SHORT REPORT

How generalised are secondarily “generalised” tonic-clonic seizures?

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In clinical practice, epileptic seizures with focal onset and subsequent generalised motor involvement are referred to as secondarily generalised seizures. The purpose of this study was to investigate the degree of electrophysiological generalisation in seizures that are clinically secondarily generalised. Intracranial EEG recordings of secondarily generalised tonic-clonic seizures were visually and quantitatively analysed for the presence of epileptiform activity. In 24 (26%) of 93 seizures recorded from 17 (27%) of 64 patients, intracranial EEG channels were found that never recorded epileptiform activity during secondarily generalised tonic-clonic seizures. Our results demonstrate that seizures that are secondarily generalised clinically are not always generalised electrophysiologically. This may have therapeutic implications.

Epileptic seizures with tonic and/or clonic manifestations of both arms, both legs, the trunk and head (ie, “general” motor involvement) are called “generalised tonic-clonic”. In “primary generalised” tonic-clonic seizures, generalised tonic occurs simultaneously at the beginning of the seizure, and non-invasive EEG shows epileptiform discharges over both cerebral hemispheres. In seizures with focal onset, different muscle groups may be involved sequentially as the seizure discharges propagate, with EEG showing localised onset and subsequent spreading of epileptiform activity. This seizure presentation is commonly referred to as “secondarily generalised” tonic-clonic. Thus the term “generalised tonic-clonic” relates to both seizure semiology and to electrophysiological findings.

However, motor manifestations that affect skeletal muscles extensively do not necessarily imply that the cerebral cortex as a whole is producing epileptiform electrical discharges. It is conceivable that epileptiform discharges confining to motor or supplementary motor areas of the frontal lobe and seizure induced changes of the activity of subcortical structures such as the basal ganglia could suffice to produce clinical signs of general motor involvement.^{1,2} Interestingly, the global involvement of the cerebral cortex has also been questioned in generalised absence seizures by Holmes and colleagues³ who found evidence for localised mesial frontal and frontopolar discharges by performing source analysis of epileptiform activity recorded with densely spaced scalp electrodes. However, even with dense array electrodes, non-invasive recordings may not detect the true extent of epileptiform activity because of the low pass filtering of the EEG signal by the anatomical structures surrounding the brain. In addition, during generalised tonic-clonic seizures, muscular artefacts may dominate the electrical signals generated by the cortex. To improve spatial resolution and to avoid muscular artefacts, the EEG has to be recorded with intracranial electrodes. Invasive EEG recording is routinely performed in patients with pharmacoresistant focal onset seizures in whom the seizure

onset zone may not be delineated precisely enough by non-invasive methods prior to surgery.

In this study, we address the question of whether secondarily generalised tonic-clonic seizures are truly generalised from an electrophysiological point of view (ie, whether the cortex is globally generating epileptiform activity). To this end we assessed whether epileptiform activity is recorded in all channels of intracranial EEGs during secondarily generalised tonic-clonic seizures. Intracranial electrodes are always placed as restrictively as possible and thus the cortex is never completely sampled. If, however, EEG channels can be identified that never exhibit epileptiform discharges during seizures, this would provide even stronger evidence that secondarily generalised seizures are not necessarily generalised from the electrophysiological point of view.

METHODS

Years 2001–2005 of the digital EEG video database of the clinic of epileptology of Bonn were screened for intracranial recordings. All patients from whom data were included in this database had given written informed consent that their data could be used for scientific analysis and publication. The videos of the intracranially recorded seizures were then reviewed (KS, HE and CE). A seizure was rated as secondarily generalised tonic-clonic according to its semiology (ie, when during its course there was simultaneous motor involvement of both arms, both legs, the head and the trunk). Symmetric versus asymmetric ictal motor manifestations were not differentiated. Motor involvement consisted of (dys)-tonic posturing evolving into clonic movements. Semiology imitating physiological movements during the seizure, such as oral or manual automatisms, were not rated as motor involvement.

To test whether clinically secondarily generalised tonic-clonic seizures may occur without epileptiform activity generated by the cortex as a whole, we assessed if there were intracranial next neighbour bipolar EEG channels that never recorded epileptiform activity during the seizure. EEG channels were visually analysed for the presence of epileptiform activity (ie, spikes, sharp waves, low voltage fast runs, rhythmic and evolving wave trains, etc). In the case of disagreement between the reviewers (KS, HE, and CE), the channel was rated as recording epileptiform activity. If there were artefacts or technical malfunctioning, such as for example, intermittent interruptions caused by violent movements, the channel was also rated as recording epileptiform activity. It is theoretically possible that widespread ictal activity might not be detected in a bipolar montage with closely spaced electrodes because of common mode rejection. Therefore, if a bipolar EEG channel appeared to record no epileptiform activity, this finding was always validated by also inspecting montages to intra- and extracranial references. In addition to visual analysis, a quantitative method detecting epileptiform activity was applied. First, the absolute slope

Figure 1 Time course of the normalised absolute slope $\tilde{S}_i(t)$ of an EEG recorded peri-ictally (frontal lobe onset seizure with rapid secondary generalisation) with 56 intracranial bipolar next neighbour channels. Forty channels did not record activity with $\tilde{S}_i(t) > 2.5$. The spatially non-contiguous appearance of epileptiform activity results from the display of channels, grouped by electrodes. Arrows indicate the beginning and end of the seizure. The white rectangle marks the reference period used for normalisation.

$$S_i(t) = \left| \frac{\Delta EEG_i(t)}{\Delta t} \right|$$

where i runs over all channels, was computed and smoothed by a lagging moving average of 5 s duration (EEG sampling rate 200 Hz, bandpass filter 0.5–70 Hz). $S_i(t)$ is an appropriate characteristic of epileptiform EEG because it increases for both high amplitude slow, but also low amplitude fast activities, as are typically observed at the onset and during intracranially recorded seizures.⁴ In a second step, $S_i(t)$ was normalised to

$$\tilde{S}_i(t) = \frac{S_i(t)}{\sigma_i^{ref}}$$

where σ_i^{ref} denotes the standard deviation of $S_i(t)$ during a reference period of 30 s duration starting 5 s after the beginning of the EEG file containing the seizure. In fig 1, $\tilde{S}_i(t)$ is displayed for a seizure recorded with 56 intracranial EEG channels. For each $EEG_i(t)$, the presence of epileptiform activity was then empirically defined as $\tilde{S}_i(t) > 2.5$. In the following, results are given as mean (SD).

RESULTS

Sixty four patients with intracranially recorded secondarily generalised tonic-clonic seizures were identified. To prevent statistical bias, not more than three seizure recordings per patient were included. The final EEG data set consisted of 93 EEG recordings. The average number of seizures per patient was 1.5 (0.6), with an average number of bipolar EEG channels of 47 (25). All the EEG channels that did not record epileptiform activity, as rated either by visual or quantitative analysis at any time during the seizures, were counted. Masking of epileptiform activity by common mode rejection was never found. In 24 (26%) seizure episodes from 17 (27%) patients, an average number of 3 (7) EEG channels (18 (15%)) were identified that never recorded epileptiform activity during the seizures. Clinical information about the patients in whom EEG channels without epileptiform activity during the seizures were found is given in table 1.

These patients suffered from different types of underlying pathology (in common with the remainder of the patients studied). The average number of EEG channels used in these patients was 60 (18) and was significantly larger ($p < 0.005$, two-tailed t test) than the average number of 43 (25) EEG channels used in the patients, in whom all the EEG channels recorded epileptiform activity. In fig 2, a representative example

Table 1 Clinical information on patients in whom EEG channels without epileptiform activity during the seizures were found

Patient No	Sex	Age (y)	MR diagnosis	Histology	Surgical procedure	Outcome*
1	F	40	Fronto-temporal atrophy left	Gliosis	Topectomy, subpial transections	Ib
2	M	15	Cortical dysplasia frontal left	Cortical dysplasia IIb†	Lesionectomy	Ia
3	M	56	Post traumatic scar fronto-basal left	Gliosis	Lesionectomy	III
4	F	8	Cortical dysplasia parietal left	Cortical dysplasia IIb	Lesionectomy	Ib
5	M	22	Hippocampal sclerosis right	Hippocampal sclerosis	sAHE right	Ia
6	M	39	Cortical malformation temporo-occipital left		No	
7	F	35	Cortical dysplasia frontal left	Cortical dysplasia IIb	Lesionectomy	Ia
8	M	30	Normal		No	
9	F	56	Bilateral hippocampal sclerosis	Hippocampal sclerosis	sAHE left	Ib
10	M	34	Normal		No	
11	M	48	Hippocampal sclerosis left	Hippocampal sclerosis	sAHE left	Ia
12	M	42	Hippocampal sclerosis right	Hippocampal sclerosis	sAHE right	Ib
13	M	27	Cortical dysplasia frontal right	Cortical dysplasia IIb	Lesionectomy	Ib
14	F	14	Hippocampal sclerosis left	Hippocampal sclerosis	2/3 ant. temp. resection	III
15	M	21	Ganglioglioma temporal left	Ganglioglioma	Lesionectomy	Ia
16	F	14	Cortical dysplasia	Cortical dysplasia IIb	Lesionectomy	Ib
17	M	27	Hippocampal sclerosis left		No	

2/3 ant. temp. resection, resection of anterior two thirds of temporal lobe; sAHE, selective amygdalo-hippocampectomy.

*According to Engel *et al.*⁵

†According to Palmini *et al.*⁶

Figure 2 (A) Clinically secondarily generalised tonic-clonic seizure. (B) Position of the intracranial electrodes. (C) At the time of general motor involvement only a subset of EEG channels records epileptiform activity. FLL, fronto-lateral left; FLR, fronto-lateral right; FPL, fronto-polar left; FPR, fronto-polar right; TBAL, temporo-basal anterior left; TBAR, temporo-basal anterior right; TBPL, temporo-basal posterior left; TBPR, temporo-basal posterior right; TL, depth electrode temporal left; TR, depth electrode temporal right; TLL, temporo-lateral left; TLR, temporo-lateral right. Informed consent was obtained for publication of part A of this figure.

of a patient (No 5, see table 1) with temporal lobe epilepsy having a secondarily generalised tonic-clonic seizure is shown. The posturing of his arms is typical of secondary generalisation and is sometimes referred to as the "figure-4-sign" because the position of the arms approximates the shape of this figure. Despite the general motor involvement, the intracranial recording (fig 2C) shows epileptiform activity only in a subset of EEG channels. When the video snapshot was taken, the epileptiform activity had already mostly terminated in the right temporal lobe region and propagated to the frontal lobes. For this seizure, visual and quantitative analysis detected six channels (in the left temporal region) that never recorded epileptiform activity during the seizure.

DISCUSSION

In approximately 25% of patients with secondarily "generalised" tonic-clonic seizures, intracranial EEG channels were found that did not record epileptiform activity at any time during the seizures. This result demonstrates that seizures that are secondarily generalised clinically are not always "generalised" electrophysiologically (ie, the present name "secondarily generalised" applies to the motor semiology only). This conclusion is corroborated by the fact that the study was strongly biased towards underestimating the extension of cortical areas not generating epileptiform activity, because intracranial electrodes are always placed as restrictively as possible, following a specific hypothesis about the location of the seizure onset zone. Therefore, the cortex will never be completely sampled by intracranial electrodes in human patients.

The notion that the cortex is not drawn into truly global epileptiform activity during "generalised" tonic-clonic seizures is important for at least two different aspects of epilepsy therapy. Firstly, it implies that animal models used to screen new substances for their potential efficacy against secondarily generalised tonic-clonic seizures should have the same electrophysiological characteristics (ie, they should display only regionalised ictal cortical activity and substances should not only be tested in models of primary generalised tonic-clonic seizures).⁸ The other point is that secondarily "generalised" seizures in humans might be prevented by targeted and localised counter measures, possibly even aimed at subcortical targets, as has already been successfully demonstrated in rats by suppressing secondary generalisation through stimulation of the subthalamic nuclei.⁹

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Informed consent was obtained for publication of fig 2A.

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