

# The Overlap between Headache and Epilepsy in the Light of Recent Advances in Medical Genetics

Alessandro Ferretti, Maria Chiara Paolino and Pasquale Parisi\*

Child Neurology, Headache Paediatric Center, Paediatric Sleep Disorders, NESMOS Department, Chair of Pediatrics, Faculty of Medicine and Psychology, Sapienza University, c/o Sant'Andrea Hospital, Rome, Italy

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Although the nature of epilepsy and headache association has not been fully understood, during the past 100 years several potential mechanisms have been proposed to explain the link between these two conditions [1]. To get a definitive international consensus on the crossover between headache and epilepsy, many authors have spent endless efforts to reach an agreement on the various aspects of this intriguing concept.

The clinical hypothesis that headache and epilepsy are related derives from 19th century literature data. Sir Gowers first suggested that "migraine is in the borderland of epilepsy", and we can say now, in the light of modern knowledge, that neurotransmitters and ion channel dysfunctions can play a leading role. Both are characterized by transient attacks of altered brain function with a spectrum of common pathophysiological, clinical and therapeutic features. Furthermore, epilepsy and migraine may mimic each other.

More than one hundred 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 not recognized), "the headache can represent the only ictal epileptic phenomenon" [2,3]. In this regard, there have been proposed new criteria for the event termed "ictal epileptic headache" (IEH) in which "headache is the sole ictal epileptic manifestation" [4].

According to our recently proposed criteria for IEH, there are serious doubts about the real existence of the phenomenon called "migralepsy" [5,6]. This term, derived from *migra(ine)* and *(epi)lepsy*, has been first used by Lennox and Lennox, in 1960 to describe a condition wherein "ophthalmic migraine with perhaps nausea and vomiting was followed by symptoms characteristic of epilepsy".

Recent scientific evidences on the IEH, 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 simply be a seizure that starts with an "ictal headache", and continues with a seizure (sensory-motor partial or generalized), fitting thus in these cases into codified criteria for "Hemicrania Epileptica" [7,8].

Moreover it is significant to underline that rarely in IEH cases, the headache ictal origin had been demonstrated (by chance in drug-resistant epileptic patients, during pre-surgical investigations) only by deep electrode studies. In other words, while epileptiform abnormalities usually sustain a diagnosis of epilepsy, not rarely IEH patients are characterized by the absence of clear epileptic spike-and-wave activity. Missed recognitions of IEH events are due to these reasons [9,10].

Highlighted these aspects, the overlap between headache and epilepsy should be analyzed from multiple points of view: epidemiological, physiological, etiopathological, and classificative.

Migraineurs show a higher frequency of epilepsy (range 1–17%) than general population (0.5–1%), and at the same time migraine prevalence among patients affected by epilepsy is also higher (range 8–15%) than that reported in healthy individuals [11–13]. Especially in children this comorbidity is found often [14].

Seizures and migraine attacks share different pathophysiological mechanisms. Both events may be sign of an underlying brain lesion, or have a probably genetic origin. In this respect, it has been shown that in epilepsy occurs hyperexcitation, while in migraine a brief hyperexcitation period (depolarization) is followed by a long hypoexcitation period (spreading depression), followed again by hyperexcitation, as rebound phenomenon. Moreover, it has been shown that a disexcitability (hyper- and hypo-excitation in the same migraineurs at different points in time) underlines both the phenomenon [1].

Cortical Spreading Depression (CSD) is believed to underlie both migraine and epilepsy [15,16], even in patients affected by migraine without aura. CSD is characterized by a slowly propagating wave of sustained strong neuronal depolarization that generates transient intense spike activity as it progresses into the brain tissue, followed by neural suppression which may last for minutes. The phase of depolarization is associated with a regional cerebral blood flow increase, whereas the phase of reduced neural activity is associated with a reduction in blood flow [17].

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 cortico-subcortical levels. Thus, the two cascades of events (headache and epilepsy) show independent ways that can crossover only at the cortical level [18,19]. When headache and epilepsy overlap, after the cortical cascade of events, their onset and propagation are triggered when CSD and epileptic focus reach a definite threshold, lower for CSD than for seizure [6,8,20,21]. Moreover, the onset of CSD and that of the epileptic seizure may facilitate each other [22].

Triggering factors may be environmental or individual (genetically determined or not), determining an ionic flow and leading to CSD, through neuronal and glial cytoplasmic bridges rather than through

**\*Corresponding author:** Prof. Pasquale Parisi, 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, Fax: 0039-6-33775941; E-mail: [pasquale.paris@uniroma1.it](mailto:pasquale.paris@uniroma1.it)

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interstitial spaces, as usually occurs in the spreading of epileptic seizures.

Strong support for a shared genetic basis between headache and epilepsy comes from clinical/EEG and genetic studies on familial hemiplegic migraine, a rare monogenic subtype of migraine [23-25], where errors in the same gene may be associated with migraine in some cases and with epilepsy in others [26].

Gene mutations have been found using positional cloning techniques, mutation analysis, and traditional linkage analysis which require testing several hundreds or thousands of genetic markers across the genome and selecting those chromosomal regions that most closely segregate with the disease. A second linkage analysis strategy is affected sib-pair analysis in which affected siblings shared chromosomal regions that occur with a probability higher than by chance alone are identified. Candidate genes in the shared regions are then characterized testing single-nucleotide polymorphism (SNPs). The objective is to identify SNPs, and thus gene alleles, whose frequency significantly differs between cases and controls and increases susceptibility to the disease. A third, hypothesis-driven approach is direct testing of candidate genes in case-control association studies [27].

Recent studies propose common genetic substrates and a correlation between phenotypic and genotypic linked to mutations in some ion transporters genes, including CACNA1A, ATP1A2, and SCN1A [28-32]. Other genotyping findings are reported in literature to explain the link between migraine and epilepsy. They include mutations on SLC1A3, a member of the solute carrier family that encodes excitatory amino acid transporter 1, 57 POLG58, C10 and F259, which encode mitochondrial DNA polymerase and helicase twinkle [33]. Recently numerous genome-wide association studies and meta-analysis are identifying loci associated migraine and epilepsy susceptibility [34].

The fundamentals of molecular genetics, are important for clinicians to understand unprecedented insights into the pathogenesis of these disorders, and reveal promising treatment targets for future drug development. Further genetic, experimental and clinical investigations (molecular and multicenter clinical trials) are necessary to better understand this complex relationship; this approach could be the basis to create a definitive international consensus on this matter.

#### Conflict of Interest

We have no conflict of interests to disclose regarding this "Invited Editorial".

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