

**Anatomo-electro-clinical correlations:
the Great Ormond Street Hospital,
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Early-onset symptomatic focal epilepsy: a dilemma in the timing of surgery

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ABSTRACT – [Case records of *Epileptic Disorders*. Anatomo-electro-clinical correlations. Case 05-2008] We report the case of a six-year-old boy who presented in infancy with infantile spasms and left focal seizures. An MR scan at two months was suggestive of a right parietal cortical dysplasia, although this was less apparent on repeat scan at 11 months. The initial response to anti-epileptic medications was good; surgery was therefore deferred at that time. Subsequently, seizure control fluctuated and developmental progress was, on the whole, good. However, ultimately seizures increased despite changing the AED, and he began showing developmental problems. Surgery was reconsidered. Again, a repeat MR scan did not define the lesion well. Following full further evaluation, including functional imaging that still implicated the right parietal cortex, subdural grid and depth electrode monitoring were undertaken at 6.5 years, which located the ictal onset zone deep within the lesion. This enabled a right inferior parietal lobe resection to be performed. Four years post-surgery he remains seizure-free and has shown progress in development.

Key words: seizures, focal cortical dysplasia, telemetry, child, epilepsy surgery

Focal cortical dysplasia (FCD) in children may present with early-onset seizures often refractory to medical treatment, or even as catastrophic epilepsies associated with development plateauing or regression. Early recognition of these lesions is essential as surgery can confer significant benefits (Lortie *et al.* 2002). The ultimate goal of the presurgical evaluation of epilepsy surgery patients consists of identifying the epileptogenic zone *i.e.* the area of the

cortex which is thought to initiate seizures, and whose removal (or disconnection) is essential for complete cessation of seizures with no or minimal detriment to function. Diagnostic protocols rely on clinical semiology, optimized MRI sequences, video-telemetry, functional neuroimaging, neuropsychology and neuropsychiatry assessments and, at times, invasive EEG monitoring. In adults, 25% of pathologically confirmed cases of focal cortical dysplasia are reported to be MRI-negative prior to surgery (Widdess-Walsh *et al.* 2006). These lesions are often poorly defined even with invasive EEG monitoring and subsequent excision has been found to be associated with less favourable outcome compared to MRI-positive cases (Cossu *et al.* 2008, Siegel *et al.* 2001). It has been suggested that MR studies performed early in life might pick up these lesions, which become less apparent with maturity (Eltze *et al.* 2005, Duprez *et al.* 1998). Occasionally, the appearances of FCD in later scans may be very

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subtle, escaping recognition and thus delaying the benefits of early surgical treatment. We report the case of a child who presented with early-onset focal epilepsy, whose lesion was more readily apparent at presentation but in whom medical treatment was of some benefit. A surgical decision was consequently delayed. However, continuing seizures and developmental compromise led to further evaluation resulting in focal resection.

Case report

The case was a term child, born of non-consanguineous union, with an uneventful neonatal period. He presented at four months following onset of seizures at eight weeks of age. There was no family history of epilepsy or neurological disorder. Presentation was with left-sided, tonic seizures and asymmetrical infantile spasms. The parents had noticed that his left leg and arm became rigid and flexed and that his head would deviate to the right. Towards the end of the episode, he would experience three to four repetitive startles. These seizures occurred every hour and would last for one to two minutes. EEG performed at that time showed epileptiform activity, with a right-sided emphasis. An MRI scan revealed changes suggestive of a right inferior parietal lobule cortical dysplasia with ill-defined margins (*figure 1A*). He was started on vigabatrin (80 mg/kg/day) and became seizure-free.

Seizures recurred however at 20 months of life. At this time, he was on vigabatrin monotherapy. These were predominantly left focal seizures involving twitching of the left side of the face with staring, followed by secondary generalization lasting a few seconds. They occurred infrequently, once a month, more commonly from sleep. His overall development and neurological examination were normal. Video telemetry performed at 27 and 36 months of age revealed seizure-onset from the right central region, with more widespread interictal discharges. A further MRI scan at 11 months however, had been less convincing of an abnormality, and was initially reported as "normal". A discussion at a multidisciplinary epilepsy surgery meeting resulted in a decision to continue to pursue medical options. Epilepsy surgery was to be considered if no progress was made and developmental problems became evident.

At five years of age, the child continued to have seizures that were infrequent but incapacitating, as the tonic spasms and subsequent falls would cause injury. The seizure episodes increased gradually and by six years of age, he had multiple seizure types consisting of vacant stares, tonic spasms, atonic falls and presumed secondarily generalized tonic-clonic seizures. They occurred both from the awake and sleep states. Many medications were tried with variable but sub-optimal response (clobazam, carbamazepine, phenobarbitone, pyridoxine, lamotrigine, valproate, topiramate and levetiracetam).

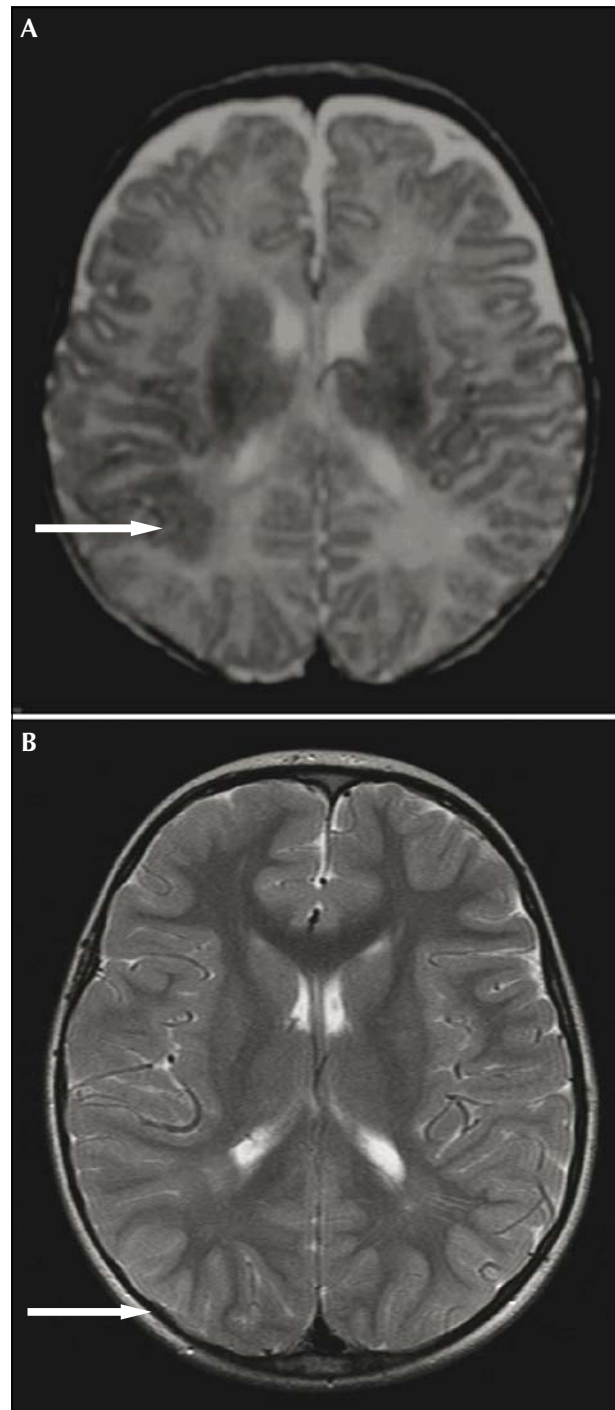


Figure 1. **A)** MRI axial T2-weighted, fast spin echo (FSE) image (0.5T) at 10 weeks showing a focal region of irregular cortical thickening, with some subcortical white matter hypointensity in the right inferior parietal lobule. **B)** MRI at five years Axial T2-weighted FSE images (1.5T) now showing only subtle grey-white matter blurring, with minimal and relative subcortical white matter hyperintensity in the right inferior parietal lobule.

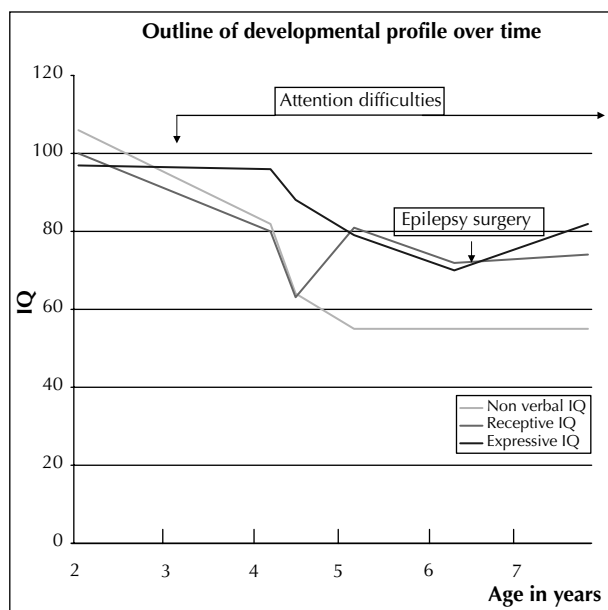


Figure 2. Outline of developmental profile over time.

Early developmental milestones had been normal and his developmental assessment at three years showed that he had age-appropriate, non-verbal reasoning skills, although his fine motor skills were less developed. He exhibited age-appropriate expressive language, although his comprehension was delayed by a few months. He was reported to be impulsive and somewhat clumsy, but there were no concerns about his social skills. However, as the seizures increased, he started to regress in both his language skills and his non-verbal learning ability (figure 2). At six years of age, he was attending a mainstream school but had a Statement of Special Educational Needs. This gave him full-time, one-to-one support. He had made some progress with his language, but was functioning approximately two years behind his chronological age in this domain. His non-verbal performance IQ remained well below average (PIQ 55). His skills ranged from below three years of age to four years. He presented with a patchy profile, with greater skills in verbal reasoning and learned general knowledge, but showing particular difficulty with visual spatial processing and discrimination. With worsening seizures, developmental regression and early MRI suggestive of a right side cortical dysplasia, he was evaluated again for epilepsy surgery. Subsequent MRIs showed only subtle evidence of the cortical dysplasia, which would have been missed without the previous scan to compare (figure 1B). Video-telemetry was very similar to the previous study, implicating the right centro-parietal region, but not clearly localizing the ictal-onset zone. Interictal discharges were maximal over the right central and parietal region, but the ictal-onset was rather diffuse (figure 3). Ictal SPECT showed increased uptake in

the right, mid-temporal parietal region when compared to the interictal SPECT.

Neuropsychiatry assessment revealed no concerns, but neurodevelopmental assessment showed lack of progress and continued difficulties with attention and staying on task (figure 2). After a multidisciplinary discussion, it was agreed that surgery was indicated but would require invasive EEG monitoring including subdural grid and depth electrode insertion into the lesion to define the limits of the epileptic zone and its relationship to sensori-motor cortex. Under MR guidance, a 48-contact subdural grid was implanted over the right parietal/occipital region (figure 4), along with two, 6-contact subdural strips over the right central and right temporal region, and a depth electrode passing through the centre of the lesion. Several seizures were recorded that were all clinically and electrographically stereotyped. Ictal EEG-onset consisted of a run of fast activity from contact three of the depth electrode associated with arousal or behavioural change (figure 4). This was followed by diffuse desynchronisation and more widespread rhythmic activity seen over other contacts of the depth electrode, both strips and the grid. Functional stimulation of motor and sensory function, intracranial SSEP, VEP and tone ARP revealed no evidence of eloquent cortex in relation to the lesion. As invasive monitoring located the ictal-onset zone to deep within the lesion and the right inferior parietal lobule (figure 4), a lesionectomy was subsequently performed. The histopathology of the lesion confirmed a Taylor-type cortical dysplasia with balloon cells (Type IIb).

At 15 months post-surgery, neurodevelopmental assessment showed a markedly uneven cognitive profile. He achieved an improved score on language-specific testing, standard score 77, and a VIQ of 85 on the verbal comprehension tasks of the cognitive assessment. However, he scored a PIQ of 55 on the non-verbal tasks. The latter showed that he had not made any significant improvement in this domain, despite making observable progress at school (figure 2). This also reflects the continuing difficulties with visual problem solving, speed of processing and motor planning skills, including handwriting, which impact on his attention and ability to access the curriculum. To date, four years post-surgery, the child has had no seizures. Parents report improvement in his learning and alertness, and he is achieving in mainstream education albeit with a high level of support. He has been weaned off lamotrigine and is currently on levetiracetam monotherapy.

Discussion

The case reported here has illustrated some of the difficulties when making surgical decisions for the treatment of epilepsy in the very young. The primary aim of surgery is seizure-freedom; secondary aims may include withdrawal from medication and improved developmental progress,

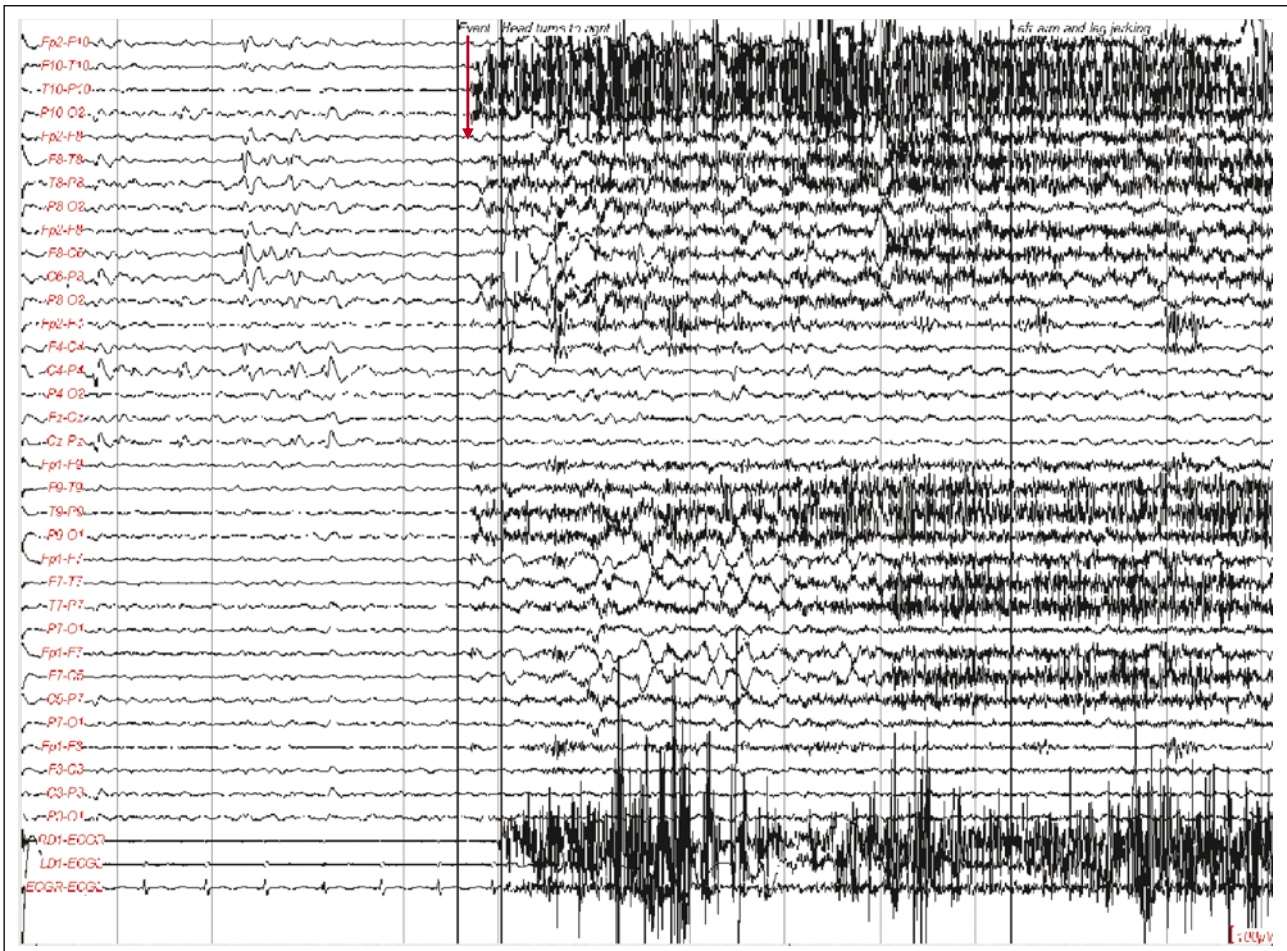


Figure 3. Telemetry at the age of five years showing diffuse ictal-onset (arrow). Note that there is an increase in right-sided discharges before the seizure.

but neither may be guaranteed. Although this case presented early with focal-onset seizures and infantile spasms, initial control with medication was achieved with apparently normal developmental progress. It was only subsequently that seizures became increasingly troublesome, and development compromised at a time when the presence of a lesion, as detected by imaging, was less convincing.

Focal cortical dysplasia is a common cause of pharmacoresistant epilepsy that may be amenable to surgical resection. In a recent multicentre survey of procedures performed for the treatment of epilepsy in children, conducted by the Pediatric Epilepsy Surgery Sub-commission of the International League against Epilepsy, malformations of cortical development were confirmed as the most common indication for surgical resections (Harvey *et al.* 2008). High-resolution MR techniques enable identification of subtle and highly localized FCD that may not be revealed by conventional MR procedures. However, studies have shown that 25% of patients with histologically

proven FCD may have normal MRI scans (Widdess-Walsh *et al.* 2006). FCD is due to abnormalities in neuronal migration, proliferation and/or differentiation that result in four different histological subtypes: cortical architectural abnormalities have been termed IA; architectural abnormalities with giant cells, but no dysmorphic neurons or balloon cells are termed IB; the presence of dysmorphic neurons defines IIA; and the presence of balloon cells classifies the pathology as IIB (Palmini *et al.* 2004).

The established criteria for Taylor FCD on MR images consists of focal cortical thickening, poorly defined transition between grey and white matter, and hyperintensity of the subcortical white matter on T2-weighted images with decreasing signal intensity on T1-weighted images (Colombo *et al.* 2003, Yagishita *et al.* 1997). These criteria are based on MRI appearance of mature brain following complete myelination. There have not been many descriptions based upon MRI images of FCD, during the early stages of myelination.

This case revealed distinct MR signal abnormalities in infancy prior to full myelination at the time of presentation with seizures. On subsequent studies performed, the MR images failed to recognize any distinct abnormality. However, comparison of signal appearances with previous images showed some subtle abnormalities. The technical difference between the scans performed could not account for the contrasting change seen in the two images. Very few cases of such “disappearing lesions” on MRI, with histologically proven cortical dysplasia, have been reported in literature (Eltze *et al.* 2005, Duprez *et al.* 1998). These chronological changes were explained by maturation of myelination, during which the white matter signal on T2WI changes from hyperintense to hypointense and *vice versa* on T1WI; these MRI changes are largely complete by the age of 2 years in normal subjects (Barkovich *et al.* 2000). The cortical and subcortical signal appearance associated with FCD can be modified as myelination advances; that the first reported cases with appearance and disappearance of FCD on MRI were performed under the age of two years supports this explanation.

The role of invasive monitoring and a complete, multidisciplinary diagnostic protocol is indispensable in the presurgical evaluation of these patients. The use of subdural EEG monitoring for patients undergoing epilepsy surgery for FCD has previously been associated with poor surgical outcome (Widdess-Walsh *et al.* 2005). However, the recent study by the same author (Widdess-Walsh *et al.* 2007) has contradicted these earlier reports and has emphasized the use of intracranial EEG recordings over MRI for demonstrating the source of the epileptiform discharges in these patients. It was found that the epileptic zone in FCD might be within an MRI lesion, adjacent to an MRI lesion or within the dysplastic tissue below the resolution of conventional MRI. Therefore, intracranial EEG is more sensitive for defining the full extent of the FCD compared with routine MRI. The ability of the subdural electrodes to map accurately eloquent cortex and allow for maximum resection of potentially epileptogenic tissue, improved the surgical outcome. The results of this study, as in our case, showed that when a combination of non-invasive EEG recording and imaging techniques failed to identify the epileptogenic zone, the use of an invasive, direct cortical recording

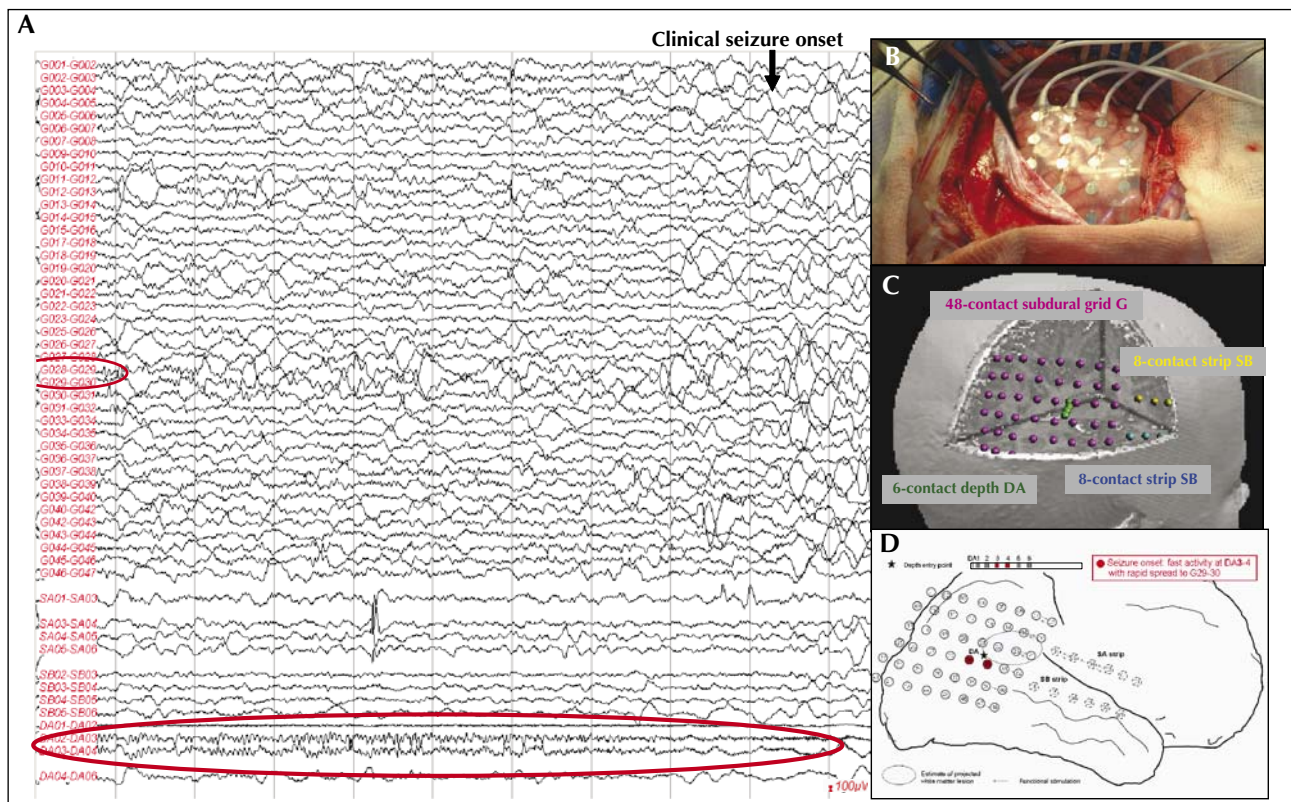


Figure 4. Invasive monitoring at the age of six years. **A)** Intracranial EEG showing seizure-onset. The first electrographic change is a run of fast activity from contacts DA3-4 of the depth electrode (encircled) with spread to contacts G29-30, leading into a more widespread slowing at the time of the first clinical change (arrow). **B)** Intraoperative placement of subdural grid. **C)** 3D reconstruction of subdural and depth electrodes. **D)** Map of subdural and depth electrodes with ictal-onset zone in red.

technique with subdural electrodes, can identify patients most likely to become seizure-free.

The question about optimal timing of surgery remains unanswered. In infants presenting or evolving into infantile spasms such as our case, medical treatment may be effective, but the likelihood of relapse is high (Lortie *et al.* 2002). Concern remains about the possible consequences of ongoing seizures on neurodevelopmental progress. The presumption in children with early-onset epilepsy is that slowing of development is the result, in part, of ongoing epileptic activity, so called "epileptic encephalopathy". Early consideration of surgery is therefore advocated to alleviate seizures and optimise the potential for cognitive development. Determining an evidence base for this however, has been more difficult. Children undergoing surgery for infantile spasms have been shown to make better developmental progress than has been documented through medical studies (Asarnow *et al.* 1997). Further, the degree of progress made postoperatively is associated with the duration of spasms before surgery; that is the shorter duration the greater progress (Jonas *et al.* 2005). In the case reported here, careful observation of developmental progress was undertaken. This was initially good and contributed to the decision to pursue medical treatment, but now, four years post-surgery there are some cognitive deficits. Early surgery could presumably have prevented some of the lasting effects of prolonged seizures on development, as seizure remission has since led to useful progress.

This case has illustrated the problems of timing of surgery in children with early-onset focal epilepsy, as well as the difficulties in defining the lesion with later imaging. A multimodal investigation led ultimately to optimal, surgical management of the case. □

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