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Peri-ictal headache due to epileptiform activity in a disconnected hemisphere

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ABSTRACT – A 4-year-old girl with intractable epilepsy due to left-side hemispheric cortical dysplasia underwent a hemispherotomy. She was seizure-free after the surgery. EEG showed persistent abundant epileptiform activity over the left (disconnected) hemisphere, including ictal patterns that neither generalised nor had clinical correlates. Antiepileptic medication was completely withdrawn four years following the surgery. One week after the withdrawal, she developed episodes of intense left-sided hemicranias (ipsilateral to the surgery) with vomiting and photophobia that did not resemble her habitual seizures and were unresponsive to non-steroidal anti-inflammatory drugs. Video-EEG showed association of the headache attacks with ictal patterns over the disconnected hemisphere. Brain MRI revealed increased signal changes in the left hemisphere. Attacks responded promptly to *i.v.* midazolam and carbamazepine at a low dose. Mechanisms underlying peri-ictal headache originating in the disconnected hemisphere are discussed. [*Published with video sequences*]

Key words: peri-ictal headache, hemispherotomy, AED withdrawal

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Headache occurring concurrently with epileptic activity is a seldom reported phenomenon that has attracted increasing attention in recent years (Parisi *et al*., 2012; Cianchetti *et al*., 2013). The third edition of the International Classification of Headache Disorders (ICHD-III) defines ictal headache as occurring during a partial epileptic seizure, ipsilateral to the epileptic discharge and remitting immediately or soon after the seizure has terminated (Headache Classification Committee of the International Headache Society, 2013).

The aetiology of ictal headache, particularly in patients exhibiting headache as the sole manifestation of the epileptic seizure, is unclear. Ictal headache manifests with diverse symptomatology. No specific type of EEG pattern or

location have been attributed to ictal headache in patients with symptomatic or idiopathic epilepsy. Regions of epileptiform EEG activity associated with ictal headache include central, parietal, and temporal regions, as well as deep structures, such as the hippocampus or amygdala, and generalised ictal activity is also reported on EEG (Cianchetti *et al*., 2013).

We report on a patient after successful hemispherotomy, who developed headaches in relation to ictal activity in dysplastic brain tissue in the disconnected hemisphere that responded to a subtherapeutic dose of carbamazepine.

Case report

The patient had intractable epilepsy from the age of 3 months. She presented with multiple seizure types, both with and without impaired consciousness, always associated with variable right-sided motor symptoms (versive, tonic and clonic). She had mild right-sided hemiparesis and central-type hypotonia. EEG consistently showed no differentiation and reactivity over the left hemisphere with frequent left-sided epileptiform activity (sharp waves, spikes, and irregular spike-wave complexes) originating from different regions of the left hemisphere and secondarily propagated to the right side. No independent right-sided spikes or seizure onsets were recorded. Brain MRI revealed left-sided hemispheric cortical dysplasia which was more prominent in the posterior part of the hemisphere, with no features of hemimegalencephaly. Multiple antiepileptic drugs (VPA, PB, PRM, TPM, VGB, PHT, DZP, and CBZ, in different combinations) were ineffective. Neuropsychological testing revealed moderate intellectual disability, mainly with communication and behavioural problems.

The patient underwent left-sided hemispherotomy from the vertical approach (performed by Olivier Delalande) at the age of 4 years. Histopathology was focal cortical dysplasia type IIb. She was seizure-free after the surgery and showed marked cognitive progress. Initial right-sided hemiplegia gradually improved. Postsurgical MRI confirmed the complete disconnection of the left hemisphere. Postoperative EEGs repeatedly showed frequent spikes as well as ictal patterns over the disconnected hemisphere that did not propagate to the right side or show clinical correlates. Anticonvulsant medication was gradually reduced: PHT, PB, and TPM were withdrawn and the patient was treated with carbamazepine monotherapy. Four years after the surgery, the remaining low dose of carbamazepine (75 mg per day) was withdrawn.

One week after the withdrawal of carbamazepine, the patient was admitted for episodes of left-sided hemicranias. She suffered from multiple daily attacks (up to 10 episodes per day) of intense headache, localised to the left temporal region, lasting for up to one minute. Nausea, vomiting, and photophobia accompanied some of the attacks. The patient did not complain of other difficulties and did not present seizures resembling those before surgery. Video-EEG monitoring (see *figure 1 and video sequence*) during the headache attacks showed an almost continuous suppression-burst pattern over the left side (*i.e.* disconnected hemisphere) and long-lasting recruiting ictal patterns (usually lasting for several minutes) that originated predominantly from the left central-parietal region, and less frequently from the left temporal and occipital regions. No independent epileptic activity was observed over the right hemisphere. Propagation of ictal patterns to the right could be explained by volume conduction because of high voltage of left-sided patterns and immediate normalisation of the background activity on the right after their cessation, in contrast to a postictal flattening of EEG activity on the left. In the majority of the attacks, ictal EEG activity preceded headache for a number of seconds (up to 2 minutes); in a few episodes, the headache started shortly after the ictal pattern manifestation. No other manifestations of seizures were identified and the patient responded normally during attacks. Brain MRI (*figure 2*) revealed a progression of signal changes (hyperintense in T2w and FLAIR images) in cortical and subcortical regions of the left hemisphere. Headache attacks did not respond to non-steroidal anti-inflammatory drugs (NSADs), but immediately resolved after *i.v.* midazolam (continuous infusion, 20 mg/day). A low dose of carbamazepine (150 mg/day) was reintroduced and the patient was rendered headache-free even after midazolam discontinuation after one week. Video-EEG performed after one month still showed almost continuous epileptiform activity over the left hemisphere, but decreased amplitude of spikes. Ictal patterns occurred less frequently with the same characteristics as described above, but with shorter duration and, importantly, were not associated with clinical manifestations. The patient has remained on the low dose of carbamazepine without clinical complications. Her mental development has proceeded.

Discussion

Headache attacks in our patient were clearly associated with epileptiform activity in the disconnected hemisphere. Features of the headache (*i.e.* brief duration, symptoms of migraine, and the temporal association between headache onset and termination of ipsilateral ictal EEG patterns) were compatible with hemicrania epileptica, as described by Isler

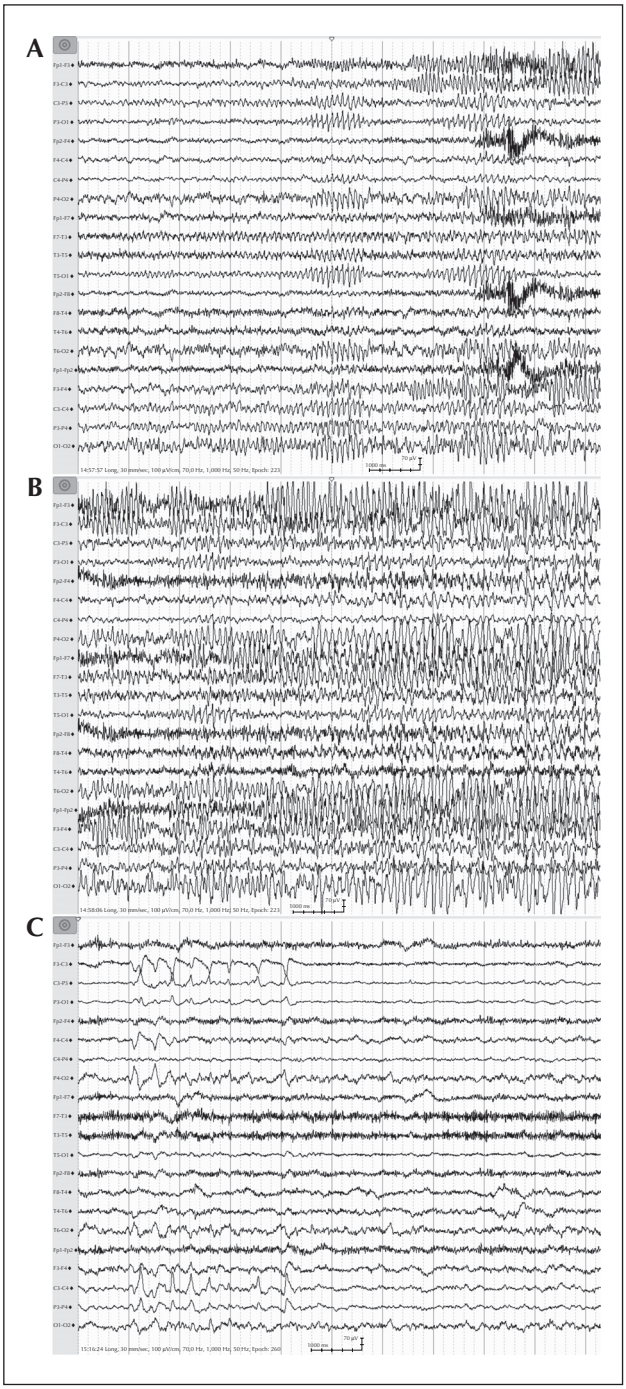

Figure 1. Interictal and ictal EEG recordings at the time of headache attacks.
(A) Seizure onset (from the left posterior quadrant on scalp EEG). (B) Evolving ictal EEG pattern during the headache attack showing the spread of ictal activity. (C) Interictal abnormality with flat non-organised background activity over the left hemisphere and central left/midline spikes.
Longitudinal bipolar montage; amplitude: 150 uV/cm; speed: 10 mm/s.

and colleagues (1987), and ictal headache, defined by ICHD-III. Furthermore, the headache attacks responded to AED therapy, but not NSADs.

Preoperative absence of any headaches in the setting of medically intractable seizures, including seizures without impaired consciousness, would suggest that either ictal headaches did not exist before the operation, or they did exist, in which case they would be the most pharmaco-responsive of all the ictal symptoms. Our patient did not complain of the headaches before the brain surgery. Severe painful sensations, as observed at the time of ictal headaches, would most probably have not been overlooked even in a preverbal child. Development of ictal headaches as a new seizure type after the operation seems less likely as the headaches appeared one week after the AED withdrawal and remitted with the use of a small dose of CBZ. Also, EEG findings recorded during ictal headaches were only quantitatively different from the EEG activity after the treatment with CBZ (lower-voltage spikes and shorter and less frequent ictal patterns). Considering the epileptic basis of the headache episodes in our patient, postoperative brain MRI was evaluated. Signs of complete hemispherotomy were confirmed. Dissection of the pathways of internal capsule prevented sensorimotor manifestations from the disconnected hemisphere. Disconnection of the corpus callosum pathways prevented spreading of the ictal activity contralaterally and sensorimotor manifestations from the preserved hemisphere. Nevertheless, we can not rule out that propagation of the ictal discharge in the dysplastic hemisphere could cause ictal headache, particularly if we accept that the ictal headache pre-existed but was suppressed by a low dose of carbamazepine.

Peri-ictal headache has been previously associated with activation of the trigeminovascular system. Cortical spreading depression (CSD), an electrophysiological phenomenon that was proposed to induce activation of the trigeminovascular system and migraine (Moskowitz *et al*., 1993), was shown to accompany epileptic discharge (Fabricius *et al*., 2008). After surgery, perivascular intracranial and meningeal neuronal branching remained preserved in the disconnected hemisphere. This supplies nociceptive innervation, provided by axons originating in the ipsilateral trigeminal ganglion, mainly through the ophthalmic trigeminal division. However, temporal association between the headache attacks and ictal discharge indicates involvement of neuro-mediated, rather than inflammatory-mediated, mechanisms and circulatory malfunction, underlying migraine pain. Furthermore, headaches in our patient did not respond to NSADs, but were well controlled by CBZ. In an experimental study, oxcarbamazepine, a derivative of CBZ, did not suppress the CSD (Hoffmann *et al*., 2011).

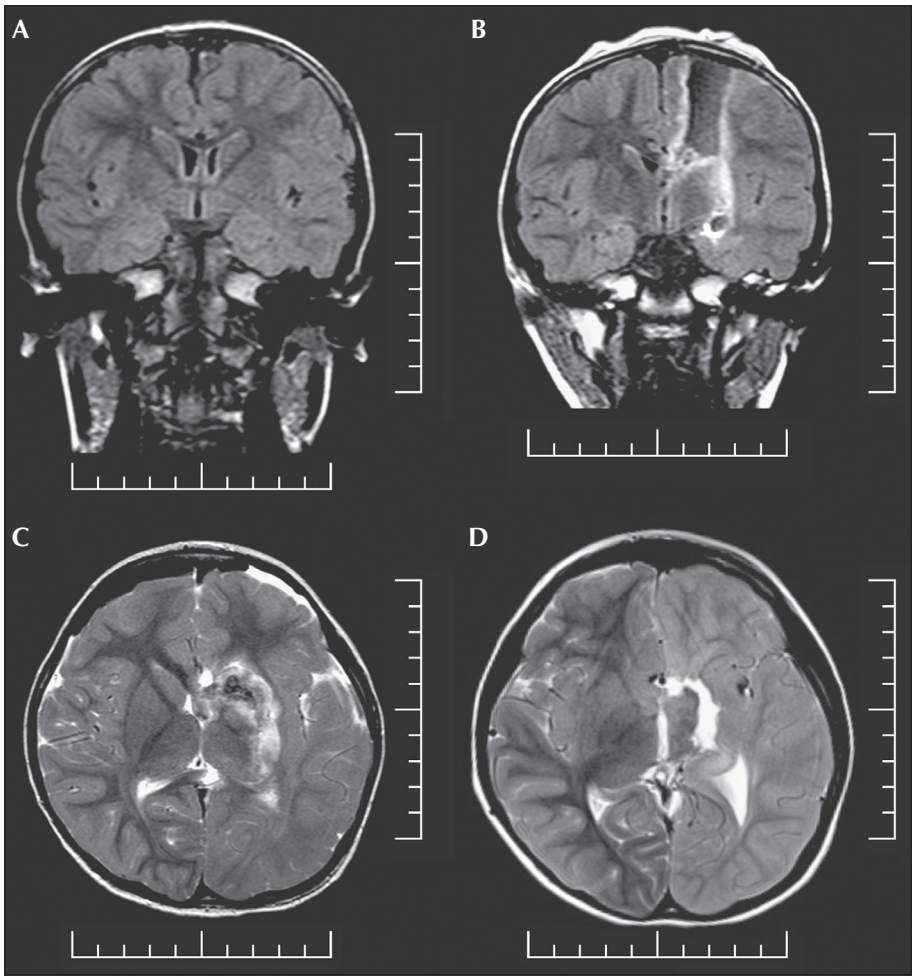

Figure 2. Brain MRI of the patient.
(A) Presurgical coronal FLAIR sequence consistent with a diagnosis of left hemispheric cortical dysplasia. (B and C) Immediate post-surgical coronal FLAIR and axial T2w sequences showing complete disconnection of the left hemisphere. (D) Axial T2w sequence performed at the time of headache attacks revealing enhanced signal changes of the grey and white matter of the left hemisphere.

Therefore, different pathophysiological mechanisms underlying the headache attacks were involved. An anti-nociceptive effect of CBZ is used for the treatment of neuralgias (particularly trigeminal neuralgia), with doses lower than those used for the anticonvulsant indication. The pain relief is believed to be associated with blockade of synaptic transmission (*via* voltage-gated sodium channels) in the trigeminal nucleus. We speculate that these mechanisms might contribute to the effect of CBZ on the headache attacks in our patient.

Brain imaging performed at the time of headache attacks showed progression of the MR signal changes over the left hemisphere. These findings were interpreted as possible oedematous changes due to abundant epileptiform activity in the disconnected hemisphere. A link between these MRI changes and the headache attacks is controversial. Nevertheless, ictal hyperperfusion in the epileptogenic brain tissue, possibly further enhanced by the AED withdrawal, may have aggravated chronic structural changes (*i.e*. dysplastic and postoperative changes) and contributed to the onset of headaches.

We are aware of one case report of epileptic headache in a patient after hemispherotomy. Fusco *et al*. (2011) reported a seizure-free child after a right-sided hemispherotomy due to Rasmussen encephalitis, who developed migraine attacks two years after the surgery. EEG showed association of the headache attacks with increasing intensity and duration of epileptiform discharges over various locations (*i.e*. frontal and occipital) of the disconnected hemisphere. Headaches disappeared after intravenous application of diazepam (Fusco *et al*., 2011).

There are both striking similarities as well as some differences between this patient and the patient reported here. We wish to emphasize that epileptiform discharges and ictal patterns over the disconnected

hemisphere were constantly present after the surgery in both children. Headache was associated with increased duration and intensity of ictal patterns. Contrary to our patient, CBZ was ineffective for the treatment of headaches in the patient with Rasmussen encephalitis. Different underlying pathophysiology (*i.e*. active inflammatory process *vs*. cortical dysplasia; migraines *vs*. brief cephalic pain) might be related to a different therapeutic effect in both patients.

Based on the experience with our patient, we would approach the option of complete AED withdrawal in hemispherotomy cases with intense epileptiform activity over the disconnected hemisphere with caution.

To summarise, ictal headache, as the sole manifestation of epileptic discharge, is rare and its underlying pathogenic mechanisms have not yet been elucidated. We believe that our case report of ictal activity-associated headache contributes to the discussion regarding such mechanisms. □

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Legend for video sequence

Video-EEG recording of a typical headache attack

The girl is lying on her back listening to her mother reading a fairy tale. With the start of the ictal EEG pattern, she indicates to the parents that she feels a headache. After approximately one minute of ongoing ictal pattern, she complains about an intense headache and points at the button to signal to her mother to mark the event. She then touches her left temporal region, grins while closing the left eye, turns her head to the pillow, and screams. Relief from the headache after cessation of the ictal pattern is apparent.

Key words for video research on www.epilepticdisorders.com

Syndrome: focal non-idiopathic (localization not specified)
Etiology: dysplasia (architectural)
Phenomenology: headache
Localization: hemispheric

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