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

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

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

1. Introduction

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

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

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

This new classification proposal (headache as an isolated ictal autonomic manifestation in IEH) has very different prognostic implications because the outcome in people with long-lasting autonomic status epilepticus is very different (i.e. benign) from that of people with additional ictal motor–sensitive semiology. We have stressed this important aspect once again more recently.
Headache and epilepsy classifications have always ignored each other.\(^2,9\) In the International League Against Epilepsy (ILAE) classification, headache is included exclusively as a possible semiological ictal phenomenon among the “non-motor” (point 2.0) features. In particular, headache is described as a “cephalic” sensation (sub-classified at sub-point 2.2.1.7) and is not considered as the sole ictal expression of an epileptic seizure. Moreover, headache is not classified as a “pain” (among the “somatosensory” features at 2.2.1.1) or “autonomic” sensation (2.2.1.8), whereas signs of involvement of the autonomic nervous system, including cardiovascular, gastrointestinal, vasomotor and thermoregulatory functions, are classified as “autonomic” features. Whilst still controversial issue, it is now generally accepted that headache pain may actually originate in the terminal nervous fibers (“vasomotor”) of cerebral blood vessels; consequently, headache should be classified as an “autonomic” sensation in the ILAE Glossary and Terminology.\(^10\)

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

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

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

2. Review of well-documented IEH cases

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

According to our criteria,\(^1\) twelve (potential or established) IEH cases have been reported since 1971 (Table 1).\(^16–28\) In addition, we have recently published a further 16 “potential” IEH cases retrospectively isolated from a large (4600 epileptic children) multicentre neuropaediatric sample.\(^4\) All 16 patients displayed focal or generalized ictal EEG abnormalities during migraine attacks. The spike or spike-and-wave pattern, which was the most commonly observed EEG pattern, was associated with both migraine with aura (MA) and migraine without aura (MO), whereas EEG theta activity was surprisingly associated exclusively with MA or a “double migraine pattern,” in which MA and MO coexisted. Fourteen of the 16 children displayed interictal EEG abnormalities\(^5\); unfortunately, we do not have any data regarding a possible therapeutic response to intravenous anticonvulsant administration in these 16 “potential retrospective” IEH cases, nor can we confirm the IEH diagnosis.

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

These published IEH cases (Table 1) unequivocally show that criterion D (“headache and EEG anomalies resolve within minutes of i.v. antiepileptic medication administration”) represents the key to diagnosing IEH. Indeed, not only is there no specific EEG picture or specific headache-pattern (tension-type headache, migraine as well as other non-typical headache patterns have been reported), but neuroradiological investigations (brain CT and MRI) can be either normal or reveal a range of structural or “transient” abnormalities. Varying associated EEG-patterns have also been recorded. Indeed, high-voltage, rhythmic, 11–12 Hz activity with intermingled spikes over the right tempo-occipital regions,\(^25,42,45\) high voltage theta activity intermingled with sharp waves over the occipital region,\(^20–22\) bilateral continuous spike- and slow wave discharges,\(^18,19,21\) 10–15 Hz paroxysmal fast activity followed by diffusely expressed slow waves\(^26\) and almost continuous ictal beta fast activity alternating with rhythmic theta discharges over the right frontotemporal regions\(^26\) have all been described; photoparoxysmal responses (PPR) associated with complaints of a light pulsating headache during intermittent photic stimulation have also been reported.\(^20,22\)

We would like to underline that the patient described by Fusco et al.\(^26\) showed the same migraine symptoms with both frontal and occipital ictal discharges, implying that the localization of the epileptogenic area was not an essential requirement for the genesis of the attack, as previously reported in ictal autonomic manifestations related to Panayiotopoulos Syndrome.\(^14\) This finding (the same migraine symptoms associated with different epileptogenic areas) has also been confirmed in the recent, above cited,\(^6\) multicentre neuropaediatric retrospective study. It is also important to stress that there have even been cases of an isolated epileptic headache without scalp EEG abnormalities; in rare cases such as these,\(^17,26\) the ictal origin of the headache has been demonstrated by deep electrode studies, as has occurred by chance in patients studied for pre-surgical investigations.\(^7,26\) In other words, while unequivocal epileptiform abnormalities usually point to a diagnosis of epilepsy, the lack of clear epileptic spike-and-wave activity is not so rare in IEH patients. It is for these reasons that IEH events will inevitably be underestimated.\(^2\) In most of the afore-mentioned patients, complete remission of both the headache and the epileptic abnormalities was achieved not by means of specific antimigraine drugs whereas intravenous administration of anticonvulsant drugs (benzodiazepines or phenytoin) was generally effective.\(^22,24–27\)

3. Discussion

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

As recently pointed out,\(^2\) there have been reports by German,\(^30\) English\(^31\) and Italian\(^32,33\) researchers since the 1950s suggesting that headache can be either simply an epileptic headache or may even be the only clinical manifestation of idiopathic epilepsy.\(^12\) Indeed, the overlap between migraine and epilepsy may be partial or complete, not necessarily synchronous (migraine mainly being a peri-ictal phenomenon), and in some cases (whose number is
Table 1
Review of the well-documented (proved or potential) “Ictal Epileptic Headache” cases.

<table>
<thead>
<tr>
<th>First author, year, reference number</th>
<th>Ictal headache features and history</th>
<th>Synchronous EEG anomalies and Physical examination*</th>
<th>Ictal AED intrav. admin. or chronic os drug therapya</th>
<th>Neurorad. investig.b</th>
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<tr>
<td>Grossmann16 (1971)</td>
<td>9-Year-old child with three episodes of headache without other signs or symptoms. Parents with migraine</td>
<td>During the three headache episodes: rhythmic sharp-waves in the right occipital region with diffusion in the right emisphere</td>
<td>AEDs administration not tried, nor during ictal phase neither as continuous anticonvulsant treatment</td>
<td>Not performed</td>
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<td>Laplante17 (1983)</td>
<td>Patient number 1 (17 year old) and 2 (28 year old): history of epilepsy and, sometimes, isolated ictal epileptic headache: duration of IEH: 30–60s</td>
<td>Most of the time no changes detected in the scalp EEG and only depth electrodes recording was able to detect EEG anomalies (3–4Hz with rapid rhythmic activity) in the right amygdala and hippocampus, synchronous with ictal headache</td>
<td>AEIDs continuous treatment was not able to stop neither seizures nor headache episodes</td>
<td>CT, bilateral carotid angiography and ventriculography showed no abnormalities</td>
</tr>
<tr>
<td>Isler18,19 (1982, 1987)</td>
<td>Bifrontal headache in six migraine patients, 13-year-old-female): impairment of consciousness and neurological deficit (dysfunction of upper brainstem and occipital and medial temporal lobes), Headaches attacks lasted from seconds - minutes to hours/days</td>
<td>Patients described in 1982: ictal EEG recorded during the episodes (migraine and neurological deficits) showed frontal intermittent rhythmic delta activity.</td>
<td>AEDs administration was not tried nor during ictal phase neither as continuous AEDs treatment</td>
<td>Not performed</td>
</tr>
<tr>
<td>Walker20 (1995)</td>
<td>31-Year-old female with occipital lobe, simple, partial status epilepticus. Since 3 years History positive for occipital seizure with secondary GTCS. From the age of 3, showed frontal migranous headache lasting hours with “silver lights” “like a camera flash”, rarely followed by visual loss and GTCS</td>
<td>The EEG recorded during headache showed runs of 4–5Hz activity on the right occipital regions. During IPS discharges were evident on the right occipital region at different rates of stimulation (3, 5 and 22Hz without associated visual symptoms)</td>
<td>Previous antimigraine treatment (analgesic, pizotifen, propranolol, sumatriptan) and AEDs failed to reach the clinical picture control</td>
<td>MRI showed enlarged sulci in the right parietal region (abnormal gyral pattern or neuroanatomical migration disorders)</td>
</tr>
<tr>
<td>Ghofrani21 (2005)</td>
<td>3 years 6 months of age: histiocytosis (1999) and started chemotherapy. 2001: two GTCS, with no involvement of CNS. 2003: because of seizure and CSF pleocytosis, intrathecal treatment with methotrexate and hydrocortisone was started. 2004: The child experienced severe and continuous headache</td>
<td>History positive for epilepsy</td>
<td>AEDs continuous polytherapy (valproic acid, phenytoin and sulthione) without antimigraine drugs, was able to stop both seizures and headache episodes</td>
<td>MRI showed brain atrophy</td>
</tr>
<tr>
<td>Parisi22 (2007)</td>
<td>14-Year-old girl with first seizure “Gastaut type” followed by GTCS. The event was preceded by migraine without aura (lasting 6h) and followed by an “ictal epileptic headache” lasting more than 72h. She had played for hours with a play station on the new color TV and she had visited an exhibition of Matisse and Bonnard with bright colors and contrast-rich text. History Family was positive for migraine</td>
<td>An EEG recording revealed an occipital status epilepticus during her migraine complaints. Standardized extensive intermittent photic stimulation, 2 days after the status migrainous, evoked besides asymmetrical right-sided driving, green spots in her left visual field, while in the EEG sharp-waves were recorded over the right parietotemporal region. After further IPS with 20Hz, she started complaining of a light pulsating headache right occipitally and in the EEG right parieto-temporal sharp-waves were seen</td>
<td>The headache continued for 3 days with nausea, repeated vomiting, photophobia and phonophobia. Neither paracetamol (15 mg/kg) and ibuprofen (10 mg/kg) consecutively administered per os, nor oxygen 10L/min. dissolved the headache Seven minutes after i.v. administration of 10 mg diazepam under continuous EEG recording, a suppression of the epileptiform discharges over the right occipital region was seen, while the headache subsided 3 min later</td>
<td>MRI of the brain, with IR and FLAIR sequences, was normal</td>
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<td>Piccioli23 (2009)</td>
<td>Among 12 subjects (mean age 30 years, range 14–46 years) proved to be photosensitive with either focial (n = 5) or generalized (n = 4) epileptiform discharges, 2 subjects showed “a documented ictal headache” occurring after IPS (lasting minutes). In this subject was proved that, in specific patients, headache could be an ictal sign of epilepsy</td>
<td>First subject (21 years-old-female): the EEG showed sharp waves over the right temporo-occipital regions, spontaneously and especially during IPS between At 12 and 25 Hz, during IPS she complained of headache. The same complaints occurred during pattern stimulation Subjects belonging to the second family had ictal headache as the only symptom of epileptic EEG abnormalities and evoked by visual stimuli</td>
<td>Continuous per os therapy with valproic acid was able to stop both epilepsy and headache AEDs i.v. administration was not tried during ictal headache phase</td>
<td>MRI were normal in all investigated subjects</td>
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<td>Belcastro27 (2010)</td>
<td>A 20-year-old right-handed woman was admitted because of right headache, throbbing, of severe intensity, with photo-, phonophobia, and vomiting, lasting for 3 days despite treatment with paracetamol and ibuprofen. Her mother suffered from migraine without aura.</td>
<td>Neurological examination revealed a left hemisynonymous Herniomanopia. EEG recording showed right posterior epileptiform activity. Photic stimulation was ineffective. The following day, the patient complained again of right unilateral painful, intense, throbbing, associated with nausea, associated with right occipital epileptic activity.</td>
<td>During EEG recording, intravenous lorazepam was administered, obtaining a complete remission of the headache and of epileptic abnormalities within 10’ During the second episode, the EEG confirmed right occipital epileptic activity and intravenous lorazepam induced again the complete regression of both migraine and EEG abnormalities. Therapy with topiramate os gave picture control.</td>
<td>MRI showed stabilized post-traumatic right parieto-occipital and left subcortical frontal lesions. Diffusion weighted imaging (DWI) showed restricted diffusion in the right occipital region. MR angiogram was unremarkable MRI examination, repeated 1 week later, showed normal diffusion-weighted sequence. The reversibility of DWI abnormalities in this patient would support the role of a wave of spreading depolarization. During headache, brain MRI documented bilateral (right/left) occipital cortex swelling with increased signal intensity on T2-weighted images, hyperintensity on diffusion-weighted images, and reduction in the apparent diffusion coefficient.</td>
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<td>Perucca25 (2010)</td>
<td>A 56-year-old woman with synthematic occipital lobe epilepsy since age 16 years, secondary to perinatal hypoxic-ischemic brain injury (and no family history of migraine nor epilepsy) was admitted for sudden onset of frequent (15/day), brief (1 min) attacks of right fronto-temporal pulsating headache associated with uncolored, scintillating, “spots” in the periphery left hemifield. Neurologic findings on admission were identical to prior evaluations (dysarthria, nystagmus, hypotonia, lower extremity hyperreflexia, dysmetria on coordination testing, and slightly unsteady gait). During the first 3 days, EEGs demonstrated that each attack coincided with 70–100s seizure patterns of high-voltage, rhythmic, 11–12 Hz activity with onset, persistence, and subsequent evolution into slow activity with intermingled spikes over the right temporo-occipital leads. Rarely, head deviation to the left was noted. No control was obtained with i.v. diazepam. On the fourth day, showed a continuous long-lasting (5h), severe, left-sided pulsating migraine-pattern headache, without scintillating scotomas. No changes were noted on neurologic examination. Os paracetamol/codeine did not relieve her symptoms. An EEG during headache revealed subcontinuous seizure activity in the right temporo-occipital region. I.V. phenytoin resulted within few minutes in cessation of both headache and ictal-EEG pattern.</td>
<td>Video/EEG recordings during two different migraine attacks, with an interval of 6 months from each other, showed, in both recordings, subsequent ictal discharges over the affected and disconnected hemisphere. Repetitive subsequent high frequency rhythmic theta discharges over the right frontal and central regions were recorded, each lasting 3–4 min and alternate with seconds to 1 min of beta activity of very low voltage, as post-ictal depression. Pain was resistant to oxygen therapy, non-steroid anti-inflammatory drugs and triptans. The patient was given, calcium-antagonist, carbamazepine, gabapentin, levetiracetam, topiramate and acetazolamide with no success. Migraine and ictal discharges in both ictal recorded episodes disappeared with 10 mg diazepam i.v. During migraine attack, 4 months later, with localization of ictal discharges over the right occipital region, disappearance of migraine and ictal discharges after 10 mg diazepam i.v. was confirmed. Several posturgical brain MRIs, showed the right hemispherotomy The interictal (out of migraine) SPECT, showed very low signal over the right temporal and parietal and occipital lobes, and a normal signal over the left hemisphere. The ictal SPECT, performed during the second migraine attack monitored by video/EEG, showed a right occipital lobe hyperperfusion, consistent with the EEG occipital ictal discharge. Brain MRI revealed hyperintense signal area on T2-FLAIR weighted images, left occipital cortico-subcortical regions, in keeping with postictal vasogenic edema. Control brain MRI performed nine days later showed almost complete resolution of the left occipital edema.</td>
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<td>Fusco26 (2011)</td>
<td>After 2 years from discontinue surgery for Rasmussen’s encephalitis, a child, 9 years old, began to present severe headache attacks, lateralized to the operated side, lasting 1–2 days with a “typical migraine pattern” presentation. It is important to stress that the patient showed, both with frontal and occipital ictal discharges, the same migraine symptoms, implying that the localization of the epileptogenic area was not an essential requirement for the genesis of the attack. Video/EEG recordings during two different migraine attacks, with an interval of 6 months from each other, showed, in both recordings, subsequent ictal discharges over the affected and disconnected hemisphere. Repetitive subsequent high frequency rhythmic theta discharges over the right frontal and central regions were recorded, each lasting 3–4 min and alternate with seconds to 1 min of beta activity of very low voltage, as post-ictal depression.</td>
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<td>Italiano27 (2011)</td>
<td>35-Year-old woman with recurrent occipital seizures, clinically presenting with seven day history of intractable headaches. Ictal EEG during headache episodes (typical migraine attack) showed a rhythmic fast activity with phase-reversal on the left occipital region, with a recruiting-dererecting pattern, gradually replaced by polyspike and polyspike-and-wave activity. The patient did not respond to common non-steroidal anti-inflammatory drugs. During the recorded ictal “migraine” a bolus of 10 mg i.v. diazepam was given with complete resolution of the electro-clinical pattern.</td>
<td>MRI showed stabilized post-traumatic right parieto-occipital and left subcortical frontal lesions. Diffusion weighted imaging (DWI) showed restricted diffusion in the right occipital region. MR angiogram was unremarkable MRI examination, repeated 1 week later, showed normal diffusion-weighted sequence. The reversibility of DWI abnormalities in this patient would support the role of a wave of spreading depolarization. During headache, brain MRI documented bilateral (right/left) occipital cortex swelling with increased signal intensity on T2-weighted images, hyperintensity on diffusion-weighted images, and reduction in the apparent diffusion coefficient.</td>
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probably largely underestimated) the headache may represent the only ictal phenomenon. We named this last type of headache an “ictal epileptic headache”.1 It is defined as a headache characterized solely by an ictal epileptic manifestation lasting from minutes to days, with evidence of ictal epileptiform EEG discharges, that resolves after administration of intravenous antiepileptic medication.1

Both, hyper- and hypo-excitation may be observed at different times in the same migraine patient affected by dysexcitability2,11,12; it is, therefore, more appropriate to consider dysexcitability as the main underlying mechanism of migraine, whose pathophysiology, though still controversial, has been explained by the widely accepted trigeminovascular theory.14–41 Accordingly, cortical spreading depression (CSD) would constitute, as it has been demonstrated more recently,36 a nociceptive stimulus capable of activating peripheral and central trigeminovascular neurons in the spinal trigeminal nucleus (C1–C2) that underlie the headache pain.36 CSD is characterized by a slowly propagating wave (2–6 mm/min) of sustained strong neuronal depolarization that generates transient intense spike activity through brain tissue (resulting in a transient loss of membrane ionic gradients and in a massive surge of extracellular potassium, neurotransmitters and intracellular calcium), 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.2 A migraine/headache attack can originate at either the cortical or subcortical level, whereas an epileptic focus arises cortically and can only be modulated at the subcortical level.2,11,12 The reasons for why headache may on rare occasions be the sole ictal epileptic manifestation have been explained previously.12 The central autonomic networks (whether cortical or subcortical) have a lower threshold for epileptogenic activation than those that produce a focal cortical sensory-motor ictal semiology; this lower threshold may be responsible for an epileptic discharge that activates the trigeminovascular system and induces a headache with any associated cortical ictal epileptic signs or symptoms. We recently reviewed the physio-pathological mechanisms that might explain why CSD and epileptic discharges may facilitate each other, though to different extents.2 The onset and propagation of CSD and an epileptic focus are triggered when these neurophysiological events reach a certain threshold, which is lower for CSD than for the seizure. Once the cortical event has started, how it spreads depends on the size of the onset zone, its velocity, semiology and type of propagation. These two phenomena may be triggered by more than one pathway converging upon the same destination: depolarization and hypersynchronization,2,11,12,41–49

4. Concluding remarks

The “migraine-epilepsy” sequence, defined as “migralepsy”, may often merely be a seizure starting with an ictal headache,2 followed by a sensory-motor partial or generalized seizure, which fits into the codified “Hemicrania Epidelatica” criteria.30 However, we recommend keeping the term “ictal epileptic headache” for cases in which headache is the sole ictal manifestation, whereas the term “ictal headache” should be applied when the headache, whether brief or long-lasting, is part of a more complex seizure including other sequential or overlapping (sensory-motor, psychiatric or non-autonomic) ictal manifestations (see “Hemicrania Epidelatica Criteria”). We believe that this separation is crucial in view of the markedly different prognosis associated with each condition.2,3,8,14 It is above all for this reason that the case described in this issue by Wang et al. should not, we believe, be classified as a case of IEH.

Animal models, molecular studies and, a multicenter approach for clinical studies may be the starting point for a definitive international consensus on this matter.

Conflict of interest

We have no conflict of interests to declare regarding the publication of this “Invited Review”.

References

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