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Stereo-EEG tailored resection in a child with presumed perinatal post-stroke epilepsy: The complex organization of epileptogenic zone

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ABSTRACT

Introduction: Only a few studies have focused on tailored resection in post-stroke epilepsy, in which hemispherectomy and hemispherotomy are the most recognized treatments.
Case description: We describe the case of a patient with drug-resistant, presumed perinatal, post-stroke epilepsy and moderate right hemiparesis. The seizures were stereotyped, both spontaneous and induced by sudden noises and somatosensory stimuli. Considering the discordant anatomic-electro-clinical data – left perisylvian malacic lesion with electrical onset over the left mesial fronto-central leads – and the patient's functional preservation, SEEG was performed. SEEG revealed sub-continuous abnormalities in the perilesional regions. Several seizures were recorded, with onset over the premotor area, rapidly involving the motor and insular-opercular regions. We decided for a combined surgical approach, SEEG-guided radiofrequency thermocoagulation, on the fronto-mesial structure but also on the central operculum, followed by resective surgery including only the fronto-mesial structures.
Discussion and conclusion: The SEEG allowed to localize the epileptogenic zone far away from the anatomical lesion but connected to part of it. A combined surgical approach tailored on SEEG results allowed a good outcome (Engel Ib) without additional deficits.

Introduction

Perinatal stroke includes all cerebrovascular events occurring between 20 weeks of gestation and postnatal day 28 [1]. Cerebrovascular events may be due to an arterial or venous process which can be either hemorrhagic or ischemic or both [2]. In some newborns, the brain injury is initially misrecognized and the diagnosis comes later, when hemiparesis becomes clinically apparent or seizures occur [2,3]. Because the clinical presentation occurs after postnatal day 28, but the neuroimaging is typical of a perinatal damage, this subtype is termed presumed perinatal strokes [1]. Post-stroke epilepsy (PSE) often has a delayed onset [4] and has been observed in approximately 70% of neonates and 30% of children after stroke [5]. The incidence of drug-resistant epilepsy (DRE) in these patients has been estimated to be around 5% [6,7]. Several surgical options have been described for drug-resistant PSE, such as cyst "uncapping", perilesional cortectomy, multilobar resection/disconnection, hemispherectomy and hemispherotomy [8,9]. Hemispherotomy is the most recognized option in the treatment of PSE, given its excellent results in seizure control [8]. Up to now, few studies have focused on tailored resection, which can limit functional impairment [8,9]. In these patients, an invasive pre-surgical investigation can be helpful to identify the EZ, which is likely be different from the perilesional area in pediatric PSE [9]. We reported the case of a patient with drug-resistant PSE who underwent a tailored surgery defined by SEEG.

Case report

We reported the case of a girl born at 37 + 4 weeks by scheduled cesarean section after a normal pregnancy. Apgar score: 8 at 1-minute and 10 at 5 min. At 3 months, the parents noticed an asymmetry in spontaneous motility, but the formal diagnosis of moderate right hemiparesis was not made until 8 months, when the patient started physiotherapy. Epilepsy onset was at 6 years, after the first focal to bilateral tonic-clonic seizure. The introduction of the first anti-seizure medication

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(valproic acid) led to seizure freedom for 3 years. Later, focal seizures appeared and persisted despite several modifications of anti-seizure medication: levetiracetam, carbamazepine, lamotrigine, perampanel, phenobarbital, zonisamide, clonazepam and clobazam. At the age of 13, the patient was admitted to our center for pre-surgical evaluation. At that time, she was on carbamazepine, zonisamide and phenobarbital. Seizures were weekly and unchanged over time, both spontaneous and induced by noise and somatosensory stimuli. Seizures were characterized by a subjective sensation of "shutting mouth" or "stiffening of the right hand", followed by a tonic contraction of the oro-facial muscles whereby she covered the mouth with her left hand, while the right arm appeared dystonic. In more intense seizures, the right arm became stiff and could be raised, or the stiffness could involve all the right hemibody resulting in a fall. All seizures were without awareness impairment.

The neurological examinations showed right hemiparesis with loss of independent finger movements. Ambulation was autonomous with internal rotation of the right foot. Visual field test was unremarkable. The mRS was 1.

Total intelligence quotient was 71 (WISC-IV): verbal comprehension 93, perceptual reasoning 80, working memory 70, processing speed 65.

Video-EEG showed a poorly organized background rhythm with asynchronous slow abnormalities over the bilateral fronto-central and vertex leads, better expressed on the left side. During hyperventilation, sequences of delta activity were observed on the left fronto-central-temporal regions. Sleep was poorly organized due to the rare representation of its physiological graph-elements. Spikes, isolated or in sequences, were observed during sleep on the left fronto-central and vertex leads (phase reversal on F3 and sometimes C3). Ten typical seizures were recorded, either spontaneous or induced by sudden auditory or sensory stimulations. The semiology was as previously described, except for the induced seizures, in which the progression of signs was faster. Regarding EEG, seizure onset was difficult to identify because of muscle artifacts, but sometimes a fast rhythmic discharge was observed mostly on anterior vertex and left fronto-central leads (Fig. 1A).

Magnetic Resonance Image (MRI) revealed a malacic cortico-subcortical lesion in the left insular and dorso-frontal regions (Fig. 1B). Fluorodeoxyglucose-positron emission tomography (PET) confirmed the presence of a hypometabolic region surrounding the ischemic area (Fig. 1C). We did not perform functional MRI for language because we assumed the dominance was in the right hemisphere. In fact, the patient had an early damage involving also the presumed pars triangularis and opercularis of the inferior frontal gyrus and she has no language impairment, even soon after seizures.

Given all these results, the localization of EZ could not be established with certainty. In fact, electro-clinical data pointed-out a possible onset in both the insular-opercular and the pre-motor region on the left side. Therefore, despite the presence of moderate hemiparesis, a hemispherotomy could not be proposed to spare visual field and cognitive function but also to not worsen motor function. For all these reasons, a SEEG exploration was performed [10,11], planned with seventeen intracerebral electrodes (Dixi Medical, 0.8 mm-diameter, 5–18 contacts) exploring the left insular-opercular region, the pre-motor and sensory-motor cortex and also the superior temporal gyrus [10–14](Fig. 2A, B, 3A, 3B). Wakefulness and sleep were characterized by frequent slow-

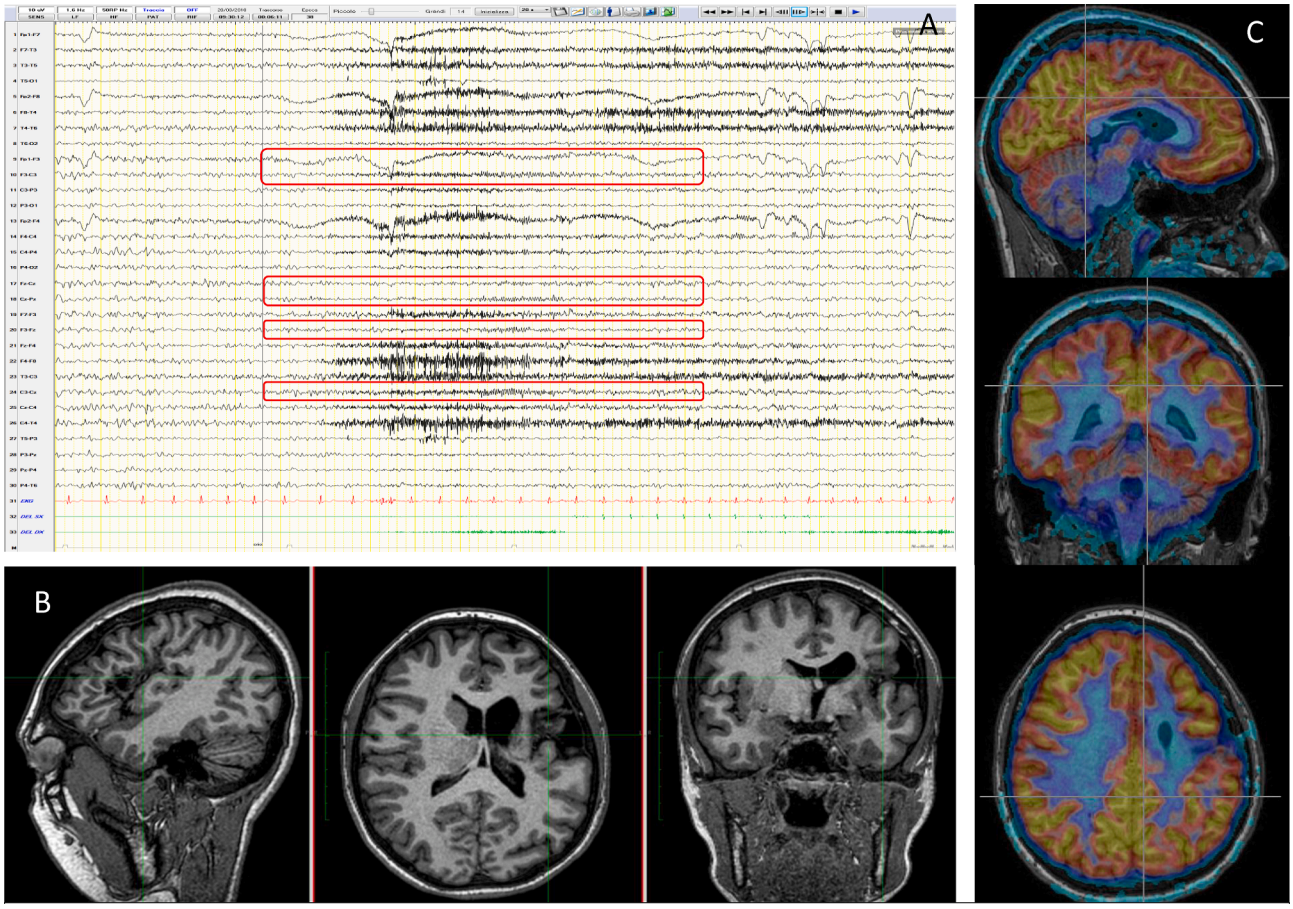


Fig. 1. A. Video-EEG Monitoring (LF 1.6 Hz, HF 5o RP Hz, sensitivity10 μV): the red rectangles showed the flattening followed by a fast rhythmic discharges over the left fronto-central leads including the vertex during a typical spontaneous seizure. The clinical onset corresponded to the appearance of muscles artifacts. 1B - 3D-T1 MRI (sagittal, axial, coronal planes): cortico-subcortical malacic lesion in left insular and dorso-frontal regions. 1C – FDG-PET (from the top to the bottom, sagittal, coronal and axial planes): hypometabolic region around the malacic lesion, the surrounding cortex had a normal metabolism, mostly over the left posterior and frontal cortex.

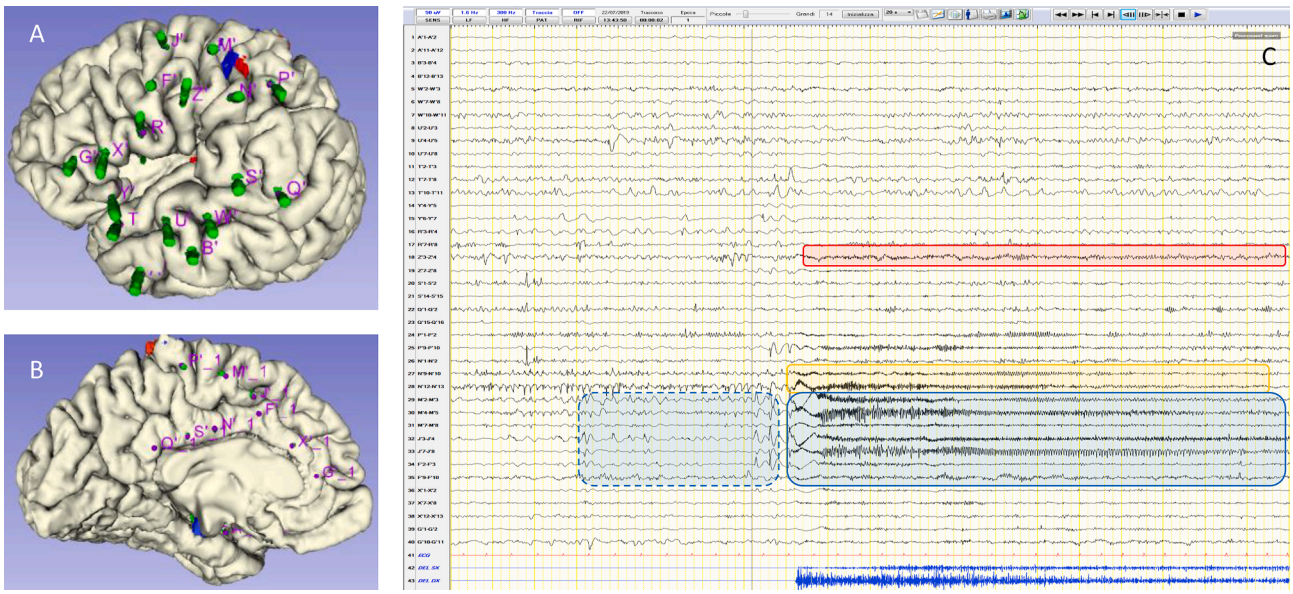


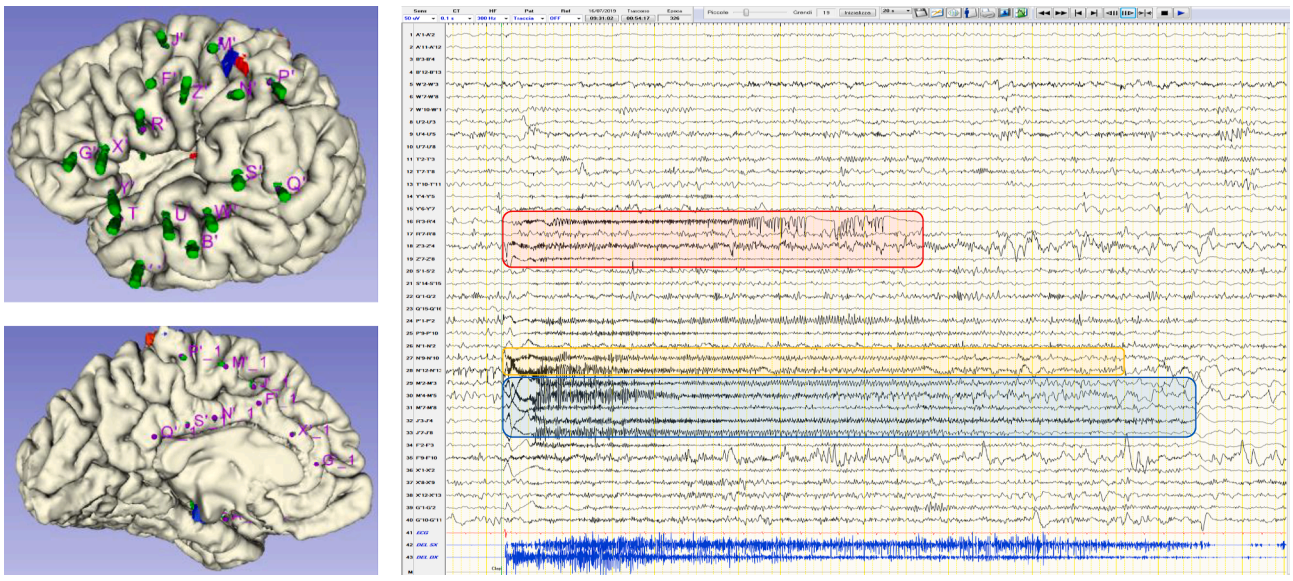
Fig. 2. A Personalized volumetric reconstruction - lateral view scheme: A' mid temporal gyrus, B' mid temporal gyrus, F' mid frontal gyrus, G' inferior frontal gyrus, J' posterior dorsal frontal gyrus, M' superior pre-central gyrus, N' post-central gyrus, P' superior parietal lobe, Q' supramarginal gyrus, R' inferior pre-central gyrus, S' posterior perilesional cortex in the inferior parietal region, T' antero-superior temporal gyrus, U' inferior perilesional cortex in the superior-mid temporal gyrus, W' inferior perilesional cortex in the superior-mid temporal gyrus, X' inferior frontal gyrus (pars opercolaris), Y' anterior perilesional cortex in the inferior frontal gyrus, Z' superior perilesional cortex in the inferior pre-central gyrus. 2B - Personalized volumetric reconstruction - mesial view scheme: A' amygdala, B' anterior hippocampus, F' cingulum sulcus, G' genus of the cingulum, J' mesial frontal gyrus, M' SSMA, N' central cingulum, P' paracentral lobule, Q' parietal cingulum, R' perilesional cortex in the insula region, S' parietal cingulum, T' orbital gyrus, U' perilesional cortex in the insula region, W' perilesional cortex in the insula region, X' frontal cingulum, Y' perilesional cortex in the inferior frontal gyrus, Z' perilesional cortex in the insula region. 2C - SEEG Monitoring (LF 1.6 Hz, HF 300 Hz, sensitivity 50 μV) of a spontaneous seizure: interictal discharges, like slow waves and some sharp-waves, involved all the peri-sylvian lesion area, both the supra-sylvian part - Z' (intermediate and external), R' (internal and external) – and the remaining superior temporal gyrus - U' and T' (internal and external). The dots blue rectangle showed the interictal spike-and-waves discharge over the fronto-mesial cortex explored by J' (internal and external) and F' internal. This phase of preparation is followed by the seizure onset characterized by a slow wave with superimposed fast activity over J', M' internal (blue rectangle) whereas the motor-cortex (N' external) was less involved (yellow rectangle). The lesion cortex explored by Z' (internal, red rectangle) was involved only in the most tonic part of the seizures. The clinical onset corresponded to the appearance of muscles artifacts on EMG traces.

waves and spike-and-waves discharges in the perilesional area (insulo-opercular region and superior temporal gyrus) (Fig. 2C). Less frequent abnormalities, such as spike-and-waves but also fast activity, were observed in the fronto-mesial cortex explored by J' and M'. We identified the same pattern in all the seizures (Fig. 2C): a slow wave with superimposed fast activity over the fronto-mesial cortex explored by J' (internal and external) and M' internal whereas the motor-cortex (N' external) was less involved. Then, recruiting fast activity was well seen on the previously described regions, but also on the perilesional opercular region (Z' and/or R' internal). The spreading over the motor cortex and the perilesional area was faster in induced seizures, with prolonged discharge over the *peri*-opercular regions (Fig. 3C). Both low and high-frequency electrical stimulations didn't induce the complete seizure, but only the subjective part in the insular-opercular region and the objective one in the fronto-mesial cortex. We were not able to induce speech problems through the stimulations of G' and X'. Low frequency stimulations and motor and sensory evoked potentials permitted to map the motor cortex over the external contact of M' and N' and the more internal one of P'. The SEEG results allowed to localize the seizure onset zone in the fronto-mesial cortex with rapid propagation to the primary motor cortex. The role of the perilesional insular-opercular cortex remained controversial; its involvement occurred only during the recruiting phase and appeared as a secondary involvement. However, we were able to reproduce the subjective part of the seizure with high-frequency stimulations of Z' and the typical electrical distribution only at very high voltage (5 mA). For all these reasons we decided to perform SEEG-guided radiofrequency thermocoagulation (RF-TC) on the posterior fronto-mesial cortex (J' 3–5, F' 1–2 and 3–5), the most posterior part of the superior frontal gyrus (J' 5–8) and the central operculum (Z'3-5 and 6–8). The latter was included for its close connection with the EZ, although during spontaneous and induced seizures its involvement was secondary. Thermocoagulation resulted in a partial but significant improvement in seizure frequency and intensity. We therefore decided to perform a left frontal cortectomy that included the Supplementary Sensori-Motor Area (SSMA) and pre-SSMA explored by J' and M', but also the cingulum explored by F' (Fig. 4). Intra-operative monitoring with somatosensory and motor evoked potentials was performed during surgery. After surgery, the patient had an expected worsening of the right motor deficit, which was fully recovered already during the week of hospitalization. The histopathological finding was gliosis. After surgery, the patient had only spontaneous catamenial (1–2/period) and very brief subjective typical manifestations, which can include mouth and right arm sensation, but for the past year she has been completely seizure free. We decided to reduce medication, discontinuing phenobarbital and zonisamide. The patient has remained on Class Ib Engel for more than three years, and currently has no more seizures.

Discussion

We described the case of a patient with drug-resistant, delayed onset PSE secondary to presumed perinatal stroke and moderate hemiparesis. The presence of discordant anatomic-electro-clinical data and the functional preservation prompted us to perform SEEG monitoring [15–20]. We identified the EZ in the fronto-mesial cortex, a structure far from the insular-opercular perilesional area, which showed inconstant involvement in seizures but induced subjective manifestations when stimulated. For all these reasons, we chose a combined surgical approach, RF-TC and resective surgery.

Only few studies have reported the use of SEEG for presurgical evaluation in PSE [8,9,21,22], whereas most teams perform large



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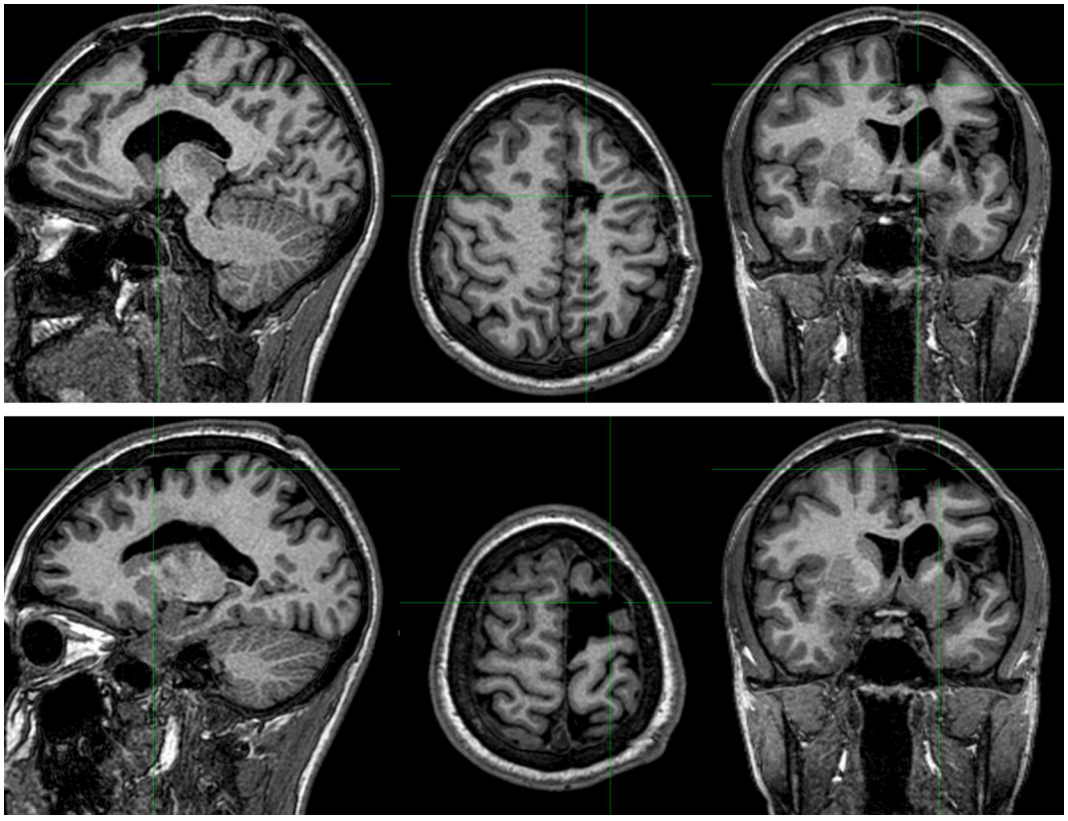

Fig. 4. Post-operative MRI performed 6 months after surgery: 3D-T1 (sagittal, axial, coronal planes) showed the detailed of the surgery consisting in a left pre-central parasagittal cortectomy.

disconnections such as hemispherotomy, considering the excellent outcome of this procedure [23]. In patient with functional preservation, invasive monitoring has been used to avoid hemispherotomy. In the first invasive study [22–24], subdural and epidural electrodes were used, revealing that seizures could come from a remote region or the border of porencephaly [22–24]. Marchi et al. [9], described a homogeneous population undergoing SEEG monitoring. Both children with perinatal and postnatal stroke were reported, only one patient had a stroke in adulthood (20 years). The use of SEEG, combined with epileptogenicity index, showed the complex organization of the EZ, which can involve both perilesional and distant structures (81%), distant regions (14.2%) and in a low percentage (4.8%) only the perilesional one [9]. No differences were found between ischemic and hemorrhagic strokes. When indicated, subsequent surgery was based on SEEG results, and in perinatal strokes it never consisted in corticectomy but in disconnection tailored to SEEG findings. Scavarda et al. [8] emphasized the importance of SEEG in establishing the anterior and posterior boundary of a more "functional" disconnection. They described a new disconnection technique guided by the SEEG results (tailored suprainsular partial hemispherotomy) that includes the perimotor cortex (suprainsular disconnection) [8]. Again, the effort to avoid hemispherotomy was due to the need to preserve visual field and cognitive function. In these patients, SEEG demonstrated the major role of premotor and precentral cortex [8]. Like the patients described by Scavarda et al. [8], our patient had a delayed presentation of drug-resistant PSE and prominent involvement of the premotor cortex [8]. Unlike that population [8], our patient did not have severe hemiplegia, so a more limited approach was deemed essential. Therefore, we decided to perform RF-TC over the opercular region explored by Z'. We tried to disconnect the network between the premotor and perilesional areas to avoid its inclusion during surgery. Considering the main role of the premotor cortex, we performed RF-TC in this area as well, followed by cortectomy. This combined approach - RF-TC followed by resective surgery - spared the visual field, cognitive function and avoided possible worsening of motor function. After surgery, our patient manifested rare subjective seizures (Engel Ib), now disappeared, probably related to the very complex organization of the EZ in PSE. Early injury of highly connected regions, such as the temporo-mesial region, insula and/or opercular region, may result in disruption and in subsequent plastic rearrangements in distant regions, including an aberrant network [23]. In our opinion, all these observations refer to the pediatric population and it is very difficult to transpose them to adulthood, especially regarding the involvement of distant regions. A recent study attempted to describe adult patients with PSE [21]. Twenty-one patients underwent intracranial EEG (subdural or SEEG), surgery or placement of vagus nerve stimulation. Twelve of these had experienced perinatal stroke. Thirteen patients underwent intracranial EEG, which showed involvement of the stroke lesion at the ictal onset (61.5%) and predominant involvement of the mesial temporal region (85%) [21]. Especially the latter result seems to be different from the previous study, probably because of the different etiology of stroke in adults. Further studies focusing on the pathogenesis of PSE would be needed to better understand the complex and widespread organization of EZ, while maintaining the differences between children, in whom brain maturity has not been achieved, and adults.

Conclusion

Considering the complexity of the EZ in patient with PSE [9] we believe that the features of pre-surgical evaluation are crucial for choosing the most adequate surgical strategy. Indeed, in patients with stereotyped seizures and only moderate motor deficit, a surgery tailored on SEEG results could avoid the resection/disconnection of both non-epileptogenic and functional area.

Ethical statement

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The informed consent was obtained by the parents of the patient. The privacy rights have been observed.

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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