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Anatomo-electro-clinical correlations: the Geneva-Lausanne, Switzerland, Case Report

Successful surgical resection in non-lesional operculo-insular epilepsy without intracranial monitoring

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ABSTRACT – Pre-operative assessment and surgical management of patients with non-lesional extratemporal epilepsy remain challenging due to a lack of precise localisation of the epileptic zone. In most cases, invasive recording with depth or subdural electrodes is required. Here, we describe the case of 6.5-year-old girl who underwent comprehensive non-invasive phase I video-EEG investigation for drug-resistant epilepsy, including electric source and nuclear imaging. Left operculo-insular epilepsy was diagnosed. Post-operatively, she developed aphasia which resolved within one year, corroborating the notion of enhanced language plasticity in children. The patient remained seizure-free for more than three years.

Key words: seizure, insular epilepsy, epilepsy surgery, presurgical assessment

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The surgical treatment of non-lesional extratemporal epilepsy (NLEE) remains challenging, mainly due to difficulties in localising the epileptic focus. The chance of improved outcome following surgery for non-lesional extratemporal lobe epilepsy is 35%, compared to 60% if an abnormality is revealed on MRI (Téllez-Zenteno *et al*., 2010). Thus, in most centres, invasive monitoring is advised. However, even with this procedure, the chance of improved outcome following surgery is, on average, no greater than 50% (Jayakar *et al*., 2008; Wetjen *et al*., 2009).

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Thus, in NLEE, the full use of complementary imaging tools is warranted in order to compensate for negative MRI results.

Our group has been actively investigating the role of electric source imaging (ESI) for presurgical evaluation over the last 10-20 years and in our experience ESI provides good to excellent results in various patient groups, including non-lesional epilepsy (Brodbeck *et al*., 2010; Brodbeck *et al*., 2011). Here, we present a child with non-lesional fronto-temporal lobe epilepsy with frequent daily seizures. ESI obtained from 256 scalp electrodes, nuclear imaging, as well as ictal and interictal EEG recordings with scalp electrodes, suggested a focus within the left insular-opercular cortex. The child received surgery and has since remained seizure-free.

Case report

A 6.5-year-old, right-handed girl suffered from intractable, partial epilepsy since the age of 4.5 years. Clinically, she presented with an undefined, unpleasant feeling, followed by hypersalivation, and left arm elevation and right arm extension (fencing position) or tonic abduction of the arms. Secondary generalisation was frequent. The seizures were almost exclusively nocturnal and exhibited a frequency of up to 20 per day. The patient had been born at term after an unremarkable pregnancy. Early psychomotor development was normal. Her older sister and brother were both healthy and family history was negative for epilepsy. Neurological examination revealed no focal neurological abnormalities. Based on initial neuropsychological evaluation at the age of 6 years and 1 month, the girl was described as shy with limited spontaneous expression, but able to produce short sentences with good phonology and simple syntax and good comprehension. Attention deficit with distractibility and impulsivity, but no major executive dysfunction, was observed. General intelligence was preserved.

Seizure control with various antiepileptic drug combinations, including carbamazepine, valproate, vigabatrin, clonazepam, levetiracetam, and topiramate, was not successful and she was referred for presurgical assessment.

The EEG showed an active left fronto-temporal focus with slow spikes during sleep. During video-EEG monitoring, 15 clinical seizures and more than 20 subclinical seizures were recorded during sleep. During the seizure, she experienced a non-specific aura, and subsequently presented with a tonic elevation of both arms and a fencing position with right arm extension, hypersalivation, and loss of consciousness. During the postictal phase, she could not speak but could understand simple orders. The ictal EEG showed left centro-temporal onset, concordant with the localisation of interictal abnormalities. The ictal ECG tracing revealed significant bradycardia (*i.e*. from 120 to 60 Hz), including brief asystole of 3-4 seconds during three seizures (*figure 1*). Subclinical seizures also showed a left centro-temporal onset. High-resolution 3T MRI did not show any abnormality (*figure 2*). A 256-channel scalp recording identified interictal spikes and sharp waves, which were localised to the left opercular region, after co-registration of the electrical source to the patient's MRI (Spinelli *et al*., 2000; Lantz and Michel, 2004) (*figure 3*).

Interictal F-18 positron-emission tomography (PET) indicated left insular and opercular hypometabolism. In addition, ictal 99mTc-ECD SPECT showed hyperperfusion in the same structures, predominant in the operculum (*figure 4*).

Overall, our work-up strongly indicated left operculo-insular epilepsy with secondary recruitment of the insular region, possibly due to focal cortical dysplasia that was not visible on MRI. Pharmaco-resistance was well documented, thus the indication for surgical treatment remained a consideration.

Although there was no visible lesion and the focus was close to Broca's area, we proceeded directly to surgical resection (with peri-operative corticography) for several reasons:

(1) the implantation of depth and/or subdural electrodes in this area is associated with a significant operative risk in itself;

(2) it was felt that the benefit of intracranial recording was relatively small, due to a significant likelihood of incomplete coverage of the area, *i.e*. despite the operative risk, an uncertainty concerning the true size of the epileptogenic zone remained;

(3) the child suffered from post-operative aphasia, *i.e*. language cortex was most likely in or nearby the epileptogenic zone. However, language mapping would have been difficult since the child spoke only rudimentary French (maternal language was Albanese). We also felt that at least partial language recovery could be expected at that age.

Operative procedure

The surgical procedure was performed under general anaesthesia. Neuro-navigation was used to determine optimal craniotomy in order to expose the cortical regions of interest. At exposure, the appearance of brain tissue was normal on inspection whereas an abnormal consistency was mostly found in the frontal operculum and superior portion of the insula. The resection of frontal and temporal operculum allowed us to demarcate the insula and the extent of the antero-posterior region. A disconnection of the insular cortex

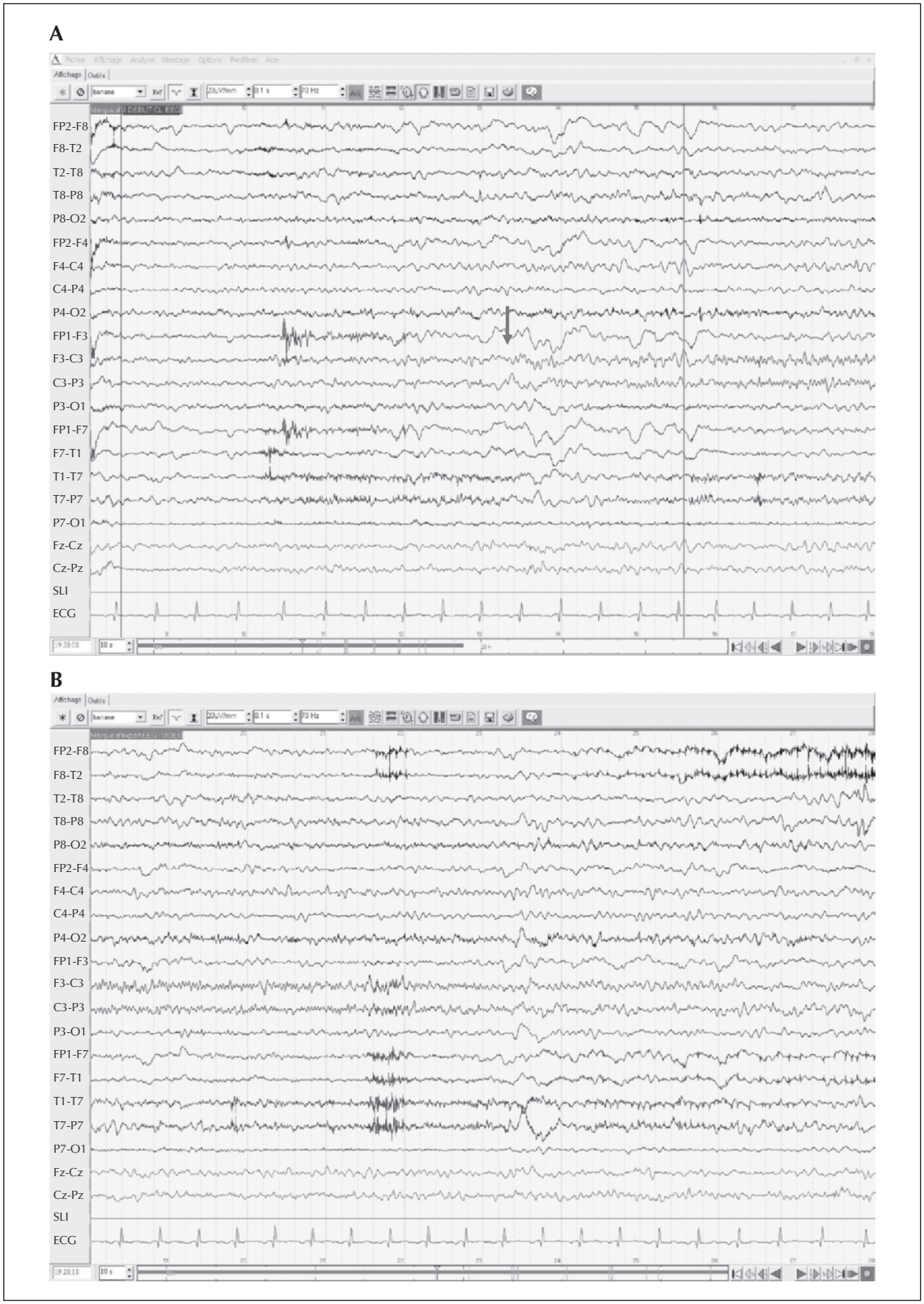
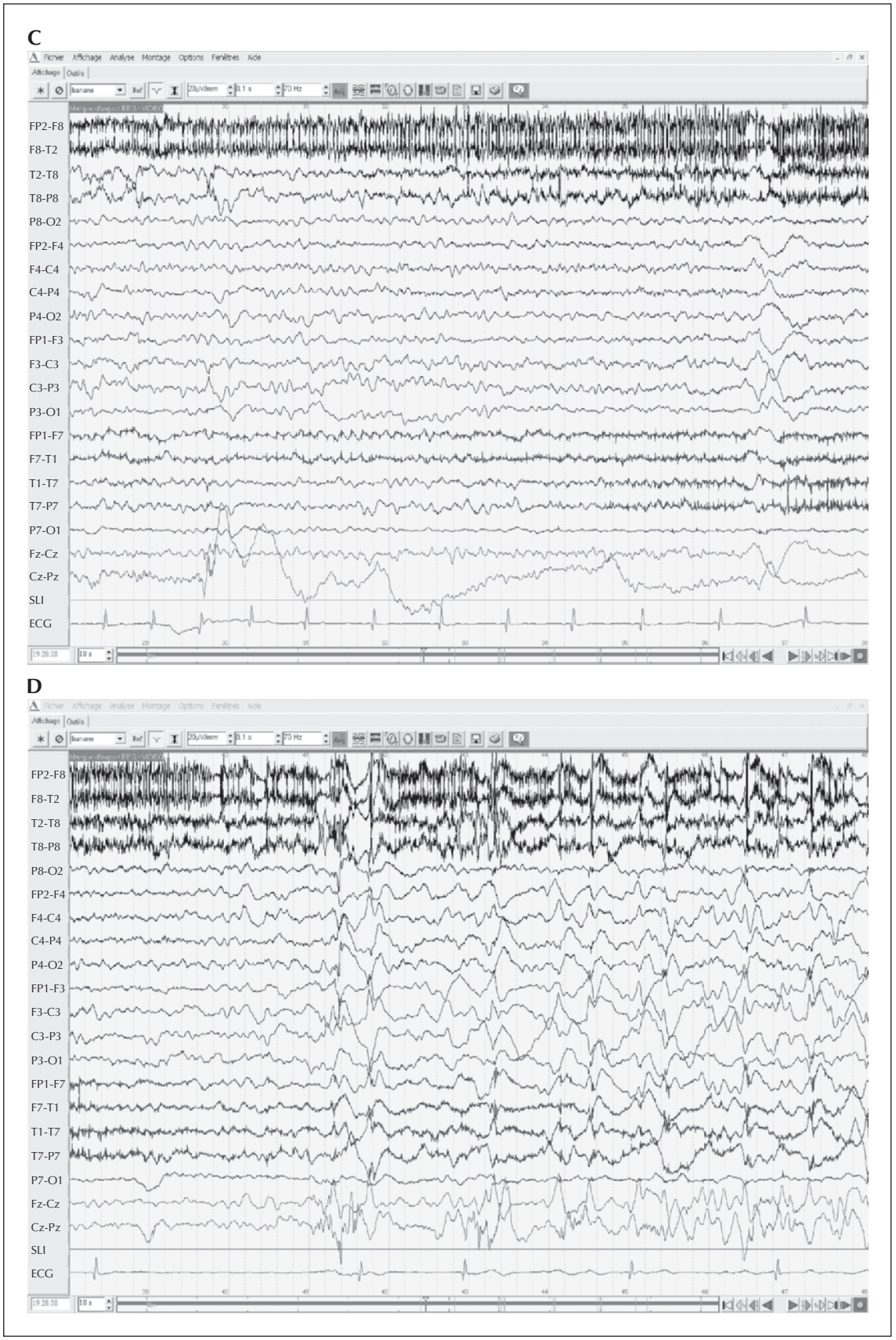


Figure 1. (A-G) Ictal EEG showing a 20-25-Hz rhythm preceding clinical onset, maximum in the left central electrode (C3; →), and progressing with irregular slowing-down in the left fronto-central region and a semirhythmic spike/polyspike-wave pattern. (A-E) Bipolar montage; (F and G) ictal onset in monopolar montage.



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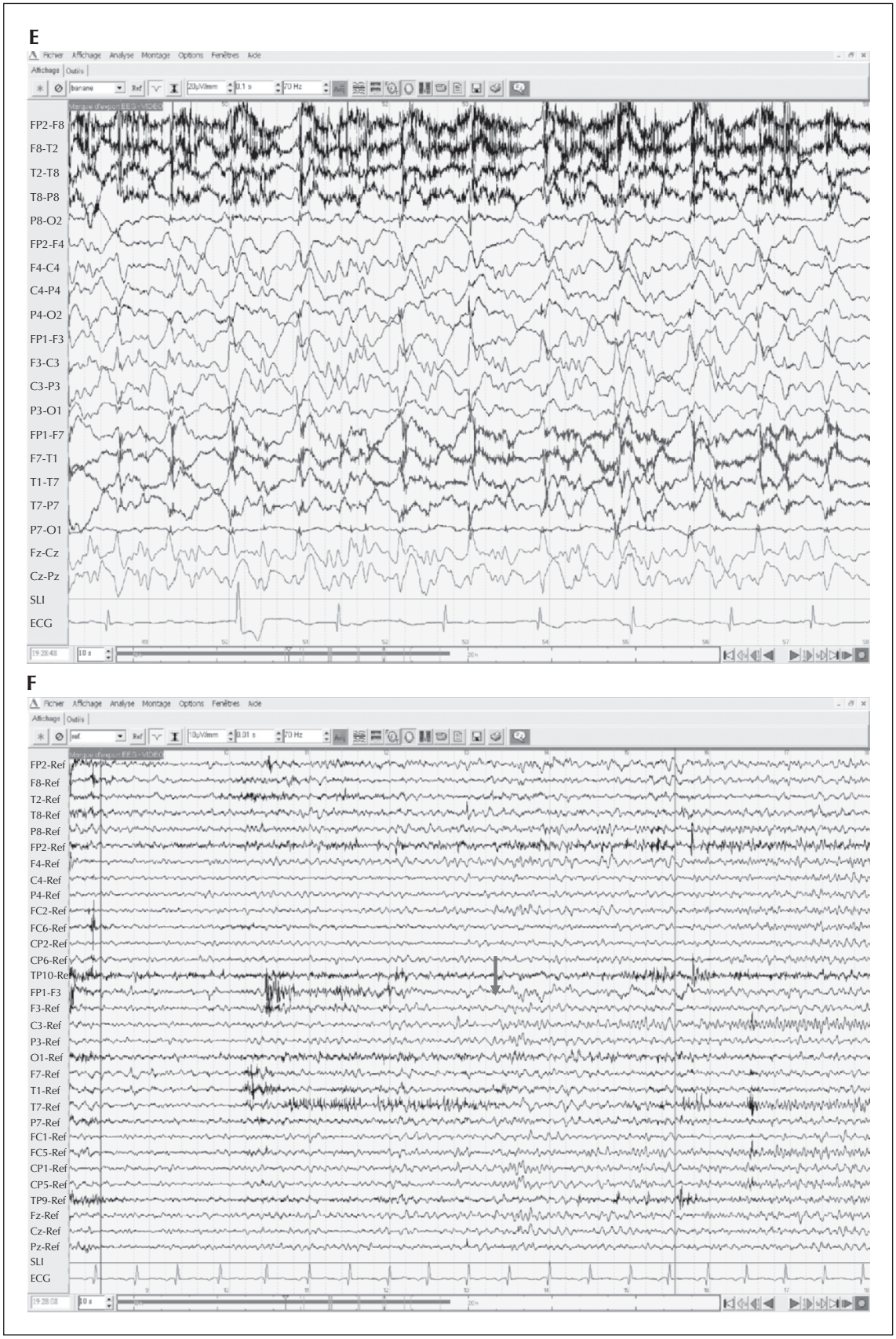

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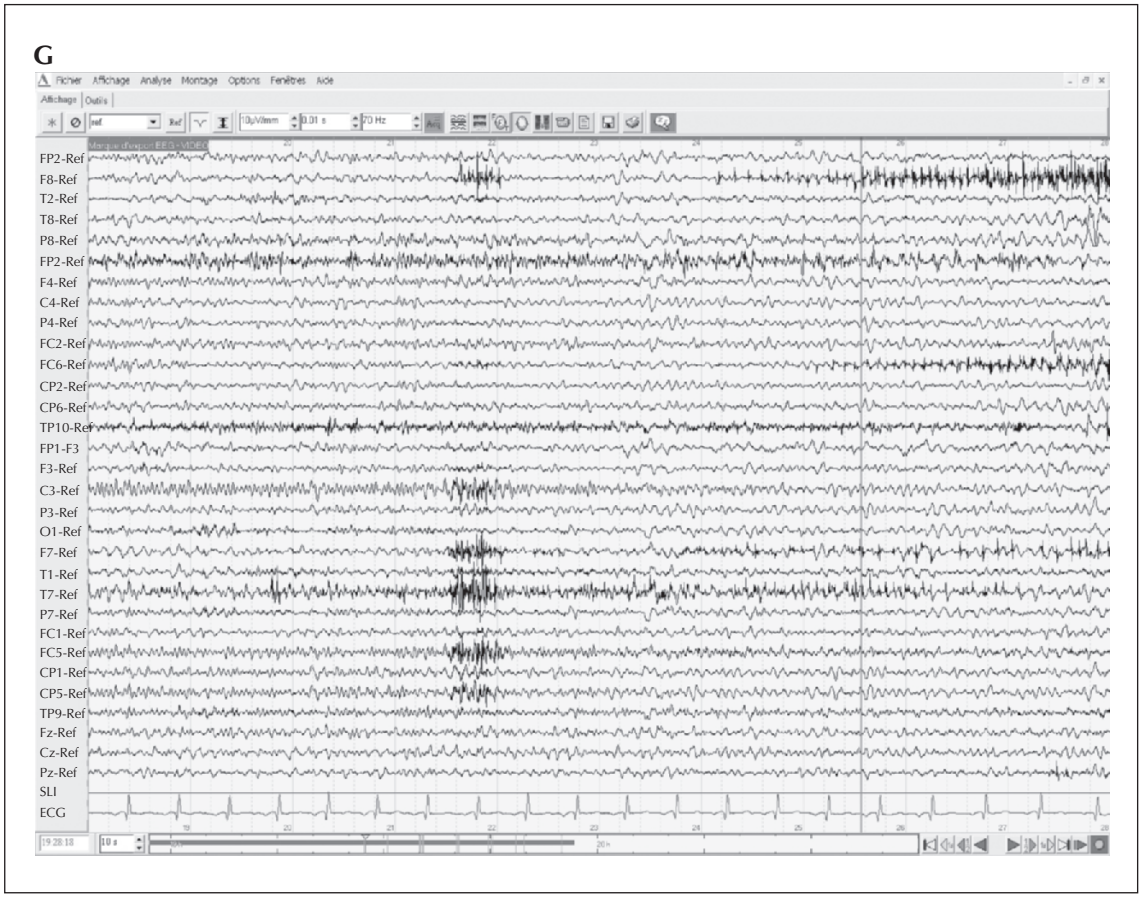

Figure 1. (*Continued*)

was then performed by aspiration of the subcortical white matter, tangentially to the insular surface from the depth of the inferior and superior semi-circular sulci.

Histopathological analysis showed the presence of ectopic neurons and gliosis in the white matter of the left frontal operculum, as well as white matter gliosis in the insula.

Outcome

The child was closely followed since her operation three years ago. She was seizure-free until her last visit. Her parents did not observe any episodes of loss of consciousness, involuntary movements, or nocturnal events.

Initially, after the neurosurgery, she presented with Broca's aphasia and right brachio-facial paresis with facial asymmetry. She was able to pronounce only a few monosyllabic or bisyllabic words and demonstrated major difficulties in lexical access and phonological errors. However, verbal comprehension was preserved. Six months post-operatively, her right face and arm paresis disappeared completely. After one year post-operation, she spoke fluently and was intelligible with residual phonological, lexical, and syntactic difficulties. She also showed deficits in writing and mathematics. Her verbal IQ was 81 and performance IQ was 102 (WISC IV). Overall, her level of speech returned to the level before the operation with unchanged comprehension.

Discussion

We report the case of a 6.5-year-old girl who underwent surgical treatment for drug-resistant left operculo-insular epilepsy, making use of the full range of non-invasive imaging techniques. The child was seizure-free at two years of follow-up. After surgery, she developed Broca's aphasia which resolved within 6-12 months.

Outcomes following extratemporal resection vary widely across the literature (Janszky *et al*., 2000; Roper, 2009). Patients with refractory extratemporal epilepsy

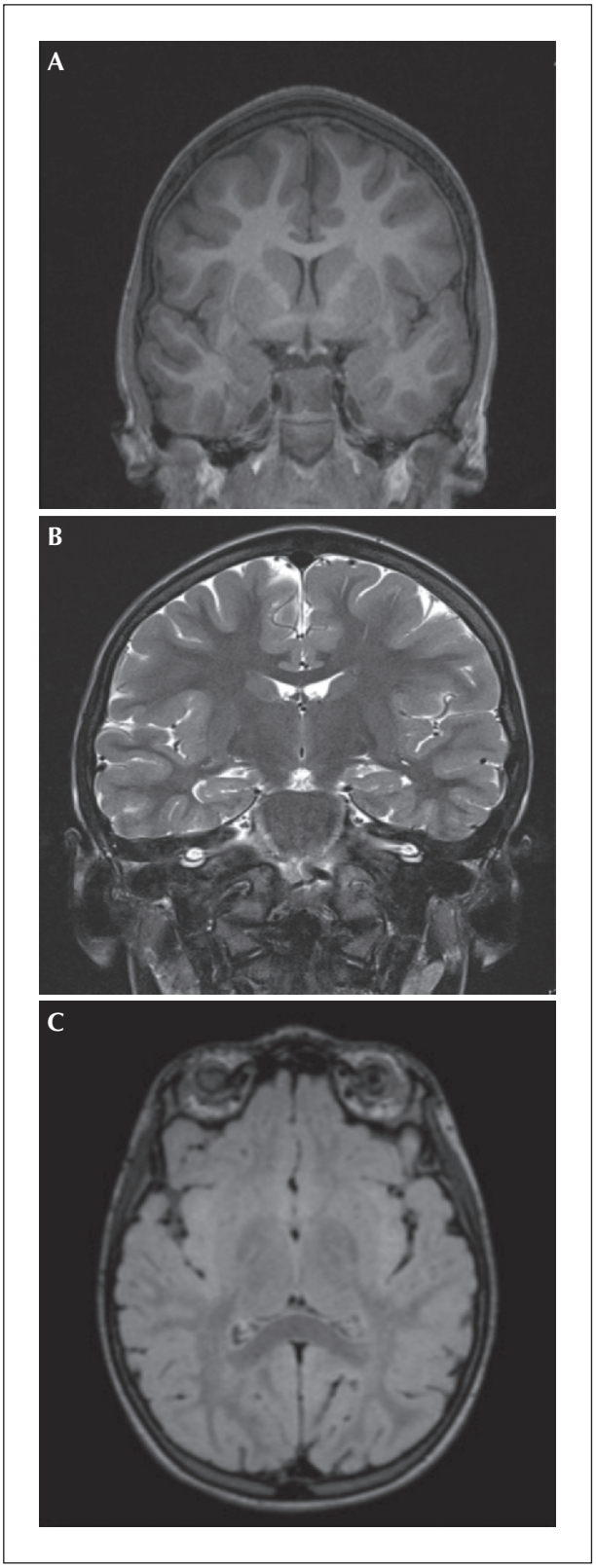

Figure 2. Pre-operative MRI. (A) T1 sequence; (B) T2 sequence, (C) axial FLAIR of the same examination.
The right side of the brain corresponds to the left side of the figure.

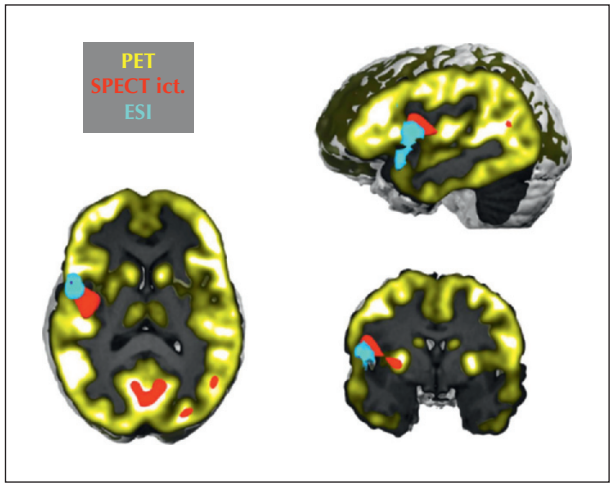

Figure 3. The maxima of the PET, SPECT, and electric source imaging (ESI) findings co-registered.
PET hypometabolism is not visible because it is relatively circumscribed and covered by the positive findings of the ESI and ictal SPECT.
The left side of the brain corresponds to the left side of the figure.

and structural lesions on MRI have the best chance of seizure freedom (Carrette *et al.*, 2010; Téllez-Zenteno *et al.*, 2010); between 60 and 70% are reported to have Engel class I outcome. Patients with non-lesional extratemporal epilepsy represent a particular difficult-to-treat patient group; on average, only 33-50% become seizure-free (Jayakar *et al.*, 2008; Wetjen *et al.*, 2009; Ansari *et al.*, 2010; Téllez-Zenteno *et al.*, 2010). Thus, additional tools for focus localisation are crucial in order to increase the yield of surgical therapy in these patients. PET and (ictal) SPECT are now well established tools and have been found to be useful for both non-lesional and lesional cases. Co-registration may increase the yield, in particular when based on the patient's individual MRI (Knowlton, 2006; Kurian *et al.*, 2007). FDG-PET remains an important clinical tool for patients with non-lesional, neocortical epilepsy in order to correctly localise the epileptogenic lobe. An overall diagnostic sensitivity of 44% for FDG-PET in patients with different forms of refractory partial epilepsy and normal MRI findings was reported, in contrast to 68% in lesional extratemporal lobe epilepsy (Kim *et al.*, 2009; Lee *et al.*, 2005).

Ictal SPECT is another useful tool with reported sensitivity and specificity of 73% and 75%, respectively (temporal and extratemporal epilepsy cases combined; Spanaki *et al.*, 1999). In patients with intractable extratemporal lobe epilepsy, a localised abnormality in around two thirds is reported, in particular, when analysed with subtraction analysis (Won *et al.*, 1999; O'Brien *et al.*, 2000). To the best of our knowledge, there are no reports of SPECT studies specifically of patients with NLEE, however, most authors agree that

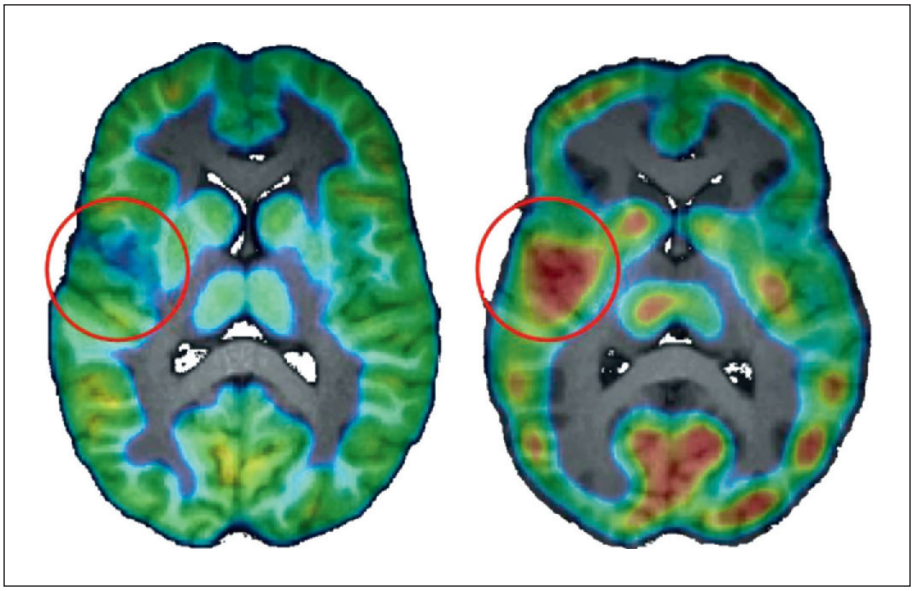

Figure 4. Left: co-registered PET demonstrating hypometabolism in the left operculo-insular region (red circle). Right: ictal SPECT showing focal hyperfusion in the same region.
The left side of the brain corresponds to the left side of the figure.

the yield is less evident in extratemporal, rather than temporal lobe epilepsy (Rathore *et al*., 2011).

ESI has become another technique with excellent sensitivity for the localisation of the epileptic focus. It is particularly useful in paediatric patients, given that sedation is not required. ESI has been shown to provide important information for focus localisation in the presurgical workup (Boon *et al*., 2002; Bast *et al*., 2006) with a sensitivity of 75% in extratemporal lobe epilepsy (Michel *et al*., 2004; Brodbeck *et al*., 2011). Even in non-lesional epilepsy, ESI has demonstrated excellent accuracy (Brodbeck *et al*., 2010). ESI was also analysed in our patient and a distinct region in the left operculo-insular area was identified by co-registration of the patient's MRI, PET, and ictal SPECT. Concordance between two or more imaging techniques was shown to be related to a greater chance of post-operative seizure freedom (Kurian *et al*., 2007). Thus, in our case, in which we found a high concordance between three imaging techniques, we felt there was no indication to proceed to phase II evaluation, for focus localisation.

Intracranial EEG may also be indicated in order to determine the extent of the epileptogenic zone, and/or presence of vital nearby cortex which is difficult to ascertain by non-invasive examination alone. However, even with subdural and/or depth electrodes, surgical Engel class I outcome in patients with extratemporal dysplasia is only reported in 30-50% patients (Wyllie *et al*., 1994; Elsharkawy *et al*., 2008; Wetjen *et al*., 2009), probably due to incomplete focus coverage. Peri-operative EEG monitoring is an alternative option, used by ourselves, but may be difficult to carry out if there are major time constraints. Motor and sensory cortex may be determined by intra-operative evoked potentials or electrical stimulation, but requires an experienced team of neurosurgeons and neurophysiologists.

Dobesberger *et al*. (2008) reported a patient suffering with non-lesional insular epilepsy who became seizure-free after a limited resection of the anterior part of the right insula and right frontal operculum. A few other case reports have provided evidence for the benefit of operculo-insular resection in cases of lesional epilepsy (Roper *et al*., 1993; Malak *et al*., 2009). Epilepsy surgery of the insula in the language-dominant hemisphere carries important risks of language deficits. However, children have an enhanced capacity for language plasticity, compared to adults, as demonstrated by their capacity to recover from brain injuries or radical surgery, such as hemispherectomy for epilepsy (Johnston, 2004; Roulet-Perez *et al*., 2010). Basic mechanisms that support plasticity during development include persistence of neurogenesis in some parts of the brain, elimination of neurons through apoptosis or programmed cell death, postnatal proliferation and pruning of synapses, and activity-dependent refinement of ipsilateral and contralateral neuronal connections. The transfer of language to the right hemisphere was identified following early injury in young children, *i.e*. before the age of 5 to 9 years (Duchowny *et al*., 1996). A functional MRI study illustrated language plasticity after left hemispherotomy at the age of 9 years for Rasmussen's syndrome of the left hemisphere, due to the ability

of the right hemisphere to take over some expressive language functions (Hertz-Pannier *et al*., 2002). These observations demonstrate the capacity of the brain to reorganise itself after removal of language-related cortex. Moreover, we were previously unable to reliably map language cortex in a patient with posterior temporal dysplasia by electrocorticography (Seeck *et al*., 2006). Thus, we felt that, in this particular case, resection without previous intracranial EEG could be envisaged, given the possible difficulties in covering the entire epileptogenic zone and the lack of a need to determine language cortex. Post-operative evolution demonstrated that language plasticity occurred reliably and that the level of speech in our patient at six months post-surgery was the same as that before surgery.

Conclusion

Here, we present a case of left operculo-insular non-lesional epilepsy, in which the patient received surgery without phase II assessment, but with ESI imaging and nuclear imaging data, with excellent neurological and cognitive outcome after two years. Extratemporal epilepsy surgery is particularly challenging, in terms of post-operative seizure control, especially in cases of non-lesional epilepsy. By using non-invasive imaging techniques, including also ESI, invasive EEG monitoring may be avoided in selected cases. However, this requires careful evaluation and co-registration of all imaging techniques, as well as the presence of a clearly defined, unifocal result. Phase II evaluation with chronic intracranial electrodes may be reserved for cases in which the determination of the extent of the epileptogenic zone or the presence of close vital cortex is not otherwise possible. □

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Disclosures.
None of the authors has any conflict of interests to declare. Margitta Seeck received speaker's fees for EISAI, UCB, EGI, GSK.

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