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LETTER TO THE EDITOR

Comment on: Generalized epilepsy or focal network? A diagnostic dilemma

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We read with great interest the recent report by Atmaca and Gurses[1] describing a patient diagnosed with genetic generalized epilepsy (GGE) with focal electroclinical features and a heterozygous CLCN2 variant who demonstrated a favorable response to perampanel. The case is valuable in highlighting the well-recognized overlap between generalized and focal epilepsy phenotypes and the limitations of rigid electroclinical classifications in certain patients. Indeed, some epileptic disorders may exhibit mixed or transitional features that challenge traditional dichotomous categorization. In this context, we would like to raise several points regarding the diagnostic interpretation of the presented case.

First, the treatment history deserves careful consideration. The patient was relatively stable under levetiracetam and carbamazepine prior to medication adjustment, and seizure frequency increased following carbamazepine withdrawal. Although sodium channel blockers may exacerbate generalized epileptiform discharges, their apparent clinical efficacy in this case may be interpreted as supportive, although not diagnostic, of a focal mechanism. In addition, the marked response to perampanel, while clinically important, does not discriminate between focal and generalized epilepsies, given its established efficacy in both conditions.[2]

Second, the clinical semiology, characterized by right arm elevation, speech arrest, and preserved awareness, strongly suggests a focal onset, likely involving the dominant frontal or perirolandic regions. Although the authors reported progression to bilateral tonic-clonic seizures, this does not in itself indicate a generalized epilepsy, as focal seizures may secondarily generalize. Importantly, no features more specific for GGE were described, such as generalized myoclonus, eyelid myoclonia, or early morning myoclonic jerks. While focal features can be observed in GGE, the relatively consistent and localized semiology in this patient more strongly supports a focal, likely nonlesional epilepsy, rather than a purely generalized onset epilepsy. Nevertheless, such cases also illustrate the growing recognition that focal and generalized epilepsies may exist along a neurobiological continuum rather than as strictly separate entities.

Third, although generalized 3-4 Hz spike-and-wave discharges were observed, the electroencephalographic (EEG) findings appear notably asymmetric, with a clear left hemispheric predominance, and interictal recordings demonstrate asymmetric left-sided discharges. This asymmetry may argue against the presence of a pure generalized epilepsy. Moreover, in at least one recorded seizure, rhythmic sharp activity was reported at F7-T3 at onset. Importantly, in other recordings, ictal onset was not clearly captured. Therefore, the available EEG data do not definitively establish a generalized onset, and a focal onset with rapid secondary bilateral synchrony cannot be excluded. This diagnostic ambiguity further illustrates the limitations of applying

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strict focal-versus-generalized classifications in selected epilepsy syndromes, particularly in cases demonstrating asymmetric generalized discharges or mixed electroclinical features. Additionally, no detailed information is provided regarding the earliest ictal changes or the evolution pattern on prolonged video-EEG monitoring, both of which are critical for distinguishing focal onset with rapid bilateral spread from generalized onset. If these findings are not clearly demonstrated or are inconclusive, advanced electrophysiological techniques, such as high-density EEG or magnetoencephalography, may be helpful for further clarification where available.[3] Furthermore, ictal single-photon emission computed tomography was not performed and could have provided valuable complementary information by demonstrating focal hyperperfusion at seizure onset, thereby aiding in differentiating focal from generalized epilepsy in this diagnostically challenging case.

Finally, caution is warranted when interpreting the identified c.1792C>T (p.Arg598Trp) variant in the CLCN2 gene, which is classified as a variant of uncertain significance. As the authors appropriately state, this variant cannot be directly associated with epilepsy or GGE; this cautious interpretation is supported by current evidence suggesting that CLCN2 variants are best regarded as potential susceptibility factors rather than causative mutations and are insufficient to define epilepsy type.[4]

Taken together, we believe that this case represents a diagnostic dilemma rather than a definitive example of GGE. The findings may also be consistent with focal epilepsy with secondary bilateral synchrony. More importantly, this case underscores the limitations of attempting to rigidly classify certain epilepsies as exclusively focal or generalized based solely on conventional electroclinical criteria. In diagnostically ambiguous cases such as this, reliance on strict dichotomous classification may risk oversimplification of the underlying epileptic network and potentially lead to overinterpretation of findings that are not definitively discriminatory. A broader network-based perspective acknowledging the overlap and coexistence of focal and generalized mechanisms may, therefore, provide a more accurate framework for interpreting such complex presentations.

We thank the authors for presenting this instructive and thought-provoking case and agree that caution is warranted when interpreting variants of uncertain significance in genes such as CLCN2. Further studies integrating electroclinical, genetic, and treatment-response data are needed to better delineate such overlapping phenotypes.

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