Anatomo-electro-clinical correlations: the Marseille, France Case Report
Case 02-2008

MRI-negative prefrontal epilepsy due to cortical dysplasia explored by stereoelectroencephalography (SEEG)

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ABSTRACT – [Case records of Epileptic Disorders. Anatomo-electro-clinical correlations. Case 02-2008] We report the case of a young boy presenting with pre-frontal seizures including singing automatisms. There was no visible lesion on MRI, but following localisation using stereoelectroencephalography (SEEG), surgery revealed an underlying dysplastic lesion. [Published with video sequences]

Key words: stereoelectroencephalography (SEEG), MRI-negative, pre-frontal, dysplasia

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Clinical history

The patient first presented to our service at the age of eight years. The product of a normal pregnancy, he had presented a single, uncomplicated febrile seizure at the age of one year in the context of a throat infection. His mother and sister also had a history of febrile convulsions, but there was no family history of epilepsy. His psycho-motor development was entirely normal until the age of 18 months, when he presented with a first diurnal seizure. This was described as an episode of staring with loss of contact lasting several seconds, associated with rubefaction, chewing and bilateral hand tapping movements. Further similar events followed (occurring in the daytime or while falling asleep) and paediatric neurology assessment resulted in a diagnosis of probable frontal lobe epilepsy. Clinical examination was unremarkable and he was right-handed. Initial surface EEG showed rare, right rhythmic anterior spikes (FP2, F4, F8) as well as bilateral polyspike wave discharges (predominant on the right side, activated by sleep). Videotelemetry at the age of two years allowed recording of two frontal seizures, one of which had apparent left-sided and one right-sided onset. Cerebral MRI was normal. Treatment with carbamazepine was commenced, resulting in a one year period of complete remission. However, seizures then recommenced at the age of three years, this time in the form of nocturnal attacks (“night terrors”), characterised by vocalisation and agitation with elevation of both upper limbs; a change in his daytime behaviour was also noted, with a tendency to hyperkinetic activity and attentional difficulty. It was noted that he seemed to remain aware or partially aware, and could ask following a seizure “why am I laughing?” Subsequent trials of various anti-epileptic drug combinations including carbamazepine, valproate, vigabatrin, clonazepam, phenytoin, topiramate and lamotrigine were unsuccessful in controlling the seizures and he was eventually referred to our centre for pre-surgical assessment. At this time, seizures often occurred in clusters of many per day, several times a month with negative consequences for his schooling.

A preliminary phase of comprehensive, non-invasive presurgical investigation was performed in our unit, the results of which are summarised below.

Non-invasive investigation

Interictal surface EEG showed bilateral frontal spikes and spike-wave discharges, predominantly right-sided; associated rapid discharges in the same region were also subsequently demonstrated using high resolution EEG (EEG-HR) (figure 1). No independent left-sided abnormality was seen. Three habitual seizures were recorded on videotelemetry, with semiology that can be summarised as follows: sudden onset of bilateral lower limb movements with asymmetric extension and/or flexion; sometimes “beating time” to the tune as he sang; less obvious bilateral upper limb movements sometimes with extension. He also presented humming or frank singing, sometimes preceded by a cry, occurring close to seizure-onset. He would then present verbal automatisms characterised by echolalia (sometimes in a sing-song style), with either comprehensible or incomprehensible words. The duration was around 20 seconds and in the post-ictal period no deficit was noted, but he would often seem euphoric or cheerful. Ictal EEG of these seizures showed a pattern of flattening in right anterior frontal regions and the anterior vertex, followed by a localised, rapid spike discharge 3-5 seconds later, in right frontal electrodes (FP2, F8, FZ) (see video sequence 1). High resolution EEG (EEG-HR) revealed that surface interictal spikes had two separate components, which, when examined sequentially and analysed using source localisation tools (MUSIC), showed antero-posterior propagation from the right medial fronto-polar region to the right superior frontal sulcus (SFS) (figure 2). Cerebral MRI, including careful review following the results of other investigations, was normal. The MR protocol used consisted of transverse diffusion images, transverse T2-weighted images, coronal T1-weighted inversion recovery images, coronal FLAIR (fluid-attenuated inversion recovery) images and a three-dimensional T1-weighted acquisition. Acquisition plans were referred to the bi-hippocampal plane for the transverse acquisitions and to the AC-PC plane for the coronal and axial acquisition. Reconstructions of the 3D T1 images were adapted to the type of epilepsy. MRI examinations were performed on a 1.5-Tesla Symphony machine (Siemens Medical Systems, Erlangen, Germany), with a 4-channel head coil being used. Interictal SPECT on two previous occasions had shown right fronto-temporal hypoperfusion (during initial paediatric assessment); at the time of pre-surgical work-up, bilateral anterior mesial frontal and right anterior temporal hypoperfusion were noted. PET and ictal SPECT were not performed. As part of a research protocol, a computerised analysis of sulcal anatomy was performed using raw MRI data, and this suggested a possibly unusual appearance of the right superior frontal sulcus. This method remains however, an as yet unvalidated research tool (Mangin et al. 2004) and the significance of this finding is therefore unclear.

Neuropsychological assessment showed intellectual capacities within the normal range, with no visuo-verbal dissociation. Although a relative preservation of executive functions was demonstrated, a deficit in visuo-spatial programming (deficit in visual exploration strategies) was present as was some mild, verbal dysfunction in terms of impaired narrative ability and difficulty in problem-solving tasks.

Stereoelectroencephalographic (SEEG) exploration

Following this non-invasive assessment, the decision was taken to perform SEEG. The main hypothesis based on electroclinical features was that of a single localised epilep-
togenic zone in the right prefrontal region, with the relative
contribution of mesial, dorsolateral and orbitofrontal struc-
tures to be determined. The exploration also aimed at
excluding a more widespread epileptogenic zone, with
electrodes therefore being placed in premotor and temporal
lobe structures. The EEG-HR was strongly suggestive of
focal right prefrontal interictal activity, and ictal EEG was
also in keeping with right prefrontal onset, such that bilat-
eral exploration was not considered necessary.

SEEG recordings were performed using intracerebral mul-
tiple contact electrodes (10 to 15 contacts, length: 2 mm,
diameter: 0.8 mm, 1.5 mm apart), placed intracranially
according to Talairach’s stereotactic method as previously
described (Talairach et al. 1992). Nine right-sided depth
electrodes were placed as follows (figure 3): electrode FP
exploring medial and lateral parts of the fronto-polar
region with medial and lateral contacts respectively;
electrode CR exploring the anterior cingulate region

Figure 1. Right frontal interictal spikes on surface EEG. Surface high resolution EEG (HREEG) using 64 electrodes; monoplar montage, average
reference. Intercitial spikes involving bilateral anterior regions, predominantly right-sided (maximum amplitude F4, F2, FC2). Amplitude
cartography (using EEGFocus; MEGIS Software, Gräfelfing, Germany) during the scalp-EEG interictal spike shown in the first panel.
Brodmann area 32) with medial contacts and the dorso-lateral prefrontal cortex (Brodmann area 9/46) with lateral contacts; electrode PS exploring the pre-supplementary motor area (SMA) with medial contacts and frontal eye fields (Brodmann area 8) with lateral contacts; electrode S exploring the SMA with medial electrodes and lateral premotor cortex (Brodmann area 6) with lateral contacts; electrode CC exploring the anterior cingulate gyrus (Brodmann area 24) with medial contacts and lateral premotor cortex (Brodmann area 6) with lateral contacts; electrode OF exploring the caudate nucleus with medial contacts and the frontal operculum with lateral contacts, passing through the insula; electrode O exploring medial and lateral orbitofrontal cortex with medial and lateral contacts respectively; electrode T exploring the medial temporal lobe with medial contacts and the superior temporal gyrus with lateral contacts; electrode TP exploring medial and lateral aspects of the temporal pole with medial and lateral contacts respectively.

Interictal SEEG (figure 4) was characterised by continuous spikes, polyspike and spike-wave activity as well as rapid discharges (35 Hz) recorded synchronously from the electrodes exploring the anterior cingulate, dorso-lateral prefrontal and fronto-polar regions (contacts CR 2-3 and 3-4, spreading to CR1-2 and CR 5-7) and FP (1-6). These spikes could spread to involve premotor regions (electrodes PS and S). The middle contacts of electrodes O, OF and TP showed interictal slow wave activity.

During SEEG, one spontaneous seizure was recorded and four seizures were provoked by electrical stimulation of selected electrode contacts. The semiology of all five seizures was comparable to those described above.

In terms of ictal SEEG, for the single spontaneous seizure, a modification of background activity was noted 2 min 30 before seizure-onset, in the form of rhythmic spikes in the middle contacts of electrodes CR and FP (dorso-lateral prefrontal region). This pre-ictal spiking then stopped abruptly, giving way to a fast tonic discharge (20 Hz) (CR 2-7 and FP 1-7), lasting eight seconds (figure 5). This was followed by a second, faster tonic discharge (80 Hz) in the same region, corresponding to the moment when the first clinical signs occurred. Following this, a clonic spike discharge was seen in the same electrodes, subsequently spreading to more lateral contacts of CR, FP then towards orbital and premotor regions (intermediary contacts of O and S).
The provoked seizures were induced by stimulation of electrodes CR 1-2, CR 5-6 and FP 1-2, 3-4 (see video sequence 2); in other words, in the same contacts as in the initial rapid discharge of the spontaneous seizure.

Conclusion following SEEG and subsequent surgical outcome

From analysis of all available data, including detailed analysis of the exact position of SEEG electrodes using 3D MRI, it was concluded that the irritative zone and epileptogenic zone were practically superimposed, involving a localised region within the right superior frontal sulcus. The preferential propagation pathway involved the orbitofrontal region. The EEG features and the localisation to the base of a sulcus raised the question of underlying dysplasia, despite the lack of any imaging abnormality. The patient subsequently underwent right, prefrontal cortectomy including the right SFS and intermediate frontal sulcus, extending posteriorly to the anterior pre-cingulate region (figure 6). Histopathology of the resected section confirmed focal cortical dysplasia type IIB (Taylor-type with balloon cells). The dysplastic lesion was relatively voluminous, being present in the bases of several adjacent sulci of the superior prefrontal cortex, particularly in their mesial aspect. The patient has been followed up in our service for four years post-operatively and has remained seizure-free since surgery. Neuropsychology assessment shows an improvement in the visuo-spatial and verbal tasks that were slightly abnormal prior to surgery. He has taken no anti-epileptic medication for the past two years and his school progress is entirely normal for his age. He is psycho-socially well-integrated within his family and school activities.
Discussion

This patient falls within the group of those presenting for surgical evaluation with normal structural imaging, but with other features indicating a likely localised region of seizure production. Frontal lobe epilepsy surgery is the second most common resective surgery performed for drug resistant epilepsy after temporal lobe resection, and the group of frontal epilepsies with normal imaging is considered to be one of the most challenging, with relatively poorer surgical outcomes reported in the literature (Jeha et al. 2007). While some authors have argued that such patients should be automatically excluded from presurgical assessment because of the low chance of success, it is however, well-recognised that selected patients can have very good surgical outcomes, dependant upon correct localisation, which usually requires intra-cranial recording. The method of SEEG, differing in many key respects from other techniques such as subdural grids, may afford certain advantages as illustrated in the current case. For example, recording from deep as well as superficial structures permits recording from buried cortex or the base of sulci (crucially, in this case, from the base of the SFS where the dysplasia was situated). In addition, simultaneous recordings from both medial and lateral structures allows a temporo-spatial pattern of activity to be characterised (here, confirming the pattern of spike propagation suggested by HR-EEG). Indeed, the current case was previously included in a reported series of 100 SEEG explorations from the Marseille group, which demonstrated no difference in localisation rates or eventual surgical outcome between those with MRI lesions and those with normal imaging (McGonigal et al. 2007).

In terms of formulating a set of hypotheses to determine a strategy for intracranial exploration in this case, a number of elements contributed. The semiology was not, in itself, clearly localising or lateralising, other than suggesting frontal and in particular prefrontal involvement. The semiology of prefrontal seizures is complex, variable and certainly remains incompletely characterised (Jobst et al. 2000, Chauvel 2003). However, some semiological ele-
ments here, namely the singing, echolalia and distal hand tapping movements, can be viewed as a form of “forced acting” or pseudo-compulsive behaviour, which has previously been described as a feature of dorsolateral prefrontal seizures (Bancaud and Talairach 1992, Chauvel and Bancaud 1994). Indeed, it has been noted that the pattern of distally driven, semi-purposeful movements seen in certain prefrontal seizures is very different from the proximal, purposeless, often violent movements that correspond to what has also been called “hypermotor seizures”, this second pattern being rather associated with prefrontal mesio-ventral cortex involvement; the difference in semiological pattern may ultimately present a means of classifying pre-frontal seizures (Chauvel 2003). The association of ictal emotional modification with stereotyped motor behaviours has been identified as a feature of epileptic activity involving the anterior cingulate region (Bancaud and Talairach 1992). Singing during seizures is rare, but in previous series has been associated with involvement of frontal, particularly right prefrontal regions (Bartolomei et al. 2007). The retained consciousness during this patient’s seizures argued against widespread seizure propagation to bilateral frontal or temporal lobe regions. The absence of significant postural features or forced eye deviation indicated a lack of involvement of frontal pre-motor areas or frontal eye fields, and no secondary generalisation occurred. In addition, there was no ictal language dysfunction or post-ictal deficit, arguing against significant involvement of dominant hemisphere language structures. Surface EEG showed rhythmic abnormalities associated with fast activity in bilateral anterior regions, predominantly right-sided. The morphology of such abnormalities was quite evocative of underlying dysplasia (Gambardella et al. 1996), whilst HR-EEG not only confirmed a clear,

Figure 5. A) Spontaneous seizure recorded on SEEG. A modification of background activity was noted 2 min 30 before the clinical seizure-onset, in the form of rhythmic spikes in the middle contacts of electrodes CR and FP (dorsolateral prefrontal region). This pre-ictal spiking then stopped abruptly, giving way to a fast tonic discharge (20 Hz) (CR 2-7 and FP 1-7), lasting eight seconds. This was followed by a second, faster tonic discharge (80 Hz) in the same region, corresponding to the moment when the first clinical signs occurred. Subsequently, a clonic spike discharge was seen in the same electrodes, subsequently spreading to more lateral contacts of CR, FP, and then intermediary contacts of O and S. B) Map of gamma activity (> 25 Hz) showing the detection of tonic rapid discharge (*) in contacts of electrodes CR and FP. Note also the pre-ictal spiking before the appearance of rapid discharge. C) Schema of electrode implantation with main electrode involvement (FP and CR) indicated in orange.
right pre-frontal pattern but also indicated a probable antero-posterior propagation of interictal activity. The HR-EEG was therefore an important argument for proceeding to intracranial exploration, with the main hypothesis being a right, pre-frontal localisation. This technique, when used in association with source localisation tools, has been previously validated in frontal lobe epilepsy by corroboration with depth EEG studies (Gavaret et al. 2006), being particularly useful in determining lateral and mesial, but not basal frontal localisations. As has been previously noted in other cases of lateral frontal epilepsy (Foldvary et al. 2001), the ictal surface EEG in this case demonstrated a likely localised onset.

In terms of SEEG data, very focal interictal spikes, combined with consistently localised seizure-onsets characterised by a rapid discharge in the same region, were recorded. In addition, stimulation of the middle contacts of the principal electrodes involved reproduced habitual seizures and showed the preferential propagation pathway involving the orbitofrontal region. These data, together with the ensemble of other elements, therefore allowed confident estimation of primary seizure organisation within a limited region centred on the right SFS. The lack of involvement of premotor or temporal regions in seizure production was also confirmed. The recording of seizure-onsets, with a clear temporal relation between rapid discharge and production of clinical signs, indicated that the choice of electrode placement appeared to have been satisfactory. Indeed, the characteristic pattern of SEEG abnormalities (Chassoux et al. 2000), including the presence of interictal and preictal rhythmic spike discharges on SEEG and the occurrence of very fast ictal discharge within the same localised region, indicated the probability of an underlying dysplastic lesion despite the normal MRI. These rhythmic discharges recorded with depth electrodes correspond to the rhythmic spiking and fast activities seen on interictal surface EEG.

This patient proved to have a type IIB focal cortical dysplasia (Taylor-type, with balloon cells) in resected tissue. Despite ongoing, rapid advances in MR techniques, an unknown proportion of all dysplasias remain undetected by magnetic resonance imaging, and it is acknowledged that even lesions visible on MRI may only be the “tip of the iceberg” (Luders and Schuele 2006); in addition, the epileptogenic zone is often greater than the lesion itself (Chassoux et al. 2000). The usefulness of SEEG in assessing dysplastic lesions has been previously confirmed (Chassoux et al. 2000), particularly with regards to permitting direct intra-lesional recording as in the present case. The presence of localised surface EEG interictal abnormalities has been associated with better prognosis in MRI-negative cases, including dysplasias (Lee et al. 2005). Despite some studies reporting poor surgical prognosis in malformations of cortical development without visible MRI abnormalities (Jeha et al. 2007), excellent outcomes in such patients have been demonstrated by others (Nobili et al. 2007), and experience in our own centre is also positive in this respect (McGonigal et al. 2007). Outcome in children
appears to be better than that reported for adults and it is argued that improved cerebral plasticity may contribute to this effect (Fauser et al. 2008). Early surgical intervention in such cases is therefore desirable. In this case, not only has the patient become and remained seizure-free, but medication has been withdrawn and his educational and neuropsychological progress is entirely normal. □

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References


