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Lesion-negative anterior cingulate epilepsy

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ABSTRACT – MRI-negative anterior cingulate epilepsy is a rare entity. Herein, we describe a case of MRI and functional imaging-negative intractable frontal lobe epilepsy in which, initially, secondary bilateral synchrony of surface and intracranial EEG and non-lateralizing semiology rendered identification of the epileptogenic zone difficult. A staged bilateral stereotactic EEG exploration revealed a very focal, putative ictal onset zone in the right anterior cingulate gyrus, as evidenced by interictal and ictal high-frequency oscillations (at 250 Hz) and induction of seizures from the same electrode contacts by 50-Hz low-intensity cortical stimulation. This was subsequently confirmed by ILAE class 1 outcome following resection of the ictal onset and irritative zones. Histopathological examination revealed focal cortical dysplasia type 1b (ILAE Commission, 2011) as the cause of epilepsy. The importance of anatomo-electro-clinical correlation is illustrated in this case in which semiological and electrophysiological features pointed to the anatomical localization of a challenging, MRI-negative epilepsy. [*Published with video sequence*]

Key words: anterior cingulate epilepsy, anterior cingulate gyrus, MRI, EEG, SEEG, focal cortical dysplasia

Anterior cingulate epilepsy (ACE), a rare entity (Garzon and Lüders, 2008; Alkawadri *et al.,* 2013), presents particular challenges in focus localization during pre-operative epilepsy surgery work-up (Garzon and Lüders, 2008; Alkawadri *et al.,* 2013). The anatomical location of the cingulate gyrus (CG), medial and distant from the cerebral surface, makes localization of the ictal onset zone difficult. The phenomenon of secondary bilateral synchrony (SBS) increases the lateralization difficulty (Cukiert *et al.,* 1991; Iwasaki *et al.,* 2011). Extensive connectivity demonstrated between homotopic cingulate and mesial frontal regions across the corpus callosum in mammals (Marcus and Watson, 1968; Musgrave and Gloor, 1980; Umeoka *et al.,* 2010; Iwasaki *et al.,* 2011) may provide the basis for the lateralization difficulties encountered in humans. Localization and lateralization challenges are compounded in MRI-negative patients (Cukiert *et al.,* 1999; McGonigal *et al.,* 2008). Although semiological descriptions of ACE exist (Bancaud and Talairach, 1992; Alkawadri *et al.,* 2013), recent reports suggest semiological

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heterogeneity between different frontal regions and even within the subgroup of ACE (Alkawadri *et al.*, 2013; Bonini *et al.*, 2014). Herein, we describe an MRI-negative ACE case in which semiology, surface EEG, and imaging were non-contributory, but the presence of extremely focal interictal and ictal high-frequency discharges and electrical stimulation of the putative ictal onset zone resulted in successful localization, lateralization, and resection of the epileptogenic zone. We posit that in ACE cases in which semiology, conventional scalp EEG and imaging are unhelpful, additional scrutiny of the EEG for high-frequency oscillations (HFOs) and the use of 50-Hz electrical stimulation for habitual seizure induction can be of critical benefit.

Case study

A 30-year-old, right-handed male with medically intractable focal epilepsy of 22 years duration was referred for pre-surgical evaluation after multiple attempts at medical control. At evaluation, he was on levetiracetam (500-500-500 mg), topiramate (50-50-100 mg) and lamotrigine (400-200-500 mg). Gestational, birth and development histories were normal and he had no history of epilepsy risk factors. He had 1-2 nocturnal seizures per month, characterized by a non-specific cephalic aura, followed by hypermotor seizures with pedalling movements in both legs and prominent gestural automatisms. Awareness was altered for less than a minute with each seizure. Neurological and neuropsychological examinations were normal. Epilepsy protocol 3T MRI was consistently normal, as was FDG-PET.

Semiology

Several seizures were captured with EEG onset, the distribution of which was the same as that for interictal discharges. Seizure semiology was characterized by a cephalic aura, followed 10-15 seconds later by prominent, repetitive, high-amplitude, proximal lower limb movement, rocking, agitation, tachycardia, pupillary dilation, and a fearful facial expression. Approximately 25 seconds after seizure onset, he had prolonged ululating palilalia of 15-18 seconds duration, accompanied by upward right conjugate gaze deviation (*see video sequence*). A decision was therefore made to evaluate the patient with stereotactic EEG (SEEG) in both frontal lobes with a putative epileptogenic zone in the mesial frontal lobe, anterior to Brodmann area 6. Adjacent dorsolateral premotor and prefrontal cortices were also covered.

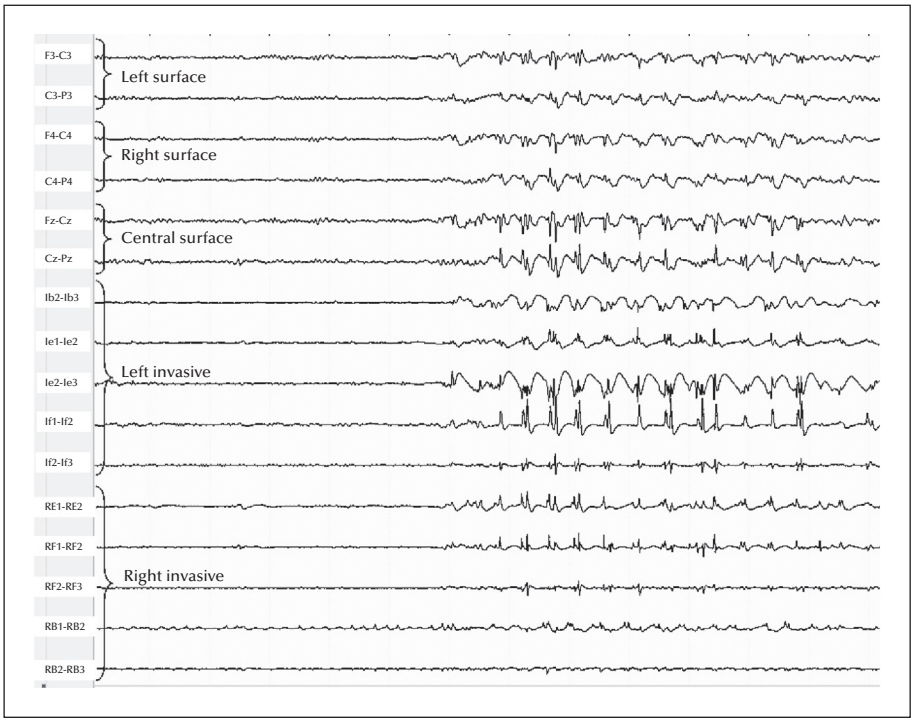

Figure 1. Interictal scalp electrode recordings of generalized spikes, maximum in the central regions (Cz>Fz), and invasive electrode recording of bilateral mesio-frontal spikes, maximum in the left anterior cingulate region (Ie2/Ie3 and If1/If2).

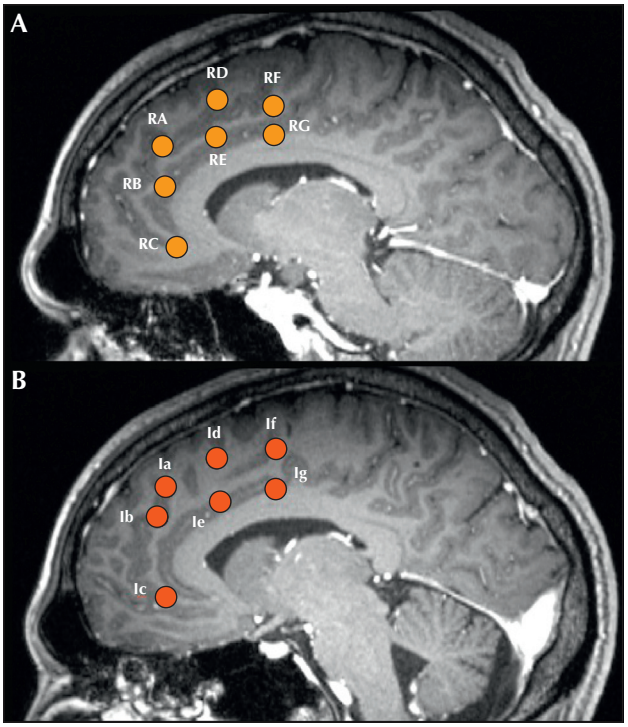

Figure 2. Second-stage bilateral EEG implantation with six orthogonally placed electrodes in the right (A) and left frontal lobe (B).

Electrophysiology

1) Interictal surface EEG revealed generalized spikes, polyspikes, and runs of spike-wave complexes, with varying left or right fronto-central emphasis (maximum at Cz>FZ on 10-20 electrode montages) (*figure 1*). EEG source imaging (Compumedics Neuroscan Curry 6.0.1; electrode locations digitized by Polhemus FastTrak electromagnetic 3D digitizer; MRI preprocessing with MPRAGE acquisition protocol) consistently localized the epileptiform discharges to deep-seated midline structures. Symmetric bifrontal SEEG evaluation with electrode coverage revealed fronto-central spikes bilaterally, similar to scalp discharges with no clear interictal or ictal lateralization. However, maximal activity was seen bilaterally in the ventro-mesial frontal, anterior peri-cingulate regions. A decision was therefore made to carry out a second SEEG evaluation, concentrating on the anterior cingulate gyrus and adjacent brain regions not targeted by the first evaluation.
2) Intracranial EEG. SEEG electrodes were placed orthogonally with mesial contacts in the mesial frontal walls of both frontal lobes, including both anterior cingulate/pericingulate regions (*figure 2*). Antiepileptic medication was reduced and stopped in a phased manner over five days. Frequent interictal bifrontal discharges, similar to the previous evaluation were seen in the anterior cingulate and adjacent cortex, again without clear lateralization, although some discharges had maximum amplitude in the left mesial frontal contacts (le2/le3/lf1/lf2; *figure 1*). However, using high-frequency analysis settings (high-cut filter: 600 Hz; high sensitivity setting; time constant: 0.0001 ms) a distinct 250-Hz high-frequency oscillation pattern was seen over-riding the sharp-wave population. These HFO were seen exclusively at RB1/RB2 electrodes in the right anterior cingulate region, in the inferior bank of the cingulate sulcus anterior to the genu of the corpus callosum (*figure 3A*). Besides, a 250-Hz fast-frequency ictal EEG onset was seen arising from the same contacts, in all habitual seizures, >20 seconds before clinical onset. Electrical stimulation was then carried out with particular emphasis on the more active electrodes on either side. Stimulation of 50 Hz (0.2-ms pulse width, 2-mAmp intensity) of electrode contacts RB1/RB2 produced the patient's habitual seizures in a consistently reproducible manner over two days of repeated testing (*figure 3B*). Current intensity of up to 20 mAmp for 10 seconds failed to produce seizures or discharges in other electrodes.

Anatomy

A consensus decision was then made to resect the right anterior cingulate region. At operation, the adjacent pericingulate areas involved in the interictal discharges were also removed to achieve a better outcome. A tailored resection of the right mesial frontal lobe was performed with the posterior resection margin at the anterior border of the supplementary motor area, inferior margin at the corpus callosum, and extending anteriorly and inferiorly to the floor of the anterior fossa, to include ictal, as well as the prominently discharging, interictal, contacts (*figure 4*). Neuropathology showed focal cortical dysplasia (FCD) type 1b (Blumcke and Muhlebner, 2011) (*figure 5*). Forty-eight hours of prolonged postoperative EEG showed absence of any interictal discharges. The patient has been seizure-free at one year follow-up.

Discussion

This case emphasizes several practical difficulties with localization and lateralization of the epileptogenic zone to the ACG in MRI-negative cases and highlights the contributory roles of clinical semiology and electrophysiology (SEEG evaluation, high-frequency discharges in invasive EEG, and electrical stimulation for habitual seizure induction) in determining the anatomical location of the epileptogenic zone.

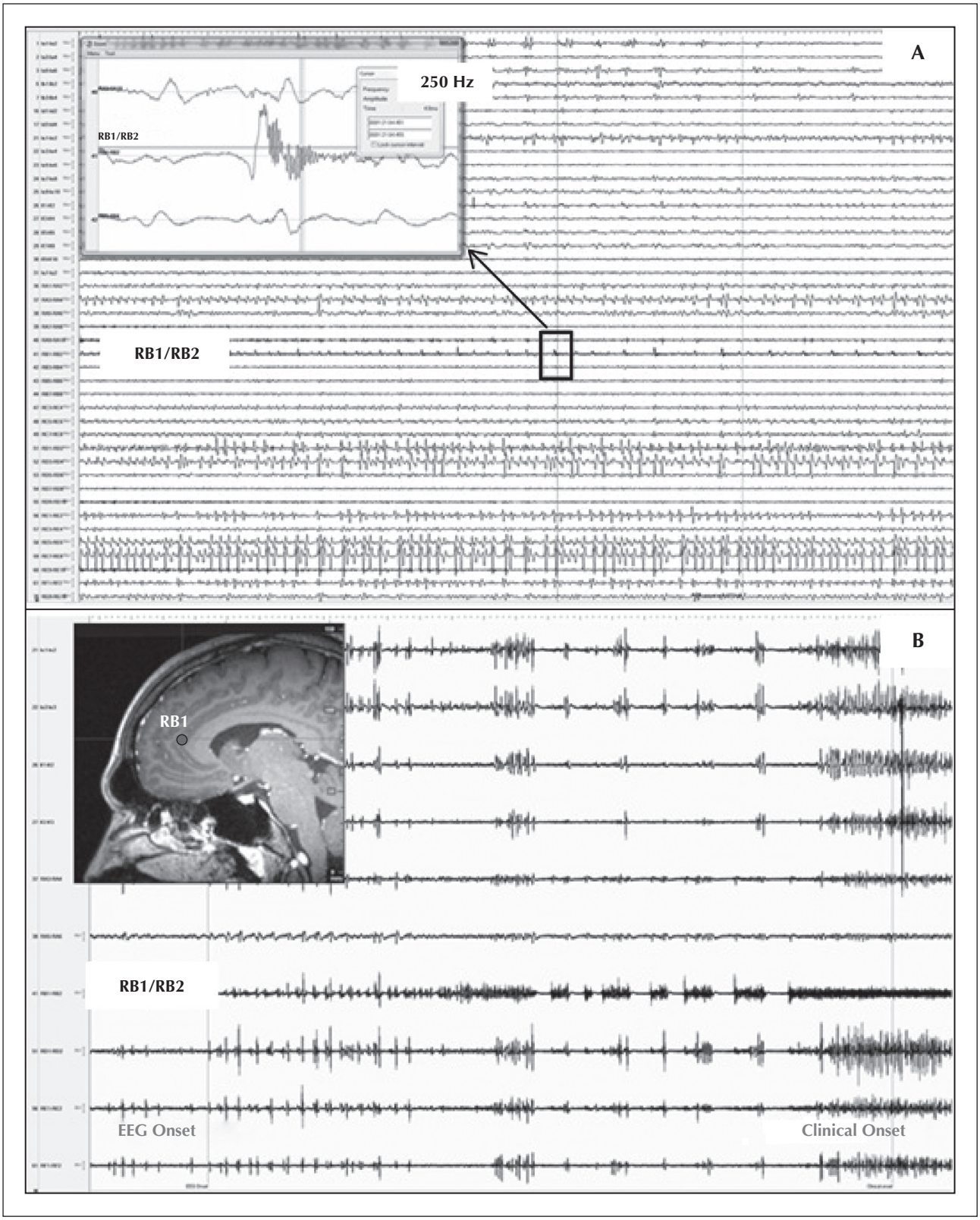

Figure 3. (A) A 250-Hz high-frequency oscillation pattern was seen over-riding the sharp-wave population arising only from the RB1/RB2 electrodes in the right anterior cingulate region, in the inferior bank of the cingulate sulcus, anterior to the genu of the corpus callosum. (B) An evolving ictal onset high-frequency discharge is seen in the same electrode contacts RB1/RB2. (High-frequency filtre: 600 Hz; time constant: 0.0001 ms).

Table 1. Non-lesional MRI Anterior Cingulate Epilepsy studies in the literature.

Study	Type	Semiology	EEG	MRI/SPECT	Brain region resection	Pathology	Outcome
Levin and Duchowny, 1991	Case report	Automotor seizures	Scalp: Fp2 EEG seizure Intracranial: Right ACG seizure	Normal MRI	Right ACG	No tissue available for pathological analysis	Sz free (follow-up: 15 mo)
San Pedro *et al.*, 2000	Case report	Automotor seizures	Scalp: Interictal: No focal or epileptiform abnormalities Ictal: No focal EEG changes. Intracranial: Subdural electrodes over the right ACG showed "spikes during seizures"	Normal MRI Ictal SPECT showed focal hyperperfusion in the right ACG	Right ACG	Neuronal loss and astrogliosis	>90% sz reduction (follow-up: 1 year)
Chassagnon *et al.*, 2003	Case report	Right shoulder somato-sensory aura → bilateral asymmetric tonic posturing → Hypermotor seizure→ gelastic seizure	Scalp: Vertex interictal spikes; precentral + vertex EEG seizure onset Intracranial: Ictal onset in SSMA contacts and in the caudal portion of the cingulate motor area. The ictal discharge originated from the SSMA. Cortical stimulation of the left SSMA evoked typical seizures.	Normal MRI	Electro-radiofrequency lesion of the left SSMA and cingulate motor area (both banks of the cingulate sulcus)	No brain tissue available for pathology	Sz free (follow-up: 27 mo)
von Lehe *et al.*, 2012	Series of 19 cases (Case 3 and 20 were non-lesional)	Case 3 →Hypermotor sz Case 20 →Bilateral arm tonic sz	Scalp: Case 3, inconclusive. Case 20, right centro-parietal seizure onset. Intracranial: Ictal onset in interhemispheric electrode in both 2 cases.	Normal MRI	Case 3→ACG Case 20 →ACG + antero- mesial frontal lobe	Case 3 → FCD Case 20→ gliosis	ILAE class 1 (follow-up: 25-106 mo).

Sz: seizure; mo: month; SSMA: supplementary sensory motor area; rCBF: regional cerebral blood flow; CG: cingulate gyrus; ACG: anterior cingulate gyrus; ACE: anterior cingulate epilepsy.

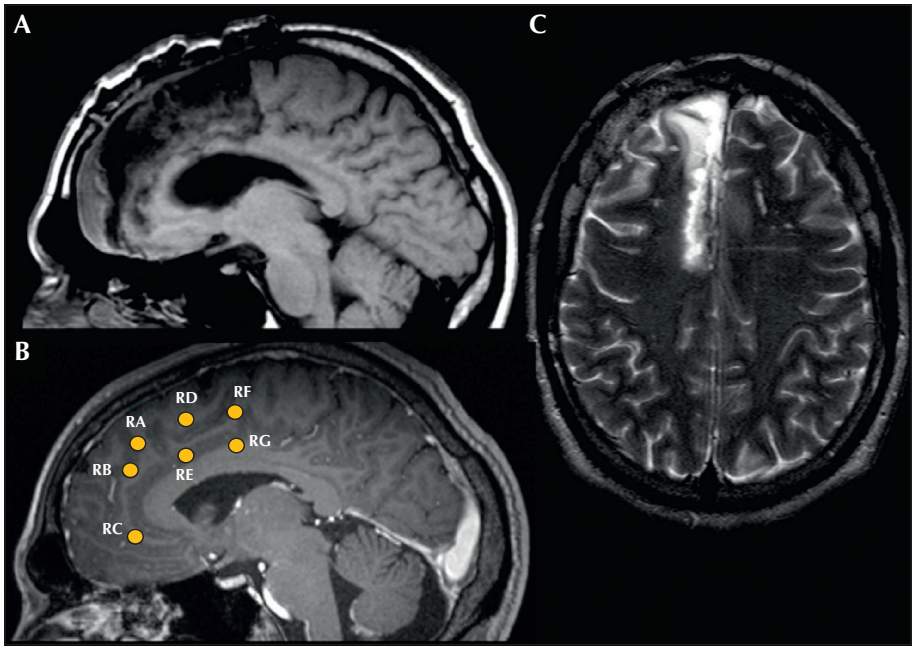

Figure 4. Post-operative MRI shows right medial frontal resection in saggital T1 (A) and axial T2-weighted (C) images. Second-stage bilateral EEG implantation with six orthogonally placed electrodes in right frontal lobe (B).

In epilepsy surgery practice, the frontal lobe is the most commonly operated brain region after the temporal lobe. However, electroclinical frontal lobe epilepsy features are less well characterized than temporal lobe epilepsy (Bancaud and Talairach, 1992; Bonini *et al.,* 2014). Several authors have differentiated between seizures arising from various regions of the frontal lobes (Bancaud and Talairach, 1992; McGonigal and Chauvel, 2004; Garzon and Lüders, 2008; Alkawadri *et al.,* 2013; Bonini *et al.,* 2014), but the anterior cingulate gyrus (ACG), appears to show significant heterogeneity in its manifestations (Alkawadri *et al.,* 2013). These semiological and other features of ACE reported in literature are detailed in *table 1*.

Ictal semiology in relation to ACE is relatively varied. The most frequent seizure types reported to originate from the ACG are hypermotor, gelastic, complex motor, and bilateral asymmetric tonic seizures (*table 1*). Bancaud's description of ACE consists of emotional symptoms, intense fright with facial expressions of fear, shouting, complex motor manifestations sometimes with aggressive verbalization, autonomic symptoms, and alteration of consciousness (Bancaud and Talairach, 1992). This was found in 6 of 10 ACE patients in a recent series (Alkawadri *et al.,* 2013) and labelled as "typical" ACE symptomatology. The remainder was classed with "atypical" seizures and characterized by tonic rather than hypermotor features, suggesting heterogeneity in ACE semiology. Moreover, "typical" ACE manifestations can also occur in other prefrontal regions (Chang *et al.,* 1991; Munari *et al., 1995*). Our patient's presentation with hypermotor seizures, fearful facial expression, and autonomic symptoms (pupillary dilation and tachycardia) is consistent with "typical" ACE. Vocalizations are consistent with both typical and atypical ACE phenotypes reported by Alkawadri *et al.* (2013). Autonomic and "neurovegetative" features, such as in our patient, are well described in ACE, as well as other brain regions (orbitofrontal, operculo-insular).

Non-invasive neurophysiological studies in patients with ACE provide only partial or inconclusive data because of the anatomical location of the CG (medial and distant form the cerebral surface). This is reflected in the secondary bilateral synchrony phenomenon, seen in our case, defined as apparent generalized epileptiform discharges triggered by a focus. It can pose significant lateralization/localization problems and often necessitates invasive evaluations (*table 1*). It is well described in frontal lobe epilepsies, especially in the mesial region and is a frequent lateralization conundrum (Marcus and Watson, 1968; Musgrave and Gloor, 1980; Cukiert *et al.,* 1991; Cukiert *et al.,* 1999; Lacruz *et al.,* 2007; Umeoka *et al.,* 2010; Iwasaki *et al.,* 2011). Extensive connectivity between homotopic regions of both frontal lobes is a likely explanation (Lacruz *et al.,* 2007; Iwasaki *et al.,* 2011). Primate studies have shown that the mesial frontal regions are very heavily supplied by reciprocal callosal connections (Karol and Pandya, 1971) although human evidence

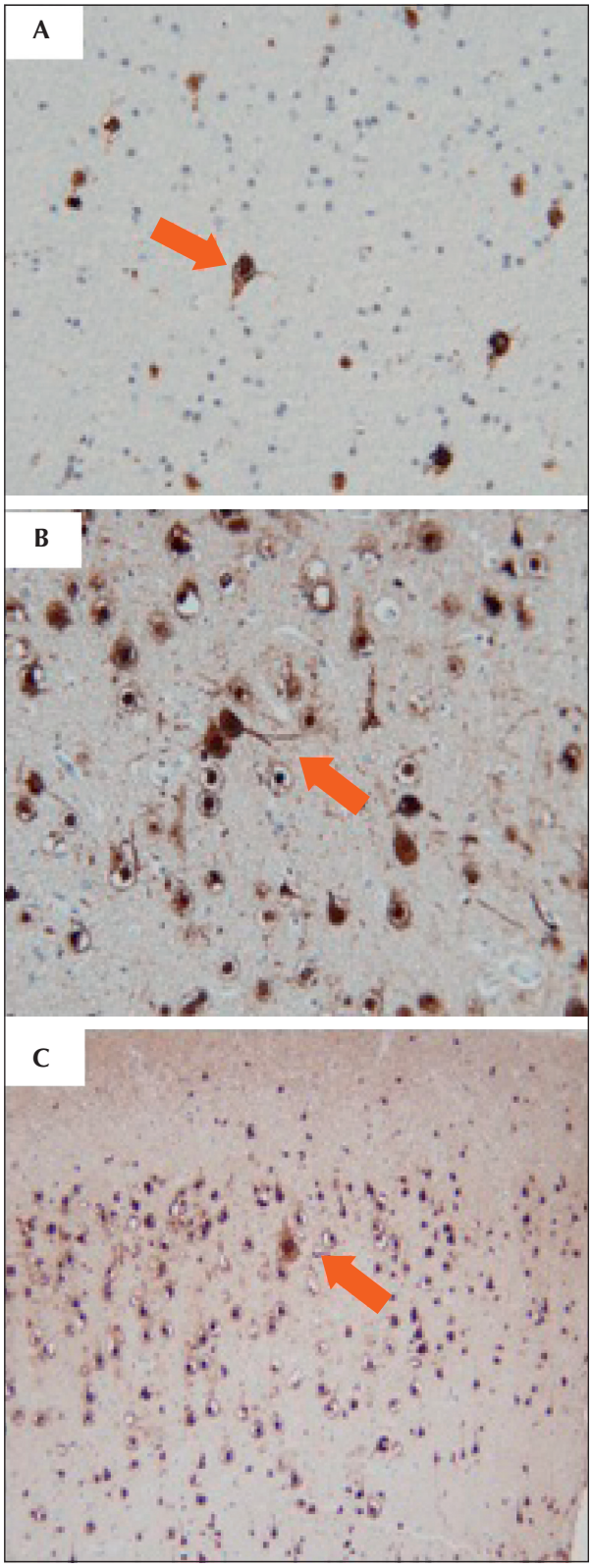

Figure 5. NeuN immunohistochemistry demonstrating several heterotopic neurons in deep white matter (200x) (A), normal neurons with disoriented dendrites (200x) (B), and hypertrophic neurons in the cortex, outside layer 5 (100x) (C).

has been mostly indirectly ascertained. Transcallosal inter-hemispheric conduction, using the relationship between axonal diameter, conduction velocity, and inter-hemispheric transfer, is estimated to be 1.5 to 24.9 ms (Aboitiz *et al.,* 1992) in humans. This is supported in one study of single-pulse 1-ms electrical stimulation of 23 medial frontal lobes assessed for epilepsy surgery which showed early responses (median: 30 ms [15-45 ms]) in the contralateral mesial frontal lobe in 14 (61%) (Lacruz *et al.,* 2007), best explained by corpus callosal connections (Buser *et al.,* 1992). EEG source imaging can contribute to localization (Brodbeck *et al.,* 2011) although in our case, the deep source was consistently unlateralized and in the midline. Indeed, some of the bifrontal interictal discharges, misleadingly, were maximum in the left frontal lobe.

HFOs (>80 Hz) are seen primarily in the epileptogenic zone (Jacobs *et al.,* 2010a, 2010b; Wu *et al.,* 2014). Furthermore, a negative correlation between HFO rates and stimulation response thresholds has been reported (Jacobs *et al.,* 2010b). Our case exhibited interictal 250-Hz HFOs in the ACG and a consistent similarly fast-frequency ictal onset discharge from the same region. Consistent with the literature, low-current intensity 50-Hz stimulation of the fast-frequency discharge interictal and ictal contacts consistently induced the patient's habitual seizures. Electrical stimulation of small, putatively epileptic cortical areas may provide data complementing that provided by spontaneous seizure recordings (Kahane, 2004). The area delineated by HFOs and electrical stimulation in our patient was therefore likely to be part of the epileptogenic zone.

The absence of an MRI lesion in this case is not surprising given that the pathology was subsequently revealed to be FCD type 1b. However, the absence of an MRI lesion posed significant difficulty in localization of the ictal onset zone, which in the absence of SEEG would not have been feasible. MRI-negative ACE is extremely rare and only a handful of cases exist in the literature (*table 1*). This case demonstrates the potential rewards of keeping this entity in mind in MRI-negative prefrontal lobe epilepsy and in particular, comprehensively targeting the ACG with SEEG electrodes (along with other candidate frontal regions), which allows for the scrutiny of HFOs, as well as provocative electrical stimulation in deep cortical structures, such as the ACG.

One limitation of this study is the relatively extensive medial frontal resection that was performed in spite of the presurgical evaluation pointing to a very focal ACE, in keeping with some of the cases detailed in *table 1*. However, the presurgical evaluation in this case strongly suggests that the epileptogenic zone was indeed limited to the ACG.

Conclusion

Our patient's evaluation and outcome suggests that although rare, MRI-negative ACE is an entity that exists and can be identified through careful anatomo-electro-clinical analysis. Patients with frontal lobe seizure semiology (hypermotor or prominent gestural automatisms, fearful expression, autonomic signs, and palilalic vocalizations), exhibiting non-lateralizable bifrontal discharges and non-contributory structural, functional or source imaging, may yet have surgically amenable ACE. Careful SEEG evaluation for interictal and ictal HFOs with additional cortical stimulation for habitual seizure induction provides the best opportunity for an accurate localization of the epileptogenic zone. □

Acknowledgements and disclosures.
None of the authors have any conflict of interest to disclose.

Legend for video sequence

Seizure semiology of the patient is characterized by a cephalic aura, followed 10-15 seconds later by prominent, repetitive, high-amplitude, proximal lower limb movement, rocking, agitation, tachycardia, pupillary dilation, and a fearful facial expression. Approximately 25 seconds after seizure onset, he has prolonged ululating palilalia of 15-18 seconds duration, accompanied by upward right conjugate gaze deviation.

Key words for video research on www.epilepticdisorders.com

Syndrome: focal non-idiopathic frontal (FLE)
Etiology: focal cortical dysplasia (type 1)
Phenomenology: hypermotor; fear
Localization: cingulate gyrus

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EDITORIAL NOTE

"Electroclinical Reasoning Reports" is a new feature of the journal. Manuscripts are expected to provide the reader with a comprehensive approach to the diagnostic or presurgical evaluation of complex epilepsy patients and epilepsy surgery strategies.

The final diagnosis or therapeutic strategy (and surgical decision or outcome) should preferably appear at the end of the report, following the electroclinical reasoning, rather than at the beginning.

The title and abstract of the submission should not contain information pertaining to diagnosis or therapeutic strategy. The template below is provided for your guidance.

All submitted manuscripts should include the following information (preferably in order):

1. Structured presentation of clinical semiology and hypotheses regarding epilepsy syndrome or epileptogenic zone(s); Justification for the investigations chosen to support the diagnostic hypotheses should be included;

2. Presentation of the results and comments on how the data contributed (or not) to the therapeutic strategy;

3. Analysis of anatomo-electro-clinical correlations (if applicable);

4. Decision regarding medical or surgical strategy;

5. Results following surgery (if applicable).

Authors are encouraged to provide comments, critical remarks, and suggestions for discussion, and to include supplementary video material and figures. Provide as supplemental data as many figures as necessary to support your arguments and select the most important to be included in the printed version of your manuscript).

More detailed instructions and a suggested template can be found on the website: www.epilepticdisorders.com