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Not Just Where, But How Does a Seizure Start?

The Repertoire of Seizure Onset Patterns in Human Focal Epilepsies: Determinants and Prognostic Values

Lagarde S, Buzori S, Trebuchon A, Carron R, Scavarda D, Milh M, McGonigal A, Bartolomei F. *Epilepsia.* 2019;60(1):85-95. doi: 10.1111/epi.14604. PMID: 30426477

Objective: In this study, we seek to analyze the determinants of the intracranial electroencephalography seizure onset pattern (SOP) and the impact of the SOP in predicting postsurgical seizure outcome. Methods: To this end, we analyzed 820 seizures from 252 consecutive patients explored by stereoelectroencephalography (total of 2148 electrodes), including various forms of focal refractory epilepsies. We used a reproducible method combining visual and time-frequency analyses. Results: We described 8 SOPs: low-voltage fast activity (LVFA), preictal spiking followed by LVFA, burst of polyspikes followed by LVFA, slow wave/DC shift followed by LVFA, sharp theta/alpha waves, beta sharp waves, rhythmic spikes/spike-waves, and delta-brush. Low-voltage fast activity occurred in 79% of patients. The SOP was significantly associated with (1) underlying etiology (burst of polyspikes followed by LVFA with the presence of a focal cortical dysplasia, LVFA with malformation of cortical development, postvascular and undetermined epilepsies), (2) spatial organization of the epileptogenic zone (EZ; burst of polyspikes followed by LVFA with focal organization, slow wave/DC shift followed by LVFA with network organization), and (3) postsurgical seizure outcome (better outcome when LVFA present). Significance: This study demonstrates that the main determinants of the SOP are the underlying etiology and the spatial organization of the EZ. Concerning the postsurgical seizure outcome, the main determinant factor is the spatial organization of the EZ, but the SOP plays also a role, conferring better prognosis when LVFA is present.

Commentary

When interpreting electroencephalograms (EEGs) in the context of the presurgical evaluation of patients with epilepsy, the critical question is most often: where does the seizure start? If scalp EEG is used, one likes to see a localized onset at the lobar, and sometimes sublobar level for the frontal lobe. With intracerebral EEG (iEEG), the region of onset can be limited to a much smaller region, possibly a fraction of a gyrus, although one has to remember that intracerebral electrodes have a field of vision of less than 1 cm (most of the cortex is not explored even with a large implantation). Once the location of presumed seizure onset is determined, an important question is: what is the EEG pattern at onset? We will only discuss iEEG here and the most common pattern is the low-voltage fast activity (LVFA) but many other patterns have been described.[1-3] Several questions have been asked regarding seizure onset patterns (SOPs): are there SOPs that are characteristic of a *true* onset and others that indicate that the *true* onset has been missed, as the apparent onset represents in fact propagated activity? Are some SOPs specific to a pathology such that one could say "if the SOP is X then the pathology must be Y"? Are some SOPs indicative of the likelihood of surgical success? Are some SOPs specific to a likely mechanism of seizure generation? Several studies have addressed these questions but the recent paper by Lagarde and colleagues reports on a particularly large group of patients (252), allowing to uncover some associations that had not surfaced before. The patients were studied with stereotaxic EEG and operated, and various characteristics of the SOPs were related to surgical success (Engel 1, 53% of patients) or failure (other Engel categories).

The study found several significant associations between SOPs and the different characteristics discussed above. What is striking however, and is in agreement with earlier studies,[2,4] is that there are practically no absolute "100%" results: no SOP guaranties that the true seizure onset was found, that a specific pathology is present, or that surgical success is guaranteed. In particular, the absence of LVFA at seizure onset is not a predictor of poor surgical outcome. The authors interestingly define 4 SOPs in which LVFA is present at the very onset or shortly after onset: LVFA at onset, preictal spiking followed by LVFA, burst of polyspikes followed by LVFA, slow wave/DC shift followed by LVFA. The other SOPs are theta/alpha sharp

waves and rhythmic slow spikes, plus a group of diverse but rare patterns. The study finds that there is a significant association between the presence of LVFA (any of the 4 above patterns) and surgical success. In particular, the "burst of polyspikes followed by LVFA" is the most frequently associated with surgical success (over 80%). The absence of LVFA was associated with poorer prognosis (31% seizure freedom) but the authors note that the absence of LVFA is certainly not a contraindication to surgery. The study does not provide evidence that the slower patterns (theta/alpha sharp waves and rhythmic slow spikes) result from propagation, although this has been reported.[3] The positive association between LVFA and surgical outcome was also noted in the meta-analysis of studies of SOPs by Singh and colleagues.[3] That study found, in addition, that the pattern called here "preictal spikes followed by LVFA" and often called in other studies "Low frequency rhythmic spikes" was a good prognosis for surgical outcome in temporal lobe epilepsy. The study of Lagarde and collaborators had a good number of patients with mesial temporal lobe epilepsy (38) and it is surprising that they did not find it to be predictive of good outcome, as it has been strongly associated with mesial temporal sclerosis.[1,2,5,6]

When examining SOPs in relation to the presence or absence of an magnetic resonance imaging (MRI)-visible lesion, the Lagarde study found a significant association, with underrepresentation of LVFA and overrepresentation of slow wave prior to LVFA in patients with negative MRI. Here again, all patterns were seen with and without MRI lesion but the proportions were a bit different. Surprisingly, the authors found no association between the presence of an MRI lesion and surgical success, an association that has been reported on multiple occasions (see the meta-analysis by Jobst and Cascino[7]). When examining the rapidity of spread outside of the onset region, Lagarde et al found a rapid spread was associated with poorer outcome, in agreement with Holtkamp et al.[8]

With respect to pathology, there were also most often several patterns associated with each pathology. The burst of polyspikes followed by LVFA was the only pattern found with only one pathology (malformation of cortical development), but it was found in only 20% of occurrences of that pathology. All pathologies were associated with multiple SOPs; LVFA at onset clearly predominated in vascular pathologies and cavernomas. These findings are essentially in agreement with the results of Perucca et al,[2] who studied SOPs in patients with lesional epilepsy, although that study found that "low frequency rhythmic spikes," which may correspond to the "preictal spikes followed by LVFA" of the Lagarde study if one judges by the illustrations given in both papers, were specific to mesial temporal atrophy (never seen in other pathologies). In the Lagarde study, the pattern of preictal spikes followed by LVFA was found in several pathologies, including quite frequently in malformations of cortical development. The apparent discrepancy may be related to the definition of patterns.

Although one feels that there must be some meaning to the SOP, it has not been possible to pin down unambiguous significance to any pattern. It has for instance been shown that most patterns seen at seizure onset can also be seen in regions of propagation, making it practically impossible to be sure that the seizure onset is found. Recent experimental work has demonstrated that the LVFA and rhythmic spikes (or preictal spikes) followed by LVFA have different mechanisms of generation,[9] a concept which could lead to SOP-specific treatment. A link has been made, through the distribution of high frequency oscillations, between these 2 patterns in animals and in humans.[10] An important difficulty in attributing a meaning to SOPs is their definition: different studies define different patterns, with some subjectivity in the definition and classification, with variable terminology (the pattern often called "low frequency repetitive spikes" is called "preictal spikes" in the Lagarde study although it is a SOP), and it is not always easy to compare studies. Much effort has been put in standardizing the nomenclature of EEG patterns seen in the intensive care unit,[11] and it may be time to standardize the definition of SOPs to facilitate the comparison between studies and reach a better understanding of the meaning of SOPs.

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