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Case Report

Is the anatomical lesion always guilty?: A case report

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ABSTRACT

During a presurgical workup, when discordant structural and electroclinical localization is identified, further evaluation with invasive EEG is often necessary. We report a 44-year-old right-handed woman without significant risk factors for epilepsy who presented at 11 years of age with focal seizures manifest as jerking of the left side of her mouth and arm with frequent evolution to bilateral tonic-clonic seizures during sleep with a weekly frequency. During video-EEG monitoring, we observed interictal left fronto-central sharp waves and some independent sharp waves in the right fronto-central region. Habitual seizures were recorded and during the post-ictal state, the patient had left arm weakness for a few minutes. The ictal discharge on EEG was characterized by a bilateral fronto-central rhythmic slow activity more prevalent over the right hemisphere. MRI of the brain revealed a left precentral structural lesion. Considering the discordant structural and electroclinical information, we performed bilateral fronto-central stereo-EEG implantation and demonstrated clear right fronto-central seizure onset. Stereo-EEG-guided radiofrequency thermocoagulation was performed in the right fronto-central leads with subsequent seizure freedom for 9 months. The patient then underwent surgery (right fronto-central cortectomy), and histology revealed focal cortical dysplasia type Ia. The post-surgical outcome was Engel Ia. This case underscores the presence of a structural lesion is not sufficient to define the epileptogenic zone if not supported by clinical and EEG evidence. In such cases, an invasive investigation is typically required.

1. Introduction

The overall lifetime prevalence of epilepsy is approximately 7.5 per 1.000 population [1] and focal seizures are the predominant seizure type in children and adults [2]. More than 30% of epilepsy patients may become drug-resistant [3]. Focal epilepsy is frequently associated with structural lesions (e.g., post-traumatic, vascular, malformation of cerebral development, low-grade tumor-associated epilepsy [LEATs], and perinatal injuries) [2,4]. Moreover, it is known that some specific lesions (e.g., focal cortical dysplasia [FCD] type II, hippocampal sclerosis [HS], and LEATs) have a high risk of inducing drug-resistance. In such conditions, epilepsy surgery should be an important treatment option, as it is frequently associated with a favorable outcome [5–7], especially in cases of short epilepsy duration [4,8–10]. When the MRI is 'negative' and fails to detect a potentially epileptogenic lesion, the chances of an excellent surgical outcome are significantly lower [9,11–13]. Anatomic-and electroclinical concordance is essential to propose a surgical procedure [14]. In patients with drug-resistant focal epilepsy, the presence of a structural lesion represents an important landmark suggesting the etiology and origin of seizures, but it cannot provide localization unless it is associated with other electroclinical features. The complexity of management increases further when confronted with two different and independent lesions (dual pathology). In such cases the clinical, semiological features, and ictal EEG are necessary to correctly interpret and define the EZ. Therefore, in the most complicated cases, the options are either eliminate the patient as a surgical candidate or perform invasive EEG to collect more information and appropriately define the EZ. We present a case report illustrating the management of drug-resistant focal epilepsy arising from the right frontal region (without a corresponding lesion on MRI) in a patient with a left frontal structural lesion.

2. Case report

A 44-year-old woman underwent presurgical evaluation at the "Claudio Munari" Epilepsy Surgery Centre at Niguarda hospital.

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She was right-handed and had no significant personal or family past medical history, except for an unspecified perinatal delay without any short- or long-term consequences. Her psychomotor development was unremarkable, and she completed high school education. She was 11 years old at the time of epilepsy onset. Her seizures were characterized by jerks of the left arm and left mouth with frequent evolution from focal to bilateral tonic-clonic seizures. Antiseizure medication (ASM) was initiated but had no significant effect on seizure frequency. Seizures were prevalent during sleep, occurring with a weekly frequency. Prolonged seizure-free periods were not reported, despite many therapeutic attempts with ASM. Focal seizures continued with a monthly frequency and stereotyped semiology, without sustaining traumatic falls despite rare evolution from focal to bilateral tonic-clonic seizures. The patient was reported to be unable to speak or understand during seizures, but able to remember what took place during seizures, so awareness was potentially unimpaired. Neither subjective symptoms nor deficits were reported at the end of the seizures. During the first outpatient visit, interictal EEGs were uninformative, whereas the brain MRI showed a FLAIR hyperintensity localized to the left precentral region, indicating a presumed epileptogenic lesion.

2.1. Presurgical work-up

The patient underwent video-EEG monitoring to collect interictal and ictal EEG findings (Nihon Kohden system, 19 electrodes placed according to the international 10–20 system, with additional polygraphic recording represented by the deltoid muscles in addition to ECG. During wakefulness, interictal video-EEG recordings demonstrated normal background activity, frequent left fronto-central sharp waves, and some rare and independent right fronto-central sharp waves. During sleep, physiological elements were recognized bilaterally, and the previously described abnormalities occurred more frequently, with a left fronto-central prevalence. Independent sharp waves, spikes, and spike-and-waves were also rarely observed in the right fronto-central regions. The ASMs were reduced (approximately halving the usual dose), and three seizures were recorded. The seizures were similar to the typical ones, being characterized by left eye and head deviation, hypertonic posturing followed by clonic movements of all four limbs, but with a clear-cut left upper limb prevalence. At the end of the seizure, the patient had dysarthria and unmistakable left arm paresis that lasted for several minutes. On EEG, ictal discharge was characterized by bilateral fronto-central rhythmic slow activity prevalent over the right hemisphere. The ictal EEG data were supported by strong clinical data identified on video recording. At the end of the video-EEG monitoring session, the patient underwent brain MRI (1.5-T Philips ACS-III-NT), targeting the alleged region of seizure origin according to Colombo et al., 2012 [15]. Accurate analysis of the brain MRI highlighted a clear-cut FLAIR hyperintensity (hypointense in T1-sequences) localized to the left precentral region. T2-weighted transverse turbo spin-echo (TSE) confirmed this finding. No other abnormal neuroradiological signs were noted. In the right hemisphere, particularly in the right frontal regions, no lesions were observed (Fig. 1). The neuroradiological interpretation of the left frontal lesion was possible type II FCD. The post-processing analysis supported this hypothesis (Fig. 1). Cerebral FDG-PET was performed and found to be uninformative. The neuropsychological assessment showed no significant abnormal alterations.

2.2. Stereo-EEG monitoring

Considering the discordance between the electroclinical data (suggesting a right frontal-central origin), neuroradiological findings (implicating the left frontal precentral lesion), and interictal EEG manifesting bilateral fronto-central epileptiform discharges with a right-sided prevalence, we performed bilateral and symmetrical fronto-central-temporal stereo-EEG implantation to verify our hypothesis and define whether a surgical plan could be considered. We extensively explored the central, precentral, and insulo-opercular regions with electrodes in the first temporal gyrus to explore the inferior part of the insula and to check for secondary propagation to temporal regions (Fig. 2). The surgical procedure of electrode implantation was performed without any complications. The interictal stereo-EEG findings consisted of epileptiform abnormalities (spike-and-waves) in the left precentral region and, in particular, on the leads exploring the structural lesion, but with maintained background activity. The abnormalities were

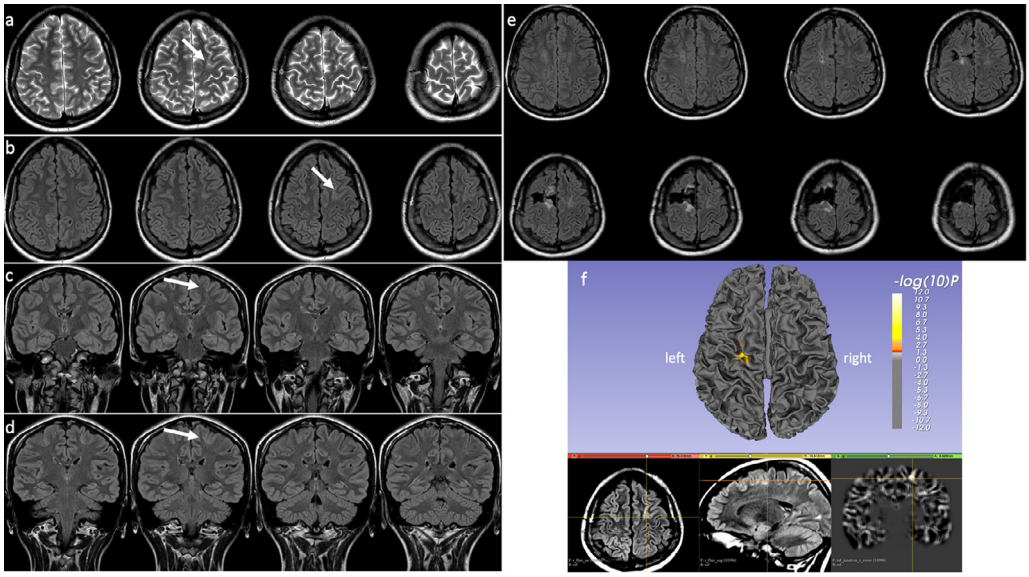

Fig. 1. Pre- and post-surgical brain MRI and post-processing analysis. Presurgical MRI: a) T2-weighted transverse turbo spin-echo (TSE) and b) T2-weighted transverse TSE fluid-attenuated inversion-recovery (FLAIR) axial sequences. c) and d) T2-weighted transverse TSE fluid-attenuated inversion-recovery (FLAIR) coronal sequences. Arrows indicate the presumed lesion. Post-surgical MRI: e) T2-weighted transverse TSE FLAIR axial sequences. f) MAP post-processing analysis.

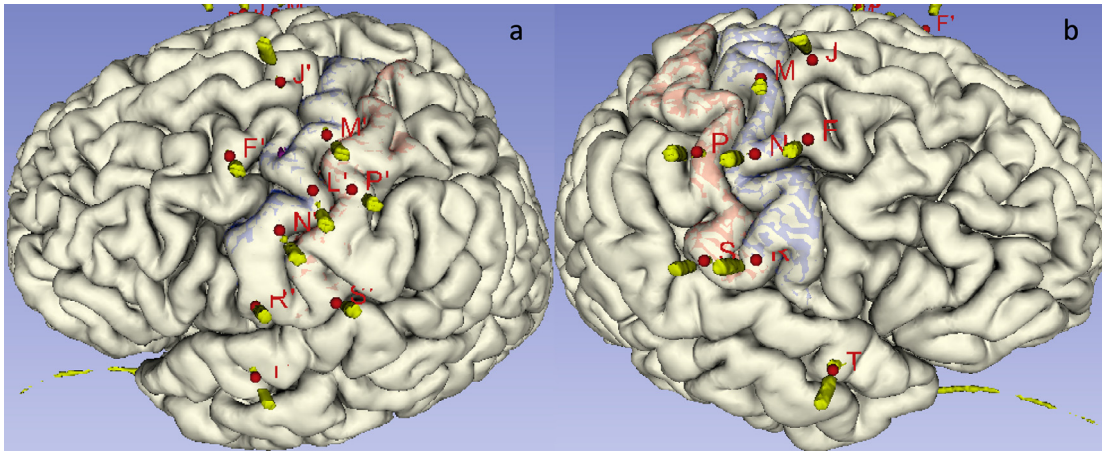

Fig. 2. 3D schema of stereo-EEG electrode implantation demonstrating the left (a) and right (b) implantations.

present mainly during sleep. These findings were not interpretable as FCD type II [16]. We recorded only one spontaneous seizure clinically as described above, clearly arising from the right precentral region with fast propagation to the homolateral primary motor cortex and with important but late contralateral hemispheric field of spread (Fig. 3). Interestingly, we induced a spontaneous seizure by stimulating electrode contact F6-7 with 1 mA at 50 Hz (Fig. 4). At 50 Hz stimulation of the contralateral homologous contacts L'6-7 with 0.8 mA of current induced motor clonic manifestations in the right hemibody, associated with a post-discharge involving only the left electrodes (Fig. 4). At the end of stereo-EEG monitoring, we performed stereo-EEG-guided radiofrequency thermocoagulation (RTC) in the leads exploring the right precentral region, which was involved in ictal discharge (Electrodes F and J). The patient was seizure-free for nine months. Due to the recurrence of the seizures, in February 2017 the patient underwent surgery (right fronto-central cortectomy). No surgical complications were noted. The histology revealed FCD Ia, and the postsurgical outcome was excellent (Engel Ia at 45-months). The doses of ASMs were substantially reduced, but treatment was continued because of the presence of the left precentral lesion.

3. Discussion

In symptomatic focal epilepsies, when caused by specific lesions (e.g. FCD type II, hippocampal sclerosis, long-term epilepsy-associated tumors), surgery should be considered because of the high predictability for patients to become seizure-free [5–7]. The best option for identifying a structural lesion is with brain MRI [17–18]. The surgical prognosis in patients with detectable lesions on MRI is favorable [4]. However, the absence of a lesion on MRI does not contraindicate the surgical procedure, despite the need for a more accurate analysis. Moreover, in selected cases, particularly temporal epilepsies, it is possible to proceed directly to

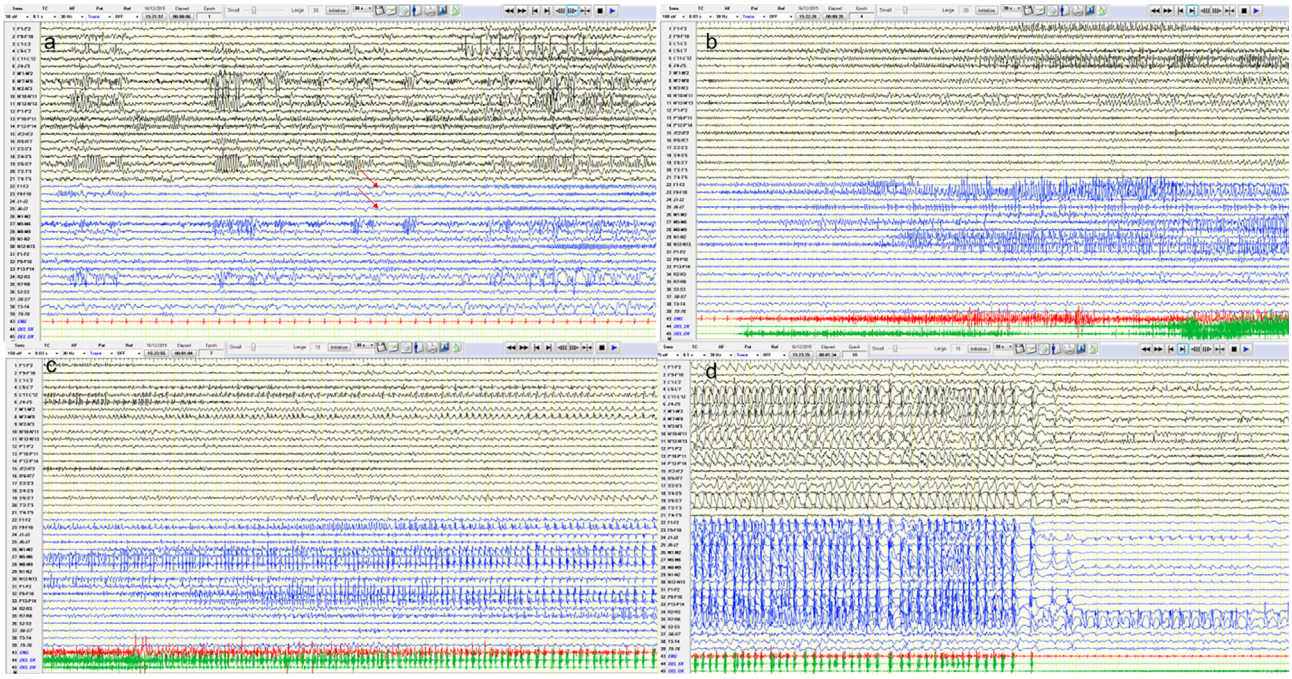

Fig. 3. Ictal stereo-EEG findings. The figure illustrates the ictal discharge during stereo-EEG. Left-sided electrodes are shown in black, right-sided ones are shown in blue. The seizure started in electrode J (mesial and lateral), one second later the mesial leads of electrode F are involved (red arrows, panel a and b). Notice the fast involvement of the right motor cortex and contralateral homologous regions. At the end of the seizure, electrical depression was evident in the right premotor and motor areas (panel c and d). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

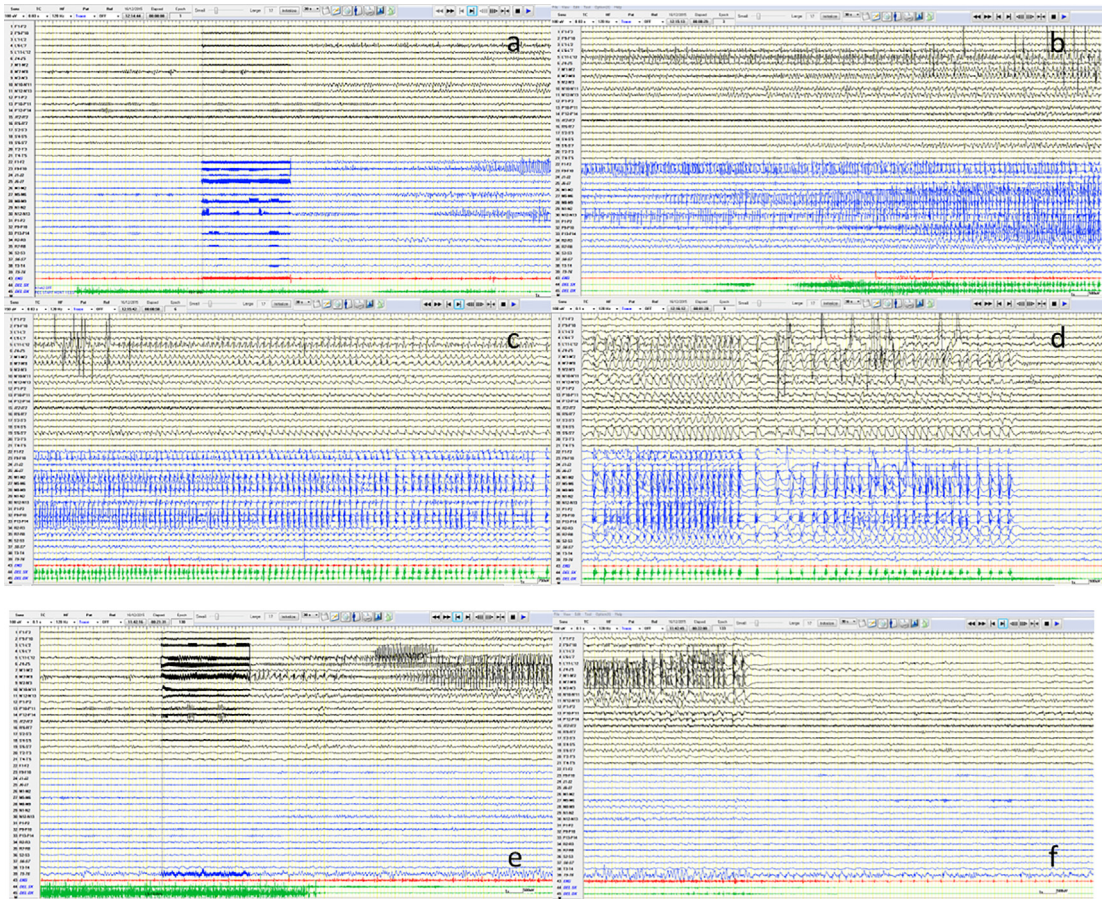

Fig. 4. Intracerebral electrical stimulations. In panels a)–d), the high frequency stimulation of F6-7 at 1 mA inducing a seizure similar to the spontaneous one. In the panels e) and f), the high frequency stimulation of L'6-7 at 0.8 mA provoked just the motor manifestations in the contralateral side. Left-sided electrodes are shown in black, right-sided electrodes are shown in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

surgery without further invasive methods [19]. However, even if a clear lesion is present, despite the importance of identifying a neuroradiological lesion, this does not represent with certainty the same site as the epileptogenic zone. Only when there is agreement between the electroclinical information and the structural lesion [20] doe this provide concordance to pursue surgery [14,21]. Also important and complementary to decision-making are post-processing neuroimaging investigations including brain PET as well as neuropsychological evaluation [14,21]. The essential prerequisite for successful epilepsy surgery is an accurate presurgical evaluation clearly defining epileptogenic brain areas to remove and designing a resection plan tailored for each patient, without producing any significant functional impairment [21–22]. Presurgical evaluation is a multidisciplinary approach based on the degree of complexity [14,21]. Little is reported in the literature regarding incidental neuroradiological lesions that are not responsible for the origin of the patients' epilepsy [23–24]. Moreover, few cases of multiple FCD have been reported [25], and invasive EEG is typically necessary to establish a solitary EZ.

Our case is exceptional. Not only were we faced with an 'innocent' lesion, but the EZ resided in the hemisphere contralateral to the visible lesion present on brain MRI in the region containing FCD type I. We initially had strong support from clinical data (lateralized jerks and postictal paresis) to support our hypothesis regarding correct localization of the EZ. Nevertheless, the scalp EEG findings (bilateral interictal abnormalities and limited localizing ability of ictal EEG recordings) with the presence of a contralateral lesion on the brain MRI placed us at a crossroads to either exclude the patient from surgery due to bilateral hemispheric involvement or perform bilateral stereo-EEG implantation in an effort to offer surgical resection. We chose the second option considering the strong clinical data and the fact that the seizures always maintained the same characteristics over time. From the stereo-EEG analysis, although the left-sided lesion had pathological electrical activity but without confirming the suspicion of FCD type II, the spontaneous seizure and the one induced by electrical stimulation, confirmed an active right precentral EZ. A further important element that indicated the right frontal EZ localization, was the very good response to the RTC performed exclusively in the right fronto-central electrode contacts.

Conclusion

This case report demonstrates that presurgical evaluation requires an organized approach and should be tailored to the individual patient. Moreover, the presence of a brain lesion on MRI should not be considered sufficient to propose epilepsy surgery, although a complete evaluation of anatomic and electroclinical data is necessary. In a presurgical evaluation, invasive methods are an important opportunity to clarify doubts and discordance. Only with an invasive evaluation with SEEG was it possible to establish the EZ in the contralateral frontal lobe in addition to validation using thermocoagulationfor localization and extent of the EZ.

We suggestion that the presence of a contralateral structural lesion on brain MRI does not contraindicate epilepsy surgery. How-

ever, this should represent a 'red flag' in tapering ASMs after surgery, even in the absence of recorded seizures, due to the inherent possibility that the lesion may have intrinsic yet unexpressed epileptogenic activity.

Ethical statement

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

The patient gave informed consent to the surgical procedure and to the reviewing of data for scientific purposes. The present retrospective study received the approval of the Niguarda Hospital ethics committee (ID 939–12.12.2013).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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