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Resective Surgery in Tuberous Sclerosis Complex, from Penfield to 2018: a critical review.

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Abstract

Medically treated patients suffering from tuberous sclerosis complex (TSC) have less than 30 % chance of achieving a sustained remission. Both the international TSC consensus conference in 2012, and the panel of European experts in 2012 and 2018 have concluded that surgery should be considered for medically refractory TSC patients. However, surgery remains currently underutilized in TSC. Case series, meta-analyses and guidelines all agree that a 50 to 60 % chance of long term seizure freedom can be achieved after surgery in TSC patients and a presurgical workup should be done as early as possible after failure of two appropriate AEDs. The presence of infantile spasms, the second most common seizure type in TSC, had initially been a barrier to surgical planning but is now no longer considered a contraindication for surgery in TSC patients. TSC patients undergoing presurgical evaluation range from those with few tubers and good anatomo-electro-clinical correlations to patients with a significant “tuber burden” in whom the limits of the epileptogenic zone is much more difficult to define. Direct surgery is often possible in patients with a good electro-clinical and MRI correlation. For more complex cases, invasive monitoring is often mandatory and bilateral investigations can be necessary. Multiple non-invasive tools have been shown to be helpful in determining the placement of these invasive electrodes and in planning the resection scheme. Additionally, at an individual level, multimodality imaging can assist in identifying the epileptogenic zone. Increased availability of investigations that can be performed without sedation in young and/or cognitively impaired children such as MEG and HR EEG would most probably be of great benefit in the TSC population. Of those selected for invasive EEG, rates of seizure freedom following surgery are close to cases where invasive monitoring is not required, strengthening the important and efficient role of intracranial investigations in drug-resistant TSC associated epilepsy.

Keywords: Epilepsy surgery, Pediatric epilepsy surgery, Childhood epilepsy, Tuberous Sclerosis, Tuberous Sclerosis Complex

Introduction

Tuberous sclerosis complex (TSC) is a rare genetic disorder occurring in about 1/5800 live births [1,2] with a population prevalence of around 1/20,000 and an estimated 1 to 2 million individuals affected throughout the world [3]. Mutations of TSC1 or TSC2 are detected in more than 95% of patients with current molecular techniques [4]. These mutations cause suppression of mTOR inhibition, producing an excessive activation of the mTOR signaling pathway and several abnormalities in cell cycle regulation. The most common findings are tumors in the skin, brain, kidneys, lung and heart that can lead to organ dysfunction. Disease manifestations in different organ systems can vary widely, however, those related to the brain result in the greatest morbidity and mortality. Specifically, epilepsy and TSC-associated neuropsychiatric disorder (TAND) cause the greatest burden [5].

The current clinical diagnostic criteria of TSC consist of 11 major features, one of which is 'cortical dysplasias' which includes tubers and cerebral white matter radial migration lines [6]. Cortical tubers, also known as glioneuronal hamartomas, are considered to be the primary lesions underlying TSC-associated epilepsy.

Cortical tubers are observed in nearly 80 to 90% of TSC patients. Seventy-five to 90% of TSC patients present with epilepsy and more than 50% of these patients develop drug-resistant epilepsy [1,7,8], underscoring the need for alternative treatments [9]. The 2012 International TSC consensus conference concluded that "epilepsy surgery should be considered for medically refractory TSC patients" [10]. Adding to this, the European panel of experts agreed in 2012 that surgery is "appropriate in TS-associated epilepsy that is inadequately controlled after trials of two anti-epileptic drugs (AEDs) and for well-defined lesions". In their recent 2018 update, they added that "early presurgical evaluation is immediately recommended after failure of two AEDs" and that "multifocal and bilateral lesions do not preclude presurgical assessment or subsequent resective surgery" [11,12] (Table 1). Surgical intervention should therefore be an essential early consideration for drug-resistant TSC patients.

When did epilepsy surgery in TSC begin?

Tuberous sclerosis complex (TSC) was first described by Friedrich Daniel Von Recklinghausen in 1862 in a newborn baby who "died after a few breaths" because of multiple cardiac "myomata". Numerous sclerotic areas were found in the baby's brain [13]. In 1880, 18 years later, Désiré-Magloire Bourneville described multiple hypertrophic sclerotic lesions affecting more or less extended parts of different circumvolutions of the brain of a deceased "mentally defective epileptic child" [14] (Figure 1). The patient presented with facial angiofibromas and renal tumors. What was especially striking for him was the localization of the sclerotic lesions in the gray matter, at the surface of the brain, as opposed to those sclerotic lesions already described in multiple sclerosis affecting essentially the white matter. Alfred Vogt then clearly defined the syndrome of "mental deficiency, epilepsy and adenoma sebaceum" in 1908 [15].

The first report of a surgical intervention for epilepsy in patients with TSC was in 1957 [16]. Ernest Adolf Spiegel reported two patients. In the first one with possible spasms and generalized tonic-clonic seizures, they performed an electrolytic lesion of a calcified nodule located in the right caudate and ansa lenticularis. The second patient with bilateral tonic seizures underwent right-sided pallidotomy. The first patient had no seizures during the two-year post-operative observation period whereas in the second patient “seizures returned after one week and further lesions seemed necessary at five months follow up”.

Two further patients, one reported by Maccagnani (1959) [17] and one by Gastaut (1965) [18], underwent surgical removal of a subependymal calcified nodule, the first of whom had an arrest of seizures, the second of which had no modification of seizures.

Finally, Jacques Achslogh, in his review of epilepsy surgery in phakomatoses in 1964 [19], described a 21-year-old patient who underwent left cortical parietal resection with a neuropathological report compatible with a tuber. Interestingly, the authors discussed that the patient had a “*forme fruste*” of TSC with no other clinical symptoms suggesting TSC, except a mild speech delay and learning difficulties and one cannot exclude that this case was not just a focal cortical dysplasia (FCD) case (see below). In fact, the hypothesized existence of “*formes frustes*” of the disease combined with the emergent concept of anatomo-electro-clinical correlations developed by Wilder Penfield and Herbert Jasper (and across the Atlantic by Jean Bancaud and Jean Talairach) lead the Montreal team to attempt to treat seizures associated with TSC neurosurgically removing the epileptogenic focus in seven patients [20]. All cases were thoroughly described; case 1 for example was a five-year-old French Canadian girl who presented with “uncontrollable burst of laughter followed by twitching of the right side of the face”. Surgery was performed in 1950 by Penfield and consisted of the “removal of a portion of the precentral and postcentral gyri for the face”. The neuropathology report revealed the presence of “giant neurons, calcium deposits and invasion of all cortical layers by very large astrocytes with bizarre forms”. Twenty-two years after this original publication, the same center re-reviewed this case series and concluded that only two of the seven cases (including the example above) had a definite diagnosis of TSC, while the others should probably have been classified not as having a “*forme fruste*” of TSC but as having an FCD [21]. These two “definite” TSC cases both had an excellent long-term outcome, for case 1 this persisted to 47 years of follow-up. Thus these two patients, one operated in 1950 and the second one operated in 1966 should therefore be considered as the first two published patients with TSC and cortectomy including tuber resections that led to seizure freedom.

Surgical series since then

Over the following 30 years, there was a paucity of publications on surgery in TSC, with only about ten new cases in the literature [22–24] until the 1993 Mayo Clinic series of nine patients [25]. All nine patients had magnetic resonance imaging (MRI), which was a first in the TSC literature. Seven of these nine patients had a follow-up of more than two years and 62% of them remained seizure free. In 2004, the long-term outcome of seven of these patients and 15 subsequent Mayo Clinic cases (22 patients total) was reported, with a 59% Engel I outcome at one-year follow up and 42% Engel I outcome at five-

year or more of follow up. Only 23% of the Engel I patients at one year had subsequent seizure recurrence when followed for five years or more [26].

The publication of numerous retrospective surgical series focusing on TSC patients then followed the development of epilepsy surgery centers across the world. We identified 22 retrospective surgical series with more than five operated patients published since 1993 (exclusion of posters, abstracts and series in review articles and if multiple publications of the same team the biggest cohort was kept), which represents a total of 380 patients, detailed in Table 2 [21,26–43][44][45,46]. The multicenter retrospective study of Madhavan with 70 patients was not included since portions of this work were published in prior reports [47]. Extremely variable time of post-operative follow-up are mentioned leading to numbers ranging from 25 to 90% seizure freedom after surgery. When restricting to series with more than ten patients with at least two -years of follow-up, seven series remain (Table 3). We chose to restrict to studies with at least two years of post-operative follow-up as this has been shown to predict longer-term outcome [48]. The number of patients in these later series range from 17 to 51 with a seizure free rate of 50 to 60% (Table 3). Interestingly, the long-term outcome series of Liang [27] has shown a statistical difference between seizure freedom of patients at one-year follow-up and five-year follow-up but not between five- and ten-year follow-up. Finally, three meta-analyses found similar results, one published in 2007 and two in 2013, with 177 [49], 181 [50] and 229 [51] patients showing 57%, 56% and 59% of patients with an Engel class 1 outcome respectively (Table 4).

This seizure freedom rate after surgery in TSC patients is in line with the 58% seizure freedom reported in surgical series in patients with other pathogenic variants of mTOR pathway genes [52]. This outcome is also in the reported range in global epilepsy surgery data [53], but around 10% lower than what was recently reported in European centers [54].

Preoperative factors that may predict surgical outcome were identified in the three previously mentioned meta-analyses (Table 4). The presence of tonic seizures and an IQ<70 were individually associated with poor seizure outcome [49], whereas the onset of seizures after one year, lateralized ictal and interictal EEG, lobectomy, absence of generalized semiology, no or mild developmental delay, unifocal ictal EEG and EEG/MRI concordance were each identified as positive predictive factors [50,51]. In a further examination of their meta-analysis data, Ibrahim et al. have applied partial least squares to reduce multicollinearity and identified focal ictal EEG and concordance of EEG and MRI abnormalities as the most predictive factors of good outcome [55]. These latter conditions are in fact those found in patients with good anatomo-electro clinical correlations and as a result the management approach mirrors that of FCD II (see below). However, the majority of TSC patients do not fall into this category [28,56] and the challenge remains to localize as best as possible the epileptogenic focus.

Are TSC2 patients poor candidates for presurgical evaluation?

Commercially available mutational analysis detects TSC1 or TSC2 mutations in 85 to 90% of patients who meet the clinical diagnostic criteria of TSC [4]. De novo mutations account for about 80% of TSC cases

and the prevalence of TSC2 mutations is four times that of TSC1 mutations among de novo cases whereas it is approximately equal among familial cases [7].

Phenotypic variability remains striking in TSC patients, as shown for example with extremely different TSC manifestations in identical twins or affected members of the same family who share the same mutation of the same TSC gene. It has been hypothesized that the variability of tumor formation from one patient to another could be explained by the “second hit” hypothesis, where a tumor arises after one or more additional mutations affects the function of the second previously normal allele in the tumor forming tissue [57]. Recent research in epigenetics might also give clues to explain this phenotypic variability [58,59].

Genotype-phenotype analyses consistently show that TSC2 mutations, the most frequently found mutation, tend to cause a more severe phenotype than TSC1 mutations. TSC2 patients having an earlier age at seizure onset, lower cognition index, and a greater tuber load than those with a TSC1 mutation [60]. The presence of a TSC2 mutation will often be associated with an increased tuber burden (both size and number) within which the epileptogenic network has developed and, therefore, finding the epileptogenic zone proves far more complex in these patients.

In our 22-series literature review (Table 2), mutational analysis was inconsistently available and while some patients with TSC2 mutations had a good outcome, there were insufficient data to draw an overall conclusion regarding the prognostic value of TSC1/TSC2 mutations. The three meta-analyses that examined predictors of seizure outcome did not separately analyze mutational genotypes. Some potential biomarkers of TSC2 mutations such as multifocal computed tomography/MRI findings [49], tuber burden [50] and number of cortical tubers (> or <4) [51]) were factors not significantly linked to seizure outcome whereas seizure onset before one year and low IQ were found to be predictors of worse outcome. Nonetheless, in the recent series of Fohlen et al., six of the 15 patients were operated before one year of age, four of them remaining Engel class I at more than two -years follow-up [43].

Considering the frequency of TSC2 mutation and these later results, TSC2 mutations should not exclude patients from surgery though these patients may need a more complex presurgical evaluation.

Should the presence of infantile spasm exclude the patient from surgery?

The second most common seizure type reported in TSC patients after focal seizure is infantile spasms [7]. The “natural” history of the advent of spasms in patients with TSC has been well described in previous reviews articles [61,62] : “Subtle focal seizures such as unilateral tonic or clinic phenomena mainly localized to the face or the limbs can be unrecognized by the parents until the third or fourth month of life when spasms occur. Isolated attacks develop within weeks into a typical cluster, especially upon awakening. However, lateralizing features such as tonic eye deviation, head turning, unilateral grimacing, and asymmetrical movements of the limbs may be observed. In the same child, focal seizures may precede, coexist or evolve into infantile spasms” [61]. These lateralizing signs have suggested a focal

origin of spasms in TSC patients and this has regularly been confirmed by seizure freedom being obtained after cortical tuber resection [29,63–65].

In their retrospective multicenter survey, Madhavan and colleagues [47] identified a “history of infantile spasms” as a poor prognostic factor with regards to post-operative seizure control. In contrast, in three meta-analyses, infantile spasms did not significantly correlate with seizure outcome after surgery [49–51]. Moreover, surgery for refractory spasms of focal onset has been recently reported in 68 patients with various pathologies with a postsurgical outcome similar to that of other seizure types [65].

The presence of infantile spasms should not exclude TSC patients from surgery. Even more, the presence of pharmaco-resistant infantile spasms could be an indicator for immediate referral to epilepsy surgery centers, considering the even further elevated risk for neurodevelopmental sequelae known to be associated with infantile spasms and that early surgery in children with infantile spasms has been shown to lead to higher gains in post-surgical cognitive development[66].

Time point to surgery regarding medical treatment

The international TSC consensus conference in 2012 concluded that “vigabatrin is the recommended first-line therapy for infantile spasms” and that “anticonvulsant therapy in TSC patients should generally follow that of other epilepsies”[10]. The European panel of experts confirmed that “vigabatrin is the first-line monotherapy in TSC related spasms or focal seizures in children under one year of age”, that “antiepileptic drug combination therapy is appropriate when first line therapy has failed” and that “early presurgical evaluation” should be the next immediate step “after failure of two AEDs”[12].

Everolimus, an mTOR inhibitor, is now available and the same panel of experts have concluded that “introduction of everolimus as add-on therapy should be considered if TSC-associated seizures are refractory to two AEDs”[12]. In the randomized, double blind EXIST-3 trial, 40% of patients treated with everolimus achieved a $\geq 50\%$ reduction in seizure frequency during a three-month maintenance period[67]. Yet, although promising, these results do not compare to the 50 to 60% long-term seizure freedom rates after surgery. Thus everolimus treatment should not delay either an invasive EEG exploration or direct surgery resection.

General surgical approach in TSC patients: in the search of the focal onset

The pre-surgical assessment of patients with TSC and intractable epilepsy begins with a careful review of the long-term video-EEG monitoring. As in all pre-surgical assessments, interictal abnormalities, ictal seizure pattern and semiology should be scrutinized. One must bear in mind that connectivity might be altered in TSC patients with multiple cortical and subcortical lesions and that semiology may not follow the same patterns observed in cryptogenic or single-focus lesion patients.

The interictal EEG will often be characterized multi-focal or diffuse abnormalities, however a prominent focal interictal abnormality can occasionally be identified within this background, providing localizing evidence for a focal epileptogenic zone. Likewise, a diffuse ictal discharge can be preceded by very focal changes (bursts of fast activity, slow/rhythmic activity or disappearance of underlying interictal rhythms). Such seizure can be associated with both focal or non-localizing semiology. Importantly, successful surgeries have indeed been reported in the setting of abundant generalized or bilateral epileptiform discharge [68].

Ultimately the electroclinical hypothesis obtained, whether unique or multiple, are confronted with the anatomical MRI of the patient in search of a correlation with the tuber(s) location(s).

Some TSC patients will have a single anatomo-electro-clinically concordant “stand out” tuber, i.e. a significantly larger, dysplastic and sometimes calcified tuber that will match the electro-clinical hypothesis, in which case, the resection of this “stand out” tuber will have a very good chance of leading to good seizure control [69][28](exemplary case 1). In others cases, including those with a single “stand out” tuber on MRI, anatomo-electro-clinical data is non-concordant and multiple tubers will be considered candidates, whether unilaterally or bilaterally [70](exemplary case 2).

When multiple seizure types are identified in a single patient, it is important to identify a ‘candidate tuber’ for each seizure type by assessing the anatomo-electro-clinical data. Likewise, when a new seizure type develops following an initially successful resection, a previously ‘quiet’ tuber may now be the epileptogenic zone and the ‘candidate tuber’.

In general, the more complex the case, the more variable the surgical approach among centers. Some teams will propose a multistep surgery where each surgery will aim at stopping a targeted seizure type, starting with the most disabling ones. Other teams have suggested that remote seizure and interictal foci may appear immediately following resection of an apparently primary focus and propose multistage surgery with grid/strips and depth electrodes being placed and replaced after a first resection during a “single” monitoring [69].

Identifying the epileptogenic zone in TSC

Over the years, numerous non-invasive tools have been used in the presurgical work-up of patients with drug-resistant TSC-associated epilepsy (Table 5). Multimodality imaging has thus proven useful in some series [30,31,71][44] and although the general principal that concordance among different modalities predicts better outcome has not been objectively demonstrated in TSC patients, when available, these tools should be considered in complex TSC cases being assessed for epilepsy surgery.

Non-invasive evaluations

MRI data

In the last 30 years, the use of clinical anatomical MRI has permitted the expansion of epilepsy surgery. The first series listed in Table 5, Guerreiro et al. [21], is the last to report cases operated without MRI (6 of 18 cases). In all the following studies MRI was performed in all patients, ranging from 0.5T to 3T MRI.

Nonetheless, when no “stand out” tuber is found, distinguishing epileptogenic and non-epileptogenic lesions on anatomical MRI remains difficult. The large size of the tubers or their location [72,73], the presence of calcification and/or “cyst-like appearance [74], the specific aspect of the tuber center [45] have been suggested to be indicators of epileptogenicity but have not been shown to be adequately predictive of epileptogenicity in a pre-operative setting [69]. With the ongoing hypothesis that the malformed tissue surrounding the cortical tuber might be part (or even the core) of the epileptogenic zone, studies have suggested that careful identification of perituberal abnormalities might be more informative in choosing the right tuber or group of tubers for investigation and/or resection than the tubers themselves. “FCD-like” changes in perituberal regions, including specifically increased cortical thickness and abnormal gyral patterns, have been described as being both more sensitive and more specific to localize the epileptogenic zone than the typical signs of tubers [75]. In this light, 7T MRI which has recently been used in 13 TS patients, might allow a better evaluation of subtle lesions and perituberal details [76].

The UCLA team has reported on the use of diffuse tensor imaging (DTI) in distinguishing epileptogenic from non-epileptogenic tubers on MRI. Chandra et al. studied 15 patients and concluded that higher apparent diffusion coefficient (ADC) was significantly increased in the subtuber white matter of epileptogenic tubers as compared to those non-epileptic tubers [71]. Yogi et al. found that maximum ADC measurements in regions of interest comprising tuber and perituberal cortex had 81% sensitivity and 44 % specificity for correctly identifying the epileptogenic tuber [77].

While possible indicators of epileptogenicity, these findings cannot be solely used to identify the tubers for resection.

Source localization procedures

The diagnosis of epilepsy and the preoperative functional evaluation of neurosurgical patients is one of the established clinical indications for magnetoencephalography (MEG) examinations [78]. Electromagnetic source imaging, whether MEG or high resolution EEG (HR EEG), has been applied to TSC surgical candidates. In most of the studies, source localization procedures used dipole modeling and have been applied on interictal spikes. More rarely, the sources of ictal signals have been assessed.

Correlations of MEG results to the localization of the ictal onset zone are available in four of the 22 retrospective studies reviewed. Among the six patients of Jansen’s series [37], five had MEGs, all had results concordant with EcoG, four of these five patients had an Engel 1 outcome and the only patient with an Engel 4 outcome had residual tuber on post-operative MRI. Wu’s series focused on surgery in TSC patients with no invasive presurgical evaluation. All 18 patients had a MEG performed: four were non-localizing, 14 localized the interictal dipole to a single tuber or to a group of closely located tubers, two patients had an ictal MEG with dipoles that matched the interictal dipoles in the same MEG study.

Complete removal of the MEG dipole clusters correlated significantly with seizure freedom [30]. Among the 37 patients of Arya's series, 20 had a MEG. In 13 (65 %) MEG dipoles were concordant with the ictal onset zone found on intracranial EEG [41]. Finally among the seven patients of Koptelova et al.'s study, MEG localized the epileptogenic zone in three seizure-free patients and mislocalized the epileptogenic zone in one other seizure-free patient [42]. Finally, the Toronto group in a prior series than that one listed in Table 2 (which comprised fewer patients) reported on eight TSC operated patients in whom the resection covered the MEG cluster in seven, six of which became seizure free [79].

Interictal HR EEG results have been reported by Kargiotis et al. in six operated patients and helped identify the epileptogenic zone in the four Engel class I patients [44]. Source modeling of ictal activities was reported in four patients by Leal et al., three of whom had subsequent lesionectomy (all three seizure free at six months to one year follow-up). Interestingly sources analysis of ictal EEG was able to localize the generator very near the suspected epileptogenic tubers, at the interface between the most dysplastic brain areas and the normal brain, outside the resection volume. Finally, Amano et al. described a nine-year-old boy in whom ictal HR EEG helped localize an ictal focus and led to invasive monitoring and to subsequent right frontal tuberectomy (associated with the removal of a subependymal giant cell astrocytoma) which led to a seven-year seizure freedom follow-up [80].

Interestingly, a large study comparing MEG and HR EEG concluded that MEG sources were closer to epileptogenic tubers than those estimated by HR EEG [81]. Nonetheless, only three of the 19 patients were operated and validation of the epileptogenic tuber was missing in most patients [81].

These results combined with the fact that MEG or HR EEG are feasible without sedation in young patients or in those patients who present cognitive impairment will probably lead to a more extensive use of MEG and HR EEG in TSC patients, when available.

Positron emission tomography (PET)

[¹⁸F]-FDG-PET will often find multiple areas of hypometabolism corresponding to multiple tubers or clusters of tubers [30,31,82][83]. Nonetheless, Chandra et al., in a series of 15 patients, described that the largest volume of hypometabolism, relative to the tuber size on coregistered [¹⁸F]-FDG-PET /MRI images corresponded to epileptogenic tubers [71]. In Wu's series, a subset of patients, who were not initially considered for surgery, were able to undergo focal resection following localization with [¹⁸F]-FDG-PET /MRI coregistration [30]. [¹⁸F]-FDG-PET has been shown to be useful in a series of seven TSC patients with particularly severe epilepsy who presented with epileptic spasms. The presumed origin of epileptic spasms determined by ictal ECoG was associated with focal [¹⁸F]-FDG-PET hypometabolism in a majority of cases [64], four of them being seizure free at two-year follow up. Thus [¹⁸F]-FDG-PET, now widely accessible in epilepsy surgery centers, is useful at an individual level in complex TSC cases.

Chugani et al. reported the first TSC case explored with [¹¹C]alpha-methyl-tryptophan (α MT-PET) in 1998 [84] and an early series of eight patients examined with α MT-PET was published by Asano et al. in 2000. They concluded that α MT-PET and FLAIR MRI improved detection of potentially epileptogenic tubers

[31]. In 2003, Fedi et al. showed a correlation between increased α MT uptake and frequency of interictal spikes in 8 TS patients [85]. Chugani's team then compared [18 F]-FDG-PET and α MT-PET in TS patients and concluded that focal cortical regions of increased α MT uptake in children is less sensitive but more specific for the lobe of seizure onset than corresponding [18 F]-FDG-PET hypometabolism. Finally, Rubi et al., in a retrospective study of 12 patients, concluded in 2013 that α MT-PET is a specific neuroimaging technique in the identification of epileptogenic tubers but offers low sensitivity [86] (Table 6). Epigenetic advances have shown that microRNA expression is often aberrant in patients with epilepsy, including those with TSC [59] and Chugani's team has recently shown that a distinct microRNA expression profile is significantly associated with α MT positive/epileptogenic tubers, as confirmed by intracranial recordings, providing new insights in mechanistic comprehension of tuber epileptogenesis [87].

Ictal SPECT

Results of ictal SPECT and SISCOM findings in TSC patients has been described in four studies. In five of six patients, Aboian et al. found a dominant SISCOM hyperperfusion lesion which provided further localizing information in three complex cases. All patients underwent surgical resection without invasive EEG monitoring. Three patients were seizure free at two-year follow-up and seizure freedom correlated with the complete resection of SISCOM abnormalities in two cases [32]. Koh et al. described the results of ictal SPECT in 15 TSC patients. In ten, with localized EEG seizure onset, five had concordant hyperperfused SPECT regions. Among five patients with non-localizing ictal scalp EEG, a focal region of hyperperfusion was found in one [88]. SISCOM was part of the presurgical workup in Arya et al.'s series of 37 patients (all of whom had subsequent invasive EEG evaluation) but its concordance with scalp ictal EEG was not significantly associated with better seizure outcome. The 11 operated patients in Kargiotis et al.'s series had a presurgical SISCOM which was concordant with the resection area in four of the seven seizure-free patients (whereas FDG-PET was concordant in six of the seven patients) [41].

EEG-fMRI

It has been shown that EEG-fMRI can provide useful additional data during presurgical evaluation. In TS, Jacobs et al. identified specific interictal active tubers in five patients using EEG-fMRI. The BOLD responses were limited to part of the lesion but extended beyond the tuber border in some cases [89].

These additional non-invasive tools (e.g. ictal SPECT, SISCOM, EEG-fMRI) can therefore assist planning an invasive exploration (positioning of grid/strips or SEEG electrodes) and/or defining the surgical boundaries of resection at an individual patient level.

Invasive presurgical workup

Given that many patients remain with multiple “candidate tubers” after non-invasive investigations, intra-cranial EEG is often required in TSC-associated epilepsy before a resection can be proposed (exemplary case 2). Invasive EEG monitoring has provided surgical treatment strategies for TSC patients previously not considered as surgical candidates. Bilateral explorations are generally used in complex cases and of the cases selected for invasive EEG, rates of seizure freedom following surgery are similar to where invasive monitoring is not required [36].

As can be seen in Table 2, the majority of series published on TSC patients are from North-American teams and as a result, the literature predominantly consists of extraoperative intracranial recordings with grids and strips. Two groups have reported on SEEG investigation in TSC patients [28] [43]. The growing number of centers using SEEG might in the future modify this equilibrium, SEEG being for example extremely useful in patients with deep mesial or insular tubers [43]. One group has reported on a single stage procedure of tuberectomy guided by intra-operative depth and grid recordings [45].

Overall the optimal implantation strategy is still not defined, resulting in wide variation in invasive EEG evaluations and subsequent operative approaches.

Although recent data might temper the conclusions of previous studies [90], it has been repeatedly suggested that high frequency oscillations (HFO) during intracranial recordings might be a specific biomarker of the epileptogenic zone [91]. Okanishi et al., retrospectively, studied the occurrence rate of interictal HFOs during intracranial monitoring in ten TSC patients and found statistically significant correlations between the resection ratio of interictal HFOs (number of channels with interictal HFOs resected/to total number of channels with interictal HFOs), whether ripples or fast ripples, and seizure outcome [92]. Similarly, Fujiwara et al., retrospectively, studied 14 TSC patients explored by grids/strips and have shown the presence of HFO, ripples and fast ripples, at ictal onset in all. Seven of the ten patients with a complete ictal HFO resection were seizure free [93].

What type of surgery?

Various surgical strategies have been described in TSC patients (Table 2) ranging from tuberectomies sparing perituberal cortex to hemispherectomies. Some teams have opted for wide resections which predominantly consist of lobectomies [35] whereas most teams have opted for focal and if possible tailored resection that may nonetheless be unilobar, bilobar or multilobar.

Limited resections were considered in most short series or case reports before 1993 and patients in Bebin et al.’s series benefited from computed tomography or MRI-based volume stereotaxic resections [23,94]. Francione et al., then reported on three patients who underwent lesionectomy associated with cortectomy [95] and in Guerreiro et al.’s series, patients with a focal resection had either lesionectomy or lesionectomy associated with resection of the surrounding cortex [21]. As discussed above, non-invasive presurgical workup usually shows more widely extended abnormalities than seen on commonly used 1.5 or 3 T anatomical MRIs and the question of tuberal or perituberal origin of seizures in TS patients has been a longstanding debate [96]. However, recent work combining strip, grid and tuber

depth electrodes appears to favor seizures arising from tubers, specifically the tuber center, rather than the perituberal cortex. These findings can have implications for both implantation and resection strategies [45,46].

Nonetheless, lobectomies have been found in Zhang et al.'s meta-analyze as a significant predictor of good seizure outcome [51] and recent European experts' recommendations have concluded that "resection beyond tuber margins is associated with greater probability of seizure freedom" (Table 1) [12].

On the surgical point of view, when considering tuber resection, the macroscopic lesion in the operating room can be variably described, such as for example "smooth, whitish, slightly raised nodules that appear as enlarged, atypically shaped gyri ". The firm texture of the tubers and the visible sulcal limits can also be clear borders for resection. As seen in Table 3, ECoG has been regularly used to confirm the epileptogenic focus and/or extend the resection to neighboring spiking cortex. EcoG was especially used when extraoperative intracranial recordings were not performed preoperatively [21,29,30] but also in some teams following these extraoperative recordings [41].

Palliative surgical treatment such as corpus callosotomy and vagus nerve stimulation are also performed in TSC patients but is beyond the scope of this paper. Indications can be found in previous reviews [8,62,70] with a special emphasis on the indication for callosotomy in patients with atonic seizures and the better results of complete versus partial callosotomy in these patients [8].

Conclusion

Case series, meta-analyses and guidelines all agree that a 50 to 60% long-term seizure freedom can be achieved after surgery in TSC patients and a presurgical workup should be done as early as possible in all TSC patients after failure of two appropriate AEDs regardless of their phenotype/genotype profile and of the presence or absence of infantile spasms. This could, in the future, lead to an increased percentage of patients undergoing resective surgery, a therapeutic strategy that is currently underutilized in drug-resistant TSC patients.

Direct surgery might be possible in patients with a good electro-clinical and MRI correlation. Invasive monitoring is often mandatory in other more complex cases and bilateral investigations can be necessary. Multiple non-invasive tools can be helpful in deciding on placement of these invasive electrodes and/or in the decision of the resection scheme and multimodality imaging has proved to be of interest at an individual level in TSC patients. Increased availability of tools that can be performed without sedation in young and/or cognitively impaired children such as MEG and HR EEG would most probably be of great benefit in the TSC population (Box 1).

Exemplary case 1: direct surgery

LB is a right-handed girl diagnosed at 18 months following the appearance of brief behavioral arrest seizures and the presence of hypomelanotic macules. A de novo TSC1 mutation was found. Over time, episodes became longer and associated with facial palor and pupil dilatation. The child could sometimes slowly respond during these seizures. She did not predict the seizure but said, at the end: "That's it, the seizure is gone". A second type of seizure, essentially during sleep, started at 3 years of age characterized by sudden wakening with an anguished look followed by ictal grunts and brief bilateral motor agitation. Long-term video-EEG revealed the presence of bifrontal interictal spikes predominantly on the right and a clear right frontal discharge during the behavioral arrest seizures. Electrographically, the second seizure type consisted of a diffuse, disorganized discharge, best organized in the right anterior region.

MRI revealed the presence of bilateral frontal and temporal tubers with a significantly larger, dysplastic and calcified tuber in the right lateral prefrontal cortex. Direct surgery was performed at age six (Figure 2 and 3) with a tailored frontal cortectomy assuring a complete resection of this right frontal "stand out" tuber. At three years post-resection the patient was free of the later onset motor seizures. Occasional behavioral arrest episodes were reported by family without EEG correlation on subsequent video-EEG.

Exemplary case 2: two-step surgery (surgery following invasive monitoring)

LM is a right-handed boy diagnosed with TSC at six months of age following clusters of seizures with upward eye deviation and a left temporal discharge recorded on his first EEG. MRI revealed multiple bilateral tubers). The patient had hypomelanotic macules and renal cysts. No TSC1 or TSC2 mutation was found. Vigabatrin was initially effective before new seizures began at six and a half years consisting of an arrest of activity, a loss of contact, a tendency to turn to the left accompanied by facial flushing and chewing automatisms. Seizures lasted from 2 to 3 min. Long-term video EEG recorded clusters of subtle spasms not previously detected by the family (Figure 4) and the habitual seizures that began with the same cluster of subtle spasms that evolved electrically into a prolonged bilateral diffuse spike and wave discharges accompanied by the recognized seizure symptomatology (Figure 5 and 6). A focal electrographic ictal onset could not be determined and a diffusion to both temporal lobes was suspected during the habitual seizures. A bilateral invasive monitoring was performed using stereo-EEG (Figure 7). A left frontal tuber showed subcontinuous spike and wave interictal activity. Both subtle spasms and prolonged seizures commenced with a long discharge in this left frontal tuber (Figure 8) that spread during the habitual seizure to both mesial and lateral temporal structures. A left tailored frontal cortectomy was performed with a complete resection of the left frontal tuber (Figure 9). The patient has been seizure free since then (five-year follow-up).

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Box. 1. Key points of this review

- Medically treated epileptic patients suffering from tuberous sclerosis complex have less than 30 % chance of achieving sustained remission
- Resective surgery offers a 50 to 60 % chance of long-term seizure freedom but is underused
- The presence of infantile spasms should not exclude tuberous sclerosis complex patients from surgery
- The presence of a TSC2 mutation, although often associated with a greater tuber burden, should not exclude patients from surgery
- Presurgical non-invasive tools may help define the epileptogenic zone at an individual level
- In complex cases, presurgical invasive recordings are effective in defining the epileptogenic zone

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PLANCHE VI

Face convexe de l'hémisphère gauche.

N, N, N, flots de sclérose.
Pc, flot occupant le pli courbe.
R, sillon de Rolando.
S, scissure de Sylvius.

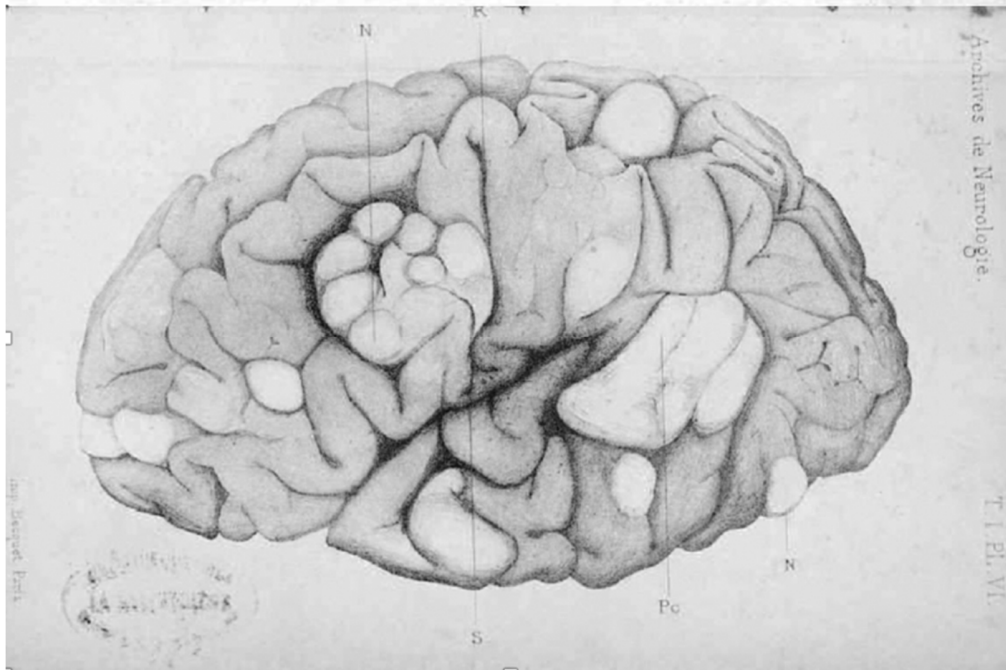


Figure 1: drawing and legend of the convexity of the left hemisphere of a 4 year old boy after autopsy. From Archives de Neurologie Tome 1: 1880-1881. Contribution à l'étude de l'idiotie par Bourneville et E. Brissaud.

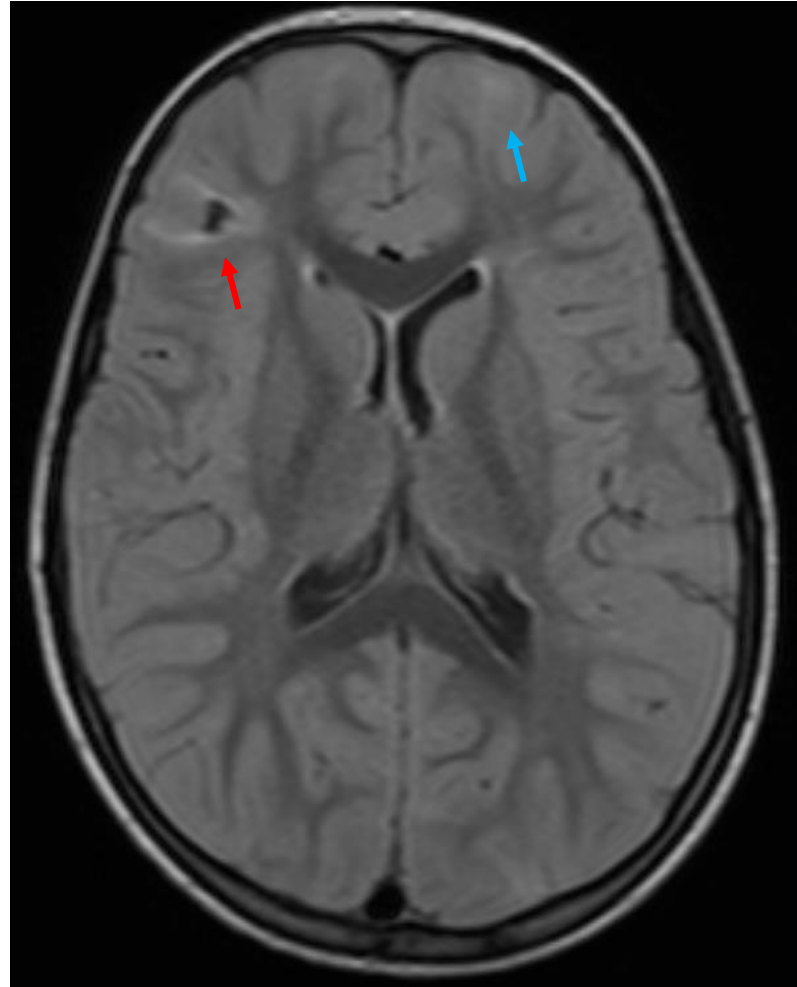


Figure 2 : Axial flair MRI going through the right frontal “stand out” tuber (red arrow). Note other smaller tubers for example in the left frontal lobe (blue arrow).

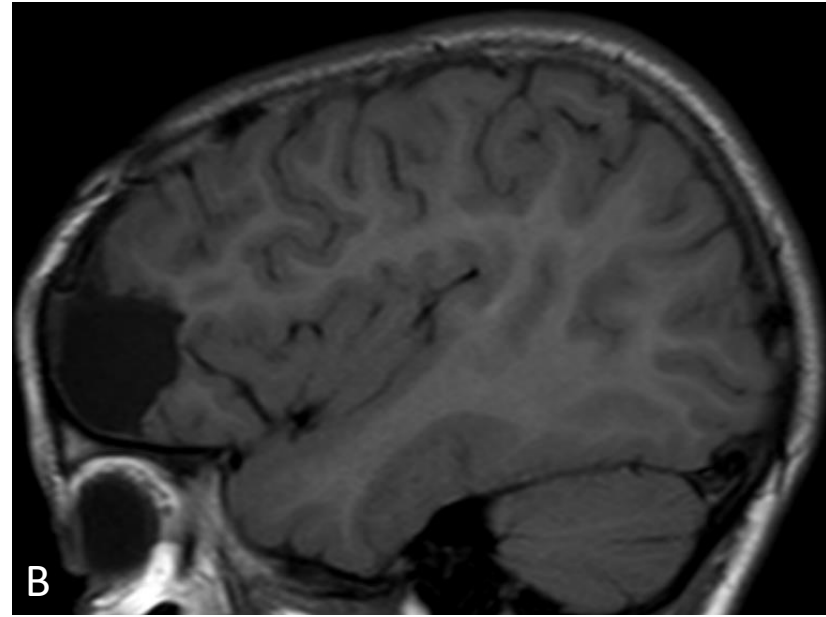
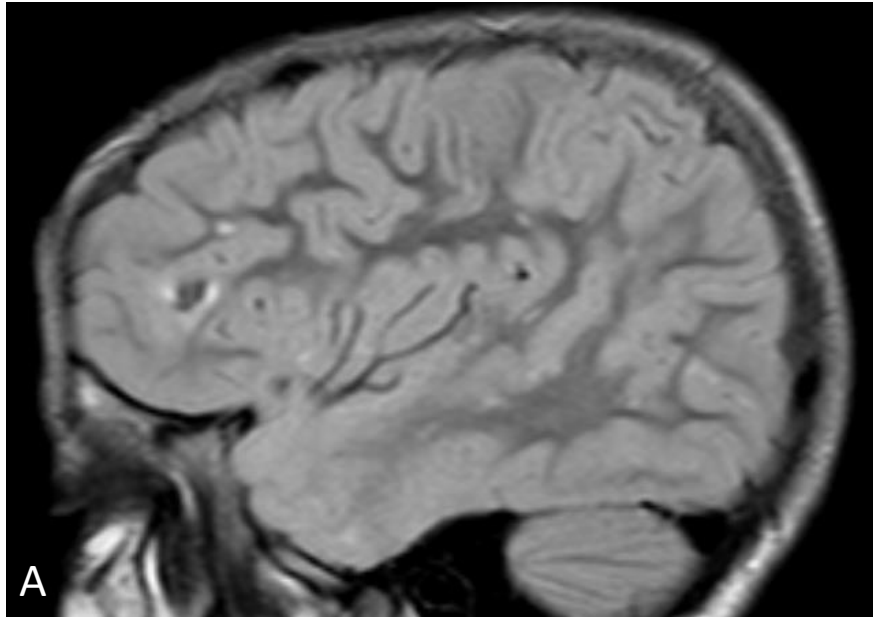


Figure 3 : A/ Sagittal flair MRI going through the right frontal “stand out” tuber, B/ T1 post-surgery MRI

Subtle spasm (head nodding)

Subtle spasm (head nodding)

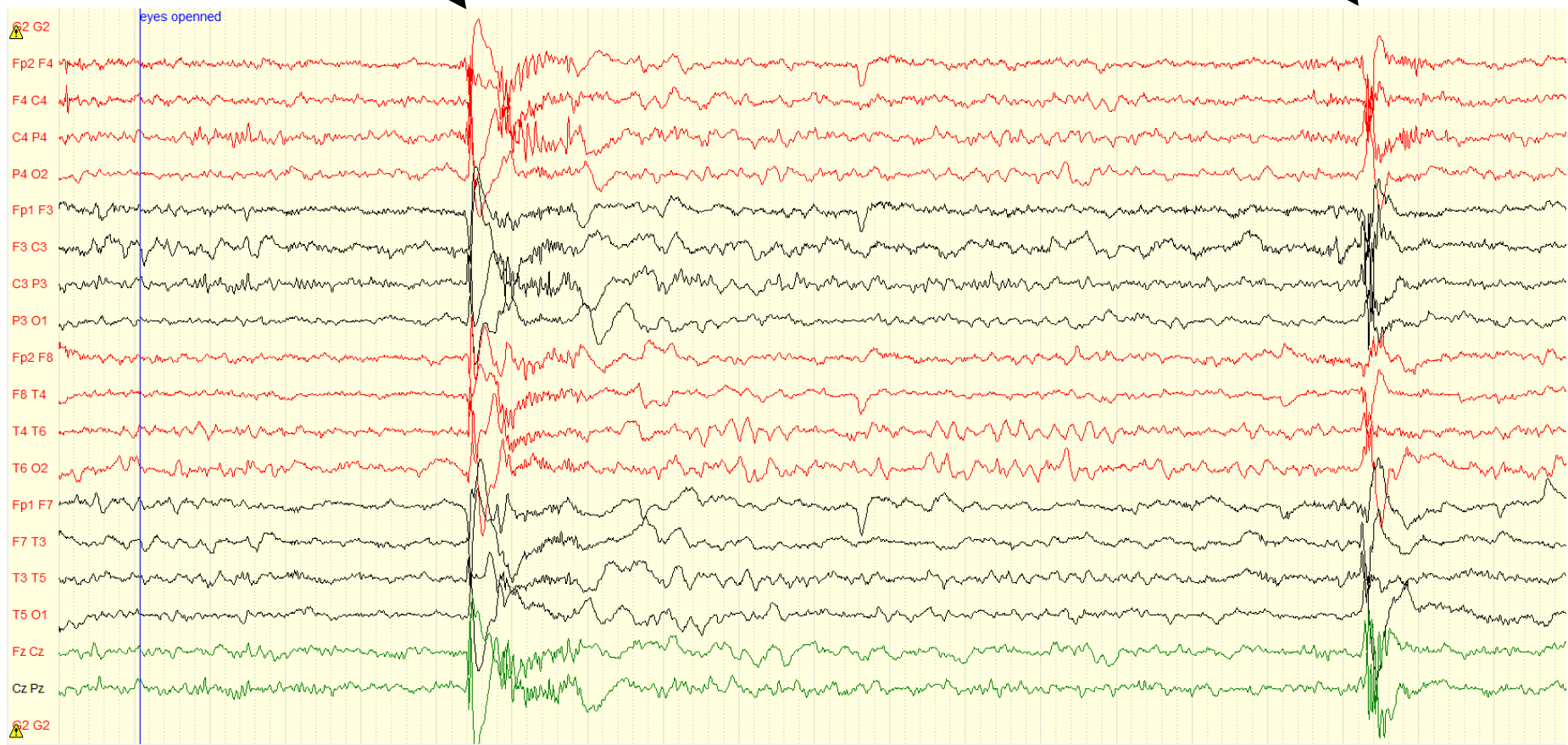


Figure 4, Scalp EEG, longitudinal bipolar montage (20sec/page) : Subtle spasms with a generalized EEG pattern.

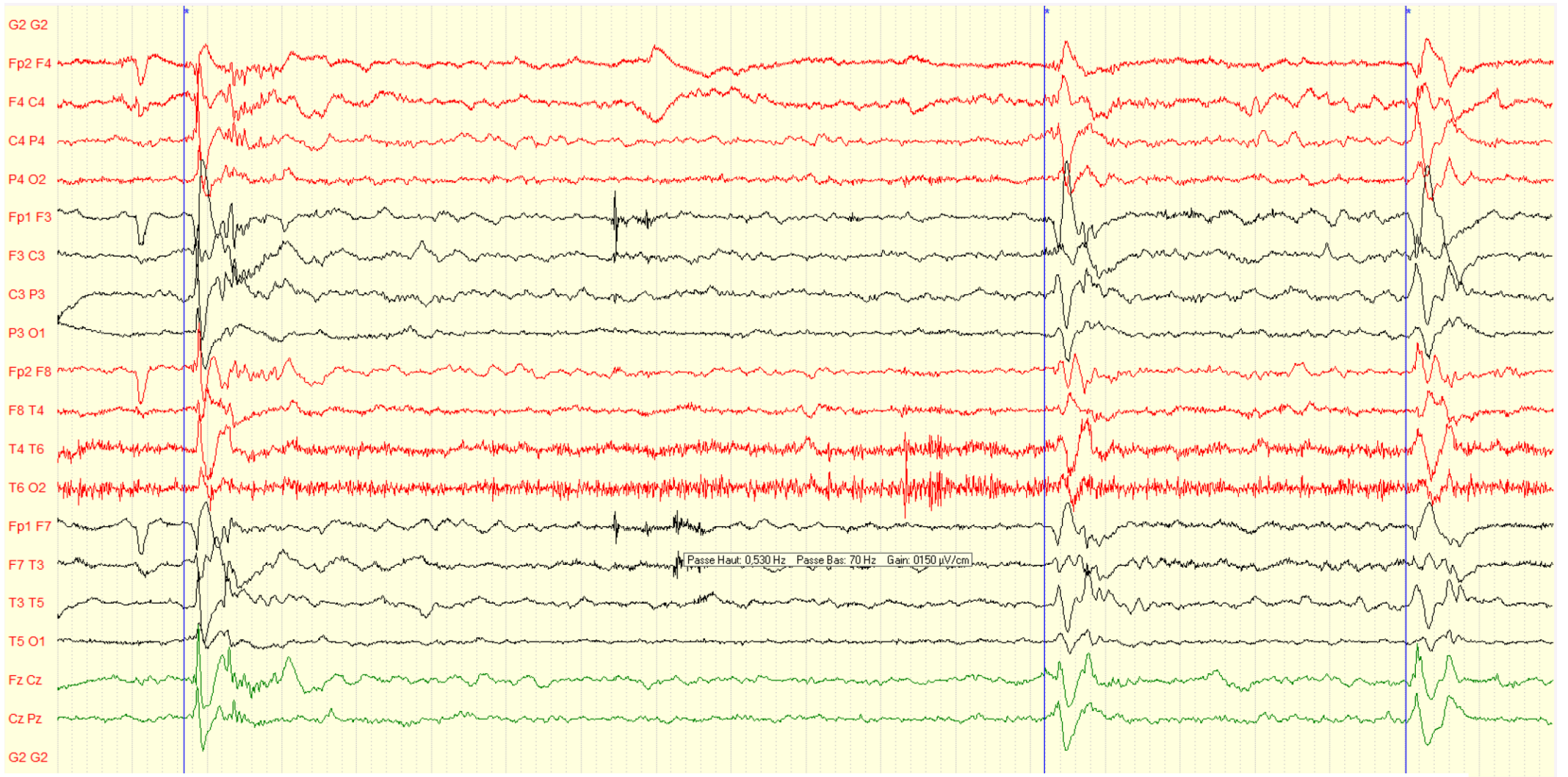


Figure 5, Scalp EEG, longitudinal bipolar montage (20sec/page) : Seizure onset of habitual seizure (begins with subtle spasms).

* subtle spasm with head nodding immediately following the asterisk (synchronous to the EEG pattern)

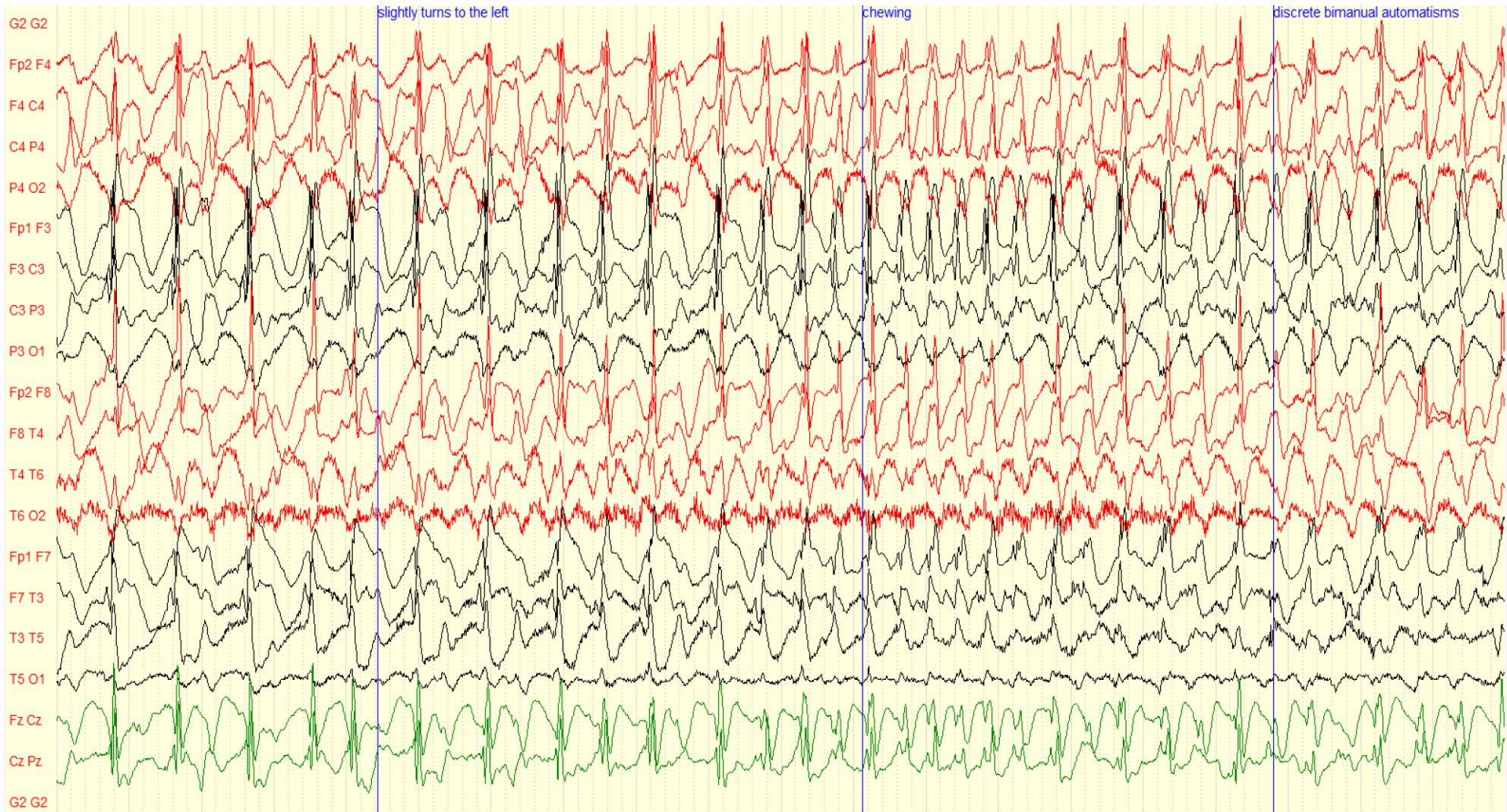


Figure 6, Scalp EEG, longitudinal bipolar montage (20sec/page) : Mid-section of habitual seizure at commencement of oro-alimentary and gestural automatisms.

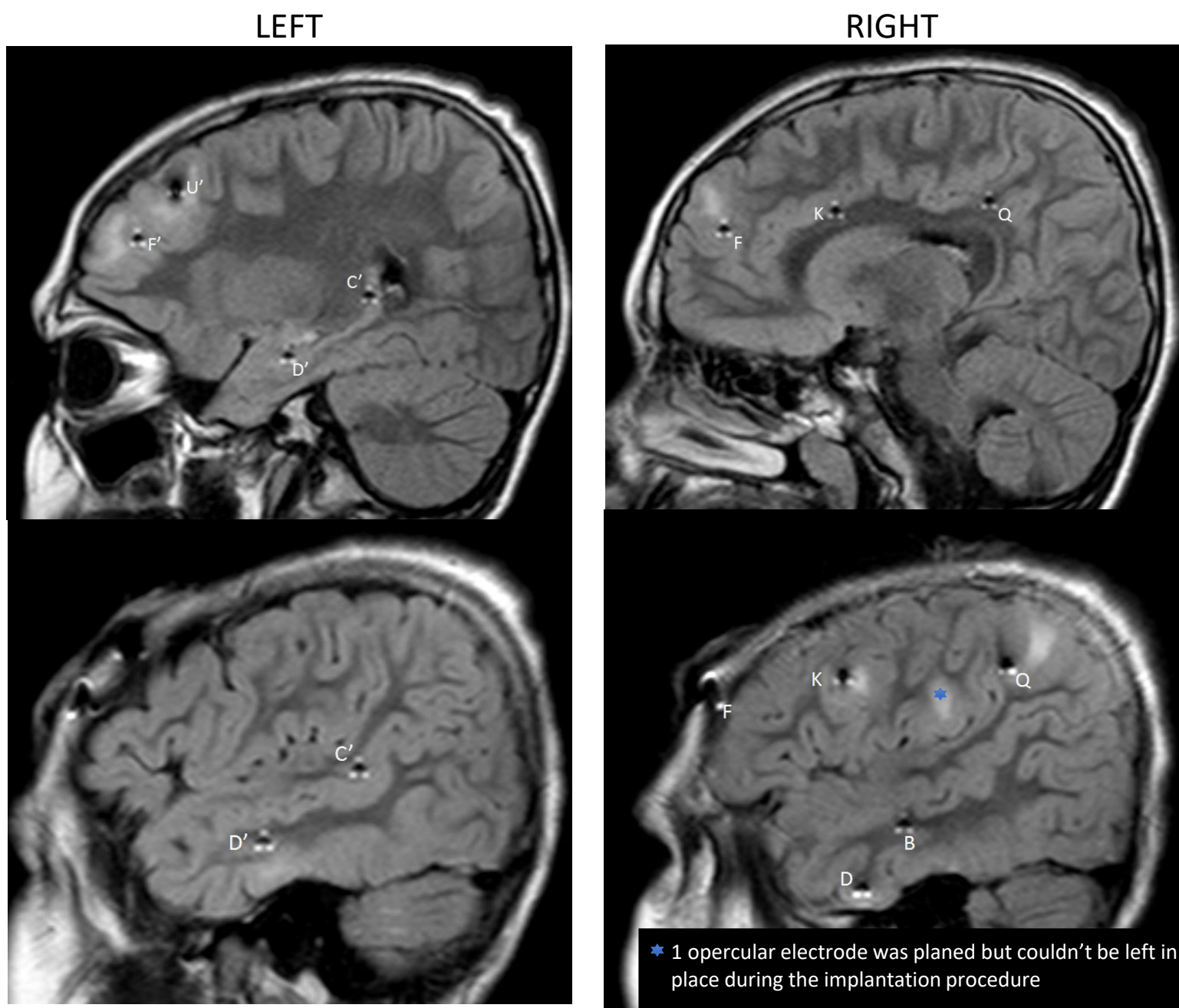


Figure 7 : SEEG investigation with 4 left and 5 right orthogonal electrodes

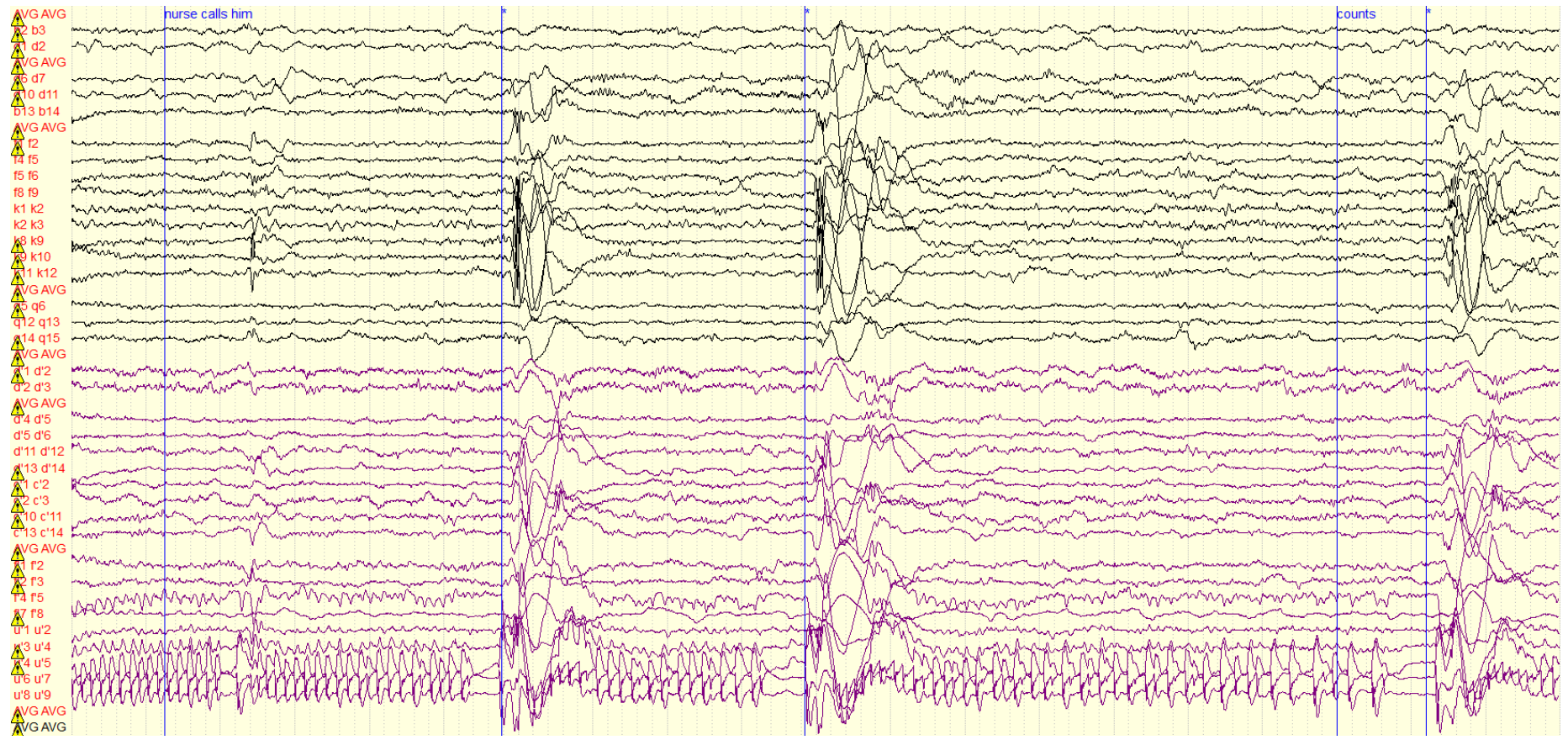


Figure 8 : Discharge in the left frontal tuber (f' and u') initiating the cluster of subtle spasms. * subtle spasm with head nodding immediately following the asterisk (synchronous to the SEEG pattern). Right contacts are in black, left contacts are in purple.

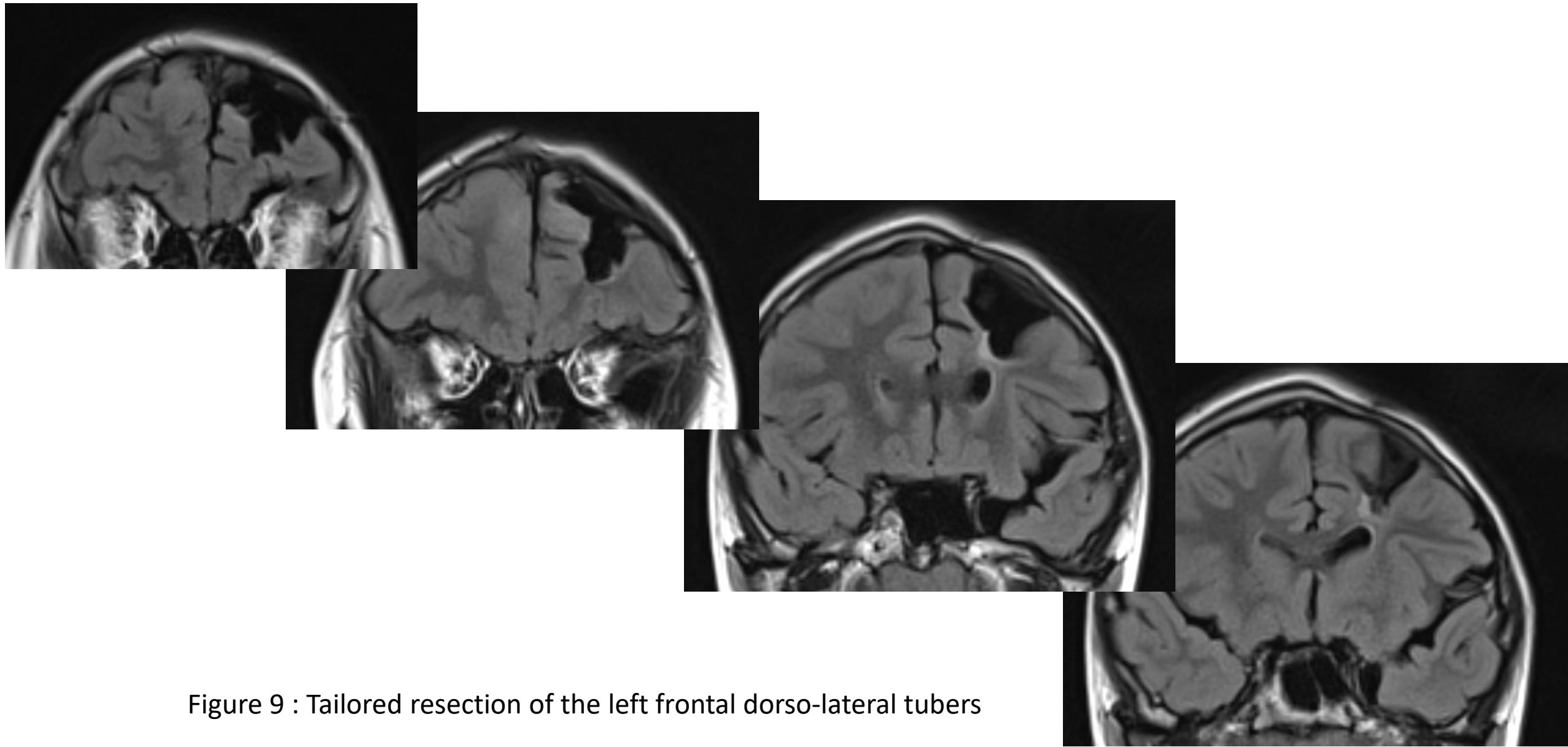


Figure 9 : Tailored resection of the left frontal dorso-lateral tubers

International TSC conference 2012 [10]	European experts Clinical recommendations 2012 [11]	European experts Clinical recommendations 2018 [12]
Epilepsy surgery should be considered for medically refractory TSC patients	Appropriate in TSC-associated epilepsy that is inadequately controlled after trials of 2 AEDs, and for well-defined lesions	Early presurgical evaluation immediately recommended after failure of 2 AEDs
	Multifocal lesions do not exclude a presurgical assessment when seizure onset is unifocal	Multifocal and bilateral lesions do not preclude presurgical assessment or subsequent surgery
Is best performed at epilepsy centers with experience and expertise in TSC	Tailored surgical resection of epileptogenic foci stopped seizure in 57 % of drug-resistant patients and improved seizure frequency by >90 % in another 18 %	Resection beyond tuber margins associated with greater probability of seizure freedom
Special consideration should be given to children at younger ages experiencing neurological regression	Success is increased by early intervention and accurate localization of the epileptogenic region.	Early surgery significantly increases probability that patients will be seizure free
		Surgery is currently underutilized in TSC-associated refractory seizures

Table 1 : Evolution in Consensus recommendations for epilepsy surgery in TSC patients

N°	First author	Year	Country, city	Journal	Number of patients operated	Age at surgery	Type of surgery	EcoG	Strip/grids or SEEG	Available FU (Engel if not precised otherwise)	Number of patients and FU at ≥2 years †
1	Guerrero	1998	Canada, Montreal MNI	Neurology	18	20 months to 54 years old	12 lesionectomy or focal resection (lesion and surrounding cortex), 5 CC, 1 focal resection and CC	10	No	FU from 1 month to 47 years. Among the 12 patients treated with resections, 7 (58%) class I, 1 (8%) class II, 3 (24%) class III, 1 lost to follow up.	7 patients 66%
2	Asano	2000	USA, Detroit	Neurology	7	1 year 1 month to 9 year 5 months	Tailored resections : 3 unilobar, 3 bilobar, 1 trilobar	NA	5 Strip/grids	FU from 3 to 28 months, 5 class I (71%), 2 class III (28 %)	2 patients 50%
3	Karenfort	2002	Germany	Neuropediatrics	8	6 months and 34 years old	4 lesionectomies, 2 hemispherotomies, 1 lobectomy (temporal), 1 partial resection of frontal and temporal lobe	3	2 Strip/grids	FU from 6 months to 4,3 years : 2 (25%) class I, 5 (62%) class II, 1 (12%) class III	3 patients 33%
4	Jarrar	2004	USA, Rochester Mayo clinic	Neurology	22	1 year to 54 years (mean 12,5)	8 tuberectomies, 12 lobar or multilobar resections, 2 CC	13	5 intracranial monitoring	FU from 1 to 14 years (mean 8,9 months) : FU at 1 year : 13 (59%) class I, 9 (41%) class III/IV, FU at 5 years or more : 9 (42%) class I, 12 (57%) class III/IV	Not available
5	Kagawa	2005	USA, Detroit	J. Child Neurol.	17	4 months to 12,3 years	13 Focal cortical resection, 1 lobectomy (frontal), 3 hemispherectomies	3	14 Strip/grids	FU from 5 to 58 months (median 15 months), 12 class I (70%), 2 (11%) class III, 3 (17%) class IV	7 patients 44%
6	Lachhwani	2005	USA, Cleveland	Neurology	17	2 months to 11 years	Resection of the tuber AND a wide margin of surrounding cortex with 14 lobectomies (5 frontal, 7 temporal, 1 TPO, 1 TP), 3 focal resections	4	4 Strip/grids	FU from 1 year to 15 years, 11 SF (65%)	9 patients 50%
7	Weiner	2006	USA, NYC	Pediatrics	20	7 months to 16,6 years (mean 4,4 years)	19 focal resection (one with additional MST) + extension during second and third stage surgery, 1 temporal lobectomy + parietal MST	No	20 Strip/grids, 9 Bilateral	FU from 6 months to 6,2 years, 17 (68%) class I, 6 (24%) in class II, 2 (8%) class III	14 patients 57%
8	Jansen	2007	Netherlands	Seizure	6	3 years to 36 years old	3 lobectomies (temporal), 1 posterior temporal resection, 1 frontopolar resection, 1 frontal corticectomy	6	No	FU from 9 to 71 months : 4 (66%) class I, 2 (33%) class IV	4 patients 50%
9	Teutonico	2008	Italy, Milano	Child Nerv Syst	21	7,11 years (SD 9,15)	21 tailored resections : 9 Lesionectomies, 12 lesionectomies and cortectomies	NA	6 Strip/grids or SEEG, 2 bilateral	FU from 6 months to 15 years : at 1 year FU, 14 (66%) class I, 6 (28%) class II to IV, 1 (4%) lost to FU	20 patients 50%
10	Wu	2010	USA , Los Angeles, UCLA	Neurology	18	0,75 to 17 years (average 5,5 years)	NA	18	No	FU from 1,75 to 8,5 years : 12 (67%) patients class I (average FU 4,1 year (+/- 1, 4 years))	NA
11	Ochi	2011	Canada, Toronto	Epilepsia	13	1,1 year to 16 years	NA	NA	12 Strip/grids and depth	FU from 14 to 70 month (Mean 32, 7 months) : 8 (62%) class I, 1 (7%) patient class II, 3 (23%) patients class III, 1 (7%) patient class 4	NA
12	Kassiri	2011	Canada, Alberta	Pediat. Neurol.	10	Not available but pediatric series	5 lesionectomies, 5 lobectomies (3 right temporal, 2 left temporal)	NA	NA	FU from 1 to 6 years (Mean 2 years), 90% class I, 10% class II	NA
13	Abolan	2011	USA, Rochester Mayo clinic	Pediat. Neurol.	6	0,7 years to 13 years	4 focal resections, 2 lobectomies (1temporal, 1TO + focal P resection)	NA	No	FU>2 years, 3 (50%) class I, 1 (16%) class III 2 (33%) class IV	6 patients 50%
14	Mohamed	2012	Australia, Melbourne	Neurology	17	1,5 to 8,8 years	Tuberectomies (1 to 9 tubers per patient)	NA	17 Strips/depths	FU 12 to 62 months (Mean 19), 6 SF (35 %)	6 patients 33%
15	Liu	2012	China, Changping	Epilepsy Res.	17	1,5 to 8 years (mean 4,23 years +/- 2,05 years)	2 focal resection, 8 multiple tuber resection, 7 multiple tuber resection and anterior callosotomy (when both hemisphere)	17	1	FU from 1,2 to 6 years (mean 2,99 years): 11 (64%) class I, 4 (23 %) class II, 2 (11%) class III	15 patients 60%
16	Kresk	2013	USA, Miami	Epilepsia	33	0,1 year to 17,6 years (median age 4,42 years)	33 tailored surgical resections : 24 unilobar, 9 multilobar	17	16 Strip/grids	18 (55%) class Ia at 2 years FU, 5 (15%) class II, 4 (12%) class III, 6 (18%) class IV	33 patients 55%
17	Karglotis	2014	Switzerland, Geneva	Epilepsy Res.	11	1 to 22 years	5 lobectomies (3 PO, 1 F, 1 T), 1 temporal polectomy, 4 lesionectomies, 1 cortectomy	NA	5 intracranial EEG	FU 1 to 7 years, 7 (63%) class I, 2 (18%) class II, 2 (18%) class IV	8 patients 60%
18	Arya	2015	USA, Cincinnati	J Neurosurg Pediat	37	Mean 6,16 years +/- 5, 96 years	7 tuber resections + adjacent cortex in single lobe, 9 ATL-AH with posterior temporal corticectomies, 6 extratemporal lobectomies, 13 multilobar resections, 2 hemispherectomies	37	37 Strip/grids	FU > 2,25 years for all patients (mean 5,6 years): 21 (57%) class I ILAE, 32 (87%) > 50 % reduction in seizure (class 4 ILAE or better)	37 patients 57%
19	Kannan	2016	Australia, Melbourne	Brain	9 (+1 in Mohamed 2012)	2,4 to 13,3 years	Tuberectomies (2 to 4 tubers per patient)	NA	10 strips/depths	FU 10 to 55 months (Mean 39), 4 SF (40%) + 3 SF from targeted seizure, 1 (10%) class II, 2 (20%) class III	6 patients 33%
20	Liang	2017	China, Beijing	J. Neurol.	51	5 years to 28 years	26 tuber resections, 15 lobectomies, 10 tuber resections and lobectomies and 11 with adjunctive CC (low IQ)	NA	33 Grids and depth	FU at 1 year : 38/51 = 75% Class I Engel, FU at 5 years 30/51 = 59% Class I Engel, FU at 10 years : 11/23 = 48% Class I Engel (no significant difference with 5 year FU)	51 patients 59%
21	Koptelova	2018	Russia and Finland	Epilep Research	7	4 years to 16,9 years	2 tuber resections, 2 multituber resection, 2 disconnection, 1 ATL	4	1 invasive	FU from 1 year to 4 year, 4 (57%) SF, 2 (28%) class II, 1 (14%) class IV	5 patients 40%
22	Fohlen	2018	France, Paris Rothschild	Seizure	15	Younger than 6 years, 5 months to 54 months	15 tailored surgical resections : 6 unilobar, 7 bilobar, 1 trilobar and in 3 patients + disconnection	1	11 Strip/grids, 3 SEEG	FU from 1,9 to 7,2 years : 9 (60%) class Ia, 4 (26%) class II, 1 (13%) class III, 1 class IV	14 patients 60%
	TOTAL				380						

Table 2

Table 2 legend: 22 Series with more than 5 patients operated. Abbreviations CC: Corpus Callosotomy, FU: Follow-up, CPS: Complex partial seizures, IS : Infantile spasms, MST: multiple subpial transection, NA: not available, SF: Seizure free, ATL-AH : anterior temporal lobectomy-amygdalo hippocampectomy, TPO: temporo-parieto-occipital, TP: temporo parietal, SD : Standard Deviation.

*Percentage of seizure free patient at >2-year FU is calculated as follows: number of patients SF at > 2 years divided by sum of (number of patients FU at 2 years + number of patients already not SF with a FU inferior to 2 years).

First Author	Year	Country	Journal	Number of patients operated	Number of patients with a Follow up ≥ 2 years	Follow up at 2 years (% Class 1 of Engel)
Weiner	2006	USA NYC	Pediatrics	25	14	57%
Teutonico	2008	Italie Milan	Child Nerv Syst	21	20	50%
Liu	2012	Chine Changping	Epilepsy Res.	17	15	60%
Kresk	2013	USA Miami	Epilepsia	33	33	55%
Arya	2015	USA Cincinatti	J Neurosurg Pediat	37	37	57%
Liang	2017	Chine Pékin	J. Neurol.	65	51	59%
Fohlen	2018	France, Paris	Seizure	15	14	60%

Table 3: 7 series since 1993 with at least 10 patients followed for at least 2 years. FU: follow-up.

First Author	Year	Journal	Number of patients	% of Patients Engel I	Bad prognosis	Good prognosis
Jansen	2003	Epilepsia	177	57%	Presence of tonic seizures IQ < 70	
Zhang	2013	Epilepsy	229	59%		Onset of seizure > 1 year Lateralized ictal and interictal EEG Lobectomy
Fallah	2013	PloS ONE	181	56%		No generalized semiology No or mild developmental delay Unifocal ictal EEG EEG and MRI concordant

Table 4 : Three Meta-analyses, prognosis factors.

N°	First author	Year	Country	Journal	Number of patients operated	Age at surgery	EcoG	Strip/grids or SEEG	If available, number of patients and FU at 2 years or more*	Non invasive presurgical methods used
1	Guerreiro	1998	Canada, Montreal MNI	Neurology	18	20 months to 54 years old	10	No	7 patients 66%	1 PEG/ 2 X rays/15 CT/12 MRI
2	Asano	2000	USA, Detroit	Neurology	7	7 months to 16 years	NA	5 strip/grids	2 patients 50 %	MRI/FDG-PET/αMT-PET
3	Karenfort	2002	Germany	Neuropediatrics	8	6 months and 34 years old	3	2 Strip/grids	3 patients 33%	MRI/2 FDG-PET
4	Jarrar	2004	USA, Rochester Mayo clinic	Neurology	22	1 year to 54 years (mean 12,5)	13	5 intracranial monitoring	Not available	MRI/4 ictal SPECT
5	Kagawa	2005	USA, Detroit	J. Child Neurol.	17	4 months to 12,3 years	3	14 Strip/grids	7 patients 44%	MRI/αMT-PET
6	Lachhwani	2005	USA, Cleveland	Neurology	17	2 months to 11 years	4	4 Strip/grids	9 patients 50%	MRI
7	Weiner	2006	USA, NYC	Pediatrics	20	7 months to 16,6 years (mean 4,4 years)	No	20 Strip/grids, 9 Bilateral	14 patients 57%	MRI/"many" ictal and interictal SPECT/"many" FDG-PET/"many" MEG
8	Jansen	2007	Netherlands	Seizure	6	3 years to 36 years old	6	No	4 patients 50%	MRI/ HR EEG/ MEG
9	Teutonico	2008	Italy, Milano	Child Nerv Syst	21	7,11 years (SD 9,15)	NA	6 Strip/grids or SEEG, 2 bilateral	20 patients 50%	CT/MRI/1 SPECT/2 MEG/1 spectroscopy
10	Wu	2010	USA , Los Angeles, UCLA	Neurology	18	0,75 to 17 years (average 5,5 years)	18	No	NA	MRI/FDG-PET/MEG
11	Ochl	2011	Canada, Toronto	Epilepsia	13	1,1 year to 16 years	NA	12 Strip/grids and depth	NA	MRI/ some MEG
12	Kassiri	2011	Canada, Alberta	Pediat. Neurol.	10	Not available but pediatric series	NA	NA	NA	MRI/NA
13	Abolan	2011	USA, Rochester Mayo clinic	Pediat. Neurol.	6	0,7 years to 13 years	NA	No	6 patients 50%	MRI/interictal and ictal SPECT + SISCOM
14	Mohamed	2012	Australia, Melbourne	Neurology	17	1,5 to 8,8 years		Strips/depths	6 patients 33%	MRI/15 SISCOM
15	Liu	2012	China, Changping	Epilepsy Res.	17	1,5 to 8 years (mean 4,23 years +/- 2,05 years)	17	1 implanted electrode	15 patients 60%	CT/MRI/5 ictal and interictal SPECT/1 spectroscopy/2 FDG-PET/ 1 BOLD fMRI
16	Kresk	2013	USA, Miami	Epilepsia	33	0,1 year to 17,6 years (medan age 4,42 years)	17	16 Strip/grids	33 patients 55%	MRI/"some" FDG-PET/"some" ictal SPECT/"some" fMRI
17	Kargiotis	2014	Switzerland, Geneva	Epilepsy Res.	11	1 to 22 years	NA	5 intracranial EEG	8 patients 60%	MRI/11 FDG-PET/11 SPECT + SISCOM/ 6 HD EEG
18	Arya	2015	USA, Cincinatti	J Neurosurg Pediat	37	Mean 6,16 years +/- 5, 96 years	37	37 Strip/grids	37 patients 57%	MRI/FDG-PET/ictal and interictal SPECT (+ SISCOM)/MEG
19	Kannan	2016	Australia, Melbourne	Brain	9 (+1 in Mohamed 2012)	2,4 to 13,3 years	NA	10 strips/depths	6 patients 33%	MRI/NA
20	Liang	2017	China, Beijing	J. Neurol.	51	5 years to 28 years	NA	33 Grids and depth	51 patients 59%	MRI/FDG-PET
21	Koptelova	2018	Russia and Finland	Epilep Research	7	4 years to 16,9 years	4	1 Invasive	5 patients 40 %	MRI/MEG
22	Fohlen	2018	France, Paris Rothschild	Seizure	15	Younger than 6 years, 5 months to 54 months	1	11 Strip/grids, 3 SEEG	14 patients 60%	CT/MRI
	TOTAL				380					

Table 5: Methods used in the presurgical workup. PEG: Pneumoencephalography, HR EEG: high resolution EEG, NA : Not available. *Percentage of seizure free patient at >2-year FU is calculated as follows: number of patients SF at > 2 years divided by sum of (number of patients FU at 2 years + number of patients already not SF with a FU inferior to 2 years).

First Author	Year	Journal	FDG PET sensitivity	FDG PET specificity	α MT PET sensitivity	α MT PET specificity
Juhasz	2003	Neurology	73%	63%	39%	100%
Rubi	2013	Epilepsia			12%	100%

Table 6: Sensibility and specificity of α MT-PET (compared to PET-FDG when available).