The Complex Relationship Between Epilepsy and Headache and the Concept of Ictal Epileptic Headache

Pasquale Parisi

Key Points

- Headache/migraine is often associated with epilepsy in children, as a pre-ictal, ictal, post-ictal or inter-ictal phenomenon.
-Epidemiological aspects of the co-morbidity between epilepsy and headache are clearly different in children and adults.
- Headache as a symptom, with migraine characteristics and/or tension-type headache characteristics, may be the only clinical ictal manifestation of an epileptic seizure: this condition is now classified as "ictal epileptic headache".
- In particular, according to published criteria, the term "ictal epileptic headache" must be used in cases of a headache/migraine attack as the sole clinical ictal symptom of epileptic origin, confirmed by ictal-EEG recording and clinical-EEG responsiveness to intravenous antiepileptic drugs.
- EEG is not recommended as a routine examination for children diagnosed with headache, but is mandatory and must be carried out promptly in cases of prolonged migraine/headache that does not respond to antimigraine drugs and in which epilepsy is suspected.
- This is not a marginal question, because these possible, isolated, non-motor, ictal manifestations (i.e. ictal epileptic headache) should be taken into account before declaring an epileptic patient as "seizure free" so as to be able to suspend anticonvulsant therapy safely.

P. Parisi (✉)
Child Neurology, Pediatric Headache & Sleep Disorders Centre, Chair of Pediatrics, NESMOS Department, Faculty of Medicine and Psychology, Sapienza University, Via Di Grottarossa, 1035–1039, 00189 Rome, Italy
e-mail: pasquale.parisi@uniroma1.it

P. Striano (ed.), *Epilepsy Towards the Next Decade,*
Contemporary Clinical Neuroscience, DOI 10.1007/978-3-319-12283-0_8

Summary

The possible link/comorbidity (causal or not causal) between epilepsy and headaches has been a topic of debate for over a hundred years, ever Since William Richard Gowers's time. In recent decades, new data have emerged in favor of a non-random relationship between these two entities. They are both characterized by transient attacks of altered brain function with a clinical, pathophysiological, genetic and therapeutic overlap, and may thus mimic each other. Indeed, the clinical distinction between headache and epilepsy may make the differential diagnosis a highly challenging task. Both are common and often co-morbid, with headache attacks in epilepsy being temporally related to the occurrence of epileptic seizures as a pre-ictal, ictal, post-ictal or inter-ictal event. Yet, they are both paroxysmal and chronic neurological disorders that share many clinical and epidemiological aspects, and they may both present with visual, cognitive, sensitive-sensorial and motor signs/symptoms; these neurophysiologicl phenomena arise from the cerebral cortex and are modulated by sub-cortical connections. Even from an epidemiological point of view, data in the literature regarding the co-morbidity between headache and epilepsy appear to be quite distinct in children. What makes this scenario even more variegated and complex are new data suggesting that a headache may, in some cases, even be the only ictal manifestation of an epileptic seizure. The latter condition, the so-called "ictal epileptic headache", is a new entity that has recently been cited in the new classification of headache disorders (ICHD-III), whose diagnostic criteria have very recently been defined and published. The data that have led, over the last decade, to the proposed "diagnostic criteria" for "ictal epileptic headache" are reported below. In this regard, it is crucial to stress that the authors who proposed the diagnostic criteria for ictal epileptic headache, have deliberately and consciously chosen "criteria" that underestimate the phenomenon so as to avoid spreading panic among both patients and physicians, who tend to be reluctant to accept this concept because of the stigma attached to the diagnosis of epilepsy. In the future, once this concept (i.e. "headache" as the sole ictal epileptic manifestation) has been more widely accepted, it will hopefully be possible to propose "different and less restrictive" criteria than those recently published.

Abstract Since William Richard Gowers' time, for over a hundred years, it has been discussing the possible link/comorbidity (causal or not causal) between epilepsy and headaches. During the latest decades, new data have emerged in favor of a non-random relationship between these two entities. They are both characterized by transient attacks of altered brain function with a clinical, pathophysiological, common genetic factors and therapeutic overlap, thus, they may also mimic each other. In fact, the clinical distinction between headache and epilepsy can be so difficult to make the differential diagnosis sometimes highly problematic. Both are common, often co-morbid and, in this latter case, headache attacks can be temporally related with the occurrence of epileptic seizures as pre-ictal, ictal, post-ictal

or inter-ictal phenomenon. Yet, they are both paroxysmal and chronic neurological disorders that share many clinical and epidemiological aspects, and they may, both, present with visual, cognitive, sensitive-sensorial and motor signs/symptoms; these neurophysiologic phenomenon arise from the cerebral cortex and are modulated by sub-cortical connections.

Even from an epidemiological point of view data from the Literature about the co-morbidity between headache and epilepsy seem to be clearly different in children.

In addition, to make this scene even more variegated and complex, new data, supporting the possibility that a headache may even be, in some cases, "*the only ictal manifestation of an epileptic seizure*", became available. This latter condition, the so-called "Ictal Epileptic Headache", is a new entity that has recently been quoted in the new classification of headache disorders (ICHD-III, third edition, published in July 2013 in Cephalalgia), whose diagnostic criteria have also been suggested and published very recently.

Here it have been reported, in their essential aspects, the available data that during the latest decade have led to propose "diagnostic criteria" for "Ictal Epileptic Headache". In this regards, in particular, it is crucial to stress that the Authors who proposed the diagnostic criteria for the "Ictal Epileptic Headache", have "deliberately" and "consciously" chose to formulate "criteria" that underestimate the phenomenon rather than to spread the "panic" among patients and physicians who are reluctant to accept this concept because the stigma attached to the diagnosis of epilepsy. In the future, when this concept (an "headache" as sole ictal epileptic manifestation) will be "metabolized", we will be able to propose "different and less restrictive" criteria than those recently published.

Keywords Ictal epileptic headache (IEH) · Epilepsy · Migraine headache · Autonomic seizures · Autonomic status epilepticus · Criteria for IEH diagnosis

Epilepsy and Headache: Diagnostic Challenges and Their Reasons

Clinical Issues

Both occipital seizures and migraine/headache may be characterized by the presence of a transitory visual disturbance that follows headache and other autonomic symptoms. A mis-diagnosis of visual seizures as migraine with visual aura is frequent and costly. The main factor that contributes to such an error is that the description of a visual hallucination is often limited to terms such as scintillations, fortification spectrum, teichopsia, phosphenes, and variations of these signs (Panayiotopoulos 1987, 1999a, b, c). Elementary visual hallucinations of occipital seizures are usually different from the visual aura of migraine. "Ictal" elementary

visual hallucinations are defined according to color, shape, size, location, movement, speed of appearance, duration, frequency and associated symptoms of progression. Elementary visual hallucinations are mainly colored and circular, develop within seconds, and are brief in duration (2–3 min); they often appear on the periphery of a temporal visual hemi-field, becoming larger and multiplying in the course of the seizure, frequently moving horizontally toward the other side (Panayiotopoulos 1987, 1999a, b, c). Significantly, post-ictal headache, which is often indistinguishable from migraine, occurs in more than half of patients, even after brief visual seizures. Post-ictal headache frequently occurs 3–15 min after the seizure ends, in a situation known in migraine as the "asymptomatic interval". Thus, occipital seizures often generate migraine-like attacks, i.e. an "epilepsy-migraine sequence" (Panayiotopoulos 1987, 1999a, b, c). In migraine, visual aura usually starts as a flickering, uncolored, zigzag line in the center of the visual field and affects the central vision. It gradually spreads over 4 min toward the periphery of one hemi-field, and usually lasts < 30 min, often leaving a scotoma. The total duration of visual auras is less than 60 min. Furthermore, migraine visual aura rarely occurs daily, and is not associated with non-visual ictal occipital symptoms, such as eye and head deviation and repetitive eyelid closures. Less typical features of migraine visual aura, such as spots, circles and beads, with or without colors, maybe experienced during migraine visual aura, though they are rarely dominant. Clustering of other symptoms, such as those described above, betray their migraine nature (Panayiotopoulos 1987, 1999a, b, c).

Electroencephalographic Issues

Children with a definitive diagnosis of epilepsy may not have epileptic EEG abnormalities recordable from the scalp (for example, as may occur in some cases of "nocturnal frontal lobe epilepsy", Nobili 2007), whereas EEG abnormalities that resemble paroxysmal abnormalities (usually present during an epileptic seizure) may be recorded during a migraine attack.

In general, EEG is of less diagnostic importance in the study of patients suffering from migraine. However, the temporal and spatial pattern of EEG anomalies in headache is usually extremely different from that observed during a real epileptic seizure (Andermann 1987; Andermann and Zifkin 1998). In the few cases of ictal epileptic headaches reported in the literature, the patients had headache/migraine as the only manifestation of a non-convulsive epileptic seizure, diagnosed on the basis of an EEG recording alone (Parisi et al. 2007, 2012a, b, 2013a, b; Parisi 2009a, b, 2011; Parisi and Kasteleijn-Nolst Trenité 2010). Intravenous administration of AEDs in these patients was able to control the seizure, as demonstrated by means of a scalp EEG as well as resolution of the headache symptoms (Parisi et al. 2012a, b). However, some isolated cases of "ictal epileptic headache" reported in the literature were incidentally detected when the critical focus was being recorded by means of deep electrodes (Laplante et al. 1983; Fusco et al. 2011). Therefore, although the EEG recording may not prove very useful as a screening instrument for migraine,

it does play a fundamental role in pediatric patients who have headache/migraine symptoms that do not respond to commonly-used anti-migraine drugs (Parisi et al. 2012a, b).

Furthermore, the ictal EEG abnormalities recorded in IEH patients display aspecific features; indeed, various ictal EEG patterns have been recorded during migraine-like complaints in both symptomatic and idiopathic cases (Belcastro et al. 2011a, b; Parisi et al. 2012a, b).

Epidemiological Issues: Beyond the Controversial Evidence

An "editorial" dedicated exclusively to these epidemiological aspects, to their possible biases and to the underestimation potentially related particularly to pediatric age has recently been published (Belcastro et al. 2012).

The prevalence and incidence of co-morbid epilepsy and headache in the general population, including all stages of life, vary (Olafsson et al. 2005). Indeed, headache predominates in males before puberty, whereas it is more common in females afterwards. By contrast, epilepsy predominates in males at all ages (Olafsson et al. 2005). The age at the peak incidence of these two conditions also differs. The peak age for migraine occurs during the working years (Lyngberg et al. 2005), whereas for epilepsy it is under the age of one year and over the age of 60 years (Hauser et al. 1993). The fact that data in the literature on this topic are somewhat conflicting (Lipton et al. 1994a, b; Andermann 1987; Tonini et al. 2012) may be attributed to the co-occurrence (synergistic and/or divergent) of confounding variables adopted in the different sampling methods and study designs. These conflicting results may partly be explained by differences in the target populations, study design, age range, methods, by inclusion criteria that are limited to referral patients with epilepsy or tertiary headache centers, by the lack of appropriate control groups, and/or by different or ill-defined diagnostic criteria (Tonini et al. 2012). Thus, these studies cannot easily be compared with one another.

Although there is not yet any conclusive evidence of a real causal relationship between the two disorders, we must bear in mind that the comorbidity of headache and epilepsy is, beyond any doubt, different in children and in adults. Children are more likely to have an autonomic symptomatology in both epilepsy and headache attacks (Fogarasi et al. 2006; Kasteleijn-Nolst Trenité and Parisi 2012). Moreover, they may have isolated, long-lasting ictal autonomic manifestations, while ictal autonomic manifestations (in both epilepsy and headache) in adults are usually associated, whether simultaneously or sequentially, with other motor or sensory ictal signs and symptoms (Fogarasi et al. 2006; Kasteleijn-Nolst Trenité and Parisi 2012). Furthermore, it should be borne in mind, despite the limited number of studies in the literature (Yamamane et al. 2004; Piccinelli et al. 2006; Toldo et al. 2010), that the framework assumes markedly different shapes in the pediatric population.

Among 50 children with epilepsy, Yamamane et al. (2004) found that 46 % had headache, and that 10 (43.5 %) out of the 23 headache sufferers had migraine. Most

patients with headache were older than 10 years (54.5%) and had idiopathic epilepsy (65.2%). In some specific childhood epilepsy syndromes, migraine/headaches appear to be more prevalent (Kinast et al. 1982; Bladin 1987; Andermann and Zifkin 1998; Panayiotopoulos 1999b; Yankovsky et al. 2005; Wirrell and Hamiwka 2006; Clarke et al. 2009). The best known of these syndromes are benign occipital epilepsy of childhood with occipital paroxysms and benign rolandic epilepsy; remarkably, in the majority of the cases reported (95%), the headache started in the same year as, or after, the diagnosis of epilepsy (Andermann and Zifkin 1998; Panayiotopoulos 1999b; (Ito et al. 1996, 2003, 2004; Leniger et al. 2001; Toldo et al. 2010; Verrotti et al. 2011a).

Piccinelli et al. (2006) found EEG interictal abnormalities in 16 (12.8%) out of 137 children and adolescents with headache, particularly in those with migraine with aura. Another intriguing issue is the comorbidity of headache in patients with idiopathic epilepsy of infancy. Indeed, it is widely known that patients with epilepsy with rolandic or occipital paroxysms, or even those without seizures, have concomitant migraine in up to 60% of cases (Panayiotopoulos 1999a, b, c; Tonini et al. 2012). When they investigated a large, consecutive, pediatric population of 1795 patients with headache under 18 years of age diagnosed at a headache center, Toldo et al. (2010) found a strong association between migraine and epilepsy. In that study, migraineurs displayed a risk for epilepsy that was 3.2 times higher than that for tension-type headache, with no significant difference between migraine with and without aura. Migraineurs affected by focal epilepsies had a risk for cryptogenic epilepsy that was three times higher than that for idiopathic epilepsy. Recently, adolescents with any headache type were reported (Lateef et al. 2012) to have significantly higher rates of epilepsy, as previously confirmed by Baca et al. (2011), who found the comorbidity of migraine and epilepsy in 15% of the children they studied. Interestingly, Colombo et al. (2011), whose data confirmed previous findings (Sasmaz et al. 2004) showing that almost 36% of parents of children with headache are unaware of the headache, stressed that pediatric headache is still under-diagnosed and is not adequately considered as a health problem either by the medical community or in social settings: on the one hand, this indicates the extent to which headache is underestimated, on the other, it confirms that the clinical picture in co-morbid cases is dominated by the diagnosis of epilepsy.

In recent years, following several reported cases of headache as the sole manifestation of an epileptic seizure (Parisi et al. 2007, 2008a, b, 2012a, b; Parisi 2009a, b; Parisi and Kasteleijn-Nolst Trenité 2010; Belcastro et al. 2011a, b; Verrotti et al. 2011b), the term ictal epileptic headache has been proposed to identify these events (Parisi 2011, 2012a, b). In particular, ictal epileptic headache is recognized as a headache ("as the sole ictal manifestation" and without presenting a "specific" clinical picture of migraine, migraine with aura or tension-type headache), lasting from seconds to days, with evidence of ictal epileptiform EEG discharges, which immediately resolve upon administration of intravenous antiepileptic medications (Parisi et al. 2012a).

In conclusion, although controversial epidemiological data in adults are often used as evidence that no association exists between these two conditions,

some studies, particularly those conducted in pediatric populations, point to the comorbidity of headache and epilepsy. Thus, further studies on larger pediatric populations are warranted to definitively confirm this comorbidity (Belcastro et al. 2012).

Shared Pathophysiology, Classification and Genetic Aspects

Common Pathways, Substrates and Genetics

Many studies support the hypothesis of excessive neocortical cellular excitability as the main pathological mechanism underlying the onset of attacks in both diseases (Somjen 2001; Berger et al. 2008). Indeed, since hypo- and hyper-excitation in migraine occur sequentially as rebound phenomena (during a spreading depression), the term "dys-excitability" may better describe migraine pathophysiology than hyper-excitability (Somjen 2001; Berger et al. 2008; Tottene et al. 2009, 2011; Fabricius et al. 2008; Parisi et al. 2012a, b). Cortical Spreading Depression (CSD), which may be considered the link between headache and epilepsy (Moskowitz et al. 1993; Bolay et al. 2002; Ayata et al. 2006; Ayata 2010; Parisi et al. 2008a, b; Parisi 2009a, b; Eikermann-Haerter & Ayata 2010; Belcastro et al. 2011a, b; Zhang et al. 2011; Parisi et al. 2012a; Ghadiri et al. 2012), is characterized by a slowly propagating wave of sustained strong neuronal depolarization that generates transient intense spike activity, followed by neural suppression, which 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. On the other hand, CSD activates the trigeminovascular system, inducing the cascade release of numerous inflammatory molecules and neurotransmitters, which results in pain during the migraine attack (Zhang et al. 2011, Parisi et al. 2012a, b).

There is emerging evidence from both basic and clinical neurosciences that cortical spreading depression and an epileptic focus may facilitate each other, though to different extents (Parisi et al. 2008; Parisi 2009a, b; Belcastro et al. 2011a, b, c; Parisi et al. 2012a). When a certain threshold is reached, the onset and propagation of neuronal depolarisation are triggered in both CSD and a seizure. The required threshold is presumed to be lower for CSD than for a seizure, which would explain why it is far more likely to observe an epileptic patient who presents a peri-ictal headache than a migraine patient who presents an epileptic seizure (Verrotti et al. 2011b, c; Parisi et al. 2012a, b).

Once the cortical event has started, spreading subsequently depends on the size of the onset zone, velocity, semiology and type of propagation (Parisi et al. 2008; Parisi 2009b). Moreover, the onset of both CSD and that of the epileptic seizure may facilitate each other (Berger et al. 2008; Fabricius et al. 2008; Zhang et al. 2011; Parisi et al. 2012b), with these two phenomena possibly being triggered by

more than one pathway converging upon the same destination: depolarization and hyper-synchronization (Parisi et al. 2008, 2012a; Parisi 2009a,b; Belcastro et al. 2011a, b; Ghadiri et al. 2012). The triggering causes, which may be environmental or individual (whether genetically determined or not), result in a flow of ions that mediate CSD through neuronal and glial cytoplasmic bridges rather than through interstitial spaces, as instead usually occurs in the spreading of epileptic seizures (Gigout et al. 2006; Parisi et al. 2008; Parisi 2009b; Tamura et al. 2011; Tottene et al. 2009, 2011). As mentioned above, the threshold required for the onset of CSD is likely to be lower than that required for the epileptic seizure. In this regard, a "migraleptic" event would be unlikely to occur (Belcastro et al. 2011a; Verrotti et al. 2011b; Parisi et al. 2012b).

As regards the role of "photosensitivity" in this topic, it should be stressed that flashes, phosphenes and other positive or negative visual manifestations are often part of the clinical picture in both headache and occipital epilepsy (Wendorff et al. 2005; Kasteleijn-Nolst Trenité and Parisi 2012). Moreover, intermittent photic stimulation (IPS) induces "flashes and phosphenes" as well as migraine/headache and seizures. Moreover, IPS may induce photoparoxysmal EEG responses (PPR), migraine and epileptic seizures (Kasteleijn-Nolst Trenité and Parisi 2012). Although occipital lobe epilepsy already has much in common with migraine (visual aura, positive and negative ictal signs, and autonomic disturbances such as pallor and vomiting), the photosensitive variant of occipital epilepsy, and photosensitive epilepsy in general, share even more similarities, such as a higher prevalence in women (female/male ratio 3:2) and a sensitivity to flickering light stimuli and striped patterns that induce attacks (Kasteleijn-Nolst Trenitè et al. 2010a, b).

Both migraine and epilepsy have an important genetic component, with strong evidence pointing to a shared genetic basis between headache and epilepsy emerging from clinical/EEG and genetic studies on Familial Hemiplegic Migraine (FHM) (Haglund and Schwartzkroin 1990; De Fusco et al. 2003; Vanmolkot et al. 2003; Kors et al. 2004; Dichgans et al. 2005; De Vries et al. 2009; Tottene et al. 2009, 2011; Gambardella and Marini 2009; Van Den Maagdenberg et al. 2010; Riant et al. 2010; Pietrobon 2010; Uchitel et al. 2012). Errors in the same gene may be associated with migraine in some cases and with epilepsy in others. Recent data suggest shared genetic substrates and phenotypic–genotypic correlations with mutations in some ion transporter genes, including CACNA1A, ATP1A2 and SCN1A (Vanmolkot et al. 2003; Kors et al. 2004; Dichgans et al. 2005; De Vries et al. 2009; Tottene et al. 2009; Gambardella and Marini 2009; Van Den Maagdenberg et al. 2010; Riant et al. 2010; Pietrobon 2010). Other genetic findings pointing to a link between migraine and epilepsy have been published. They include mutations on SLC1A3, a member of the solute carrier family that encodes excitatory amino acid transporter 1, and 57 POLG58, C10 and F259, which encode mitochondrial DNA polymerase and helicase twinkle (Tzoulis et al. 2006; Lonnqvist et al. 2009).

In addition, glutamate metabolism (Jen et al. 2005), serotonin metabolism (Johnson and Griffiths 2005), dopamine metabolism (Chen 2006) and ion channel (sodium, potassium and chloride) function might be impaired in both epilepsy and migraine (Steinlein 2004; Pietrobon 2010). In particular, it is likely that voltage-

gated ion channels play a critical role in the pathways associated with migraine and epilepsy (Vanmolkot et al. 2003; Kors et al. 2004; Dichgans et al. 2005; De Vries et al. 2009; Tottene et al. 2009; Gambardella and Marini 2009; Van Den Maagdenberg et al. 2010; Riant et al. 2010; Pietrobon 2010).

Temporal Relationship and Classification Issues

Seizures and epilepsy syndromes are classified according to guidelines of the ILAE (Panayiotopoulos 2012), and headaches according to the International Classification of Headache Disorders (ICHD). The current version, the ICHD-III, was published in Cephalalgia in July 2013 (Headache Classification Committee of the International Headache Society 2013).

Seizure-related headaches may be peri-ictal (40–75 %) or inter-ictal headaches (25–60 %) (Verrotti et al. 2011a; Cai et al 2008; Ito et al 1996, 2003, 2004). Peri-ictal headache can be divided into pre-ictal, ictal and post-ictal headache; among the peri-ictal forms, the "post-ictal" is, without doubt, the most frequently reported (15–50 %), probably because both children and adults tend to remember the events more easily once the seizure has resolved (post-ictal). (Verrotti et al. 2011a; Cai et al. 2008; Ito et al. 1996, 2003, 2004). "Ictal Headache" (i.e. a "headache" with either migraine or tension-type characteristics associated with other sensory–motor–autonomic–psychiatric ictal epileptic manifestations) occurs in as few as 3–5 % of cases (Forderreuter et al. 2002).

The latest edition of the International Headache Classification (ICHD-III) (Headache Classification Committee of the International Headache Society 2013) makes a distinction between three entities (Table 1): (1) epilepsy induced by migraine with aura or "migraine-triggered seizure" (previously referred to as migralepsy) (code 1.4.4); (2) epileptic migraine (code 7.6.1); (3) post-convulsive headache (code 7.6.2). Diagnostic criteria for the new entity ictal epileptic headache (IEH) (Table 1) have recently been proposed (Parisi et al. 2012a) and more recently cited in the Appendix of the new ICHD-3 edition (Headache Classification Committee of the International Headache Society 2013).

Hemicrania Epileptica or "Epileptic Migraine" (code ICHD-3 7.6.1)

This condition, despite being very rare, has been included in the ICHD Classification and confirmed in the new ICHD-III classification. The diagnostic criteria are: (a) headache lasting seconds-to-minutes, with migraine features that satisfy criteria C and D; (b) patient presenting a partial seizure; (c) the headache develops together with the seizure and is homo-lateral to the ictal event; (d) headache resolves immediately after the convulsion.

Table 1 Current ICHD-3 classification of headache-related seizures and proposed criteria for ictal epileptic headache (IEH)

Current ICHD-3 classification of headache-related seizures
Migraine-triggered seizure (Migralepsy) (1.4.4)
Diagnostic Criteria:
A. Migraine fulfilling criteria for 1.2 ("*Migraine with aura*")
B. A seizure fulfilling diagnostic criteria for one type of epileptic attack occurs during or within 1 h of a migraine aura
Hemicrania Epileptica or "Epileptic Migraine" (7.6.1)
Diagnostic Criteria:
A. Headache lasting seconds to minutes, with features of migraine fulfilling criteria C and D
B. The patient is having a partial epileptic seizure
C. Headache develops synchronously with the seizure and is ipsilateral to the ictal discharge
D. Headache resolves immediately after the seizure
Post-ictal Headache (7.6.2)
Diagnostic Criteria:
A. Headache with features of "*tension-type headache*" or, in a patient with migraine of "*migraine headache*" and fulfilling criteria C and D
B. The patient has had a partial or generalized epileptic seizure
C. Headache develops within three hours of the seizure
D. Headache resolves within 72 h of the seizure
Proposed criteria for ictal epileptic headache (IEH)
Diagnostic criteria A-D must all be fulfilled to make a diagnosis of "IEH"
A. Headache[a] lasting minutes, hours or days;
B. Headache that is ipsilateral or contralateral to lateralised ictal epileptiform EEG discharges (if EEG discharges are lateralised);
C. Evidence of epileptiform (localised[b], lateralised or generalised) discharges on scalp EEG concomitantly with headache; different types of EEG anomalies may be observed (generalized spike-and-wave or polyspike-and-wave, focal or generalised rhythmic activity or focal sub-continuous spikes or theta activity that may be intermingled with sharp waves) with or without photoparoxysmal response (PPRs)
D. Headache resolves immediately (within minutes) of i.v. antiepileptic drug administration

[a] A specific headache pattern is not required (Migraine with or without aura, or tension-type headache are all admitted)

[b] Any localisation (frontal, temporal, parietal, occipital) is admitted

Post-ictal Headache (code ICHD-3 7.6.2)

Headache with migraine characteristics that manifests itself in about 50% of patients after a convulsive epileptic seizure. The criteria of ictal headache in the ICHD classification are: (1) tension headache, or migraine that satisfies criteria C and D; (2) the patient presents a partial or general epileptic seizure; (3) headache develops

within 3 h of seizure onset; (4) headache resolves within 72 h of the convulsion. Post-ictal headache, though often associated with symptomatic epilepsy, is a frequent event in idiopathic occipital epilepsy in children.

Epilepsy Induced by Migraine with Aura ("migralepsy") (code ICHD-3 1.4.4)

According to the ICHD-III, migralepsy is a recognized complication of migraine (Table 1).

It does not exist in the international classifications of epilepsy (ILAE).

The term migralepsy, which was first used in 1960 (Lennox and Lennox 1960) to define a condition of "opthalmic migraine with associated nausea and vomiting followed by symptoms characteristic of epilepsy", was reintroduced in 1993 by Marks and Ehrenberg (1993). However, the term migralepsy used to refer to a temporal sequence of a migraine with aura attack that evolves into tonic-clonic seizures was widely criticized by many authors, and patients classified as having migralepsy were subsequently defined as having epileptic seizures of the occipital lobe. Unfortunately, there is no clear EEG documentation of cases of migralepsy showing a critical surge of the scalp EEG in patients in whom migraine with aura is followed by a tonic-clonic seizure. Despite the skepticism expressed by various authors regarding the concept of "migralepsy", this clinical condition was inserted in the ICHD-2 classification (Headache Classification Committee of the International Headache Society 2004) as a complication of migraine (code 1.5.5), whereas in the latest revision of the ICHD-3 classification (Headache Classification Committee of the International Headache Society 2013), this condition is codified as epilepsy induced by migraine with aura (code 1.4.4), the term migralepsy being omitted. According to the ICHD-III criteria (Headache Classification Committee of the International Headache Society 2013), epilepsy induced by migraine with aura is defined as an epileptic fit that manifests itself within an hour of a migraine with aura attack in the absence of other causes. Although epilepsy and migraine are among the most common neurological illnesses, this event is very rare in children. Indeed, Sances et al. (2009) recently demonstrated that of the 50 cases of migralepsy mentioned in the literature, only two patients satisfied the migralepsy criteria according to ICHD 2 (Headache Classification Committee of the International Headache Society 2004)

Sunset of the "Migralepsy" Concept

Most reported cases of "migralepsy" do not allow a meaningful and unequivocal migraine-epilepsy sequence to be detected (Sances et al. 2009; Verrotti et al. 2011b, c). There are approximately 50 cases of potential migralepsy reported in the literature (Sances et al. 2009). The majority of these cases have been the subject of criticism by various authors because the diagnosis in the majority of the patients is uncertain for the following reasons: the information available is not clear (38%),

the cases do not fulfil the current ICHD-III criteria (30 %), the diagnosis is questionable (28 %). Indeed, most previous reports of "migralepsy" may have been occipital seizures imitating migraine with aura (Verrotti et al. 2011a, b, c; Barrè et al. 2008).

It has recently even been suggested (Belcastro et al. 2011a; Parisi et al. 2012b) that many of the "published" migralepsy cases may be an "ictal epileptic headache" followed by other sensori-motor or autonomic ictal signs/symptoms. Indeed, although unequivocal epileptiform abnormalities in patients with paroxysmal sensations or behavioural changes usually point to a diagnosis of epilepsy, the lack of clear ictal epileptic spike-wave activity is frequent in autonomic epilepsies, such as Panayiotopoulos syndrome (Koutroumanidis 2007), or even in frontal lobe epilepsy (Nobili 2007). In such cases, ictal epileptic EEG activity might be recorded as unspecific slow wave abnormalities without any spike activity (Belcastro et al. 2011a; Parisi et al. 2012b). Interestingly, there may, on rare occasions, be an isolated epileptic headache that has no associated ictal epileptic manifestations or scalp EEG abnormalities but whose ictal epileptic origin can be demonstrated by depth electrode studies, even purely by chance (Laplante et al. 1983; Fusco et al. 2011).

This misunderstanding has perpetuated the concept of "migralepsy" since the 1960s (Lennox and Lennox 1960) to the detriment of the entity we now define as ictal epileptic headache. We believe that this has led to ictal epileptic headache being severely underestimated, on the one hand, and to migralepsy being clearly overestimated, on the other (Parisi et al. 2012b, 2013a, b).

The Rise of the "Ictal Epileptic Headache" Concept: "A Long and Winding Road…."

Sir Gowers's famous book, published in 1907 (Gowers 1907), first stated that "migraine is in the borderland of epilepsy", and in an epoch before electroencephalography (EEG), Gowers stated: "…the most frequent relation of migraine to epilepsy is as source of error;….in extremely rare instances one affection may develop while the other goes on".

More than 100 years later, we can firmly state that on occasion "migraine itself may be epilepsy" (Parisi et al. 2007, 2008a, b, 2012a, b, 2013a, b). The overlap between these two conditions is partial or complete, not always synchronous (i.e. mainly a peri-ictal phenomenon), but in some cases (whose number is probably largely underestimated) "the headache represents the only ictal phenomenon": we recently named this condition "ictal epileptic headache" (Parisi et al. 2012a). Since 1971, fewer than 20 IEH cases diagnosed according to proposed criteria (Table 1, Parisi et al. 2012b) have been reported (Grossman et al. 1971; Walser and Isler 1982; Laplante et al. 1983; Isler et al. 1987; Niedermeyer 1993; Marks and Ehrenberg 1993; Walker et al. 1995; Ghofrani et al. 2006; Parisi et al. 2007; Piccioli et al. 2009; Perucca et al. 2010; Belcastro et al. 2011c; Fusco et al. 2011; Italiano et al. 2011; Fanella et al. 2012; Cianchetti et al. 2013). Verrotti et al. recently published 16 other potential ictal epileptic headache cases from a large multicentre

neuropediatric sample (Verrotti et al. 2011b), stressing the concept of "probable underestimate phenomenon" (Parisi et al. 2012a; Parisi et al. 2013a, b).

Nonetheless, this belief goes back a long way. Indeed, it is ever since the 1950s that cases have been reported in German (Heyck and Hess 1955), English (Nymgard 1956) and Italian (Lugaresi 1955; Morocutti and Vizioli 1957) literature in which it has been suggested that "headache" may actually be "an epileptic headache" and "… may even be the only clinical manifestation of idiopathic epilepsy" (Morocutti and Vizioli 1957). Thus, the concept of "ictal headache" dates from a long time ago (Lugaresi 1955; Heyck and Hess 1955; Nymgard 1956; Morocutti and Vizioli 1957). However, the term migralepsy was subsequently coined in the 1960s (Lennox and Lennox 1960) and has permeated the epilepsy and headache culture ever since.

With regard to migralepsy cases reported in the literature, recent articles (Sances et al. 2009; Verrotti et al. 2011a, b, c) have provided a clear demonstration of the inadequacy of both the ICHD-2 and ICHD-3 definitions of this condition. Following the introduction of the migralepsy concept by Lennox and Lennox (1960), an increasing number of ictal epileptic headaches have been reported since the 1970s (Grossman et al. 1971; Walser and Isler 1982; Laplante et al. 1983; Isler et al. 1987; Niedermeyer 1993; Marks and Ehrenberg 1993; Walker et al. 1995; Ghofrani et al. 2006; Parisi et al. 2007; Piccioli et al. 2009; Perucca et al. 2010; Belcastro et al. 2011c; Fusco et al. 2011; Italiano et al. 2011; Fanella et al. 2012; Cianchetti et al. 2013). It has also been suggested (Parisi and Kasteleijn-Nolst Trenité 2010; Belcastro et al. 2011a; Verrotti et al. 2011a, b; Striano et al. 2011, 2012; Parisi et al. 2012a, 2013a, b) that the migralepsy sequence may not exist at all and that the initial part of the "migralepsy sequence" may merely be an "ictal epileptic headache" (Parisi et al. 2012a) followed by other ictal autonomic, sensory, motor or psychic features.

It should be borne in mind that cortical and subcortical areas appear to be hierarchically divided according to how likely they are to develop CSD, with the occipital lobe appearing to be the most likely area (Verrotti et al. 2011a, b; Parisi et al. 2012b).

How can CSD and epileptic discharges facilitate each other, though to a varying extent? In other words, why may the onset of an epileptic seizure facilitate the onset of CSD to a greater extent that CSD facilitates the onset of an epileptic seizure (Belcastro et al. 2011a; Parisi et al. 2012b)? Some experimental and clinical data in the literature discuss this topic. The most interesting data on genetic defects leading to both epilepsy and migraine are related to FHM, as stated above (Haglund and Schwartzkroin 1990; De Fusco et al. 2003; Vanmolkot et al. 2003; Kors et al. 2004; Dichgans et al. 2005; De Vries et al. 2009; Tottene et al. 2009; Gambardella and Marini, 2009; Van Den Maagdenberg et al. 2010; Riant et al. 2010; Pietrobon 2010; Escayg and Goldin2010; Uchitel et al. 2012).

With regard to the concept of "cortex dys-excitability" in migraine subjects, new advances now support this point of view (Berger et al. 2008; Fabricius et al. 2008; Tottene et al. 2009, 2011; Faragauna et al. 2010; De Souza et al. 2011). Indeed, if we consider the specific polysynaptic inhibitory sub-circuit involving fast-spiking (FS) inter-neurons and pyramidal cells (PC) that have been investigated in FHM1

mice (Berger et al. 2008; Fabricius et al. 2008; Tottene et al. 2009, 2011; Faragauna et al. 2010; De Souza et al. 2011), the gain in function following glutamate release at the recurrent synapses between pyramidal cells would certainly increase network excitation; by contrast, the gain in function following glutamate release at the PC-FS synapses would lead to enhanced recruitment of inter-neurons and enhanced inhibition. Although this analysis is restricted to a specific sub-circuit, it does raise the important point that the differential effect of FHM1 mutations on excitatory and inhibitory neurotransmission may produce over-excitation in certain brain conditions, while leaving the excitation-inhibition balance within physiological limits in others. This would explain the episodic nature of the disease with alternate hyper-excitation and hypo-excitation in the same subject at different times (thus supporting the dis-excitability concept in migraine subjects) (Pinto et al. 2005; Berger et al. 2008; Fabricius et al. 2008; Tottene et al. 2009, 2011; Faragauna et al. 2010; De Souza et al 2011; Tamura et al. 2011; Escayg and Goldin 2010; Uchitel et al. 2012).

A possible explanation for the clearly different extent to which CSD and epileptic seizures facilitate each other is that although these two conditions are triggered by similar mechanisms, their evolution is different depending on whether the neuronal hyperactivity and consequent increase in (K+) exceed a critical level that causes self-regeneration of the depolarization; according to this hypothesis, CSD may be defined as "a poorly-controlled seizure" in which (K+) regulation is completely disrupted. Indeed, local neuronal hyperactivity that progressively recruits a synchronous discharge via recurrent excitatory collaterals and (K+) accumulation has been hypothesized to initiate epileptic discharge in slice models (Pinto et al. 2005). CSD, experimentally induced in rats, increases cortico-cortical evoked responses and strongly induces "brain-derived neurotrophic factor" with synaptic potentiation in vivo (Faraguna et al. 2010), while the induction of a "long-term potentiation-like" (LTP-like) phenomenon by CSD receives support from experimental evidence. In vivo data that lend support to the idea of a CSD-induced LTP-like phenomenon also exist (De Souza et al. 2011). Another recent and intriguing finding regarding CSD propagation is the model according to which interstitial (K) diffusion initiates the positive feedback cycle that ignites CSD in adjacent dendrites, and which is in contrast to the hypothesis that CSD spreads through gap junctions. In particular, according to this hypothesis, the opening of the gap junctions would not be required for CSD propagation, but is instead required for extracellular homeostasis following CSD (Tamura et al. 2011). A causative link between enhanced glutamate release and CSD facilitation has been demonstrated by means of an in vitro model of CSD (Tottene et al. 2009). The synapse-specific effect of FHM1 mutations points to the disruption of the excitation-inhibition balance and neuronal hyperactivity as the bases for episodic vulnerability to CSD ignition in migraine. This finding provides direct evidence that the gain in function following glutamate release at synapses onto pyramidal cells is likely to facilitate experimental CSD in FHM1 mutant mice, and thus provides novel insights into the controversial mechanisms of CSD initiation and propagation.

These data are consistent with and support a model of CSD initiation, in which activation of pre-synaptic voltage-gated Ca channels, and the consequent release of

glutamate from recurrent cortical pyramidal cell synapses and activation of NMDA receptors, are key components of the positive feedback cycle that ignites CSD. In this regard, the role of different voltage-gated Ca2+ channels in CSD has recently been investigated (Tottene et al. 2011). After blockade of either the P-/Q-type Ca2+ channels or the NMDA receptors, CSD cannot be induced in wild-type mouse cortical slices. By contrast, the blockade of N- or R-type Ca2 channels only has a slight inhibitory effect on the CSD threshold and velocity of propagation. These findings support a model according to which the initiation and propagation of the CSD involved in migraine require the influx of Ca2+ through pre-synaptic P-/Q-type Ca2+ channels, which in turn releases glutamate from the recurrent cortical pyramidal cell synapses and activates NMDA receptors (Tottene et al. 2009, 2011).

The temporal and spatial associations between CSD and seizures have been studied by means of electro-corticographic (ECoG) recordings in patients with acutely injured cerebral cortex (Fabricius et al. 2008). The authors reported clinically overt seizures in only one patient, while each of the patients with both CSD and seizures displayed one of the following four different patterns of interaction between CSD and seizures: (a) in four patients, CSD was immediately preceded by prolonged seizure activity; (b) in three patients, the two phenomena were separated in time, with multiple CSDs being replaced by ictal activity; (c) in one patient, seizures appeared to trigger repeated CSDs at the adjacent electrode; (d) in two patients, ongoing repeated seizures were interrupted whenever CSD occurred. These four patterns were consistent within recordings from the same patient, but were different in each of the patients.

Patients 3 and 4 described by Fabricius et al. (2008) are particularly interesting as seizure activity in these two subjects spread from electrode to electrode at the same slow speed as CSD, but preceded it by several minutes. This is noteworthy because seizure activity under other conditions spreads much faster than CSD. To better understand the relevance of this finding, it should be borne in mind that a Ferrari can be driven at the top speed of a Fiat 500, though not vice versa. This example may help to understand why the onset of an epileptic seizure facilitates the onset of CSD to a greater degree than CSD facilitates the onset of an epileptic seizure. Indeed, a Ferrari is usually driven on fast roads, such as highways (myelinic), whereas a Fiat 500 tends to be driven on minor roads (amyelinic), though it must be stressed that a Ferrari can easily be driven on roads (amyelinic) usually taken by a Fiat 500, while the reverse is not true. According to these reflections, it is noteworthy that the patterns recorded by Fabricius et al. (2008) were consistent within the same patient, but differed between patients: highways (myelinic) and minor roads (amyelinic) within the same patient do not usually vary to any great extent, at least not over a relatively short period of time.

Yet another important finding reported by Fabricius et al. (2008), which confirmed our hypothesis (Parisi et al. 2008, 2012a, b, 2013a, b; Belcastro et al. 2011a, 2013; Kasteleijn-Nolst Trenité et al. 2010), is that CSD in their sample was encountered more often than seizures, as demonstrated by the fact that there were twice as many patients with CSD/peri-infarct depolarization alone than with CSD/peri-infarct depolarization plus seizures. Moreoever, 10 of the 11 patients with sei-

zure activity also had CSD, while clinical overt seizures were only observed in 1 of the 11 patients, and seizures were not suspected on clinical grounds in any of the remaining 10 patients.

Interestingly, in the so-called IEH case reports (Grossman et al. 1971; Walser and Isler 1982; Laplante et al. 1983; Isler et al. 1987; Niedermeyer 1993; Marks and Ehrenberg 1993; Walker et al. 1995; Ghofrani et al. 2006; Parisi et al. 2007; Piccioli et al. 2009; Perucca et al. 2010; Belcastro et al. 2011c; Fusco et al. 2011; Italiano et al. 2011; Fanella et al. 2012; Cianchetti et al. 2013), patients were both idiopathic (whether photosensitive or not) and symptomatic; moreover, they also often presented a clinical history (personal and/or familial) of epilepsy and migraine. Intermittent photic stimulation evokes headache in patients with a positive photo-paroxysmal response, who may also have visually induced seizures (Table 1) (Parisi et al. 2012b). With regard to the EEG abnormalities recorded in "ictal epileptic headache" cases (Grossman et al. 1971; Walser and Isler 1982; Laplante et al. 1983; Isler et al. 1987; Niedermeyer 1993; Marks and Ehrenberg 1993; Walker et al. 1995; Ghofrani et al. 2006; Parisi et al. 2007; Piccioli et al. 2009; Perucca et al. 2010; Belcastro et al. 2011c; Fusco et al. 2011; Italiano et al. 2011; Fanella et al. 2012; Cianchetti et al. 2013), the same wide spectrum of different EEG patterns (spike-wave activity, "theta" or even "delta" shape, without any spike activity) associated with both CSD and/or seizures were also confirmed "in vivo" by electrocorticography (Fabricius et al. 2008).

Drawbacks: The Current "Ictal Epileptic Headache" Definition Will Inevitably Underestimate the Phenomenon

The proposed IEH criteria are reported in Table 1. Nonetheless, we wish to stress that the IEH criteria inevitably underestimate the number of cases with "ictal epileptic headache" events. Besides highlighting the strengths of "our published criteria" (Parisi et al. 2012a), we would also like to point out "their inevitable drawbacks".

Headache and epilepsy classifications have so far ignored each other. In the ILAE classification, headache is considered exclusively as a possible semiological ictal phenomenon that is included among the "non-motor" features. In particular, headache is described as a "cephalic" sensation, but is not considered as the sole ictal expression of an epileptic seizure. Moreover, headache is not classified as a "pain" (among the "somatosensory" features) or "autonomic" sensation, whereas signs of involvement of the autonomic nervous system, including cardiovascular, gastrointestinal, vasomotor and thermoregulatory functions, are classified as autonomic features. Despite still being considered a controversial issue, we must consider that headache pain may actually originate in the terminal nervous fibers ("vasomotor") in cerebral blood vessels; consequently, headache should be classified as an "autonomic" sensation in the ILAE Glossary and Terminology (Berg et al. 2010). It may thus be possible to interpret headache as the sole expression of an epileptic seizure and classify it as an autonomic seizure.

To explain why headache may be the sole ictal epileptic symptom, Parisi et al. (2012a, b, 2013a, b) previously suggested that an autonomic seizure (i.e. in IEH) remains purely autonomic if ictal neuronal activation of non-autonomic cortical areas fails to reach the symptomatogenic threshold, as previously described for other ictal autonomic manifestations in Panayiotopoulos syndrome (Koutromanidis 2007). In this regard, Parisi et al. have suggested that ictal epileptic headache may be considered an autonomic form of epilepsy, like Panayiotopoulos syndrome, and cases with long-lasting ictal epileptic headache episodes may accordingly even fulfil the criteria that allow them to be considered as "autonomic status epilepticus" (Ferrie et al. 2007).

In addition, it has been suggested (see all Papers by Parisi et al. from 2008 to 2013) that the social stigma attached to epilepsy may explain a general reluctance (Parisi 2009a) (not only in the general public, but even among physicians) to recognize the growing number of documented cases of IEH. Another noteworthy point is that while unequivocal epileptiform abnormalities usually point to a diagnosis of epilepsy, the lack of clear epileptic spike-and-wave activity is frequent in other ictal autonomic manifestations, as well as in patients with a deep epileptic focus arising, for example, from the orbitomesial frontal zone (Nobili 2007). In such cases, ictal epileptic EEG activity may be recorded from the scalp or exclusively by means of deep stereo-EEG recording, sometimes purely by chance (Laplante et al. 1983; Fusco et al. 2011).

Yet another point that deserves attention is the lack of a clear, repetitive EEG headache-associated pattern owing to the fact that ictal EEG recording in such patients does not yield a specific EEG picture. Indeed, different EEG patterns have been recorded during migraine-like complaints in both symptomatic and idiopathic cases (Grossman et al. 1971; Walser and Isler 1982; Laplante et al. 1983; Isler et al. 1987; Niedermeyer 1993; Marks and Ehrenberg 1993; Walker et al. 1995; Ghofrani et al. 2006; Parisi et al. 2007; Piccioli et al. 2009; Perucca et al. 2010; Belcastro et al. 2011c; Fusco et al. 2011; Italiano et al. 2011; Fanella et al. 2012; Cianchetti et al. 2013). Moreover, when EEG anomalies are recorded, no specific cortical correlations emerge (e.g. focal frontal, parietal, temporal, occipital and primary or secondary generalized), as has also been reported (thus confirming our hypothesis) for autonomic manifestations in children affected by Panayiotopoulos syndrome. Lastly, the criteria we propose do not offer the possibility of confirming all suspected cases of ictal epileptic headache by means of intravenous anticonvulsant administration, just as it is not always possible for other types of epileptic seizures; indeed, although there appears to be a clinical response in the vast majority of published cases affected by autonomic seizures as well as in ictal epileptic headache, we cannot be sure whether intravenous anticonvulsant drug administration has the ability to stop a seizure.

For all the afore-mentioned reasons, we firmly believe that the diagnosis of IEH (even according to our proposed new criteria) will remain an underestimated phenomenon owing, in particular, to:

a. the psychosocial stigma attached to this disease;
b. the fact that IEH cannot always be detected from the scalp by means of EEG recording;
c. IEH is rarely refractory to i.v. antiepileptic drug administration, as can instead occur in other type of seizures.

Conclusions

A clear clinical picture of IEH appears to be difficult to obtain. Since its epileptic nature can only be documented by means of ictal EEG recording and simultaneous intravenous antiepileptic drug administration, it is difficult to obtain firm conclusions regarding the frequency of IEH in epidemiological studies. Headache/migraine of epileptic origin must always be suspected in pediatric patients who do not respond to treatment with anti-migraine drugs in order to promptly perform an EEG and thus make a correct diagnosis.

Moreover, ictal epileptic headache may not have the characteristics of migraine with or without aura, or those of a tension headache; indeed, any "type" of headache may be defined as an ictal epileptic headache in the presence of symptoms associated with ictal EEG anomalies (whether focal or generalized) that resolve immediately after i.v. administration of an anticonvulsant drug.

On the basis of current knowledge and clinical experiences, "migralepsy" or a migraine-triggered seizure is highly unlikely to exist. We thus believe that these terms should be removed from the Appendix of International Headache Disorders Classifications until clear evidence is provided of the existence of such conditions.

Ictal Epileptic Headache criteria (Table 1) should be used to classify the rare events in which headache may represent the sole ictal epileptic manifestation. "These findings further highlight the important role of EEG recording in patients with headache, which has traditionally been opposed by fierce ancestral adversity (Parisi 2009a) against the possible link between headache and epilepsy".

We as a group thus suggest that the term ictal epileptic headache be maintained for cases in which headache is "the sole ictal manifestation", and that the term "ictal headache" be maintained for cases in which the headache, whether brief or long-lasting, is merely part of a more complex seizure including ictal manifestations that are either sequential or overlapping (sensory–motor, psychiatric or other non-autonomic manifestations). In our opinion, this distinction is crucial, as has been explained in detail in this chapter, owing to the markedly different prognosis it entails. In fact, this is not a marginal question, because these possible, isolated, non-motor, ictal manifestations (i.e. ictal epileptic headache) should be taken into account before declaring an epileptic patient as "seizure free" so as to be able to suspend anticonvulsant therapy safely.

In conclusion, by applying the ictal epileptic headache criteria proposed here (Table 1) to a large pediatric population in the future, we should be able to understand whether ictal epileptic headache is a marginal phenomenon or is, instead, an underestimated event that deserves greater attention.

Acknowledgments My interest and my commitment to research in the field of pediatric neurology have been made possible only by the patience, trust and love of my parents, Maria and Alfonso, my son, Eduardo Alfonso, and my wife, Loredana, to whom I will forever be indebted, as well as by the support of all the people I have met over the years.

References

Anderman F (1987) Clinical features of migraine-epilepsy syndrome. In: Andermann F, Lugaresi E (eds) Migraine and epilepsy. Butterworth Publishers, Boston, pp 20–89

Andermann F, Zifkin B (1998) The benign occipital epilepsies of childhood: an overview of the idiopathic syndromes and of the relationship to migraine. Epilepsia 39:9–23

Ayata C (2010) Cortical spreading depression triggers migraine attack: pro. Headache 50(4):725–730

Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz MA (2006) Suppression of cortical spreading depression in migraine prophylaxis. Ann Neurol 59(4):652–661

Baca CB, Vickrey BG, Caplan R, Vassar SD, Berg AT (2011) Psychiatric and medical comorbidity and quality of life outcomes in childhood-onset epilepsy. Pediatrics 128(6):e1532–e1543

Barré M, Hamelin S, Minotti L, Kahane P, Vercueil L (2008) Epileptic seizure and migraine visual aura: revisiting migralepsy. Rev Neurol (Paris) 164:246–252

Belcastro V, Striano P, Kasteleijn-Nolst Trenite DGA, Villa MP, Parisi P (2011a) Migralepsy, hemicrania epileptica post-ictal headache and ''ictal epileptic headache'': a proposal for terminology and classification revision. J Headache Pain 12:289–294

Belcastro V, Striano P, Parisi P (2011b) Seizure or migraine? The eternal dilemma. Comment on: "recurrent occipital seizures misdiagnosed as status migrainosus". Epileptic Disord 13(4):456

Belcastro V, Striano P, Pierguidi L, Calabresi P, Tambasco N (2011c) Ictal epileptic headache mimicking status migrainosus: EEG and DWI-MRI findings. Headache 51:160–162

Belcastro V, Striano P, Parisi P. (2012) "Ictal epileptic headache": beyond the epidemiological evidence. Epilepsy Behav 25(1):9–10

Belcastro V, Striano P, Parisi P (2013) From migralepsy to ictal epileptic headache: the story so far. Neurol Sci 34(10):1805–1807

Berg AT, Berkovic SF, Brodie MJ et al (2010) Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 51:676–685

Berger M, Speckmann EJ, Pape HC, Gorji A (2008) Spreading depression enhances human neocortical excitability in vitro. Cephalalgia 28:558–562

Bladin PF (1987) The association of benign rolandic epilepsy with migraine. In: Andermann F, Lugaresi E (eds) Migraine and epilepsy. Butterworth Publishers, Boston, pp 145–52

Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA (2002) Intrinsic brain activity triggers trigeminal meningeal afferents in migraine model. Nat Med 8:136–142

Cai S, Hamiwka LD, Wirrell EC (2008) Peri-ictal headache in children: prevalence and character. Pediatr Neurol 39:91–96

Chen SC (2006) Epilepsy and migraine: the dopamine hypotheses. Med Hypotheses 66:466–472

Cianchetti C, Pruna D, Porcu L, Peltz MT, Ledda MG (2013) Pure epileptic headache and related manifestations: a video-EEG report and discussion of terminology. Epileptic Disord 15(1):84–92

Clarke T, Baskurt Z, Strug LJ et al (2009) Evidence of shared genetic risk factors for migraine and rolandic epilepsy. Epilepsia 50:2428–2433

Colombo B, Dalla Libera D, De Feo D, Pavan G, Annovazzi PO, Comi G (2011) Delayed diagnosis in pediatric headache: an outpatient Italian survey. Headache 51(8):1267–1273

De Fusco MM, Silvestri L et al (2003) Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump a2 subunit associated with familial hemiplegic migraine type 2. Nat Genet 33:192–196

de Souza TK, e Silva MB, Gomes AR, de Oliveira HM, Moraes RB, de Freitas Barbosa CT et al (2011) Potentiation of spontaneous and evoked cortical electrical activity after spreading depression: in vivo analysis in wellnourished and malnourished rats. Exp Brain Res 214:463–469

De Vries B, Frants RR, Ferrari MD, van den MAM (2009) Molecular genetics of migraine. Hum Genet 126:115–132

Dichgans M, Freilinger T, Eckstein G, Babini E, Lorenz-Depiereux B, Biskup S (2005) Mutations in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. Lancet 366:371–377

Eikermann-Haerter K, Ayata C (2010) Cortical spreading depression and migraine. Curr Neurol Neurosci Rep 10(3):167–173

Escayg A, Goldin AL (2010) Critical review and invited commentary: sodium channel SCN1A and epilepsy: mutations and mechanisms. Epilepsia 51:1650–1658

Fabricius M, Fuhr S, Willumsen L, Dreier JP, Bhatia R, Boutelle MG et al (2008) Association of seizures with cortical spreading depression and peri-infarct depolarisations in the acutely injured human brain. Clin Neurophysiol 119(9):1973–1984

Fanella M, Fattouch J, Casciato S, Lapenta L, Morano A, Egeo G et al (2012) Ictal epileptic headache as ''subtle'' symptom in generalized idiopathic epilepsy. Epilepsia 53(4):e67–e70

Faraguna U, Nelson A, Vyazovskiy VV, Cirelli C, Tononi G (2010) Unilateral cortical spreading depression affects sleep need and induces molecular and electrophysiological signs of synaptic potentiation in vivo. Cereb Cortex 20:2939–2947

Ferrie CD, Caraballo R, Covanis A et al (2007)Autonomic status epilepticus in Panayiotopoulos syndrome and other childhood and adult epilepsies: a consensus view. Epilepsia 48(6):1165–1172

Fogarasi A, Janszky J, Tuxhorn I (2006) Autonomic symptoms during childhood partial epileptic seizures. Epilepsia 47:584–588.

Forderreuther S, Henkel A, Noachtar S et al (2002) Headache associated with epileptic seizures: epidemiology and clinical characteristics. Headache 42:649–655

Fusco L, Specchio N, Ciofetta G, Longo D, Trivisano M, Vigevano (2011) Migraine triggered by epileptic discharges in a Rasmussen's encephalitis patient after surgery. Brain Dev 33:597–600

Gambardella A, Marini C (2009) Clinical spectrum of SCN1A mutations. Epilepsia 50:20–23

Ghadiri MK, Kozian M, Ghaffarian N, Stummer W, Kazemi H, Speckmann EJ et al (2012) Sequential changes in neuronal activity in single neocortical neuron after spreading depression. Cephalalgia 32(2):116–124

Ghofrani M, Mahvelati F, Tonekaboni H (2006) Headache as a sole manifestation in nonconvulsive status epilepticus. J Child Neurol 21:981–983

Gigout S, Louvel J, Kawasaki H, D'Antuono M, Armand V, Kurcewicz I (2006) Effects of gap junction blockers on human neocortical synchronization. Neurobiol Dis 22:496–508

Gowers WR (1907) The border-land of epilepsy, Chapter V. Reprint 1995. Arts & Boeve, Nijmegen, pp 76–102

Grossman RM, Abramovich I, Lefebvre AB (1971) Epileptic headache: report of a case with EEG recorded during the crisis. Arq Neuropsiquiatr (San Paulo) 29:198–206

Haglund MM, Schwartzkroin PA (1990). Role of Na-K pump potassium regulation and IPSPs in seizures and spreading depression in immature rabbit hippocampal slices. J Neurophysiol 63(2):225–239

Hauser AW, Annegers JF, Anderson EV, Kurlan LT (1993) The incidence of epilepsy and unprovoked seizure in Rochester, Minnesota, 1935–1984. Epilepsia 34:453–468

Heyck H, Hess R (1955) Vasomotoric headaches as symptom of masked epilepsy. Schweiz Med Wochenschr J Suisse Med 85(24):573–575

International Headache Society (2004) The international classification of headache disorders: 2nd edition. Cephalalgia 24(1):9–160

International Headache Society. (2013) The international classification of headache disorders: third edition. Cephalalgia 33(9):629–808

Isler H, Wieser HG, Egli M (1987) Hemicrania epileptica: synchronous ipsilateral ictal headache with migraine features. In: Andermann F, Lugaresi E (eds) Migraine and epilepsy. Butterworth Publishers, Boston, pp 249–263

Italiano D, Grugno R, Calabro' RS, Bramanti P, Di Maria F, Ferlazzo E (2011) Recurrent occipital seizures misdiagnosed as status migrainosus. Epileptic Disord 13:197–201
Ito M, Schachter SC (1996) Frequency and characteristics of interictal headaches in patients with epilepsy. J Epilepsy 9:83–86
Ito M, Adachi N, Nakamura F et al (2003) Multi-center study on post-ictal headache in patients with localization-related epilepsy. Psychiatry Clin Neurosci 57:385–389
Ito M, Adachi N, Nakamura F et al (2004) Characteristics of postictal headache in patients with partial epilepsy. Cephalalgia 24(1):23–28
Jen JC, Wan J, Palos TP (2005) Mutations in the glutamate transporter EAAT1 causes episodic ataxia, hemiplegia, and seizures. Neurology 65:529–534
Johnson MP, Griffiths LR (2005) A genetic analysis of serotonergic biosynthetic and metabolic enzymes in migraine using a DNA pooling approach. J Hum Genet 50:607–610
Kasteleijn-Nolst Trenité DGA, Verrotti A, Di Fonzo A et al (2010a) Headache, epilepsy and photosensitivity: how are they connected? J Headache Pain 11:469–476
Kasteleijn-Nolst TDGA, Cantonetti L, Parisi P (2010b) Visual stimuli, photosensitivity and photosensitive epilepsy. Chapter 94. In: Shorvon S, Guerrini R, Andermann F (eds) Common and uncommon causes of epilepsy. Cambridge University, Cambridge
Kasteleijn-Nolst Trenité DGA, Parisi P (2012) Migraine in the borderland of epilepsy: "migralepsy" an overlapping syndrome of children and adults? Epilepsia 53(Suppl 7):20–25
Kinast M, Lueders H, Rothner AD et al (1982) Benign focal epileptiform discharges in childhood migraine. Neurology 32:1309–1311
Kors EE, Melberg A, Vanmolkot KR, Kumlien E, Haan J, Raininko R, Flink R, Ginjaar HB, Frants RR, Ferrari MD, van den Maagdenberg AM (2004) Childhood epilepsy, familial hemiplegic migraine, cerebellar ataxia, and a new CACNA1A mutation. Neurology 63(6):1136–1137
Koutroumanidis M (2007) Panayiotopoulos syndrome: an important electroclinical example of benign childhood system epilepsy. Epilepsia 48:1044–1053
Laplante P, Saint-Hilaire JM, Bouvier G (1983) Headache as an epileptic manifestation. Neurology 33:1493–1495
Lateef TM, Cui L, Nelson KB, Nakamura EF, Merikangas KR (2012) Physical comorbidity of migraine and other headaches in US adolescents. J Pediatr 161(2):308–313
Leniger T, Isbruch K, Driesch S, Diener HC, Hufnagel A (2001) Seizure-associated headache in epilepsy. Epilepsia 42:1176–1179
Lennox WG, Lennox MA (1960) Epilepsy and related disorders. Little Brown, Boston, p 451
Lipton RB, Silberstein SD (1994) Why study the comorbidity of migraine? Neurology 44(10, Suppl 7):S4–S5
Lipton RB, Ottman R, Ehrenberg BL, Hauser WA (1994a) Comorbidity of migraine: the connection between migraine and epilepsy. Neurology 44(Suppl 7):S28–S32
Lonnqvist T, Paeteau A, Valanne L, Pihko H (2009) Recessive twinkle mutations cause severe epileptic encephalopathy. Brain 132:1553–1562
Lugaresi E (1955) EEG investigations in monosymptomatic headache in infants. Riv Neurol 25(4):582–588
Lyngberg AC, Rasmussen BK, Jørgensen T, Jensen R (2005) Incidence of primary headache: a Danish epidemiologic follow-up study. Am J Epidemiol 161(11):1066–1073
Marks DA, Ehrenberg BL (1993) Migraine-related seizures in adults with epilepsy, with EEG correlation. Neurology 43:2476–2483
Morocutti C, Vizioli R (1957) Episodes of paroxysmal headache as the only clinical manifestation of idiopathic epilepsy. Riv Neurol 27(4):427–430
Moskowitz MA, Nozaki K, Kraig RP (1993) Neocortical spreading depression provokes the expression of C-fos proteinlike immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms. J Neurosci 13:1167–1177
Niedermeyer E (1993) Migraine-triggered epilepsy. Clin EEG 24:37–43
Nobili L (2007) Nocturnal frontal lobe epilepsy and non-rapid eye movement sleep parasomnias: differences and similarities. Sleep Med Rev 11:251–254
Nymgard K. (1956) Epileptic headache. Acta Psych Neurol Scand: Suppl 108:291–300

Olafsson E, Ludvigsson P, Gudmundsson G, Hesdorffer D, Kjartansson O, Hauser WA (2005) Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study. Lancet Neurol 4(10):627–634

Panayiotopoulos CP (1987) Difficulties in differentiating migraine and epilepsy based on clinical EEG findings. In: Andermann F, Lugaresi E (eds) Migraine and epilepsy. Butterworth Publishers, Boston, pp 142–151

Panayiotopoulos CP (1999a) Visual phenomena and headache in occipital epilepsy: a review, a systematic study and differentiation from migraine. Epileptic Disord 1:205–216

Panayiotopoulos CP (1999b) Differentiating occipital epilepsies from migraine with aura, acephalic migraine and basilar migraine. In: Panayiotopoulos CP (ed) Benign childhood partial seizures and related epileptic syndromes. John Libbey & Company Ltd, London, pp 281–302

Panayiotopoulos CP (1999c) Elementary visual hallucination, blindness, and headache in idiopathic occipital epilepsy: differentiation from migraine. J Neurol Neurosurg. Psychiatry 66:536–540

Panayiotopoulos CP (2012) The new ILAE report on terminology and concepts for the organization of epilepsies: critical review and contribution. Epilepsia 53(3):399–404

Parisi P (2009a) Who's still afraid of the link between headache and epilepsy? Some reactions to and reflections on the article by Marte Helene Bjørk and co-workers. J Headache Pain 10(5):327–329

Parisi P (2009b) Why is migraine rarely, and not usually, the sole ictal epileptic manifestation? Seizure 18(5):309–312

Parisi P (2011) Comments on the article by Fusco L. et al. entitled "Migraine triggered by epileptic discharges in a Rasmussen's encephalitis patient after surgery". Brain Dev 33(8):704–705

Parisi P, Kasteleijn-Nolst Trenite DGA. (2010) "Migralepsy": a call for revision of the definition. Epilepsia 51(5):932–933

Parisi P, Kasteleijn-Nolst TDG, Piccioli M et al (2007) A case with atypical childhood occipital epilepsy ''Gastaut type'': an ictal migraine manifestation with a good response to intravenous diazepam. Epilepsia 48:2181–2186

Parisi P, Piccioli M, De Sneeuw S, de Sneeuw S, de Kovel C, van Nieuwenhuizen O, Buttinelli C, Villa MP, Kasteleijn-Nolst Trenité DG (2008a) Redefining headache diagnostic criteria as epileptic manifestation? Cephalalgia 28:408–409

Parisi P, Piccioli M, Villa MP, Buttinelli C, Kasteleijn-Nolst Trenéte DGA (2008b) Hypothesis on neurophysiopathological mechanisms linking epilepsy and headache. Med Hypoth 70:1150–1154

Parisi P, Striano P, Kasteleijn-Nolst Trenite DGA et al (2012a) "Ictal Epileptic Headache": recent concepts for new classifications criteria. Cephalalgia 32(9):723–724

Parisi P, Striano P, Negro A, Martelletti P, Belcastro V (2012b) Ictal epileptic headache: an old story with courses and appeals. J Headache Pain 13(8):607–613

Parisi P, Striano P, Belcastro V (2013a) The crossover between headache and epilepsy. Expert Rev Neurother 13(3):231–233

Parisi P, Striano P, Verrotti A, Villa MP, Belcastro V (2013b) What have we learned about ictal epileptic headache? A review of well-documented cases. Seizure 22(4):253–258

Perucca P, Terzaghi M, Manni R (2010) Status epilepticus migrainosus: clinical, electrophysiologic, and imaging characteristics. Neurology 75:373–374

Piccioli M, Parisi P, Tisei P, Villa MP, Buttinelli C, Kasteleijn-Nolst Trenité DGA (2009) Ictal headache and visual sensitivity. Cephalalgia 29:194–203

Piccinelli P, Borgatti R, Nicoli F et al (2006) Relationship between migraine and epilepsy in paediatric age. Headache 46:413–421

Pietrobon D (2010) Biological science of headache channels. Handb Clin Neurol 97:73–83

Pinto DJ, Patrick SL, Huang WC, Connors BW (2005) Initiation, propagation and termination of epileptiform activity in rodent neocortex in vitro involve distinct mechanisms. J Neurosci 25(36):8131–8140

Riant F, Ducros A, Ploton C, Banbance C, Depienne C, Tournie-Lasserve E (2010) De novo mutations in ATP1A2 and CACNA1A are frequent in early-onset sporadic hemiplegic migraine. Neurology 75:967–972

Sances G, Guaschino E, Perucca P, Allena M, Ghiotto N, Manni R (2009) Migralepsy: a call for revision of the definition. Epilepsia 50:2487–2496

Sasmaz T, Bugdayci R, Ozge A, Karakelle A, Kurt O, Kaleagasi H (2004) Are parents aware of their schoolchildren's headaches? Eur J Public Health 14(4):366–368

Somjen GG (2001) Mechanisms of spreading depression and hypoxic spreading depression-like depolarization. Physiol Rev 81:1065–1096

Steinlein OK (2004) Genetic mechanisms that underlie epilepsy. Nat Rev Neurosci 5:400–408

Striano P, Belcastro V, Parisi P (2011) Status epilepticus migrainosus: clinical, electrophysiologic, and imaging characteristics. Neurology 76:761

Striano P, Belcastro V, Parisi P (2012) From ''migralepsy'' to ''ictal epileptic headache'' concept. Epilepsy Behav 23(3):392

Tamura K, Alessandri B, Heimann A, Kempski O (2011) The effects of a gap-junction blocker, carbenoxolone, on ischemic brain injury and cortical spreading depression. Neuroscience 194:262–271

Toldo I, Perissinotto E, Menegazzo F et al (2010) Comorbidity between headache and epilepsy in a pediatric headache center. J Headache Pain 11:235–240

Tonini MC, Giordano L, Atzeni L (2012) Primary headache and epilepsy: a multicenter cross-sectional study. Epilepsy Behav 23:342–347

Tottene A, Conti R, Fabbro A, Vecchia D, Shapovalova M, Santello M, van den Maagdenberg AM, Ferrari MD, Pietrobon D (2009) Enhanced excitatory transmission at cortical synapses as the basis for facilitated spreading depression in Ca(v)2.1 knockin migraine mice. Neuron 61(5):762–773

Tottene A, Urbani A, Pietrobon D (2011) Role of different voltage-gated Ca2+ channels in cortical spreading depression. Channels (Austin) 5(2):110–114

Tzoulis C, Engelsen BA, Telstad W (2006) The spectrum of clinical disease caused by the A467T and W748S POLG mutations: a study of 26 causes. Brain 129:1685–1692

Uchitel OD, Inchauspe CG, Urbano FJ, Di Guilmi MN (2012) Ca(V)2.1 voltage activated calcium channels and synaptic transmission in familial hemiplegic migraine pathogenesis. J Physiol Paris 106(1–2):12–22

Van Den Maagdenberg AM, Terwindt GM, Haan J, Frants RR, Ferrari MD (2010) Genetics of headaches. Handb Clin Neurol 97:85–97

Vanmolkot KR, Kors EE, Hottenga JJ, Terwindt GM, Haan JJ, Hoefnagels WA (2003) Novel mutations in the Na+/K+-ATPase pump gene ATP1A2 associated with familial hemiplegic migraine and benign familial infantile convulsions. Ann Neurol 54:360–366

Verrotti A, Coppola G, Spalice A et al (2011a) Peri-ictal and inter-ictal headache in children and adolescents with idiopathic epilepsy: a multicenter cross-sectional study. Childs Nerv Syst 27:1419–1423

Verrotti A, Coppola G, Di Fonzo A et al (2011b) Should "migralepsy" be considered an obsolete concept? A multicenter retrospective clinical/EEG study and review of the literature. Epilepsy Behav 21(1):52–59

Verrotti A, Striano P, Belcastro C et al (2011c) Migralepsy and related conditions: advances in pathophysiology and classification. Seizure 20:271–275

Walker MC, Smith SJM, Sisodya SM, Shorvon SD (1995) Case of simple partial status epilepticus in occipital lobe epilepsy misdiagnosed as migraine: clinical, electrophysiological, and magnetic resonance imaging characteristics. Epilepsia 36:1233–1236

Walser H, Isler H (1982) Frontal intermittent rhythmic delta activity. Impairment of consciousness and migraine. Headache 22(2):74–80

Wendorff J, Juchniewicz B (2005) Photosensitivity in children with idiopathic headaches. Neurol Neurochir Pol 39(4 Suppl 1):S9–S16

Wirrell EC, Hamiwka LD (2006) Do children with benign rolandic epilepsy have a higher prevalence of migraine than those with other partial epilepsies or nonepilepsy controls? Epilepsia 47:1674–1681

Yamamane LE, Montenegro MA, Guerreiro MM (2004) Comorbidity headache and epilepsy in childhood. Neuropediatrics 35(2):99–102

Yankovsky AE, Andermann F, Bernasconi A (2005) Characteristics of headache associated with intractable partial epilepsy. Epilepsia 46:1241–1245

Zhang X, Levy D, Kainz V, Noseda R, Jakubowski M, Burstein R (2011) Activation of central trigeminovascular neurons by cortical spreading depression. Ann Neurol 69(5):855–865