

Atonic seizures in children with surgically remediable epilepsy: a motor system seizure phenotype?

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ABSTRACT – *Aim.* Atonic seizures are common in some epileptic syndromes beginning in infancy or early childhood but they are rarely described in epilepsy with focal seizures of structural aetiology. We aimed to characterize the electroclinical features of atonic seizures in surgically remediable paediatric patients and to study the spatiotemporal organization of the underlying epileptogenic networks.

Methods. We retrospectively analysed two consecutive, longitudinally evaluated and surgically treated paediatric patients presenting with atonic seizures as a manifestation of pharmacoresistant epilepsy of structural aetiology, evidenced by scalp- and stereotactic intracerebral video-EEG-recordings. A quantitative analysis of the epileptogenic zone organization was performed using the “epileptogenicity index”.

Results. Long-lasting generalized ictal atonia, occurring in infancy, was a predominant clinical feature in both patients, with some hints of focal origin present in one case. The seizure phenotype evolved at later age into subtle segmental atonia, associated with prominent positive motor signs. The epileptogenic zone was localized within the dorsolateral or mesiolateral premotor region. Its spatial organization was focal, matching the lesional cortex in one and distributed involving several lesional and non-lesional structures in the other case. The emergence of atonic semiology temporally correlated with involvement of both lateral and mesial premotor, as well as primary motor areas.

Conclusion. We hypothesize that atonic seizures may be considered as a motor system seizure phenotype in the setting of structural epilepsy. Complete removal of the epileptogenic area provided excellent seizure control.

Key words: atonic seizure, premotor cortex, negative motor area, intracerebral EEG, epileptogenicity index

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Atonic seizures are common in several electroclinical epileptic syndromes that begin in infancy or early childhood, such as Dravet syndrome, epilepsy with myoclonic atonic seizures, and Lennox-Gastaut syndrome. Negative motor phenomena may be encountered in atypical benign epilepsy with centrotemporal spikes. However, atonic seizures are also observed in epilepsy with focal seizures of structural aetiology. Whereas focal atonic phenomena characterized by ictal limb or facial paresis, or negative myoclonus are well described in this setting (Abou-Khalil *et al.*, 1995; Noachtar and Lüders, 1999; Matsumoto *et al.*, 2005; O'Donovan *et al.*, 2007), only few video-EEG documentations of focal seizures with axial or generalized ictal atonia are available (Satow *et al.*, 2002; You *et al.*, 2007; Zhao *et al.*, 2010; Kovac *et al.*, 2012). The latter phenotype might be difficult to recognize as a focal seizure if the precise electroclinical characteristics are lacking. These aspects are particularly relevant in early-onset pharmacoresistant epilepsies associated with MRI-obscure cortical developmental malformations.

The pathophysiological basis of ictal atonia is still under debate. In seizures with focal atonic semiology, there is growing evidence for a predominant location of the epileptogenic areas within the frontal or peri-central part of the cortical motor system (Tinuper *et al.*, 1998; Noachtar and Lüders, 1999; Matsumoto *et al.*, 2000; Rubboli and Tassinari, 2006; Kovac *et al.*, 2012; Maillard *et al.*, 2014). Alteration in electrical activity within the distinct areas of dorsolateral or mesial associative motor cortex, defined as primary and supplementary negative motor areas (Lim *et al.*, 1994; Lüders *et al.*, 1995), or within the primary motor or sensory cortex (Ikeda *et al.*, 2000; Matsumoto *et al.*, 2000; Kovac *et al.*, 2012), may produce focal atonic signs. Moreover, the frequency content of the ictal discharge within the primary motor cortex could be important for the semiological expression of ictal phenomenon as positive or negative motor signs (Maillard *et al.*, 2014). As for generalized atonia, the few available human intracerebral EEG studies have analysed cases of epilepsy with hypothalamic hamartoma and demonstrated that atonic seizures in this particular context were associated with extended bilateral frontal cortical discharges (Munari *et al.*, 1995; Kahane *et al.*, 2003). An acute perturbation in the corticoreticulospinal regulatory pathway has been hypothesized as a possible mechanism underlying a sudden loss of postural tone, being a hallmark of some generalized epileptic syndromes (Elger *et al.*, 1981; Mori *et al.*, 1995; So, 1995; Kovac and Diehl, 2012).

Our objectives were to assess the electroclinical phenotype of atonic seizures in surgically remediable

paediatric patients and to study the organization of the underlying epileptogenic zone defined by intracerebral EEG (icEEG) recordings.

Methods

Patients and EEG recordings

In this retrospective study, we analysed two consecutive, serially evaluated paediatric patients presenting with atonic seizures as a manifestation of pharmacoresistant epilepsy of structural aetiology, as evidenced by scalp- and stereotactic intracerebral video-EEG-recordings (SEEG). Both patients underwent presurgical assessment, followed by resective surgery at the Epilepsy Unit of the Strasbourg University Hospital (France). They were identified from 114 intracerebral EEG investigations performed at our unit between 2004 and 2015.

We used the ILAE definition of atonic seizures (Blume *et al.*, 2001) to distinguish seizures that are characterized by a sudden loss or diminution of muscle tone without apparent preceding myoclonic or tonic event, involving the head, trunk, jaw, or limb musculature.

Presurgical evaluation included detailed clinical history, physical examination, long-term video/scalp-EEG recordings according to the 10-20 system with simultaneous bipolar surface EMG recording from the right and left deltoid muscles, neuropsychological evaluation, high-resolution 1.5 Tesla MRI, and metabolic imaging using FDG-PET.

Both patients required icEEG to allow more precise definition of the epileptogenic zone (EZ) and subsequent tailored resection. SEEG recordings were performed at the Epilepsy Unit of the Strasbourg University Hospital. Intracerebral multiple contact electrodes (5-18 contacts of 2 mm length; diameter: 0.8 mm; 1.5 mm apart; Dixi Medical, France) were implanted unilaterally in different cortical areas, using a frameless stereotactic surgical robot ROSA™. The placement of electrodes was guided in each patient by the hypotheses for EZ localization, based on available non-invasive data. The frontal, insular, and temporal regions were explored in the first patient and the frontal and insular regions in the second patient. A cranial CT scan was performed after intracerebral electrode implantation to verify the absence of any complication and the spatial accuracy of the implantation. 3D CT/MRI data fusion was used for the accurate anatomical localization of each electrode contact.

Long-term scalp and icEEG recordings were performed using a Deltamed™ system (SEEG signal sampling rate: 256 Hz; high-pass filter cut-off: 0.16 Hz).

Both families gave their written informed consent prior to investigation.

Seizure analysis

For each patient, scalp video-EEG and SEEG recordings of all seizures were reviewed. The clinical duration and the topography of the muscle atonia (generalized or segmental), the presence of other clinical ictal phenomena, as well as the order of appearance of atonic semiology during the seizure were analysed.

In this retrospective study, the polygraphic monitoring, performed within the frame of a routine presurgical work-up, was limited to bilateral EMG recordings from the deltoid muscles in Patient 1 and additionally covered the neck muscles in Patient 2. However, the ILAE definition of atonic seizures does not formally require an extended polygraphic documentation. The ictal atonia definition was based on clinical observation of loss of posture on video recording, as well as on absence of myographic activity demonstrated on the EMG traces. The atonic phase comprised the whole period of muscle atonia, with absence of visible voluntary movements, including the fall period. Total seizure duration was defined as the period between the electrographic seizure onset and its termination.

Analysis of anatomo-electroclinical organization of the epileptogenic zone

The hypothesis for the localization of the EZ was made based upon icEEG and neuroimaging data. For the purpose of the anatomo-electroclinical correlations, the boundaries and subdivisions of dorsolateral (lateral Brodmann area 6 [BA6] and Brodmann area 8 [BA8]) and mesial (supplementary motor area [SMA], pre-supplementary motor area [preSMA], and cingulate motor area [CMA]) premotor cortex were defined according to previous proposals (Rizzolatti *et al.*, 1998; Matsumoto *et al.*, 2007; Bonini *et al.*, 2013). The primary motor (MI) and the primary sensory (SI) areas were defined according to cortical electrical stimulations, performed as a part of the routine pre-surgical SEEG evaluation.

We determined a quantitative definition of the EZ based on the estimation of a mathematical quantity referred to as the “epileptogenicity index” (EI) in brain structures, involved (or not) with the ictal discharge. Epileptogenicity index is a novel quantitative measure that characterizes the epileptogenicity of brain structures recorded by depth electrodes, with the aim of objectively quantifying and defining a neuronal network underlying seizure generation. In this method, each recorded SEEG signal is analysed in the transition period from interictal to ictal activity and two parameters are evaluated and combined into a single quantity: – the propensity of a given brain structure to generate rapid discharges (beta [12.4-24 Hz] and gamma [24-90 Hz] bands), considered as a typical electrophysiological

pattern of the EZ in focal epilepsies, replacing background activity (delta [1-3.4 Hz], theta [3.4-7.4 Hz], and alpha [7.4-12.4 Hz]);

– the delay of appearance of this rapid discharge in a given structure with respect to the first structure, itself involved in a “rapid discharge mode” (Bartolomei *et al.*, 2008a).

In this respect, the EI is built on the same information as that used during visual review of EEG seizure recordings. In practice, we use a semi-automatic approach involving a handy graphical user interface; the user can easily inspect and validate automatically-detected change points indicating the accurate onset of rapid discharges. From this validation performed on a “structure-by-structure” basis, the EI is then computed.

The EI estimation can be used as a classification measure to distinguish between epileptogenic and non-epileptogenic structures independently of the underlying pathological substrate or the patient’s age (Aubert *et al.*, 2009; Bartolomei *et al.*, 2011; Bonini *et al.*, 2013; Sevy *et al.*, 2014). The method has been recently validated in the setting of epileptogenic neurodevelopmental disorders (de la Vaissière *et al.*, 2014; Gollwitzer *et al.*, 2016; Lagarde *et al.*, 2016).

A normalized EI value is used, ranging from 0 to 1. If there is no involvement of the brain structure, EI=0 (no epileptogenicity), whereas if the brain structure generates a rapid discharge and the time to seizure onset is minimal, EI=1 (maximal epileptogenicity). An EI between 0 and 1 corresponds to secondary involvement of the brain structure concerned (*for detailed methodology, see Bartolomei et al. [2008a]*). We arbitrarily set a cut-off EI value, *i.e.* a value above which we considered a structure as highly epileptogenic and thus belonging to the epileptogenic zone, as EI>0.4. This cut-off was defined as optimal based on a previous study on epileptogenicity of developmental lesions (Aubert *et al.*, 2009), where this value corresponded to the 90th percentile of EI values in the intrinsically epileptogenic lesional sites. EI values from brain structures investigated were computed and averaged for all invasively recorded seizures in each patient.

Results

Clinical data

The patients were aged 6 months and 36 months, respectively, at epilepsy onset. Atonic seizures were first reported at age 16 months and 36 months, respectively. Both patients had uneventful personal history with uncomplicated pregnancy and birth. Neither had a family history of epilepsy. Neuropsychological evaluation demonstrated moderate developmental

Table 1. Main characteristics of studied patients.

Pt no.	Gender	Age at epilepsy onset (months)	Age at onset of atonic seizures (months)	Age at recordings	Neuropsychological evaluation	MRI: suspected lesion/localization	Surgery/age	Histopathology (ILAE)	Postsurgical follow-up (years)	Outcome (Engel class)
1	M	6	16	1 st evaluation: 24 months 2 nd evaluation: 7 years	Moderate developmental delay (Brunet-Lézine)	FCD/L dorsolateral premotor cortex (SFG, MFG & superior bank of the IFG), next to the preCG Residual FCD with elusive borders within the dorsal aspect of the L SFG	1 st surgery: L dorsolateral premotor corticectomy up to the preCG/25 months 2 nd surgery: L dorsolateral premotor (SFG-MFG) and mesial premotor (SMA) corticectomy (EZ defined by SEEG)/8.5 years	FCD 2a	4	1a
2	M	36	36	1 st evaluation: 5 years 2 nd evaluation: 16 years	Average cognitive performances (WPPSI-III) Normal intelligence, working memory and executive function deficits (WISC-IV)	Considered as normal Profound L SFS, abnormal gyration of adjacent premotor cortex (SFG, MFG)	L dorsolateral premotor corticectomy along the SFS (EZ defined by SEEG)/17 years	FCD 1a	5	1a

EZ: epileptogenic zone; FCD: focal cortical dysplasia; IFG: inferior frontal gyrus; L: left; M: male; MFG: medial frontal gyrus; preCG: precentral gyrus; SEEG: stereotactic intracerebral EEG; SFG: superior frontal sulcus; SFS: superior frontal sulcus; SMA: supplementary motor area; WISC-IV: Wechsler Intelligence Scale for Children; WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence.

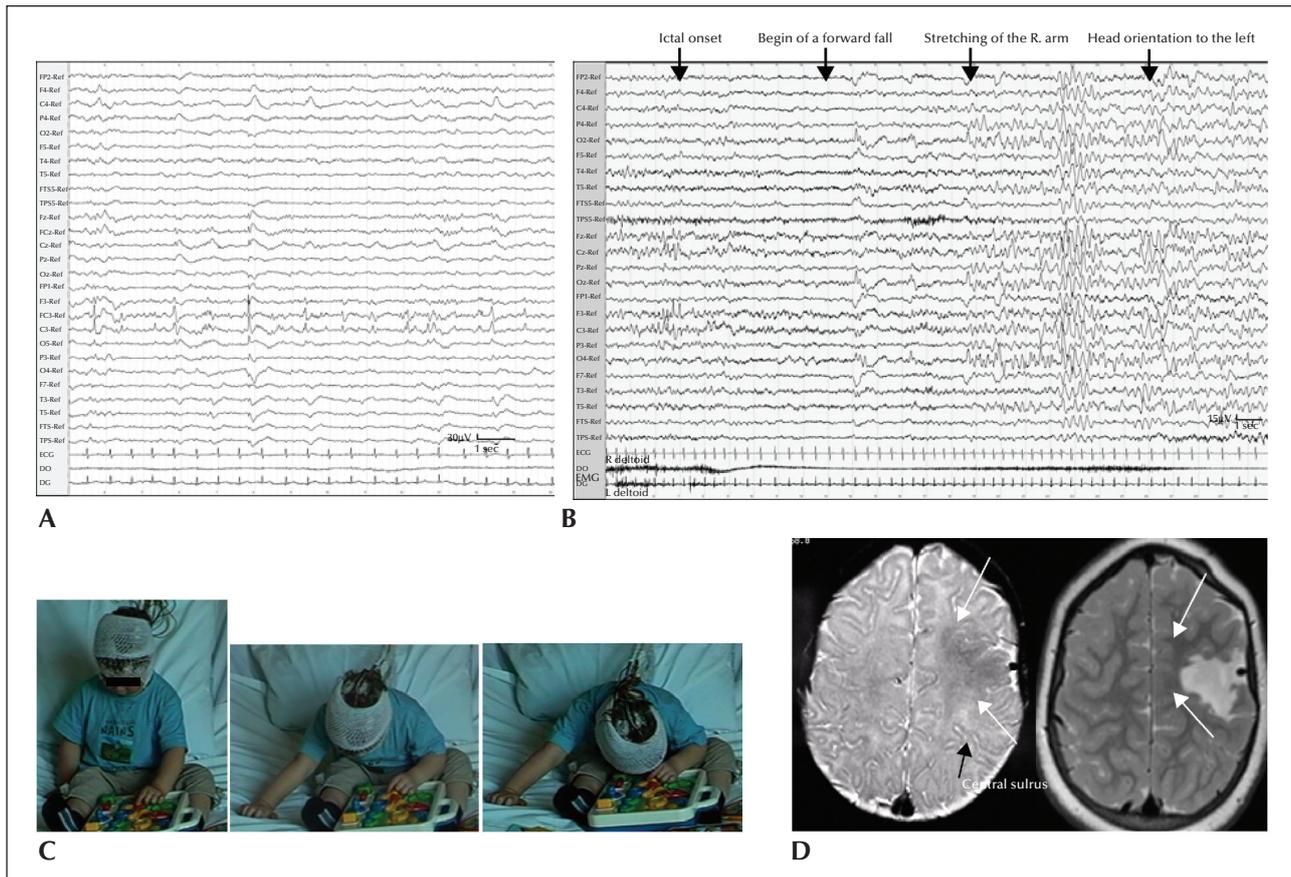


Figure 1. Scalp electroclinical findings and neuroimaging of Patient 1. (A) Interictal scalp EEG at age 24 months (referential common average montage: 30 mV/mm, 0.3 seconds, 70 Hz, during non-REM sleep) showing left precentral and median pseudorhythmic spikes and polyspikes with recurrent bursts of low-voltage fast activity of the same topography. (B) Seizure recorded by scalp video-polygraphic EEG at age 24 months (referential common average montage: 15 mV/mm, 0.3 seconds, 70 Hz), showing ictal onset (arrow) involving a rhythmic recruiting left precentral fast polyspike discharge preceding the onset of atonic phenomenon. (C) The atonic phenomenon was associated with “positive motor” signs; “slow” forward fall with concomitant stretching of the right arm, then slight head orientation to the left (arrows). (D) MRI at age 9 months (left) showing a lesion within the left dorsolateral premotor region BA6 (white arrows), and at age 8 years (right) revealing a suspicion of residual cortical dysplasia with elusive borders close to the dorsal limit of the first resection (white arrows).

delay (Patient 1) or deficits in executive functions and working memory (Patient 2), which installed after epilepsy onset. Clinical data are summarized in *table 1*.

Scalp electroclinical findings

In Patient 1, interictal EEG showed focal pseudorhythmic epileptiform discharges and slowing over left precentral and vertex regions, with presence of recurrent bursts of low-voltage fast activity of the same topography (*figure 1A*). This periodic pattern increased and became continuous during non-REM sleep, suggesting a characteristic surface EEG aspect of focal cortical dysplasia (FCD) type 2 (Palmini *et al.*, 1995; Chassoux *et al.*, 2000; Tassi *et al.*, 2012). In Patient 2, scalp EEG showed both regional (bilateral frontal) and

generalized interictal epileptiform discharges (*figure 2A*). Generalized polyspike bursts were sometimes symptomatic of the myoclonia of the isolated head, face, or arms. This patient was initially misdiagnosed with progressive myoclonic epilepsy.

A total of nine atonic seizures (3-6 per patient) were analysed. The negative motor semiology comprised sudden generalized atonia with drooping of the head and arms and loss of postural tone, leading to a fall. The duration of the atonic phase was 47.5 ± 21.0 seconds in Patient 1 and 23.6 ± 3.2 seconds in Patient 2. Representing more than 70% of the total seizure duration (63.8 ± 13.1 seconds and 30.0 ± 1.7 seconds, respectively), it was the core but not the only ictal phenomenon. In both patients, the atonic phase was preceded by a brief behavioural arrest. In Patient 1, a subtle concomitant “positive motor” sign (slight

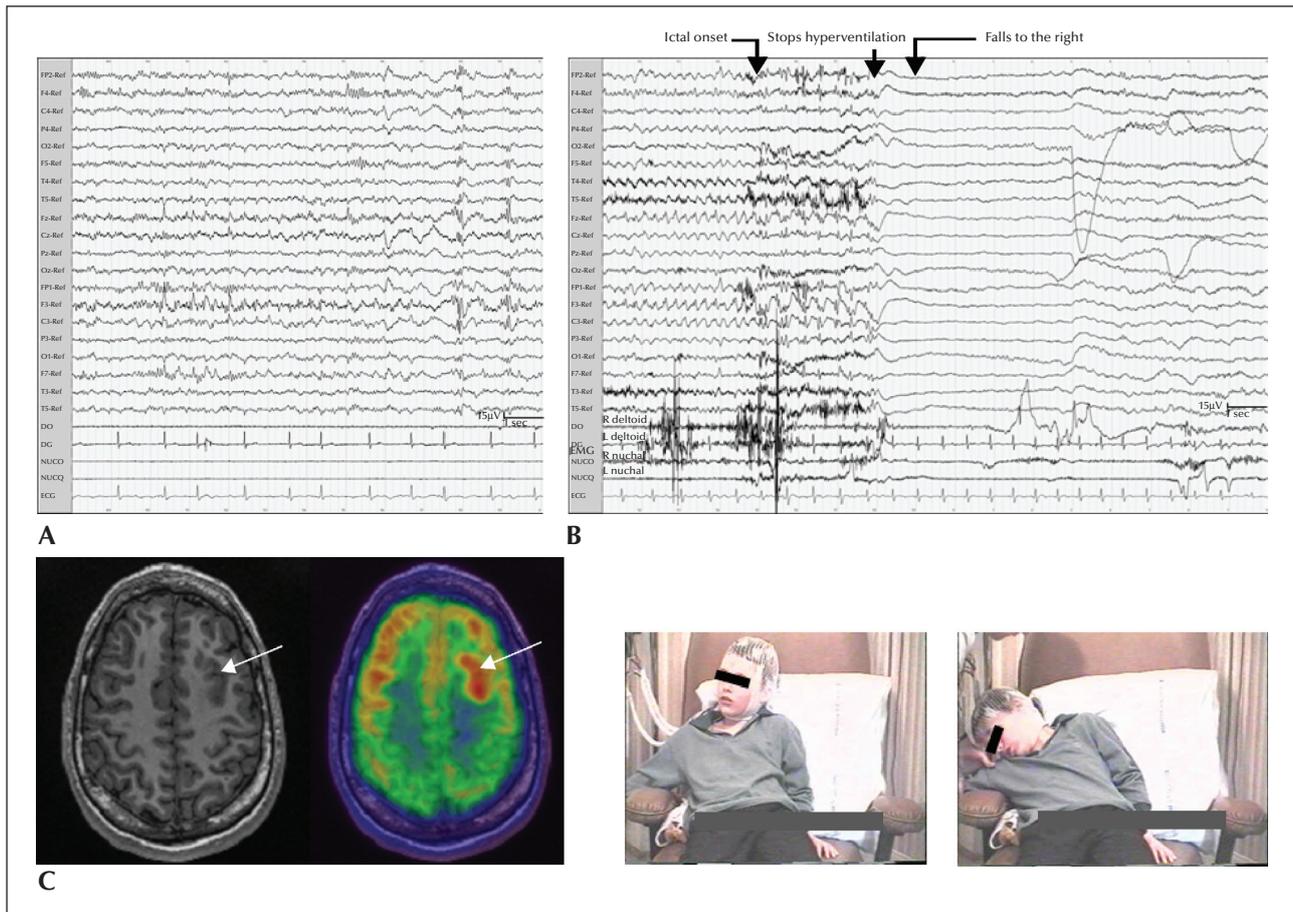


Figure 2. Scalp electroclinical findings and neuroimaging of Patient 2. (A) Interictal scalp EEG at age 8 years (referential common average montage: 15mV/mm, 0.3 seconds, 70 Hz, during a non-REM sleep) showing the coexistence of long-lasting sequences of left fronto-central and median slow waves with superposed spikes and polyspikes, and generalized left frontal predominant fast polyspike bursts. The latter were sometimes symptomatic of the isolated myoclonia of the head, face or arms. This patient was initially misdiagnosed with progressive myoclonic epilepsy. (B) Seizure recorded by scalp video-polygraphic EEG at age 8 years (referential common average montage: 15 mV/mm, 0.3 s, 70 Hz) showing ictal onset involving a brief bilateral, left frontal predominant polyspike-and-wave discharge, followed by generalized background deflection and low-voltage fast polyspike activity, simultaneously with the atonic fall (arrows). The atonic phenomenon was characterized by a sudden generalized hypotonia with “rapid” fall to the right. Note the absence of myographic activity on the EMG traces during the atonic phase. (C) MRI (left) and MRI-PET-fusion image (right) showing a well-delimited hypermetabolic area in the left dorsolateral premotor cortex, with abnormal gyration of superior frontal sulcus in this area (arrows).

stretching of the contralateral arm) was observed during the atonic phase, followed by contralateral dystonic arm posturing and contralateral head orientation.

The ictal EEG onset patterns were immediately bilateral, predominant over frontal regions (Patient 2; figure 2B), or localized over a precentral region on the lesion side with fast bilateral spread (Patient 1; figure 1B).

Neuroimaging findings

In Patient 1, MRI displayed an extended lesion, suggestive of FCD, located in the dorsolateral

premotor region, adjacent to the primary motor cortex (figure 1C). In Patient 2, initial MRI at age 5 years was considered normal. At age 16 years, FDG-PET revealed a well-delimited hypermetabolic area in the left dorsolateral premotor cortex corresponding to the abnormally deep superior frontal sulcus (figure 2C).

SEEG electroclinical findings

Patient 1 did not become seizure-free after the first cortectomy at age 25 months that targeted the epileptogenic zone, as determined by the MRI lesion and concordant scalp video-EEG. He was investigated using SEEG at age 7 years. Four invasively recorded habitual

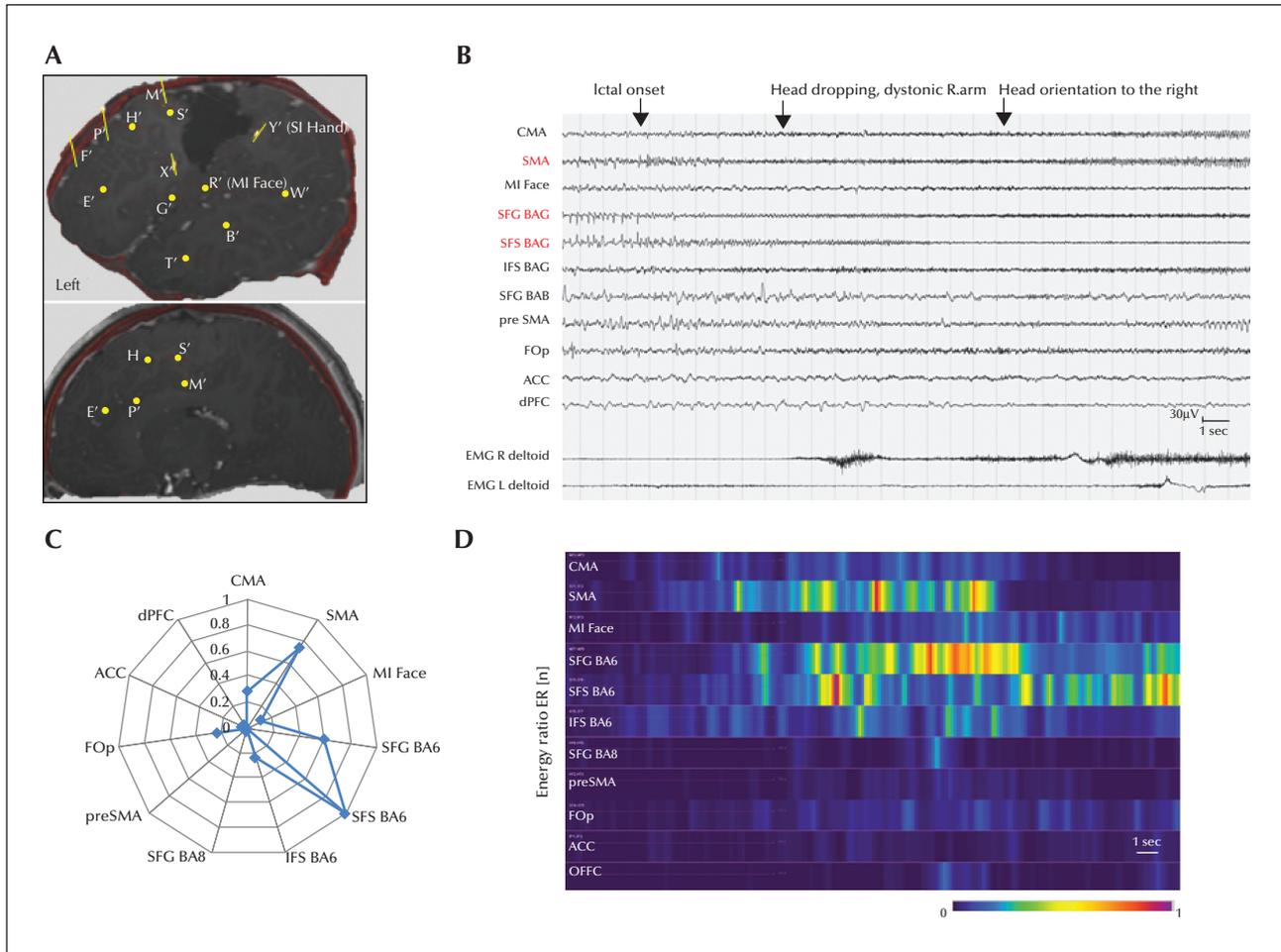


Figure 3. SEEG recordings of Patient 1. (A) Location of the SEEG electrodes used to investigate the left hemisphere, shown on the sagittal planes of 3D CT/MRI fusion images. Electrode entry points are represented as circles or lines that correspond to orthogonal or to oblique electrode trajectories, respectively. Electrode Y' was used to investigate the posterior insula (internal contacts) and hand SI area (lateral contacts); R' the superior insula (INS) and face MI area; M' the cingulate motor area (CMA) and the premotor part of the superior frontal gyrus (SFG BA6, residual lesion on MRI); S' the supplementary motor area (SMA), the premotor part of the superior frontal sulcus (SFS BA6, residual lesion on MRI) and the premotor part of the middle frontal gyrus; X' the anterior insula, as well as the premotor parts of the inferior frontal sulcus (IFS BA6) and of the middle frontal gyrus; G' the anterior insula and the frontal operculum (FOp); and H' the pre-supplementary motor area (preSMA) and the premotor part of the superior frontal gyrus, rostral to M' (SFG BA8). Internal contacts of electrodes P' and E' were used to investigate the rostral part of the anterior cingulate cortex (ACC). The lateral contacts of P', F' and E' recorded the dorsolateral prefrontal cortex (dPFC). Internal contacts of F' were used to investigate the orbitofrontal cortex. Electrodes T', B' and W' sampled the mesial and lateral structures of the left temporal lobe. (B) Seizure onset within the "lesional" dorsolateral premotor cortex (SFG, SFS BA6), with early implication of the SMA, showing increasing synchrony of interictal spikes and transition to rhythmic polyspike activity, followed by a low-voltage rapid discharge. A subtle atonic phenomenon (head dropping) with concomitant dystonic right-arm posturing was associated with a vast tonic discharge affecting mesial and lateral premotor cortices, and a less tonic low-voltage fast activity in the primary motor face area. (C) Quantification of the rapid discharge at seizure onset. Changes in energy ratio of high frequencies (25-90 Hz; ER[n]) in the selected SEEG signals from primary motor, premotor, and prefrontal regions are depicted in a colour scale. Maximal increase in ER is observed in the superior premotor cortex (SFG, SFS BA6) and the SMA. (D) The epileptogenicity index (EI) values quoted on the web chart demonstrating maximal epileptogenicity in the superior dorsolateral premotor cortex BA6.

seizures were analysed. The ictal semiology comprised behavioural arrest, followed by head dropping with dystonic stretching of the right arm, head orientation to the right, and bilateral inferior facial contraction. The duration of this subtle segmental atonic phenomenon was significantly shorter than in infancy:

10.5±2.0 seconds (51% of total seizure duration) versus 47.5±21.0 seconds (75%), respectively. SEEG recordings (figure 3) revealed a mesiolateral premotor epileptogenic network with seizure onset in the lesional dorsolateral premotor cortex (BA6) next to the anterior and superior borders of the first resection, with

rapid involvement of the SMA (<0.5 sec), as well as of the inferior dorsolateral premotor cortex, rostral to the first resection. A vast spread of rapid discharge affecting mesial and lateral premotor (lateral BA6, SMA, and CMA), as well as the MI areas, preceded the emergence of ictal atonia.

Patient 2 remained misdiagnosed with progressive myoclonic epilepsy until the age of 16 years when a potential structural abnormality was finally suspected on FDG-PET-guided MRI that encouraged subsequent SEEG exploration. Four habitual seizures were analysed. The initial semiology comprised a behavioural arrest, followed by slow head dropping. As for Patient 2, the duration of the negative motor phenomenon became much shorter, compared to the first evaluation: 4.3 ± 1.0 seconds (15% of total seizure duration) versus 23.6 ± 3.2 seconds (79%), respectively. The seizure then evolved with rubefaction and contralateral tonic head and gaze deviation. Ictal SEEG showed seizure initiation within the premotor part of the superior frontal sulcus and rapid implication (<0.5 seconds) of the adjacent superior frontal gyrus (BA8). A tonic discharge then rapidly invaded both lateral and mesial premotor areas (lateral BA8 and BA6, and SMA), as well as the MI, in temporal correlation with the emergence of segmental atonia (figure 4).

In both patients, no isolated atonic phenomena could be elicited by cortical electrical stimulations.

Organization of the epileptogenic zone

The epileptogenicity profiles of the analysed patients are illustrated in figure 5A. The mean EI values of recorded seizures were maximal in the lateral premotor cortex in both patients (0.90 ± 0.15 and 0.78 ± 0.27 , respectively). In Patient 1, the quantitatively defined EZ (EI values >0.4) included several lesional and non-lesional structures within the lateral (BA6) and mesial (SMA) premotor cortex (figure 5B). In Patient 2, it was restricted to a part of the lateral premotor cortical area within the “lesional” part of superior frontal sulcus and the adjacent superior frontal gyrus (BA8; figure 5C).

Surgery and outcome

Both patients underwent subsequent tailored resections of the invasively defined epileptogenic zone. Pathological examination of resected specimens showed FCD in both cases. Postoperative seizure outcome corresponded to Engel Class Ia (Engel et al., 1993) at the last follow-up visit. Patient 1 presented with moderate, partially reversible right-sided hemiparesis after the first surgery; no transient or permanent postoperative neurological deficits were reported in Patient 2. Neuropsychological outcome one year after surgery was favourable, with improvement of partial scores

(verbal comprehension), but persistence of moderate developmental delay in Patient 1 and normalization of previously deficient scores (backward verbal and spatial working memory spans and cognitive flexibility) in Patient 2.

Discussion

Our study demonstrates that different electroclinical phenotypes might be encountered in focal-onset atonic seizures occurring in infancy or early childhood. The first presented phenotype comprised an ictal atonic phenomenon associated with some lateralizing clinical features and focal scalp EEG abnormalities; the second was characterized by “pure” atonic semiology without lateralizing clinical signs and by the presence of bilateral ictal and interictal EEG patterns. However, long-lasting (over dozens of seconds) generalized atonia was a predominant feature in both cases. This clinical aspect is of particular interest as it corroborates the previously postulated hypothesis that long duration of an atonic phenomenon might be a feature distinguishing the phenotype of focal-onset atonic seizures from that of atonic seizures within the frame of generalized epileptic syndromes, in which brief atonia lasting from milliseconds to 1-2 seconds has been classically reported (Gastaut et al., 1966; So, 1995; Oguni et al., 2001; Satow et al., 2002). Nonetheless, this requires further investigation using a larger patient cohort.

The epileptogenic zone underlying atonic seizures was localized within the premotor regions, rostral or adjacent to the primary motor cortex. Using a quantitative analysis of the intracerebral EEG recordings, we identified a “focal”, dorsolateral premotor EZ in one case and a more distributed mesiolateral premotor EZ in the other case. These findings are in good agreement with previously described motor seizure network subtypes (Bonini et al., 2013). In both situations, the emergence of atonic semiology temporally correlated with nearly simultaneous spread of the tonic ictal discharge to the lateral and mesial premotor and primary motor areas, as demonstrated by SEEG recordings.

According to the recent concept proposed by Bartolomei et al. (2008b), the emergence of clinical signs in a focal seizure depends on the phenomena of synchronized or transiently desynchronized activity in the cortical structures, defined as the “epileptogenic zone network”, followed by synchronized rhythmic modifications of the other cortical and subcortical structures belonging to the “propagation network”. A recent study based on direct cortical stimulations suggested the possible integrative role of higher-order associative fronto-parietal cortices in producing negative motor signs that would result from impairment

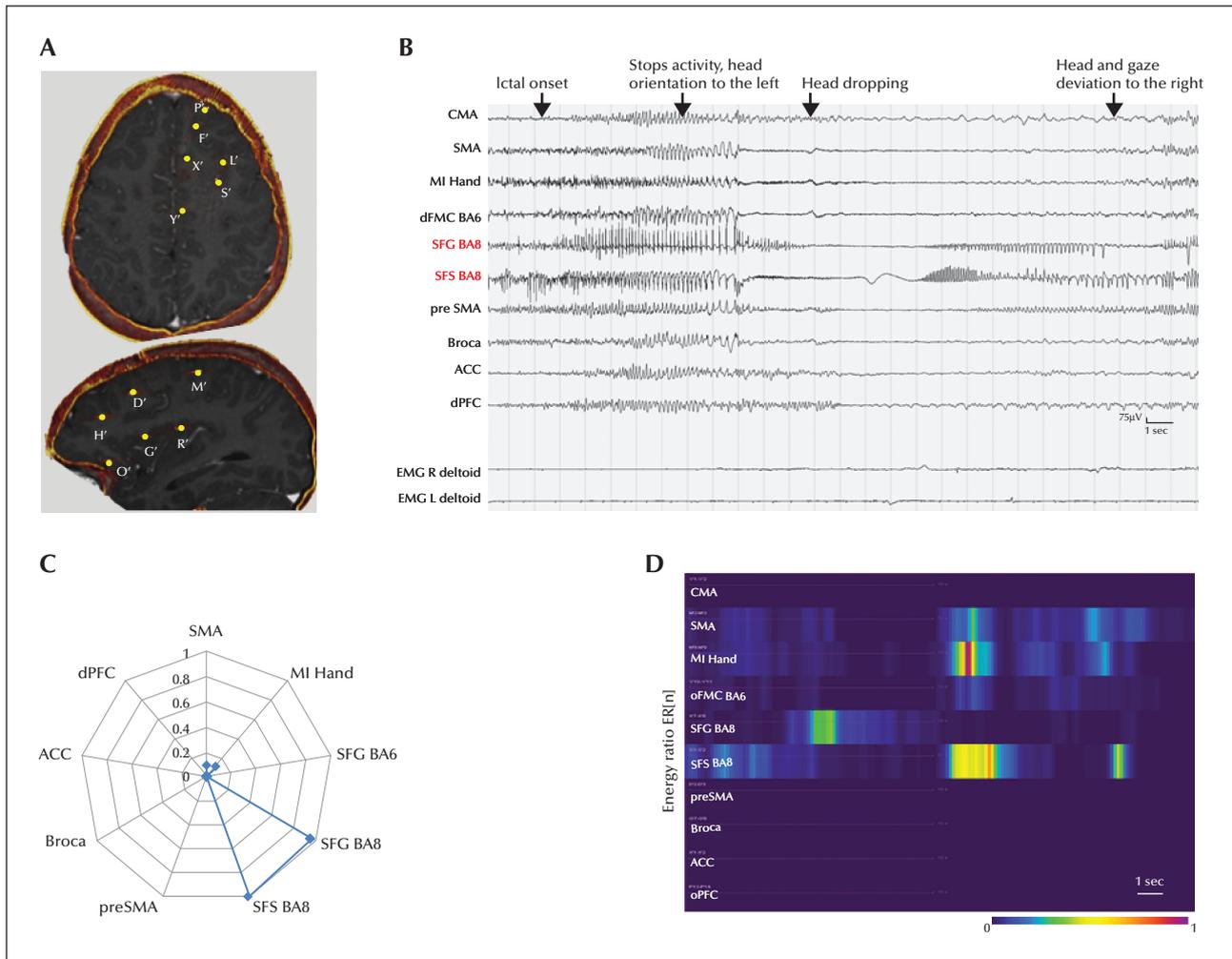


Figure 4. SEEG recordings of Patient 2. (A) Location of the SEEG electrodes used to investigate the left hemisphere, shown on the sagittal (orthogonal electrode entry points) and axial (oblique electrode entry points) planes of 3D CT/MRI fusion images. Electrode M' was used to investigate the SMA (internal contacts) and hand MI area (lateral contacts); Y' the cingulate motor area (CMA, internal contacts) and the caudal premotor part of the superior frontal gyrus (SFG BA6, lateral contacts); X' the rostral part of the anterior cingulate cortex (BA24) and the rostral premotor part of the superior frontal gyrus (SFG BA8); electrodes S' and L' the "lesional" aspect of the superior frontal sulcus in the area of the metabolic PET abnormality (SFS BA8); electrodes F' and P' the orbitofrontal cortex and the dorsolateral prefrontal cortex; D' the preSMA (internal contacts), the "lesional" aspect of the SFS (intermediate contacts), and the premotor part of the medial frontal gyrus (BA8, lateral contacts); R' the superior insula (INS) and rolandic operculum; C' the anterior insula and the Broca area (BA44); H' the anterior cingulate cortex (ACC, BA32, internal contacts) and the dorsolateral prefrontal cortex (BA9, lateral contacts); and O' the ACC (BA25, internal contacts), medial, and lateral orbitofrontal cortex (BA47/12, intermediate and lateral lids). (B) Seizure onset within the rostral dorsolateral premotor cortex (BA8), showing recruiting polyspike activity within the "lesional" part of the SFS, with rapid involvement of the adjacent SFG, followed by a slower rhythmic activity involving the rest of the lateral and mesial premotor areas, while a non-sustained slow rhythmic pattern was observed in the prefrontal areas. The seizure then evolved with a low-voltage tonic discharge affecting the dorsolateral premotor (BA8 and BA6), mesial premotor (SMA), and the primary motor cortices, with subsequent appearance of an atonic phenomenon (arrow). (C) Changes in energy ratio of high frequencies (ER[n]) in the above-selected SEEG signals from different frontal regions are disclosed with a colour scale. Increase in ER is seen first in the rostral dorsolateral premotor cortex (BA8) and secondarily in the MI and SMA regions. (D) The epileptogenicity index (EI) values quoted on the web chart demonstrating maximal epileptogenicity in the superior dorsolateral premotor cortex BA8.

of movement organization (Enatsu *et al.*, 2013). Thus, ictal negative motor semiology might not correspond to the involvement of just an isolated brain area (e.g. the so called negative motor areas [Lüders *et al.*, 1995] that would elicit negative motor responses when stim-

ulated), but could reflect a larger perturbation of the cortico-subcortical motor networks.

In the light of these concepts, we hypothesize that atonic seizures might represent a motor system seizure phenotype in the setting of structural epilepsy.

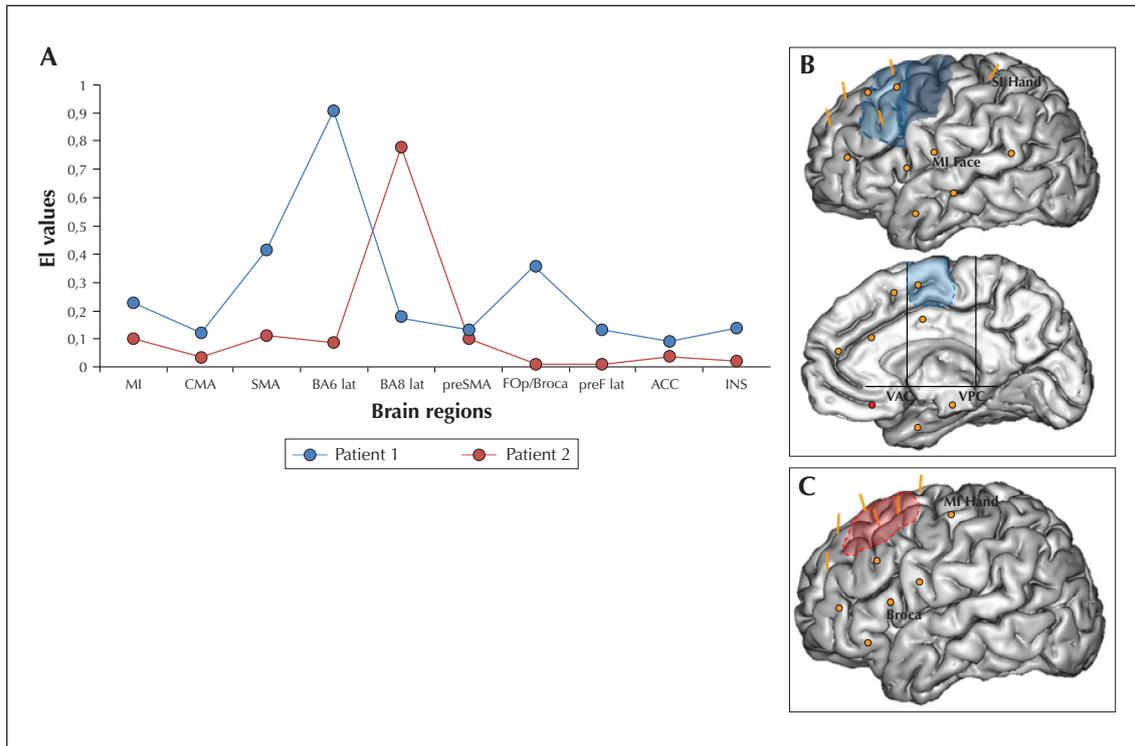


Figure 5. Quantitative analysis and anatomo-electroclinical organization of the invasively defined epileptogenic zone. (A) Profiles of epileptogenicity of Patients 1 and 2. The EI values (mean of four seizures) in 10 explored brain regions are indicated for each patient. The EI profiles are characterized by maximal epileptogenicity in dorsolateral premotor regions. While a “focal” (lateral BA8) EI profile is observed in Patient 2, a more distributed, mesiolateral premotor (lateral BA6, SMA) epileptogenic profile, with globally higher EI values, is disclosed in Patient 1. (B) Topography of the quantitatively defined EZ in Patient 1 (blue-coloured area) with lateral and medial view of all implanted depth electrodes on a 3D-reconstruction of the neocortical surface of the left hemisphere. The grey-coloured area corresponds to the first MRI lesion-guided cortectomy before the SEEG. (C) Topography of the quantitatively defined EZ in Patient 2 (red-coloured area) with lateral view of all implanted depth electrodes on a 3D-reconstruction of the neocortical surface of the left hemisphere. ACC: anterior cingulate cortex; BA: Brodmann area; CMA: cingulate motor area; EI: epileptogenicity index; EZ: epileptogenic zone; FOp: frontal operculum; INS: insula; lat: lateral; MI: primary motor cortex; preF lat: dorsolateral prefrontal cortex; preSMA: pre-supplementary motor area; SMA: supplementary motor area; VAC: vertical anterior-commissural line; VPC: vertical posterior-commissural line.

A vast initial spread of the high-frequency desynchronizing discharge, arising from the motor areas (whether corresponding to the negative motor area or not), would lead to a functional decoupling between the primary, lower-order, and higher-order associative cortical and subcortical (the fast corticoreticular pathway) parts of the motor system, resulting in disorganization of postural control that underlies generalized atonia. The subsequent decrease in discharge frequency and increase in network synchronization between the specific cortical (the SMA and dorsolateral premotor cortex) and subcortical (the basal ganglia) nodes might mediate the emergence of positive motor signs, such as contralateral tonic/dystonic arm posturing, the M2e posture, or head version (Ajmone-Marsan and Ralston, 1957; Bancaud and Talairach, 1992; Rusu et al., 2005; Bonini et al., 2013; Marashly et al., 2016).

As far as the developmental aspect is concerned, it should be accepted that atonic seizures are not exclusively seen in infants and children, but may also be observed in epilepsy with focal seizures in adulthood. However, in an adult cohort, they were mostly reported as focal and, only exceptionally, as generalized atonia (So, 1995; Kovac and Diehl, 2012). Our findings in two serially evaluated patients suggest a possibility of age-dependent evolution of atonic seizures from prolonged generalized atonia with a few subtle positive motor signs at early age to brief segmental atonia with prominent positive motor signs in later life, along with the maturation of the physiological brain motor networks throughout childhood, adolescence, and early adulthood (Chugani et al., 1987; Chiron et al., 1992; Schäfer et al., 2014). Finally, our data demonstrate that atonic seizures, commonly associated with generalized syndromes,

may have a focal onset and be amenable to surgery. Surgical outcome was excellent in both our cases suggesting that early-onset pharmacoresistant epilepsy manifesting with atonic seizures should be considered for presurgical evaluation if some clinical, EEG or neuroimaging features are in favour of a focal origin.

Conclusion

Long-lasting generalized atonia was a predominant clinical feature of focal-onset atonic seizures occurring in infancy. This ictal semiology evolved into subtle segmental atonia associated with prominent positive motor signs at later age. The spatio-temporal organization of the underlying epileptogenic networks supports the hypothesis that atonic seizures may represent a motor system seizure phenotype in structural epilepsy. Sustained seizure freedom could be achieved by complete removal of the epileptogenic zone. □

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References

- Abou-Khalil B, Fakhoury T, Jennings M, Moots P, Warner J, Kessler RM. Inhibitory motor seizures: correlation with centroparietal structural and functional abnormalities. *Acta Neurol Scand* 1995;91(2): 103-8.
- Ajmone-Marsan C, Ralston BL. *The Epileptic Seizure. A Clinical-electrographic Analysis of Metrazol Attacks*. Springfield, IL: Charles Thomas Publisher, 1957.
- Aubert S, Wendling F, Regis J, et al. Local and remote epileptogenicity in focal cortical dysplasias and neurodevelopmental tumours. *Brain* 2009;132(11): 3072-86.
- Bancaud J, Talairach J. Clinical semiology of frontal lobe seizures. *Adv Neurol* 1992;57: 3-58.
- Bartolomei F, Chauvel P, Wendling F. Epileptogenicity of brain structures in human temporal lobe epilepsy: a quantified study from intracerebral EEG. *Brain* 2008a;131(7): 1818-30.
- Bartolomei F, Wendling F, Chauvel P. The concept of an epileptogenic network in human partial epilepsies. *Neurochirurgie* 2008b;54(3): 174-84.
- Bartolomei F, Gavaret M, Hewett M, et al. Neural networks underlying parietal lobe seizures: a quantified study from intracerebral recordings. *Epilepsy Res* 2011;93: 164-76.
- Blume WT, Lüders HO, Mizrahi E, et al. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. *Epilepsia* 2001;42(9): 1212-8.
- Bonini F, McGonigal A, Wendling F, et al. Epileptogenic networks in seizures arising from motor systems. *Epilepsy Res* 2013;106(1-2): 92-102.
- Chassoux F, Devaux B, Landre E, et al. Stereoelectroencephalography in focal cortical dysplasia: a 3D approach to delineating the dysplastic cortex. *Brain* 2000;123: 1733-51.
- Chiron C, Raynaud C, Mazière B, et al. Changes in regional cerebral blood flow during brain maturation in children and adolescents. *J Nucl Med* 1992;33(5): 696-703.
- Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. *Ann Neurol* 1987;22(4): 487-97.
- de la Vaissière S, Milh M, Scavarda D, et al. Cortical involvement in focal epilepsies with epileptic spasms. *Epilepsy Res* 2014;108(9): 1572-80.
- Elger CE, Speckmann EJ, Prohaska O, Caspers H. Pattern of intracortical potential distribution during focal interictal epileptiform discharges (FIED) and its relation to spinal field potentials in the rat. *Electroencephalogr Clin Neurophysiol* 1981;51(4): 393-402.
- Enatsu R, Matsumoto R, Piao Z, et al. Cortical negative motor network in comparison with sensorimotor network: a cortico-cortical evoked potential study. *Cortex* 2013;49(8): 2080-96.
- Engel Jr. J, Van Ness PC, Rasmussen TB, Ojemann LM. Outcome with respect to epileptic seizures. In: J Engel, ed. *Surgical Treatment of the Epilepsies*. New York: Raven Press, 1993, 609-21.
- Gastaut H, Tassinari CA, Bureau-Paillas M. Étude polygraphique et clinique des effondrements atoniques épileptiques. *Rev Neurol* 1966;36(1): 5-21.
- Gollwitzer S, Valente I, Rodionov R, et al. Visual and semi-automated evaluation of epileptogenicity in focal cortical dysplasias - An intracranial EEG study. *Epilepsy Behav* 2016;58: 69-75.
- Ikeda A, Ohara S, Matsumoto R, et al. Role of primary sensorimotor cortices in generating inhibitory motor response in humans. *Brain* 2000;123(8): 1710-21.
- Kahane P, Ryvlin P, Hoffmann D, Minotti L, Benabid AL. From hypothalamic hamartoma to cortex: what can be learnt from depth recordings and stimulation? *Epileptic Disord* 2003;5(4): 205-17.
- Kovac S, Diehl B. Atonic phenomena in focal seizures: nomenclature, clinical findings and pathophysiological concepts. *Seizure* 2012;21(8): 561-7.
- Kovac S, Nachev P, Rodionov R, et al. Neck atonia with a focal stimulation-induced seizure arising from the SMA: pathophysiological considerations. *Epilepsy Behav* 2012;24(4): 503-6.

- Lagarde S, Bonini F, McGonigal A, et al. Seizure-onset patterns in focal cortical dysplasia and neurodevelopmental tumors: relationship with surgical prognosis and neuropathologic subtypes. *Epilepsia* 2016; 57(9): 1426-35.
- Lim SH, Dinner DS, Pillay PK, et al. Functional anatomy of the human supplementary sensorimotor area: results of extraoperative electrical stimulation. *Electroencephalogr Clin Neurophysiol* 1994; 91(3): 179-93.
- Lüders HO, Dinner DS, Morris HH, Wyllie E, Comair YG. Cortical electrical stimulation in humans. The negative motor areas. *Adv Neurol* 1995; 67: 115-29.
- Maillard L, Gavaret M, Régis J, Wendling F, Bartolomei F. Fast epileptic discharges associated with ictal negative motor phenomena. *Clin Neurophysiol* 2014; 125(12): 2344-8.
- Marashly A, Ewida A, Agarwal R, Younes K, Lüders HO. Ictal motor sequences: Lateralization and localization values. *Epilepsia* 2016; 57(3): 369-75.
- Matsumoto R, Ikeda A, Ohara S, et al. Nonconvulsive focal inhibitory seizure: subdural recording from motor cortex. *Neurology* 2000; 55(3): 429-31.
- Matsumoto R, Ikeda A, Hitomi T, et al. Ictal monoparesis associated with lesions in the primary somatosensory area. *Neurology* 2005; 65(9): 1476-8.
- Matsumoto R, Nair DR, LaPresto E, Bingaman W, Shibasaki H, Lüders HO. Functional connectivity in human cortical motor system: a cortico-cortical evoked potential study. *Brain* 2007; 130(1): 181-97.
- Mori S, Iwakiri H, Homma Y, Yokoyama T, Matsuyama K. Neuroanatomical and neurophysiological bases of postural control. *Adv Neurol* 1995; 67: 289-303.
- Munari C, Kahane P, Francione S, et al. Role of the hypothalamic hamartoma in the genesis of gelastic fits (a video-stereo-EEG study). *Electroencephalogr Clin Neurophysiol* 1995; 95(3): 154-60.
- Noachtar S, Lüders HO. Focal akinetic seizures as documented by electroencephalography and video recordings. *Neurology* 1999; 53(2): 427-9.
- O'Donovan CA, Chan A, Maxwell S. Focal akinetic seizures as the only clinical manifestation of partial epilepsy. *Seizure* 2007; 16(6): 542-4.
- Oguni H, Fukuyama Y, Tanaka T, et al. Myoclonic-astatic epilepsy of early childhood-clinical and EEG analysis of myoclonic-astatic seizures, and discussions on the nosology of the syndrome. *Brain Dev* 2001; 23(7): 757-64.
- Palmini A, Gambardella A, Andermann F, et al. Intrinsic epileptogenicity of human dysplastic cortex as suggested by corticography and surgical results. *Ann Neurol* 1995; 37: 476-87.
- Rizzolatti G, Luppino G, Matelli M. The organization of the cortical motor system: new concepts. *Electroencephalogr Clin Neurophysiol* 1998; 106(4): 283-96.
- Rubboli G, Tassinari CA. Negative myoclonus. An overview of its clinical features, pathophysiological mechanisms, and management. *Neurophysiol Clin* 2006; 36(5-6): 337-43.
- Rusu V, Chassoux F, Landré E, et al. Dystonic posturing in seizures of mesial temporal origin: electroclinical and metabolic patterns. *Neurology* 2005; 65(10): 1612-9.
- Satow T, Ikeda A, Yamamoto J, et al. Partial epilepsy manifesting atonic seizure: report of two cases. *Epilepsia* 2002; 43(11): 1425-31.
- Schäfer CB, Morgan BR, Ye AX, Taylor MJ, Doesburg SM. Oscillations, networks, and their development: MEG connectivity changes with age. *Hum Brain Mapp* 2014; 35(10): 5249-61.
- Sevy A, Gavaret M, Trebuchon A, et al. Beyond the lesion: the epileptogenic networks around cavernous angiomas. *Epilepsy Res* 2014; 108: 701-8.
- So NK. Atonic phenomena and partial seizures. A reappraisal. *Adv Neurol* 1995; 67: 29-39.
- Tassi L, Garbelli R, Colombo N, et al. Electroclinical, MRI and surgical outcomes in 100 epileptic patients with type II FCD. *Epileptic Disord* 2012; 14(3): 257-66.
- Tinuper P, Cerullo A, Marini C, et al. Epileptic drop attacks in partial epilepsy: clinical features, evolution, and prognosis. *J Neurol Neurosurg Psychiatr* 1998; 64(2): 231-7.
- You SJ, Lee J-K, Ko T-S. Epilepsy surgery in a patient with Lennox-Gastaut syndrome and cortical dysplasia. *Brain Dev* 2007; 29(3): 167-70.
- Zhao J, Afra P, Adamolekun B. Partial epilepsy presenting as focal atonic seizure: a case report. *Seizure* 2010; 19(6): 326-9.

TEST YOURSELF



- (1) Are there distinct electroclinical features of atonic seizures in early-onset structural epilepsy and can they change with age?
- (2) Which cortical regions might be involved in ictal discharge during the emergence of atonic semiology?
- (3) Can a paediatric patient with pharmacoresistant epilepsy and clinically generalized atonic semiology be a candidate for resective surgery?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".