Cortical involvement in focal epilepsies with epileptic spasms

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Summary The pathophysiological mechanisms of epileptic spasms are still poorly understood. The role of subcortical structures has been suggested on the basis of non-localized EEG features and from experimental data. The description of asymmetric spasms associated with lateralized EEG patterns has challenged this view and raises the possibility of a cortical origin. This study investigated the cortical organization of partial seizures associated with epileptic spasms in children undergoing intracerebral EEG recordings for presurgical evaluation. Eleven children with drug resistant epileptic spasms and for whom depth electrode recordings were performed were retrospectively studied. In all children several features suggested a focal origin. Cortical involvement was studied using the "Epileptogenicity Index" (EI). A focal origin was finally demonstrated in 10/11 patients. Seven patients demonstrated pre-ictal changes in the seizure onset zone area. EI analysis showed maximal values in the temporal (n=5), parietal (n=1) or frontal (n=5) cortices. EEG changes were also observed in the premotor cortex during spasms.

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Introduction

Since the most recent classification proposed by the ILEA, the clinical entity of epileptic spasms (ES) has been separated from West syndrome and constitutes a distinct type of seizure (Berg et al., 2010). However, their pathophysiology remain unknown such that at present it has been difficult to class them as either generalized or partial seizures.

The following clinical description is commonly recognized: an axial contraction, more often flexion than extension, brief and sudden, lasting from 0.2 to 2 s, occasionally recurring in short clusters separated by periods lasting between 5 and 20 s (Holmes and Vigevano, 1997). They occur typically in infancy (6–12 months) but they may occur at a later stage of life (Gobbi et al., 1987). In addition, some patients with ES may have other types of epileptic seizures, most commonly partial seizures (Kubota et al., 1999; Pachatz et al., 2003). In these cases surgical treatment may lead to seizure remission and neurocognitive improvement (Jonas et al., 2005; Ricard-Mousnier et al., 2012).

Epileptic spasms were initially considered as originating sub-cortically (Gastaut et al., 1964), but a cortical origin of the spams has alternatively been suggested, in particular from the results of cortical surgery (Asano et al., 2001). Furthermore, more recent animal models also support the hypothesis of cortical involvement in the genesis of ES (Scantlebury et al., 2010).

Few studies have analyzed intracerebral EEG recordings in this context (Asano et al., 2005; Ricard-Mousnier et al., 2012). A corticographic study of 62 spasms from patients suffering from tuberous sclerosis suggested that spasms were elicited by a cortical onset (Asano et al., 2005). Two patterns of discharges were described in this study, a first type with a localized spike followed by fast activity or a second type without a focal spike.

Our objective was to study the cortical organization of partial seizures associated with ES in children undergoing intracerebral EEG recordings for presurgical evaluation. We have analyzed the ictal IcEEG characteristics in children with pharmacoresistant ES, for whom intracerebral EEG recordings were proposed due to a suspected focal onset.

Material and methods

Patients and EEG recordings

This retrospective study analyzed the IcEEG of children with pharmacoresistant ES recorded at the hospital La Timone in Marseilles, France. They were selected from 280 intracerebral investigations between 2002 and 2012. All the patients with ongoing ES that had IcEEG were included in this retrospective study.

Non-invasive pre-surgical recordings (pre-surgical assessment Phase 1) were performed at the hospitals Henri Gastaut or La Timone in Marseilles. The EEG trace was performed using 20 scalp electrodes, following the international 10–20 system. Additional polygraphic recordings were composed of EMG of both deltoids and ECG.

Pre-surgical assessment phase 2 consisted of IcEEG recordings over a number of days. It is performed following discussion by a multidisciplinary team, utilizing the clinical and imaging data, and the results from phase 1. The number and position of the implanted electrodes were also discussed.

The implantation of the intracerebral electrodes was performed in the neurosurgery departments. The adequate localization of the electrodes in the cerebral space was checked using 1.5 MRI or using a fusion of preimplantation MRI and CT scan with electrodes in place. IcEEG recordings were performed using intracerebral multiple contact electrodes (10–15 contacts: 2 mm diameter; 0.8 mm and 1.5 mm apart). The anatomical targeting and number of necessary electrodes was established in each patient according to the hypotheses for localization of the epileptogenic zone determined by the clinical data and EEG recordings from phase 1. Each electrode comprised of multiple contact points numbered 1 to 15.

The signals were recorded on a 196 channels Deltamed™ system. They were sampled at 512 Hz or 1024 Hz and recorded on hard disk (16 bits/sample) using no digital filter. The only filter present in the acquisition process was a high-pass analog filter (cut-off frequency equal to 0.16 Hz) used to remove very slow non-physiological variations that sometimes contaminate the baseline. The video-EEG recordings were prolonged as long as necessary to capture several of the patient’s habitual seizures.

Intracerebral EEG signal analysis: determination of the Epileptogenicity Index (EI)

For each seizure, the corresponding IcEEG trace was studied and the Epileptogenic Index (EI) was calculated. The objective was to better characterize the regions involved at seizure onset.

This quantification has been proposed in order to characterize the propensity of a given brain structure to generate a ‘rapid discharge’ (the high frequency oscillations observed during the transition between ictal and interictal activity) and takes into account the delay of appearance of this discharge with respect to seizure onset (Bartolomei et al., 2008, 2010, 2011). The purpose of this index is to provide quantified information about the behavior of brain structures recorded from signals they generate during the seizure process. This index summarizes two pieces of information.
Table 1 Main clinical characteristics of studied patients. Cognitive evaluation was assessed for each patient using first the Weschler Intelligence Scale for Children (WISC IV) (Parkin and Beaujean, 2012). Intelligence quotients using the Wisc IV were Total IQ (TIQ), Verbal IQ (VIQ), Non verbal IQ (NVIQ).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at onset</th>
<th>Neuropsychological Testing (preop) TIQ, VIQ, NVIQ</th>
<th>Neuropsychological Testing (postop) TIQ, VIQ, NVIQ</th>
<th>Normal MRI</th>
<th>Histopathology</th>
<th>Hypometabolism PET-scan</th>
<th>Age at iEEG</th>
<th>Age at surgery</th>
<th>Surgery</th>
<th>Outcome/FU (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>5 months</td>
<td>60, 75, 58</td>
<td>ND</td>
<td>No</td>
<td>Right frontal MCD (heterotopia)</td>
<td>Left frontal</td>
<td>12 years 3 months</td>
<td>12 years 9 months</td>
<td>Right frontal lobectomy</td>
<td>IV(3)</td>
</tr>
<tr>
<td>P2</td>
<td>12 months</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
<td>Left temporal DNET</td>
<td>Left temporal</td>
<td>7 years</td>
<td>8 years</td>
<td>Left temporal lobectomy</td>
<td>III(4)</td>
</tr>
<tr>
<td>P3</td>
<td>Neonatal period</td>
<td>45, 45, 45</td>
<td>ND</td>
<td>No</td>
<td>Non specific</td>
<td>Left frontal</td>
<td>8 years 4 months</td>
<td>9 years 2 months</td>
<td>Right frontal (premotor cortex) cortectomy</td>
<td>IV(3)</td>
</tr>
<tr>
<td>P4</td>
<td>8 months</td>
<td>96, 116, 90</td>
<td>86, 116, 77</td>
<td>No</td>
<td>Right temporal DNET</td>
<td>Right temporal posterior</td>
<td>7 years 3 months</td>
<td>8 years 5 months</td>
<td>Lesionectomy</td>
<td>IA(2)</td>
</tr>
<tr>
<td>P5</td>
<td>2 years 5 months</td>
<td>NA</td>
<td>47, 47, 45</td>
<td>Yes</td>
<td>Right frontal FCD (type 1 histopathology)</td>
<td>No</td>
<td>6 years 4 months</td>
<td>7 years 11 months</td>
<td>Right prefrontal cortectomy</td>
<td>IA(2)</td>
</tr>
<tr>
<td>P6</td>
<td>5 months</td>
<td>93, 104, 81</td>
<td>78, 90, 67</td>
<td>Yes</td>
<td>Normal (FCD type 1 histopathology)</td>
<td>NP</td>
<td>7 years 1 months</td>
<td>17 years</td>
<td>Right prefrontal cortectomy</td>
<td>IIA(10)</td>
</tr>
<tr>
<td>P7</td>
<td>9 months</td>
<td>49, 58, 58</td>
<td>ND</td>
<td>Yes</td>
<td>–</td>
<td>Left temporal DNET</td>
<td>7 years</td>
<td>NF</td>
<td>Left temporal-frontal cortectomy</td>
<td>IB(4)</td>
</tr>
<tr>
<td>P8</td>
<td>4 years</td>
<td>NA</td>
<td>50, 63, 50</td>
<td>No</td>
<td>Left temporal DNET</td>
<td>Left temporal</td>
<td>6 years 4 months</td>
<td>6 years 10 months</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>P9</td>
<td>7 years</td>
<td>85, 86, 81</td>
<td>88, 92, 82</td>
<td>No</td>
<td>Right parietal DNET</td>
<td>Right internal parietal</td>
<td>11 years 4 months</td>
<td>11 years 9 months</td>
<td>Parietal cortectomy aNF Lesionectomy</td>
<td>IA(1)</td>
</tr>
<tr>
<td>P10</td>
<td>2 years</td>
<td>72, 76, 69</td>
<td>58, 79, 79</td>
<td>No</td>
<td>Right temporo mesial DNET</td>
<td>Right temporal</td>
<td>5 years 9 months</td>
<td>6 years</td>
<td>Leisionectomy</td>
<td>IB(1)</td>
</tr>
<tr>
<td>P11</td>
<td>2 years 3 months</td>
<td>78, 82, 82</td>
<td>70, 82, 72</td>
<td>No</td>
<td>Right temporo mesial DNET</td>
<td>Right temporal</td>
<td>7 years 2 months</td>
<td>7 years 6 months</td>
<td>ATL+ Lesionectomy</td>
<td>IA(1)</td>
</tr>
</tbody>
</table>

Abbreviations: NA: not applicable, non testable because of major cognitive or/and behavioral problems. ND: not done. iEEG: intracerebral EEG figures.
Figure 1  Example of Stereotactic EEG (SEEG) recordings in a patient with a DNET located in the left temporo-basal cortex (Pt 8). (A) SEEG scheme showing the location of the electrodes and MRI showing the lesion. (B) Infraclinical discharges affecting the lesion site (electrodes L′ and OT′) (C) Ictal discharge associated with clinical spasms. This discharge is localized to the premotor cortex (electrode SA) in addition to the temporal region.

into a single quantity: (1) whether or not the recorded brain structure is involved in the generation of a high frequency discharge and (2) when involved, whether or not this rapid discharge is delayed with respect to rapid discharges generated by other structures. A normalized value is used ranging from 0 to 1. If there is no involvement of the brain structure, the EI = 0 whereas if the brain structure generates a rapid discharge and the time to seizure onset is minimal, the EI = 1. An EI between 0 and 1 corresponds to secondary involvement of the brain structure concerned (for detailed methodology, see Bartolomei et al. (2008) and supporting methods).

This index therefore allows a semi-automatic characterization of the anatomical zone from which the epileptic process originates. In this study it was calculated for each seizure in each child recorded by IcEEG. The data was subsequently integrated into graphical form representing the ‘epileptogenic’ zone.

Results

Clinical data

The clinical data has been summarized in Table 1. Eleven patients (four girls, seven boys) presenting with spasms were investigated in our unit between 2002 and 2012 and selected for this study. The average age at time of IcEEG was 7 years 10 months (range 5 years 9 months–12 years 3 months). The average age of onset of epilepsy was 22.5 months (ranging from birth to 7 years). The epilepsies of all the children commenced with ES. Temporary epilepsy remission was reported in one patient with appropriate neurodevelopment associated with the period of seizure freedom. At the preoperative neuropsychological evaluation, only 3 patients had scored at a normal/subnormal level (see details in Table 1). Hypsarhythmia was initially present in one patient. Of the 11 patients, three patients had normal Magnet Resonance Imaging (MRI) despite repeated imaging. In one, post-operative histological analysis demonstrated a dysplastic lesion. Imaging in the other patients revealed focal malformation of cortical development (n = 2) or a dysembryoplastic neuroepithelial tumor (DNET) (n = 6). The lesions, identified or suspected, were situated in the frontal (n = 4), temporal (n = 6) or parietal (n = 1) regions. Metabolic imaging (PET scan) revealed areas of hypometabolism corresponding to a focal region in eight patients.

The description of the spasms recorded at presurgical assessment (Phases 1 and 2) for each patient is reported in supporting Table 1 and supporting Table 2. An axial contraction was present in all patients. The average duration was 0.5 s, ranging between 0.2 and 3 s. Short clusters of spasms were observed in seven patients. Only one patient presented with asymmetrical spasms.

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Cortical involvement during epileptic spasms

Intracerebral EEG recordings

IcEEG was obtained in the 11 consecutive patients. The results have been separated into location of the epileptogenic zone as defined by IcEEG findings.

Temporal lobe cases

Seizures were localized to the temporal region in 5 cases (cases P2, P4, P8, P10, P11). Complete sequences of seizures and spasms were recorded in 3 patients (cases P2, P8, P10) while only brief facial minimal contractions (that did not reproduced the complete ES features) was recording in another patient (4). No spasms were recorded during IcEEG in patient 11.

In the three cases with IcEEG recorded typical spasms, the occurrence of spasms was associated with a discharge affecting both the temporal lobe and the premotor cortex. Involvement of the premotor cortex was delayed (mean 264 ms ± 0.09). Spasms were generally grouped into clusters. Figs. 1–2 show two examples of this pattern. In these two cases, the ES coincided with a discharge extending the limit of the temporal lobe, in particular affecting the electrode exploring the premotor region. The appearance of ictal spasms (cases P2, P8, P10) or more subtle manifestations (case P4) was preceded by repetitive rapid discharges (with no clinical changes) into the lesion (cases P4 and P8, see Fig. 1b) or by partial seizures (cases P2 and P10). In case P11, isolated subclinical discharges were recorded in the lesion and the hippocampal region with no clinical changes.

Frontal cases

In 4 cases, the origin of the ictal discharge was found to be the frontal cortex (cases P1, P3, P5, P6). In all these cases, a preictal phase was observed, characterized by the appearance and the gradual extension in the frontal lobe of isolated rapid discharges and/or spikes. Examples of such preictal changes are depicted in Fig. 3. Spasms were found to be the main manifestation of seizures in these cases and were associated with a discharge affecting the premotor cortex (Figs. 3–4).

Other cases

Patient 9 presented with seizures involving both parietal and premotor cortex. Clusters of spasms followed partial seizures and were characterized by brief discharges over parietal and premotor cortices. Patient P7 had an isolated cluster of spasms with a discharge affecting a large part of the cortical regions with no clear focal onset.

Figure 2 (A) SEEG scheme showing the location of the electrodes in a patient with temporal lobe seizures and spasms (Pt 2). The electrodes explore the temporal region. (NA, B, TB, TP) and the frontal lobe (SA, OF and OR). Seizures initially involve the internal temporal region (internal leads of electrodes TP, NA, B and TB) before spreading to the SMA regions (blue arrow, internal leads SA electrode). Clinical spasm appears subsequently (red arrow). (B) Quantification of the rapid discharge at seizure onset in two internal regions (Hip and EC) and two frontal regions (SMA and Orbitofrontal cortex, OFC). The changes in energy ratio of high frequencies (25–90 Hz, ER(n)) are depicted in a color scale. Increased in ER is seen first in Hip and EC and secondarily (delay 800 ms) in the OFC and SMA regions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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Epileptogenicity index analysis

The Epileptogenicity profiles of the analyzed patients (62 seizures) are indicated in Fig. 5a. They reflect the average values of recorded seizures in the 10 patients in whom a localized onset was found.

EL values were often maximal at the sites of the suspected lesion or lesion reported on MRI. In the temporal cases, the values in the premotor cortex were found to be generally low and lower than in the frontal cases (mean 0.05 ± 0.07 in temporal cases versus 0.48 ± 0.2 in extra-temporal cases).

Most of the patients disclosed a focal pattern with epileptogenicity restricted to lesional sites (cases P10, P4, P8, P10, P11, P5, P9). Only 3 cases disclosed more complex patterns with high values outside the lesion site (P1, P3, P6). Interestingly, these three cases corresponded to extra-temporal cases and were not rendered seizure free after surgery.

Surgery and outcome

Following IcEEG, 10 patients benefited from surgical treatment, two patients required repeat surgery due to seizure recurrence and consisted in an extension of the previous surgery according to the IcEEG results (to the premotor cortex more posteriorly in P1 and to the frontal region in P8). The surgery, guided by the results of the IcEEG, consisted of a corticectomy encompassing the MRI evident lesion and/or the region considered epileptogenic in six children and purely a lesionectomy in three children (Table 1). Average age at time of surgery was 9 years 1 month (ranging between 6 years 10 months to 12 years 9 months 17y 9). The average duration of post-surgical follow-up was 3 years (1–10). Among the 10 operated patients, 7 have a good outcome (5 Engel IA, 1 Engel Ib, 1 Engel IIA). Among the patients with frontal lobe epilepsy and poor outcome, one had post-operative contralateral seizures that were recorded during video EEG session (P1) and one had a resection that was limited to the anterior part of the epileptogenic zone given the risk of motor deficit (P2).

Discussion

This study investigated the cortical organization of partial seizures associated with epileptic spasms. Patients were included in this study when IcEEG was decided after non-invasive data in which a possible focal origin of the ES was
suspected. This is a well recognized situation (Asano et al., 2005; Fogarasi et al., 2003; Gobbi et al., 1987; Holmes and Vigevano, 1997; Kamei et al., 1996; Kubota et al., 1999; Pachat et al., 2003; Ricard-Mousnier et al., 2012) but to our knowledge, there is no report of depth electrodes investigations in such cases with the exception of a recent case report (Ricard-Mousnier et al., 2012). Visual analysis was complemented by signal EEG analysis based on the epileptogenic index method that is particularly suited to detect the increase in high frequencies at seizure onset (Aubert et al., 2009; Bartolomei et al., 2008, 2010, 2011; Bonini et al., 2013).

In the present series, ES occurred with a variable temporal relationship with partial seizures (PS): being part of the seizures; preceding the partial seizures; or following the seizures. This has been already reported. For example in a previous paper (Kubota et al., 1999), authors reported eight cases associated with various etiology, that had ES associated with PS. Three types of seizure sequence were identified: PS followed several seconds later by ES (two patients), alternating PS and ES starting with PS (three patients), and PS gradually replaced by ES with overlapping of the two (three patients).

In another report, (Pachat et al., 2003) investigated with video EEG 13 children with partial seizures and ES. Authors identified three groups with different seizure patterns regarding the temporal association of ES and partial seizures: (a) PS followed by ES; (b) PS appearing during a cluster of ES without interrupting the cluster; and (c) complex seizure interaction with a succession of ES and partial seizures in a close but variable temporal association.

In this context, our series also confirms that there is no specific etiological factor associated with ES from focal origin even if we found a majority of patients, having late onset ES, absence of hypersynchrony and presenting with a neurodevelopmental tumors (6/11 cases). Early injury or developmental disorders were generally found in the previous series including cortical dysplasia or tubers, cerebral malformations, perinatal anoxic-ischemic injuries (Pachat et al., 2003).

In this series, we also observed that ES may be associated with seizures from various cortical origins since temporal lobe seizures as well as extra temporal lobe seizures may be associated with this clinical manifestation. ES values were high and restricted to the lesional site in 7 patients. This demonstrates that despite the clinical symptoms and often wide diffusion of ictal EEG patterns, the epileptic disease can be quite focal in these children. A recurring issue has been to question the cortical origin of the clinical phenomenon. In our frontal lobe cases with ES, premotor and/or primary motor regions involvement was found to be associated with the ES occurrence. In these cases, the ES are finally very close to patterns involved in motor cortex seizures as recorded during presurgical evaluation. In particular, tonic postural seizures are the most frequent pattern of seizures involving premotor or premotor and primary motor cortices (Bonini et al., 2013). In the case with parietal epilepsy, the ES were also coincident with a discharge affecting both parietal and premotor cortex. This pattern has been already described in parietal seizures and is closely related to the large connectivity between parietal and premotor cortices (Bartolomei et al.,...
In patients with temporal lobe origin the mechanisms of spasms are less evident. In three of our cases, propagation of the discharges to the premotor area suggested an involvement of the cortical motor system. Therefore, a common pathway including an involvement of premotor cortex seems to be involved in the ES whatever the cortical origin.

This pathophysiological hypothesis agrees with works from animal models of ES. A model (Velisek et al., 2010) demonstrating the role of corticotropin-releasing hormone (CRH) supports the hypothesis of a subcortical origin for spasms and hypsarrhythmia. The other models display results supporting the hypothesis of a cortical origin. Lee et al (Lee et al., 2008) described a rat model with ES secondary to cortical developmental abnormalities. Another group also published an animal model in which cortical lesions were created with injections of lipopolysaccharide and doxorubicin (Scantlebury et al., 2010). The rats initially presented with ES, though then developed other types of epileptic seizures. Finally another model was a knockout mouse for the ARX gene involved in neuronal migration. The mutation of this gene is associated with cerebral malformations and functional abnormalities of interneurons and thus supports involvement of the cortex in ES (Marsh et al., 2009).

Surgical outcome was good in our series. 70% were largely improved. These results compare well with previous data (Asano et al., 2001; Jonas et al., 2005; Pachatz et al., 2003) and seem particularly favorable in temporal lobe cases, where the relationship between lesion and the epileptogenic zone was more simple and direct. Larger epileptogenic networks as found in the cases with poor outcome may explain the limited effect of surgery. The extension of the epileptogenic networks has been already shown to have a negative impact on the surgical prognosis in other forms of focal epilepsies (Aubert et al., 2009; Bartolomei et al., 2010) (Bonini et al., 2013)

In conclusion, this study confirms that seizures associated with spasms may originate from various cortical regions and reflects the primary or delayed involvement of premotor cortices. Good surgical outcome may be obtained

Figure 5  (A) Profiles of epileptogenicity in patients with ES and Temporal lobe seizures. Mean values of EI is indicated for 15 brain regions explored by depth electrodes. EI profiles show maximal epileptogenicity in temporal regions and lower values in the frontal regions. (B) Profiles of epileptogenicity in patients with ES and extra-temporal seizures (13 brain regions are depicted). Abbreviations: EC: entorhinal cortex, Amy: amygdala, Hip:hippocampus, TP: temporopolar cortex, TBC: temporobasal cortex, Ins: insula, STG: superior temporal gyrus, PHG: parahippocampal gyrus, Fus: fusiform gyrus, SMA: supplementary motor area, BA6: lateral premotor cortex, aCG: anterior cingulate gyrus BA32, pCG: cingulate gyrus BA 24, OFC: orbitofrontal cortex, preF: prefrontal cortex, Rol: rolandic cortex, Par(SPL): parietal cortex, superior parietal lobe; contra: contralateral side. (C) Mean (±SD) of EI values in lesional sites (blue bars), non lesional sites (orange bars) and in motor cortices. Values are obtained from the 62 analyzed seizures. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
when the epileptogenic zone is well restricted to lesional sites.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eplepsyres.2014.08.008.

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