Current Literature

In Clinical Science

The Role of Semiology in the Work-Up of Frontal Lobe Epilepsy: In the Eye of the Beholder

Frontal Lobe Seizures: From Clinical Semiology to Localization.

Bonini F, McGonigal A, Trébuchon A, Gavaret M, Bartolomei F, Giusiano B, Chauvel P. *Epilepsia* 2014;55:264–277

OBJECTIVE: Frontal lobe seizures are difficult to characterize according to semiologic and electrical features. We wished to establish whether different semiologic subgroups can be identified and whether these relate to anatomic organization. **METHODS:** We assessed all seizures from 54 patients with frontal lobe epilepsy that were explored with stereo-electroencephalography (SEEG) during presurgical evaluation. Semiologic features and concomitant intracerebral EEG changes were documented and quantified. These variables were examined using Principal Component Analysis and Cluster Analysis, and semiologic features correlated with anatomic localization. **RESULTS:** Four main groups of patients were identified according to semiologic features, and correlated with specific patterns of anatomic seizure localization. Group 1 was characterized clinically by elementary motor signs and involved precentral and premotor regions. Group 2 was characterized by a combination of elementary motor signs and nonintegrated gestural motor behavior, and involved both premotor and prefrontal regions. Group 3 was characterized by integrated gestural motor behavior with distal stereotypies and involved anterior lateral and medial prefrontal regions. Group 4 was characterized by seizures with fearful behavior and involved the paralimbic system (ventromedial prefrontal cortex $\pm$ anterior temporal structures). The groups were organized along a rostrocaudal axis, representing bands within a spectrum rather than rigid categories. The more anterior the seizure organization, the more likely was the occurrence of integrated behavior during seizures. Distal stereotypies were associated with the most anterior prefrontal localizations, whereas proximal stereotypies occurred in more posterior prefrontal regions. **SIGNIFICANCE:** Meaningful categorization of frontal seizures in terms of semiology is possible and correlates with anatomic organization along a rostrocaudal axis, in keeping with current hypotheses of frontal lobe hierarchical organization. The proposed electroclinical categorization offers pointers as to the likely zone of organization of networks underlying semiologic production, thus aiding presurgical localization. Furthermore, analysis of ictal motor behavior in prefrontal seizures, including stereotypies, leads to deciphering the cortico-subcortical networks that produce such behaviors.

Commentary

The most fundamental basis of the study of epilepsy relies on a solid and accurate understanding of two concepts: the central neuronal networks that govern human behavior and the brain's anatomy that provides the structural framework for various patterns of connectivity. A thorough analysis of a seizure's semiology is therefore an essential foundation in the attempt to localize and define a patient's epilepsy because it provides a unique and precious opportunity to appreciate this critical and dynamic duo of function and anatomy as it pertains to an individual clinical scenario. While this is a self-evident fact, it is often overlooked in the current era of "high-tech"—expensive neuroimaging and diagnostic tests that overshadow the current conduct of presurgical work-ups for intractable epilepsy. This commentary will use a growing body of literature—in-

cluding the work by Bonini et al. highlighted here—to achieve two goals: 1) to address the diagnostic and localizing role of semiology in epilepsy surgery evaluations, and 2) to highlight the mechanistic and clinical benefits of a more comprehensive view of the systems underpinning ictal manifestations.

Let's define first the question at hand. Although the *lateralizing* value of several semiological signs—such as clonic head version, hand dystonia, postictal aphasia, and Todd's palsy—are well-established (1), the value of semiological signs to *localize* epilepsy has been more controversial, particularly in the context of the frontal lobe epilepsies. The study at hand by Bonini et al. and several others with similarly stated goals (2–5) share many similarities in their methodology: all analyze semiological signs using some variation of the statistical methods of cluster analysis, and all rely on the investigator's interpretation of recorded video-EEG evaluations in patients with a presumed frontal lobe epilepsy localization. Similarly, their findings highlight some common themes: First, somatosensory and Jacksonian clonic semiology supported a perirolandic localization with 22 out of 24 lesional cases involving this region in Manford et al.(2)

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and 16 patients “clustering” in Group 1 with elementary motor signs involving the precentral and premotor regions in Bonini et al. Second, seizures characterized by general motor agitation suggested an orbitofrontal and frontopolar epilepsy, consistent with lesions (2) or with stereo-EEG patterns involving these regions, as in Type 1 hypermotor seizures (HMS1)—as described in Rheims et al. (3), and Group 4 seizures described by Bonini et al. Yet, the conclusions drawn by the authors on the significance of their findings and the value of semiology are markedly different. On one hand, some concluded that “relatively few seizures can be localized reliably on clinical grounds” (2); on the other hand, the current work by Bonini et al. concludes that “meaningful categorization of frontal seizures in terms of semiology is possible . . . thus aiding presurgical localization.” Understanding the apparent discrepancy between these two extremes seems to be critical in building consensus and helping us—the population of “epileptologists at large”—in advancing the conduct of presurgical evaluation. The first hint helping us to tackle these differences lies in the methodology: particularly, in the definition of the “frontal lobe localization” itself.

Studies eventually doubting the localizing value of semiology usually attempted to validate semiological signs by evaluating their relationship to the localization of a frontal lobe lesion or to the ictal onset region (2, 4, 5), often defining a reliable localizing semiological sign as one that can be dependably reproduced by direct cortical stimulation (6). In this context, the underlying hypothesis assumes that the clinical manifestations during a seizure are mainly the direct result of electrically activating the underlying cortex of interest (the lesion at hand or the ictal onset zone). This would easily account for the strong localizing value and reliable reproducibility with cortical stimulation of “simple” sensory ictal manifestations such as visual, auditory, or somatosensory auras, but inevitably falls short in explaining more complex behaviors such as automatisms or psychomotor ictal changes. In fact, recent neurobehavioral work interestingly brings in additional layers defining human action beyond the anatomical localization of the cortex activated. One example includes the concept of “frequency gating”: in a recent study of the primary sensorimotor network, isometric contraction of the forearm showed dominant coupling within the β -band (13–30 Hz) between the primary motor cortex (M1) and the supplementary motor area (SMA), whereas fast repetitive finger movements were characterized by strong coupling within the γ -band (31–48 Hz), mainly seen in connections from lateral premotor cortex to SMA and to M1. All three structures (M1, SMA, and lateral premotor cortex) are components of the “same” sensorimotor network, yet they were activated to a different degree and “connected” differently in different motor tasks with these variations in connectivity potentially gated by varying their underlying firing frequency (7). Another example includes a tremendous body of work illustrating how complex behavior is truly the result of the interactions among various brain regions, rather than the activation of any single area (8). An ictal recording—whether with scalp or with invasive EEG—actually requires, by definition, an evolution in the frequency and distribution of the electrical activity, starting from a restricted area of ictal onset. Therefore, patients practically demonstrate semiological signs in various combinations and sequences, and not usually in isolation. Furthermore, at the point in time when

any semiological sign emerges, there is a lot more in the cortex that is being activated besides the ictal onset zone. The brain’s symptomatogenic “state” rather than the localization of a single symptomatogenic “zone” is logically then more relevant to a patient’s clinical behavior at any point during a seizure’s evolution. This line of thought likely explains why studies eventually touting the localizing value of semiological manifestations evaluated them in relation to the activated ictal networks rather than the ictal focus.

Given the richness of the epileptic and functional networks alluded to earlier, one would then naturally understand and even expect that a given isolated semiological sign occurs with epilepsies that may arise from different areas of the brain. In that sense, there is no semiological sign with a perfect correlation to a given epilepsy localization. This observation should not, however, “limit” the value of semiology any more than the 50% seizure recurrence rate following temporal lobectomy for hippocampal sclerosis should limit the value of neuro-imaging to identify mesial temporal pathology. A surgical work-up is akin to solving a puzzle, with each piece serving its purpose—no more but also no less.

For frontal lobe epilepsy where a growing proportion of patients with intractable epilepsy are presenting for a presurgical evaluation without a clear lesion and where delay in resection worsens the chances of surgical success (9, 10), time is indeed of the essence, and the use of every piece of noninvasively acquired information—including semiology—should be optimized.

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