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# The crossover between headache and epilepsy

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**“The relationship between headache and epilepsy is complicated and although the nature of this association is not yet fully clear, several plausible explanations have been proposed.”**

The relationship between headache and epilepsy is complicated and although the nature of this association is not yet fully clear, several plausible explanations have been proposed. To achieve a definitive international consensus on the crossover between headache and epilepsy, during the last 100 years, many authors have devoted countless efforts to reach an agreement on the multiple aspects of this intriguing topic [1].

The clinically based hypothesis that headache and epilepsy are related dates back to the 19th century, when Sir William Richard Gowers' famous book, published in 1907, first suggested that “migraine is in the borderland of epilepsy” [1], sharing several pathophysiological mechanisms related above all – “we can say today in the light of modern knowledge” – to neurotransmitter and ion channel dysfunctions. If we compare the current knowledge with those of Gowers' times, the etiopathogenesis of headache and of epilepsy are nowadays, in the most important aspects, well known. However, in his own time, during an epoch before EEG, Gowers stated that “...in extremely rare instances one affection may develop while the other goes on,” suggesting a possible partial overlap between them. More than 100 years later, in the era of digital EEG recordings, we can firmly report that sometimes “headache itself can even be epilepsy,” and, in certain cases (probably largely underestimated), “the headache can represent the only ictal epileptic phenomenon” [1,2].

There are insufficient etiopathological studies of the pediatric population

for tension-type headache and other primary headache (cluster headache and other trigeminal autonomic cephalalgias), which are so rare or even exceptional in pediatric age; so, here we can discuss only data related to the physiopathology of migraine. In this respect, it has been shown that hyperexcitation occurs in epilepsy, while in migraine a brief hyperexcitation period (depolarization) is followed by a long hypoexcitation period (spreading depression), followed again by hyperexcitation as a rebound phenomenon. Moreover, a disexcitability (hyper- and hypo-excitation in the same migrainous patient at different points in time) condition has even been demonstrated [1].

**“Cortical spreading depression seems to be the connecting point between migraine and epilepsy...”**

Cortical spreading depression (CSD) seems to be the connecting point between migraine and epilepsy [3,4], even in patients suffering from migraine without aura, whereas the presence of CSD in silent cortical areas has been hypothesized as a possible underlying mechanism. CSD is characterized by a slowly propagating wave (2–6 mm/min) of sustained strong neuronal depolarization that generates transient intense spike activity as it progresses into the brain tissue, followed by neural suppression that may last for minutes. The depolarization phase is associated with an increase in regional cerebral blood flow, whereas the phase of reduced neural activity is associated with a reduction in blood flow [5].

**KEYWORDS:** classification criteria • comorbidity • epidemiology • epilepsy • headache • ictal epileptic headache • migraine

It is crucial to remark that while an epileptic discharge can originate exclusively in the cortex, the physiopathogenesis of headache has its origin at multiple corticosubcortical levels. Therefore, the two cascades of events (headache and epilepsy) show independent ways that can crossover only at a certain point: at the cortical level [6,7]. The numerous other subcortical and peripheral neurovascular steps in the activation of the cascade run through independent ways that do not cross.

However, when headache and epilepsy overlap as a result of the crossing of the cascade of events at the cortical level, in both of the events (CSD and epileptic focus), their onset and propagation are triggered when these events reach a certain threshold, which is lower for CSD than for seizure [6–12]. These two phenomena may be triggered by more than one pathway converging (at cortical level) upon the same destination: depolarization and hypersynchronization.

**“...the conflicting literature data on this topic can be explained by ... the different sampling and study design”**

Why could the onset of epileptic seizure facilitate the onset of CSD to a greater degree than the onset of CSD facilitates the onset of epileptic seizure? Recently, we have studied this aspect in depth and, due to lack of space, here we refer to the recently published [6–12]. In this respect, we consider of particular interest the patients reported by Fabricius *et al.*, “...whose seizure activity spread from electrode to electrode at the same slow speed as CSD...” [13]. This is noteworthy, as the march of seizure activity under other conditions spreads much faster than a CSD; this experimental observation can justify why two neurophysiological events (epileptic discharge and CSD), which normally run at significantly different speeds, in certain conditions can meet and trigger each other.

With regards to the epidemiological literature findings on comorbidity between headache and epilepsy, the major discrepancies and conflicting data are due to: the confusion and mixture of epidemiological data between adults and children across studies, and the significant underestimation of headache when it is comorbid in populations with epilepsy; in addition, it is likely that the comorbidity is higher in children than in adults, as is the case for all other ictal autonomic manifestations [10–12,14]. Indeed, the conflicting literature data on this topic can be explained by the co-occurrence (synergistic and/or divergent) of confounding variables according to the different sampling and study design. These results may also be partly explained by differences in the target populations, study design, age range, methods and inclusion criteria limited to referral epilepsy patients or just tertiary headache centers, or not having appropriate control groups and/or using different or ill-defined diagnostic criteria [14]. Therefore, due to the different methodologies and criteria used, these studies are quite difficult to compare.

Children are more likely to have an autonomic symptomatology both in epilepsy and headache attacks, and moreover, they can experience isolated long-lasting ictal autonomic manifestations, while in adults ictal autonomic manifestations (both in

epilepsy and headache) are usually associated, simultaneously or sequentially, with other motor or sensory ictal signs and symptoms [15]. In this regard, we have recently suggested to include ‘ictal headache’ among the ictal autonomic manifestations in both headache and epilepsy international classifications, which until now have always ignored each other [1,6–8,10–12,16]. In particular, we have proposed new criteria for the event termed ‘ictal epileptic headache’ (IEH) in which “headache is the sole ictal epileptic manifestation” [1,2]. On the other hand, we should consider that headache pain originates in the terminal nervous fibers (vasomotor) in cerebral blood vessels; consequently, headache should be classified as an ‘autonomic’ sensation in the International League Against Epilepsy (ILAE) Glossary and Terminology. Conversely, in the ILAE classification, headache is considered exclusively as a possible semiological ictal phenomenon among the ‘nonmotor’ features. In particular, headache is described as a ‘cephalic’ sensation and is not considered as the sole ictal expression of an epileptic seizure. In this respect, we suggested that ‘ictal epileptic headache’ events could thus be interpreted as the sole expression of an epileptic seizure and classified as an autonomic seizure. 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 is very different (i.e., benign) from that of people with additional ictal motor-sensitive semiology. In addition, headache as an autonomic phenomenon is crucial when attempting to understand why headache may be the sole ictal epileptic manifestation [1]: the reasons have been thoroughly explained in Panayiotopoulos syndrome, whereas 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.

**“Recent scientific evidences on the ictal epileptic headache have convinced us that the ‘migralepsy’ concept is exceptional or even it does not exist.”**

According to our recently proposed criteria [2] for IEH, there are serious doubts about the real existence of the phenomenon called ‘migralepsy’ [1,10,15]. Recent scientific evidences on the ictal epileptic headache’ have convinced us that the ‘migralepsy’ concept is exceptional or even it does not exist.

In our opinion, the ‘migraine–epilepsy’ sequence, defined as ‘migralepsy’, could merely be a seizure starting with an ‘ictal headache’, followed by a sensory-motor partial or generalized seizure, thus fitting, in these cases, the codified ‘hemicrania epileptica’ criteria [1,10,12,16].

It is also important to stress that rarely in IEH cases, the ictal origin of the headache has only been demonstrated (by chance in drug-resistant epileptic patients, during the presurgical investigations) by deep electrode studies. 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 [1,17–19].

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