifestation has been excluded.

Comment Headache and epilepsy are both paroxysmal brain disorders. Migraine with visual aura and occipital epileptic seizures share a common site of origin with probably partially similar mechanisms. Seizures beginning with visual symptoms and migraine-like attack, immediately followed by other epileptic manifestations, may occur in occipital epilepsy, including symptomatic cases. In this condition, the migraine-like manifestation is an epileptic phenomenon, part of the epileptic seizure as an initial pain phase of it, that is head pain as an epileptic aura (see “Epileptic headache (EH)”).

The definition “pre-ictal migraine” requires the absence of ictal-epileptic EEG features during aura and migraine in the cases where the phenomena occur in a direct sequence. A time interval following the aura/migraine before the epileptic seizure should exclude an epileptic origin of the sequence also in absence of an EEG record.

Pre-ictal migraine with aura is more frequent than without aura. Reported auras are visual, although rarely also paresthetic.

A triggering effect of migraine, rather than an occasional association, is suggested in cases lacking a history of epilepsy, or of repeated occurrence, although it is generally difficult to establish with certainty; therefore, in most cases the term pre-ictal migraine should be preferred, instead of “migraine aura-triggered seizure”.

The term “*migralepsy*” was originally used in reference to the condition of visual symptoms followed by migraine and subsequently an epileptic seizure; the term may be applied both to an epileptic migraine evolving with other types of epileptic manifestation, both to a true migraine followed by a seizure. Therefore, it is a term requiring a better and consensual definition.

Ictal headache

Epileptic headache (EH)

Description Headache is a possible manifestation of an epileptic seizure.

It is characterized by head pain (whether migraine-like or not) with onset, and cessation if isolated, coinciding with a scalp EEG pattern consistent with an epileptic seizure

(cases are reported in which EEG alterations may only be detectable using intracranial electrodes).

It may present as an isolated manifestation (“pure” or “isolated epileptic headache”), or it may directly precede other manifestations of an epileptic seizure (in this condition, headache more clearly appears as an “aura” of the seizure, an “epileptic aura”). When isolated, it is not distinguishable from other types of headache, and only an EEG during the manifestation can lead to the correct diagnosis.

The immediate pain cessation at the infusion of an antiepileptic therapy helps to confirm the diagnosis.

“Hemicrania epileptica” is a very rare variant of epileptic headache, characterized by ipsilateral location of a hemicranial headache and ictal EEG paroxysms.

Diagnostic criteria:

- (A) Headache attack of any type fulfilling criterion B.
- (B) Onset, and cessation if isolated, coinciding with a scalp or intracranial EEG pattern of epileptic seizure.

Variants:

- (a) Pure or isolated (Isolated Epileptic Headache, IEH), when headache is the only manifestation of a seizure (minor additional manifestations, like nausea, vomit, phono-photophobia, agitation or irritability or hypersensitivity to noises or dyspnea, may be present).
- (b) Epileptic headache followed without discontinuity by other epileptic manifestations, thus headache representing actually the initial manifestation of an epileptic seizure.

Ictal non-epileptic headache

Description Headache occurring during an epileptic seizure, but not being epileptic in nature, therefore not showing strict coincidence with epileptiform EEG features.

The presence of this kind of headache in epidemiological studies is reported with a frequency from 0.5 to 5%. In practice, it can be differentiated from the epileptic headache when ictal headache onset clearly precede and/or continues after cessation of the seizure.

Diagnostic criteria:

- (A) Headache attack of any type occurring during an epileptic seizure, fulfilling criterion B.
- (B) Onset and/or cessation not coinciding with the seizure, or not coincidence with the EEG pattern of epileptic seizure.

Post-ictal headache (PIH)

Description The occurrence of headache after an epileptic seizure is frequent, ranging between 12 and 52%.

PIH occurs (conventionally) within 3 h following a seizure, and may last up to 72 h. Headache may have migrainous or tension-type features and is usually of moderate to severe intensity. PIH is more frequent after generalized tonic–clonic, prolonged and repetitive seizures; moreover, it occurs more frequently in subjects suffering from inter-ictal headache.

Diagnostic criteria:

- (A) Headache of any type fulfilling criterion B.
- (B) Headache occurring within 3 h after any type of epileptic seizure.

Inter-ictal headache

Description Patients suffering from epilepsy may also suffer from any type of headache, having its occurrence independent of the epileptic seizures, although occasionally near it. This is a comorbid condition, to be kept separated from the above-reported peri-ictal and ictal headaches.

Diagnostic criteria:

- (A) Headache of any type in a patient suffering from epilepsy.
- (B) Headache attacks and epileptic seizures occur independently, although headache may be rarely pre-ictal and frequently post-ictal.

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