

**Anatomo-electro-clinical correlations:  
the Melbourne, Australia Case Report  
Case 06-2008**

# Multifocal epilepsy: the role of palliative resection - intractable frontal and occipital lobe epilepsy secondary to radiotherapy for acute lymphoblastic leukaemia

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**ABSTRACT – [Case records of *Epileptic Disorders*. Anatomo-electro-clinical correlations. Case 06-2008]** Patients with multifocal epilepsy are often considered unsuitable for epilepsy surgery. We report an adolescent with intractable frontal and occipital lobe seizures, secondary to complications of treatment for acute lymphoblastic leukaemia as a young child. Chemotherapy and radiotherapy were complicated by bilateral, posterior leukoencephalopathy and later an acquired frontal cerebral cavernous malformation (CCM). Detailed electro-clinical and imaging studies showed multiple, frontal lobe seizures per day with less frequent and non-debilitating, simple, occipital lobe seizures. Focal resection of the frontal CCM abolished the socially-disabling seizures with resultant marked improvement in the patient's quality of life at 12 months. Careful analysis of the type and impact of focal seizures in the setting of multifocal epilepsy may demonstrate that one seizure type is more deleterious to quality of life and may be amenable to surgery. In this situation, the patient may benefit significantly from surgery to resect the more active epileptic focus. [*Published with video sequences*]

**Key words:** cerebral cavernous malformation, acute lymphoblastic leukaemia, refractory seizures, multifocal epilepsy, epilepsy surgery

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Patients with refractory multifocal epilepsy are not usually considered as surgical candidates. Detailed evaluation may show that specific seizures have a greater impact on the quality of life than others. In such cases, targeted surgery may hold benefits for the patient even when full control of seizures is not anticipated. An example of such an approach is corpus callosotomy to treat disabling drop attacks in an individual with symptomatic, generalised epilepsy with multiple seizure types.

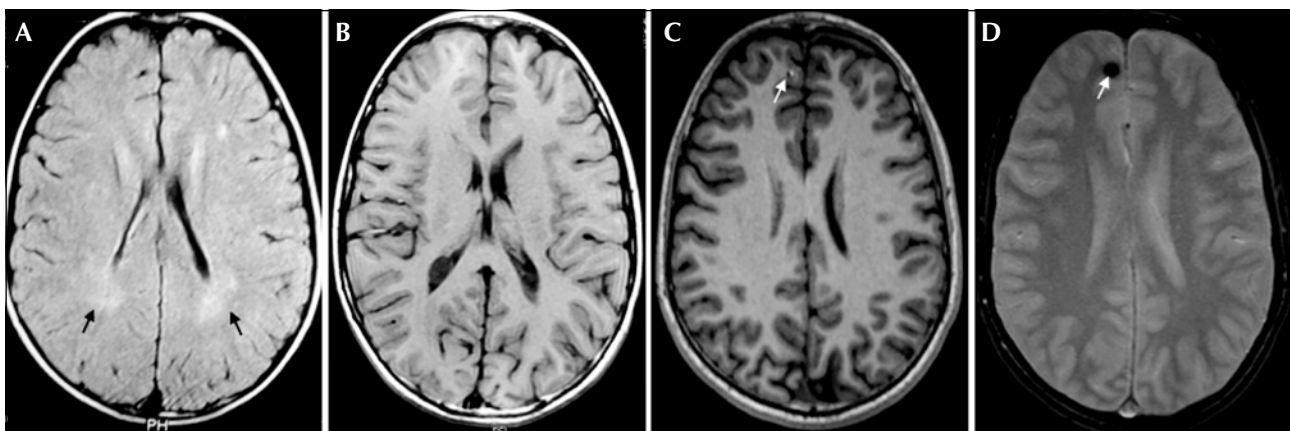
Here, we describe a patient with multifocal epilepsy comprising discrete occipital and frontal lobe seizures. The recent development of frontal lobe seizures had markedly affected the patient's functioning. The frontal lobe seizures were due to a CCM that developed following irradiation for acute lymphoblastic leukaemia (ALL). The patient also had occipital lobe seizures associated with MRI abnormalities thought to be delayed sequelae of chemotherapy or radiotherapy. Surgery for the CCM produced marked improvement in the patient's quality of life, although it was expected that he would not be rendered seizure-free due to the ongoing occipital seizures.

## Case report

An 18-year-old, right-handed boy, presented with an antalgic gait, thigh pain, malaise and refusal to walk at 18 months of age following an illness with coryza and mild fever. He had had a normal birth and unremarkable developmental history. He was diagnosed with ALL of the L1 type (Bennett *et al.* 1976), with 88% blasts at 20 months. Tumour markers showed a pre- $\beta$  lineage, and the bone marrow karyotype showed one normal cell line and another abnormal cell line containing a chromosome 1/19 translocation, known to be associated with pre- $\beta$  ALL (Carroll *et al.* 1984). His white cell count was 28,000/cmm, with haemoglobin of 9.7 gm% with normal

platelets. He received cranial irradiation at a dose of 18 Gray in 15 fractions over eight months. His chemotherapy regimen included an induction phase with vincristine, cytosine arabinoside, followed by maintenance treatment with E-asparaginase, oral and intrathecal methotrexate, 6-mercaptopurine, cyclophosphamide, cytosine arabinoside, and prednisolone over two years. His leukocyte count and bone marrow normalized by four years. He had normal developmental milestones. Fine motor concerns with writing became apparent when he started school at age six years. An MRI brain scan showed increased signal involving the white matter bilaterally, both in the periventricular regions and peripherally with confluent, increased signal within the occipital lobes and was consistent with leukoencephalopathy due to radiotherapy and chemotherapy. Brain CT did not show calcification.

His epilepsy began at eight years with visual auras characterised by flashing or flickering images moving across his vision such as images of clouds (seizure type 1). He reported macropsia, for example "a tap appearing large or distorted". He had a feeling of falling forward as though his head was forced forward, or his head and eyes would deviate to either side with loss of awareness for 30-60 seconds. Postictally, he vomited and was confused for a few minutes. Seizures typically occurred daily on becoming drowsy or awakening. Triggers included changes in lighting, splashing in the shower or swimming. No photosensitivity was noted on EEG; however, discharges appeared on eye closure. At the age of 10 years, brain MRI showed bilateral, periventricular white matter hyper-intensities in the parieto-occipital regions (*figure 1A*). He was refractory to the following anti-epileptic drugs: carbamazepine, topiramate, lamotrigine, valproate, gabapentin and clobazam. The visual seizures did not impact markedly on his daily life as they were limited to periods around sleep, and they did not affect his schoolwork.



**Figure 1.** Serial MRI studies. **A**) (Age 10 years) Axial FLAIR image demonstrating increased signal in the parieto-occipital regions bilaterally (black arrows). **B**) (Age 13 years, 2003) Axial T1-weighted image showing the absence of the right mesial frontal CCM. **C**) (Age 16 years, 2006) Axial T1-weighted image showing right mesial frontal CCM with increased signal intensity (arrow). **D**) (Age 16 years, 2006) Gradient echo (GE) axial image with blooming and low signal over right mesial frontal CCM (arrow).

At 15 years, he developed a new type of focal seizure (type 2). These began with an aura of nausea and vomiting, and he felt a tightness in his chest and abdomen "as if my stomach is pushed together" accompanied by a feeling of anxiety and palpitations. This evolved to loss of awareness with facial grimacing, bilateral upper limb automatisms and left hand dystonia. If standing, he would walk away. If he was sitting, he had axial rocking and bipedal automatisms, more marked on the right. Type 2 seizures were triggered by exercise such as running around, and occurred whenever he played sport. These seizures gradually escalated over eight months, eventually occurring every two hours throughout the day by 16 years. These seizures compromised his daily life such that he showed a dramatic decline in academic performance from being an A grade student to struggling with schoolwork, in part due to difficulty concentrating. He experienced increasing isolation from his peers, low mood and self-esteem. His frequent attacks meant that he required constant supervision and could not do any activities alone such as walking to the shops.

In 2006, at 16 years, he underwent detailed epilepsy characterization. An MRI brain scan showed a right frontal CCM (*figure 1C,D*) that had not been present on the most recent, previous MRI in 2003 (*figure 1B*). The posterior periventricular abnormalities had resolved when repeat imaging was performed at 13 years. Neuropsychological assessment showed a focal visuo-perceptual deficit on a background of normal cognitive function.

The patient underwent two periods of video-EEG monitoring, and 48 seizures were captured. Interictal EEG showed active, right posterior temporo-occipital epileptiform discharges, and intermittent theta and rare left occipital discharges (*figure 2A*). No interictal frontal discharges were seen. Two type 1 seizures and 46 type 2 seizures were captured (*see video sequences*). The type 1 seizures had no observable clinical features, changes in heart rate or EEG changes (*see video sequences*). The type 2 seizure started with the patient experiencing an aura and tachycardia (resting heart rate 70-80, ictal heart rate 140-160 beats/minute). He then lost awareness, with bipedal and left hand automatisms, and head deviation to the left. He clutched his abdomen with both hands, leant forward bending his head, coughed, retched, and rubbed his right eye with his right hand (*see video sequences*). The EEG of the type 2 seizures showed right frontal onset of diffuse, non-lateralized attenuation followed by rhythmic, low voltage bifrontal fast activity (*figure 2B, C*).

The interictal, single photon emission computed tomography (SPECT) study showed subtle, focal hypoperfusion of the right mesial frontal region (*figure 3A*). An ictal SPECT study was performed during a type 2 seizure (injected 44 seconds from seizure-onset during a seizure lasting 84 seconds). This showed hyperperfusion of the right mesial frontal cortex (*figure 3B*). An interictal FDG-PET scan showed hypo-

metabolism of the right mesial temporal and posterior temporo-occipital regions (*figure 4A*) and subtle hypometabolism in the right mesial frontal region (*figure 4B*).

Co-registration of interictal EEG-functional MRI (EEG-fMRI) studies showed blood oxygen-level-dependent (BOLD) signal changes in the right parieto-occipital region, which correlated with the frequent, right parieto-occipital interictal discharges (*figure 5A*). A type 2-seizure ictal EEG-fMRI study showed a diffuse bilateral network of increased BOLD signal with a right-sided emphasis. There was involvement of the right frontal, central, parietal and temporal regions and the motor strips bilaterally (*figure 5B*).

The patient underwent right mesial frontal lesionectomy in August 2006. Histopathology showed a partially thrombosed cavernous angioma with evidence of previous haemorrhage.

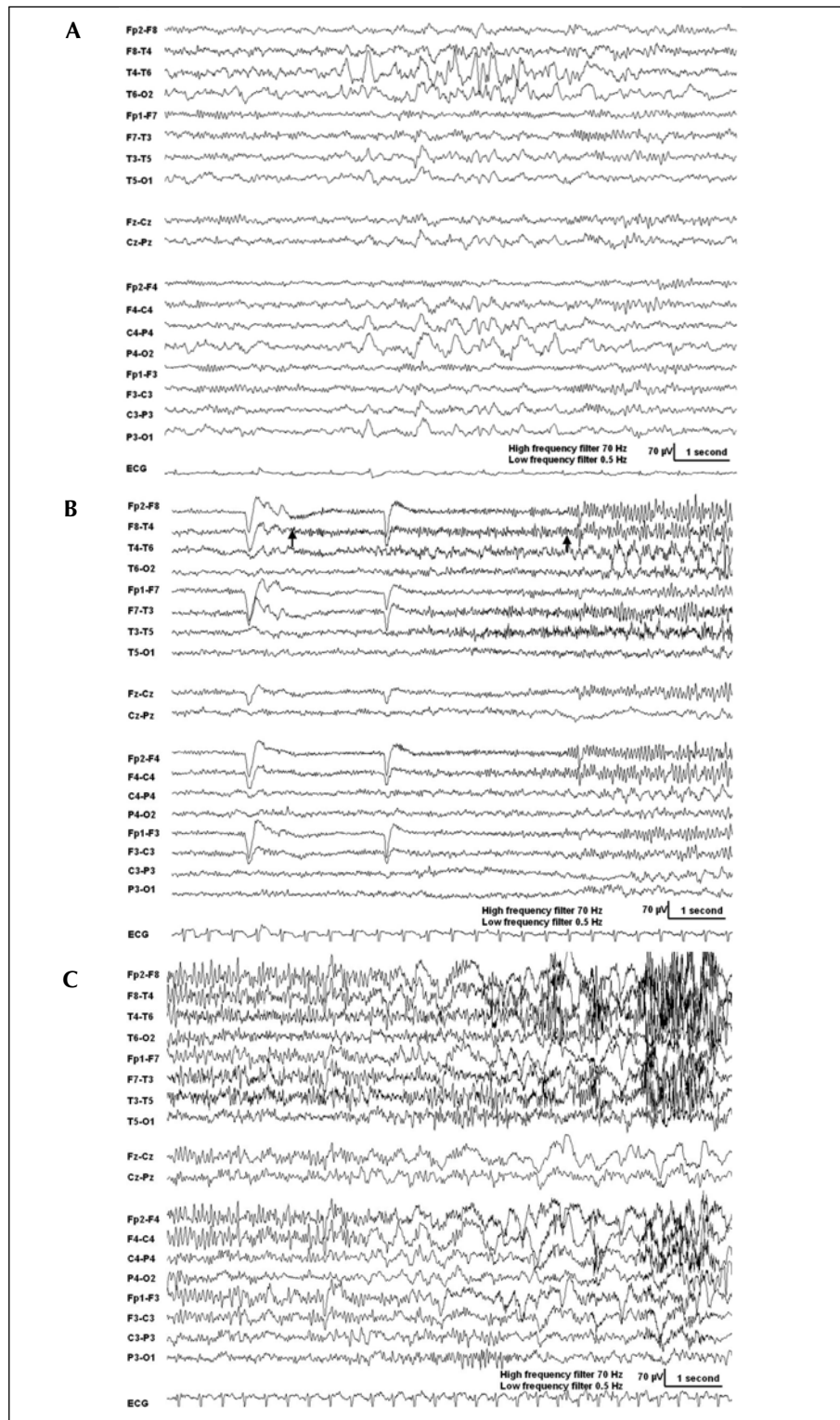
In the 22 months following surgery, the frontal seizures ceased although with ongoing, daily, visual auras due to occipital lobe seizures. His quality of life significantly improved after surgery. He became more alert and interactive, his mood improved and he was able to return to normal school life. He became independent, wrote poetry and short stories. Life for the whole family improved in the context of his improved seizure control as he was able to carry out activities independently.

## Discussion

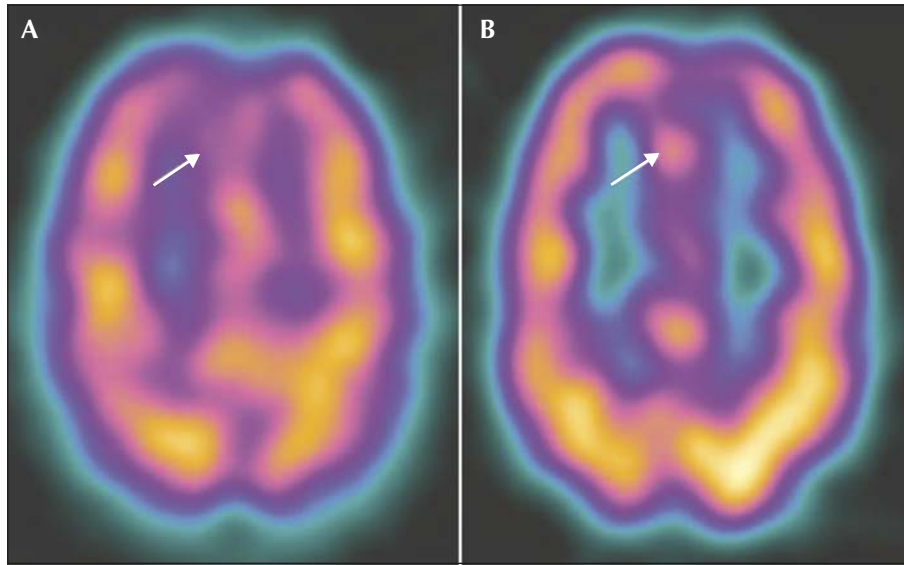
### Late sequelae of radiotherapy and chemotherapy

Cerebral cavernous malformations (CCMs) are angiographically occult vascular lesions that are found in 0.5% of the general population. CCMs occur either as isolated lesions in sporadic individuals or as multiple lesions with a genetic basis. Acquired causes of CCMs are recognised. For example, CCMs may develop as late sequelae after irradiation of the brain. Post-irradiation CCMs are more frequently reported in children with ALL as this is the most common group to receive radiotherapy (Larson *et al.* 1998, Heckl *et al.* 2002, Maeder *et al.* 1998). More than 3% of children receiving radiotherapy for brain tumours develop CCM (Burn *et al.* 2007); this complication is much rarer in the adult population (Furuse *et al.* 2005). The average time interval between irradiation and the detection of a CCM in children varies from 3 to 22 years after exposure to radiation doses of 24 to 60 Gray (Megdiche Bazarbacha *et al.* 2004, Duhem *et al.* 2005, Baumgartner *et al.* 2003).

The late effect of irradiation-induced CCM occurs predominantly in children; however, the mechanism is unknown. Heckl and colleagues postulated that a small, pre-existing CCM not visible on MRI could grow secondary to irradiation (Heckl *et al.* 2002). Irradiation causes adventitial fibrosis and endothelial oedema, resulting in narrowing of the vascular lumen.



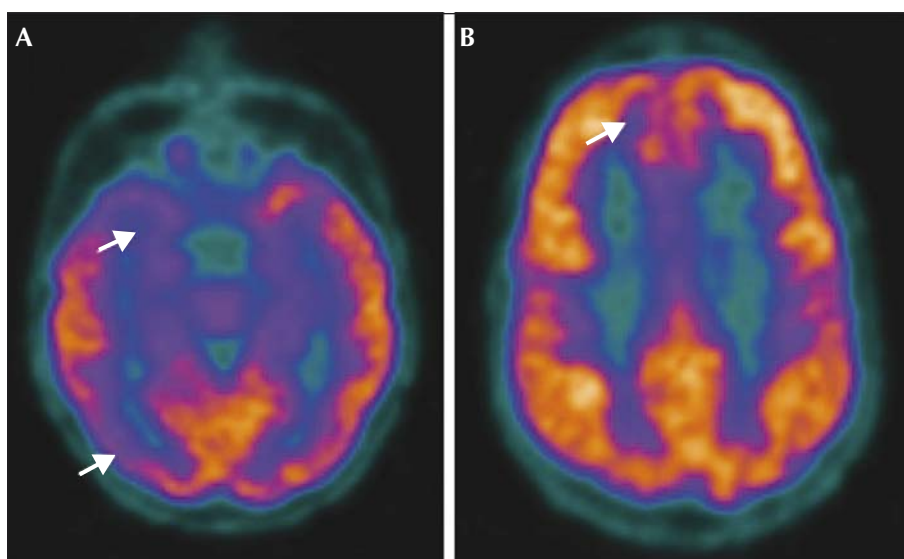
**Figure 2.** EEG studies. **A)** Interictal recording showing sharp and slow wave discharges in the right posterior temporo-occipital region (T6, O2) with intermittent theta and delta transients. **B)** Ictal recording of a type 2 seizure with diffuse, non-lateralized attenuation followed by rhythmic, low voltage, bifrontal fast activity, more prominent on the right (arrows). Note ictal tachycardia of ~ 140/minute. **C)** Continues from 2B showing evolution of ictal recording of type 2 seizure with sinusoidal 17 Hz fast activity over the frontal regions, higher in amplitude on the right (Fp2, F8, F4) progressing to prominent postictal delta slowing over the frontal regions. Note ictal tachycardia of ~ 160/minute.



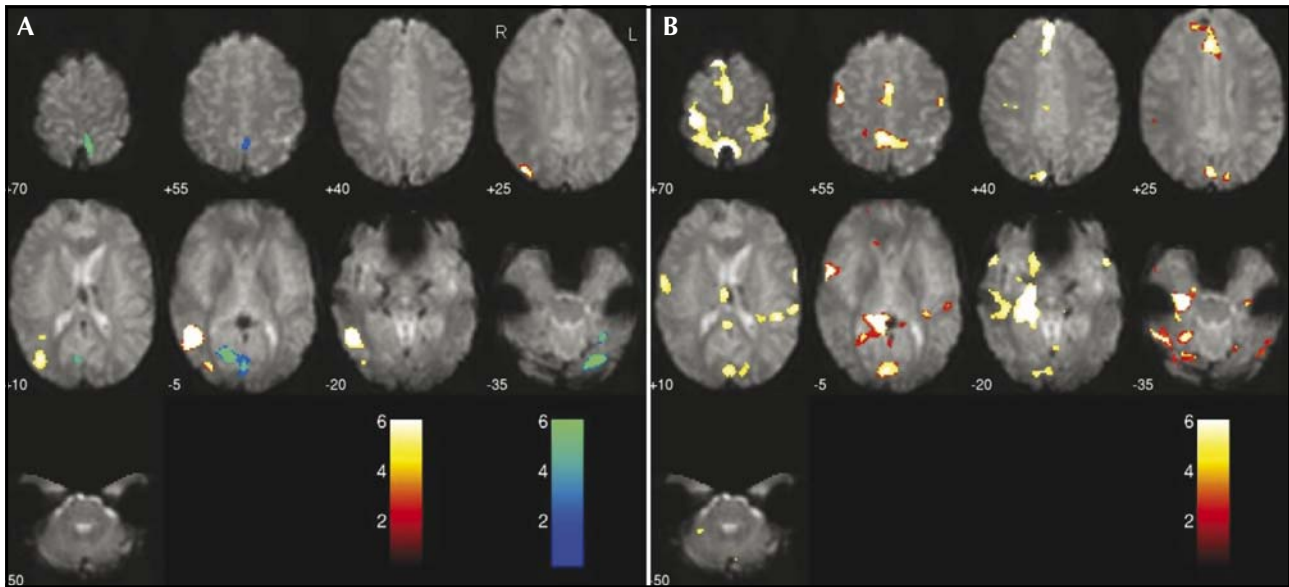
**Figure 3.** SPECT studies. **A)** Interictal SPECT study showed focal hypoperfusion of the right mesial frontal cortex and frontal pole (670 MBq of Tc-99m ECD administered intravenously with the patient resting quietly with eyes opened). **B)** Ictal SPECT performed during a type 2 seizure (720 mBq of Tc-99m ECD administered intravenously 44 seconds from seizure-onset, seizure duration 1:24 minutes), showed hyperperfusion of the right mesial frontal cortex.

Toxic leukoencephalopathy may occur secondary to radiotherapy or chemotherapy, and may be clinically, radiologically and pathologically indistinguishable between the two aetiologies (Filley 1999). The severity may be more severe where chemotherapy is administered intra-

thecally or intravenously in combination with radiotherapy. Intrathecal methotrexate in particular may be associated with leukoencephalopathy. Most commonly, radiation exposure is associated with a late, delayed leukoencephalopathy with neurobehavioural changes such



**Figure 4.** Interictal FDG-PET study. **A)** PET study showing marked hypometabolism of the right mesial temporal and posterior temporo-occipital regions (arrows). **B)** PET study demonstrating subtle hypometabolism of the right mesial frontal region (arrow).



**Figure 5.** Interictal and ictal EEG-fMRI study. **A)** Statistical parametric map (SPM) of significant BOLD signal changes ( $p < 0.05$  corrected for multiple comparisons) associated with the interictal discharges (left of brain on right of image). Increased BOLD signal is in warm colours (red-yellow), decreased BOLD signals are presented in cool colours (blue-green). Significant, increased BOLD signal extends from the right parietal to lateral temporal areas. Associated deactivation near this is consistent with discharges arising from the right posterior quadrant. **B)** Statistical parametric map (SPM) of significant BOLD signal changes ( $p < 0.05$  corrected for multiple comparisons) associated with an ictal recording of a type 2 seizure. Image layout is the same as the previous image. Significant, increased BOLD signal is seen bilaterally, but with a right-sided emphasis that involves the perilesional area as well as the thalamus, medial temporal lobe and patches in the cortex. This suggests a predominantly unilateral cortical-thalamic network that includes the lesion.

as learning disabilities in children. Milder neurobehavioural effects are associated with a greater likelihood of reversibility as noted in our patient (Filley 1999).

### Surgical decision-making

The decision to progress to epilepsy surgery in this young man involved multiple admissions for video-EEG monitoring, a range of investigations and many complex discussions.

Initially, we had to delineate whether there were actually two types of seizures or simply different spread patterns emanating from a single epileptogenic focus. The recent-onset attacks differed from the long-standing seizures, most notably with a different aura, evolution and triggers. The semiology of the recent, disabling seizures began with an aura of fear, palpitations, a sensation of tightness in the chest and abdomen, and nausea, followed by pedal automatisms and hyperkinetic behaviour. The clinical features were clearly those of frontal seizures (Jobst *et al.* 2000), compared with his original occipital (Taylor *et al.* 2003) seizures characterised by a visual aura. The frontal lobe seizures had a characteristic ictal EEG onset pattern and an associated lesion. The occipital seizures did not have an EEG signature, but it is well known that simple partial seizures can be silent on surface EEG. Also, there was no history of one seizure type progressing to the other.

Multiple investigations were performed and closely scrutinised to confirm the clinical impression of two discrete seizure types rather than spread from the occipital focus to the frontal region. Thus, the close attention to the video-EEG data was crucial to determining suitability for epilepsy surgery. The EEG showed frequent, right temporo-occipital interictal epileptiform discharges (IED) and infrequent left occipital discharges; interictal frontal discharges were not seen. The presence or absence of IED in FLE indicative of an "irritative zone" does not crucially influence surgical decision-making and outcome (Worrell *et al.* 2002).

In comparison with the interictal recordings, ictal studies gave evidence to support the case for epilepsy surgery. The frontal lobe seizures showed high frequency, low amplitude beta discharge over the right frontal electrodes (Fp2-F8-F4) within 2-3 seconds of seizure-onset in all 46 of the type 2 seizures (*figure 2B, C*). In contrast, there was no ictal rhythm seen in the two recordings of the type 1 seizures. The focal beta discharge at the onset of the frontal lobe seizures was highly indicative of seizure origin in terms of spatial and temporal resolution. The focal beta discharge served as a marker of the epileptogenic zone in frontal lobe resections and was associated with excellent seizure-free outcome following surgical resection (Worrell *et al.* 2002, Kazemi *et al.* 1997).

Our patient was referred from the northern part of Australia with his MRI reported as showing posterior abnormalities only. With the identification of frontal lobe seizures, we scrutinised his MRI carefully and compared his serial studies over 10 years. We found a right mesial frontal lesion that had only emerged in the preceding three years. It is critical that MRI studies are reviewed in the light of electro-clinical seizure semiology as subtle lesions may be easily missed.

Functional imaging is helpful in localising seizure-onset. Comparison of ictal to interictal SPECT in our patient added considerable weight to seizure localization (*figure 3A, B*). In frontal lobe seizures in children, ictal SPECT demonstrated unilateral frontal hyperperfusion in 91%, which was concordant with electroclinical lateralisation in 95% of cases (Harvey *et al.* 1993). EEG-fMRI provided supportive information about the right posterior quadrant interictal epileptiform discharges, presumably relevant to the occipital seizures (*figure 5*). The probable type 2 seizure recorded during fMRI was supportive of perilesional involvement, but was not considered for clinical decision-making because it was performed purely for research.

The epilepsy surgery discussion centred around whether there were sufficiently convincing data to show that the type 2 seizure arose independently in the frontal lobe rather than representing spread from a single focus in the occipital lobe, and whether the patient would benefit from epilepsy surgery directed solely at the frontal focus. To address the first question, it is clear that the type 2 seizure was frontal in nature with frontal lobe semiology, ictal EEG frontal lobe signature, SPECT localisation to the frontal lobe and a MRI mesial frontal lesion. Rather than spread from the occipital lobe, there was evidence of frontal onset as the aura was different, the two seizure semiologies did not occur together and a highly epileptogenic lesion was found in the frontal lobe. In answer to the second question, the patient's quality of life had deteriorated since onset of the FLE in terms of school and social functioning. He had coped well with daily, mild occipital seizures for many years. Here we showed that the vast majority (46/48) of seizures arose in the frontal lobe. The issue of surgery was broached and it was carefully explained that occipital seizures would continue at the same frequency but hopefully, the frontal lobe seizures would cease or occur at a far reduced frequency with resection of the frontal lesion, allowing resumption of previous activities.

Considerable time was spent discussing the value of intracranial monitoring. In a patient with multifocal or dual pathology, further delineation of the exact ictal-onset zone with invasive strategies, such as implantation of intracranial electrodes, is regarded as the gold standard. This is essential when clinical, electrophysiological and neuroimaging data are ambiguous or discordant (Dubeau *et al.* 2000, McLachlan 2000, Worrell *et al.* 2002, Romanelli *et al.* 2004, Cross *et al.* 2006). However, careful analysis of

non-invasive evaluation incorporating seizure semiology, scalp EEG, neurophysiological and neuroimaging techniques can localize epileptic foci accurately and determine likely benefit of surgery (Koh *et al.* 2000, Karenfort *et al.* 2002, Francione *et al.* 2005). Here, our patient had concordant clinical semiology, EEG data and a congruent lesion on structural and functional imaging, such that invasive studies were not essential and carried risks of complication (Harvey *et al.* 1993, Cascino *et al.* 1992, Pondal-Sordo *et al.* 2007, Shukla *et al.* 2003). Equally, it was important that the clinical team made it clear to the patient and his family not to expect seizure-freedom from the surgical resection in view of his multifocal epilepsy.

### Surgery for multifocal epilepsy

Multifocal epilepsy does not preclude successful epilepsy surgery. Studies of patients with tuberous sclerosis show that benefit can be gained from resection of one tuber in

### Legends for video sequences

#### Video sequence 1

Frontal seizures. The seizure started with the patient having an aura while eating, he pressed the seizure button (six seconds from the start of the video). He then lost awareness (12 seconds), developed prominent bipedal automatisms (13 seconds), left hand automatisms (19 seconds), head deviation to the left (22 seconds), and then he held his abdomen with both hands (25 seconds), leant forward with his head bent down (34 seconds), coughed (38 seconds), retched (44 seconds), and later rubbed his right eye with his right hand. The seizure ended with retching and chewing automatisms. The patient responded to his mother at 67 seconds.

Figure 2B: ictal EEG recording of a type 2 seizure, with diffuse, non-lateralized attenuation followed by rhythmic, low voltage, bifrontal fast activity, more prominent on the right (arrow).

Figure 2C: the ictal EEG continues from 2B showing evolution of ictal recording of a type 2 seizure with sinusoidal, 17 Hz fast activity over the frontal regions, higher in amplitude on the right (Fp2, F8, F4), progressing to prominent postictal delta slowing over the frontal regions.

#### Video sequence 2

Occipital seizures. The patient was watching television and experienced a visual aura of "flashes", and informed his father. The patient remained fully aware throughout the aura with no other clinical manifestations. No electroencephalographic changes were seen.

children with multiple tubers or even multiple tuberec-tomies (Weiner *et al.* 2006).

Here, we were not attempting to resect multiple abnormal regions. Rather, we focused on removing the epileptogenic lesion responsible for the prominent and disabling frontal seizures of recent onset. Surgery for the occipital seizures was not indicated for several reasons: seizures were not disabling, seizure-onset was not lateralized nor was a discrete lesion present, and surgery would have produced an unacceptable visual defect. Detailed analysis may show that a patient has seizures arising from different cortical foci that occur at different frequencies. If one seizure focus is more active and those seizures are more disruptive to daily function, surgery may still prove beneficial. If surgery is offered with appropriate counselling, the patient may elect to undergo surgery despite the expectation of ongoing epilepsy. As seen here, surgery may significantly improve the patient's quality of life even though seizures from the remaining foci continue to occur. Our case highlights the benefits derived from: (1) careful evaluation of multiple seizure types, in terms of their origin and impact, (2) the importance of patient auras, seizure semiology and evolutions, (3) the search for an occult epileptogenic lesion that, once found, obviated the need for intracranial EEG monitoring, and (4) the application of surgery to one of multiple seizure foci, resulting in striking improvement in the patient's quality of life. This case illustrates the importance of not dismissing patients with multifocal epilepsy as unsuitable surgical candidates and emphasizes that in some cases, seizure freedom is not always the endpoint that is sought. Such surgery should be considered curative for the disabling epilepsy, rather than "palliative". □

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