Surgical indication and controversies in temporal lobe epilepsy of uncertain lateralisation associated with a unilateral glioneuronal lesion: report of two cases

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Abstract
Surgery is the therapy of choice in patients with drug-resistant temporal lobe epilepsy. The best outcome is obtained when clinical data, EEG and neuroimaging correlate in pointing out a unilateral involvement. In some cases, however, seizures can arise in an apparently independent manner from both temporal lobes, featuring a bitemporal epilepsy. In these cases, patients are frequently considered not eligible for surgery. However, several studies have shown that scalp-EEG appears not reliable in lateralizing the epileptogenic focus. On the contrary, invasive EEG has been proven able to identify a unilateral origin of seizures in more than 70% of patients who had been classified as bilateral with the non-invasive monitoring. We report two cases with similar features: drug-resistant temporal lobe epilepsy, a temporal epileptogenic lesion on brain MRI, non-invasive Long-Term Monitoring Video-EEG evidence of seizures originating from the temporal lobe contralateral to the lesion and bilateral interictal EEG abnormalities.

KEY WORDS: bitemporal epilepsy, temporal lobe epilepsy, video-EEG, epilepsy surgery.

Introduction
Temporal lobe epilepsy (TLE) is known as one of the best indications for surgery: 60-90% of patients suffering from mesio-temporal epilepsy are seizure-free after unilateral temporal lobe resection (1-3). However, patients in which clinical data and presurgical investigations suggest a bitemporal epilepsy (BiTLE), may not be ideal surgical candidates since they have worse surgical outcomes due to the difficulty in identifying a unilateral seizure onset, or due to the presence of a genuinely bitemporal seizure origin (4). On the other hand, recent studies have demonstrated that seizure reduction and/or seizure freedom are possible in patients with features of BiTLE on EEG monitoring (5). According to a recent meta-analysis, 73% of patients defined as bitemporal after scalp EEG recordings, are discovered to be unilateral on intracranial EEG (iEEG); indeed 67% of them have a good outcome (Engel's class Iand II) after temporal lobectomy (6). The presence of an epileptogenic lesion on the MRI examination such as glioneuronal tumors (GNTs), focal cortical dysplasia (FCD) or hippocampal sclerosis (HS) in a patient with features of BiTLE on non invasive EEG poses a further challenge with regards to management strategy: should we consider these lesional patients suitable for an epilepsy surgery directly, without further investigations? Do we have to differentiate these three different lesions in the decision-making process since the evidence of a glioneuronal tumor could justify an early first-step lesionectomy in order to characterize histological and molecular features for a more precise diagnosis and a better definition of tumor behaviour and epileptogenic mechanisms? (7-9). We report two challenging cases with epilepsy of uncertain lateralisation and MRI suspicion of unilateral glioneuronal tumor and we discuss the possible indications for surgery.

Case report 1
A 46-year-old right-handed man with drug-resistant epilepsy was brought to our attention for a pre-surgical evaluation. Seizures had started at the age of 37 and were initially characterized by sudden loss of consciousness, diffuse stiffening, tongue biting, followed
by post-ictal wandering. Seizure frequency was of 3-4 per year. He was initially treated with topiramate without efficacy, and afterwards with carbamazepine obtaining a seizure-free period of six months followed by the reappearance of episodes with increased frequency (1 or more per week) and with different semiotic features: seizure onset usually during meals with incongruous speech, staring, bilateral gestural automatisms (perhaps with right prevalence), lasting a few seconds, followed by a quick recovery, with amnesia of the event. Levetiracetam was introduced as an adjunctive therapy with a mild decrease of seizure frequency. Also an attempt with lacosamide and then perampanel was made in the following months but both drugs had been suspended for lack of effect and lack of tolerance respectively. A brain MRI (Fig. 1 B) revealed a lesion in the right amygdala and hippocampal head resembling a Dysembryoplastic neuroepithelial tumour (Dnet). Neuropsychological assessment showed a low cognition level (Q.I. = 57) and specific deficits in long-term visuo-spatial memory, and constructive praxis. Long-Term Monitoring Video-EEG (LTM-VEEG) with 10-10 system showed interictal polyphasic sharp waves over both the temporal lobes, in a synchronous and asynchronous manner, with no prevalence in frequency. We recorded six seizures similar to the habitual ones, characterized by motor arrest, staring, followed by bilateral gestural automatisms, prevalent on the right and sometimes oro-alimentary automatisms. In one case, we recorded orientation of the head to the right and unilateral right gestural automatisms. From an EEG point of view seizures were all characterized by the appearance of a short desynchronization on T3, followed by a burst of rhythmic, sustained theta-delta activity at 4-5 Hz, clearly arising from the left temporal regions with maximum amplitude on T3 and T5. About 4-8 seconds after the onset, the discharge spread to the homologous regions of the contralateral hemisphere appearing visible mostly on F8, T4 and F10 (Fig. 1 A). Brain FDG-PET scan showed hypometabolism in the anterior neocortex of left temporal lobe (Fig. 1 C).

Case report 2

The second patient is a right-handed 54-year-old man who had his first seizure at the age of 18 with loss of consciousness without prodromal signs. After about 3-4 months, while he was participating in a bicycle race, he had a second seizure similar to the previous

Figure 1 A-C - A. Seizure discharge arising from the left temporal regions; about 4-8 seconds after the onset, the discharge spreads to the homologous regions of the contralateral hemisphere; B. MRI IR Coronal (on the left) and T2 Axial (in the middle) showing a lesion in the right amygdala and hippocampal suggestive for Dnet; C. Brain FDG-PET scan showing hypometabolism in the anterior neocortex of left temporal lobe.
episode. An EEG identified epileptogenic abnormalities therefore antiepileptic treatment was started. After the introduction of therapy (phenobarbital, primidone, diontoine, gabapentin, oxcarbazepine, levetiracetam, all without full benefit) seizures semiology changed: he manifested staring, continued his momentary action but was unable to comprehend or speak. The patient had no prodromal signs nor memory of the episode, but after each episode (which lasted about 3-4 minutes), he was aware that something had happened. Seizure frequency was about one every month. He came to our attention for a surgical evaluation, 36 years after the onset. At that time, he was taking lacosamide and oxcarbazepine.

A brain MRI revealed a lesion in the left temporal pole compatible with Dnet (Fig. 2 B).

Neuropsychological assessment showed a mild low cognition level (Q.I. = 86) and specific deficits in executive functions.

LTM-VEEG showed an interictal epileptiform activity present only during sleep and characterized by polyphasic sharp waves often followed by slow wave over the right temporal region (maximum amplitude on F8, T4 and F10). Less frequently, epileptiform interictal activity (spikes, sharp waves, short bursts of low voltage rapid activity) were present over the left temporal region (maximum amplitude on F7, T3 and F9). We recorded two seizures having different clinical features compared to the usual ones. Both seizures occurred during sleep: the patient lifts up his right hand flexed to the head, after a few seconds he has a tonic deviation of the head to the left followed by generalised tonic-clonic jerks. From an EEG point of view seizures were characterized by a theta-rhythmic discharge, arising from the right anterior temporal region spreading to the whole brain area; in one case the discharge appears to be preceded by a desynchronisation of the background activity on the anterior left temporal region (Fig. 2 A).

Brain FDG-PET/MRI co-registration showed a clear hypometabolism corresponding with the lesion (Fig. 2 C).

Discussion

We described two patients affected by drug-resistant temporal lobe epilepsy, with presence of a temporal epileptogenic lesion on MRI and LTM-VEEG evidence of contralateral seizure onset and bilateral interictal abnormalities.

In patients with temporal lobe epilepsy, a bilateral
independent temporal lobe epileptiform activity is frequently found (10-11). In cases in which clinical findings and presurgical examinations lead to a bitemporal or undefined epilepsy, the selection of suitable surgical candidates can be difficult and debatable to the point that some authors consider BiTLE a contraindication to surgical treatment (4, 12, 13). Nevertheless, many studies indicate that the evidence of bilateral or ambiguous laterality of temporal lobe seizure onset on scalp EEG should be considered as a poor indicator of uni- or bilaterality of seizure onset (13-17). According to these studies, the diagnostic confirmation of bilateral temporal lobe epilepsy requires iEEG, which can lead patients to be considered for surgery although seizure-freedom in these cases is less probable than expected in unilateral temporal lobe epilepsy (13-17).

Moreover, a recent meta-analysis concluded that in 73% of patients with presumed BiTLE on the basis of scalp EEG recordings, were actually affected by unilateral temporal epilepsy when studied with iEEG (6).

In both our cases, MRI showed a lesion, a feature which is usually associated with a good outcome even in the presence of discrepancy with the EEG data (6, 14). The presence of GNT can be often associated with FCD (usually type I) or, less frequently, with HS; the specific role of each lesion in epileptogenesis is still undefined and may underlie a widespread epileptogenic network (7, 8). Although GNT are low grade tumors, they may eventually incur a malignant transformation (18, 19): for this reason and also for the evidence of good outcome after surgery, an early surgical approach can be an appropriate therapeutic option in the decision-making process although the optimal surgical strategy (lesionectomy or tailored resection) remains controversial (8, 20).

In our opinion, these patients can be considered as affected by a potentially unilateral temporal lobe epilepsy in relation to the presence of an epileptogenic temporal lesion. In these cases, as suggested by recent literature, we could therefore choose between performing iEEG in order to possibly confirm our hypothesis and then proceed with surgical treatment or we could directly proceed to surgery, which, as a first-step, could be a lesionectomy. We think that performing an iEEG in a setting like that as in our two patients is eventually the better option as opposed to directly proceeding to surgery. Although certainly a surgical procedure on its own, iEEG does not entail any ablation or excision of tissue and is a low risk, minimally invasive procedure. The benefit of this procedure, as opposed to direct surgical lesionectomy, is that both the treating physicians and the patient are thoroughly informed on the nature of epileptogenesis and on what to expect from a hypothetical surgical procedure in terms of probability of seizure freedom. Direct surgical resection of the lesion will most certainly lift the doubt on the nature of the lesion and reduce or eliminate the threat of future malignant transformation, but on the other hand, it could be a frustrating experience, at the least, both for the patient as well as for the treating physicians, to perform a lesionectomy just to find out that the nature of the lesion poses no threat at all but the seizures continue due to a clear contralateral origin. iEEG is therefore, in our opinion, the initial procedure of choice and the preferable method for both cases would be the Stereo-EEG instead of the subdural electrodes implantation since the first method would provide more information allowing the exploration of deep regions such as the mesial structures; moreover, considering a bilateral exploration, the SEEG has definitely a lower complications rate than subdural electrodes implantation (21). If the iEEG evaluations showed unilateral ictal onset contralateral to the lesion we would not consider the patients suitable for epilepsy surgery and we would perform MRI follow-ups of the lesions instead.

References

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