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LETTER TO THE EDITOR

Response to Letter to the Editor: Generalized epilepsy or focal network? A diagnostic dilemma

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We thank the authors for their thoughtful and constructive comments on our case report. We fully agree that the distinction between genetic generalized epilepsy (GGE) with focal electroclinical features and focal epilepsy with rapid bilateral synchrony may be challenging in selected patients. Our intention was not to present the focal features as irrelevant, but rather to emphasize that focal semiology and asymmetric electroencephalographic findings may occur in generalized epilepsies and may lead to diagnostic uncertainty.

The authors argue that the patient's semiology, including right arm and index finger elevation, speech arrest, and preserved awareness, strongly favors focal epilepsy. We agree that these features should raise the possibility of focal onset. However, the current literature also shows that focal semiological features are not exclusive to focal epilepsies. Christie et al.[1] reviewed 13 studies including 952 participants and demonstrated that several focal signs may occur in generalized-onset tonic-clonic seizures, including early head version, figure-of-four sign, asymmetric seizure termination, auras, and automatisms. Importantly, although combinations of focal signs may favor focal to bilateral tonic-clonic seizures, the same review cautioned against differentiating generalized-onset and focal-onset bilateral tonic-clonic seizures on semiology alone because of substantial overlap.

Similarly, Seneviratne et al.[2] showed that certain signs, such as head version, preceding automatisms, eye version, unilateral facial clonic activity, and mouth deviation, were significantly more frequent in focal-onset bilateral tonic-clonic seizures. However, the same study also confirmed that focal signs may occur in generalized-onset bilateral tonic-clonic seizures. Therefore, the presence of focal semiology increases diagnostic suspicion for focal epilepsy, but does not by itself exclude GGE.

The electroencephalographic findings also require careful interpretation. The commentators suggest that left hemispheric or left frontocentral predominance argues against a generalized epilepsy. We agree that asymmetry should not be ignored. Nevertheless, asymmetric and focal EEG features are well documented in idiopathic/genetic generalized epilepsies. In childhood absence epilepsy, a prototypical GGE, interictal focal spike-wave discharges were observed in 49% of patients during wakefulness and in 85.1% during sleep; focal seizure onset was observed in 14.9%, and bilateral symmetric as well as asymmetric seizure onset was also reported. The authors concluded that asymmetric and/or focal seizure onset and interictal focal spike-wave discharges are commonly observed in drug-naive childhood absence epilepsy.[3]

Although childhood absence epilepsy is not identical to the present adult case, this study illustrates an important principle: focal or asymmetric EEG expression does not automatically establish focal epilepsy. In our patient, repeated EEGs demonstrated

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generalized 3.5-4 Hz spike-and-wave discharges, occasionally with left-sided predominance, and ictal recordings were interpreted as generalized epileptiform discharges with left frontocentral predominance. We acknowledge that one seizure showed rhythmic sharp activity at F7-T3 at onset; however, this isolated finding should be interpreted in the context of the overall electroclinical picture rather than used alone to reclassify the patient as having focal epilepsy.

We also agree that normal cranial MRI and PET do not exclude focal epilepsy. Nonlesional focal epilepsy, including focal cortical dysplasia, may be MRI-negative. However, the absence of a structural or metabolic lesion, together with recurrent generalized spike-and-wave discharges and the absence of a clearly demonstrated focal epileptogenic lesion, supported our interpretation of GGE with atypical focal electroclinical features rather than definite focal epilepsy.

Regarding treatment response, we agree that the worsening of seizures after carbamazepine withdrawal may be interpreted as supportive of a focal mechanism. However, treatment response is not sufficiently specific to determine epilepsy type. Carbamazepine withdrawal may increase seizure frequency because of loss of antiseizure coverage rather than because the epilepsy is necessarily focal. Conversely, improvement of generalized epileptiform discharges after replacing carbamazepine with lamotrigine supports the possibility that carbamazepine had aggravated the generalized EEG abnormality. Therefore, the treatment response in this case should be regarded as supportive but not diagnostic. Likewise, we agree that the favorable response to perampanel does not distinguish focal from generalized epilepsy, because perampanel is effective in both focal-onset seizures and generalized tonic-clonic seizures. This was also stated in our report.

We further agree with the authors that the CLCN2 variant should be interpreted cautiously. In our report, we explicitly stated that the identified c.1792C>T p.(Arg598Trp) variant was a variant of uncertain significance and that it could not be directly associated with epilepsy or GGE. We considered it only as a possible supportive finding in the context of the electroclinical phenotype, not as definitive genetic proof of GGE.

We acknowledge that advanced investigations such as high-density EEG, magnetoencephalography, or ictal SPECT might have provided additional information. Their absence is a limitation of the case. However, in routine clinical practice, epilepsy classification is often based on the integration of history, seizure semiology, scalp video-EEG, neuroimaging, treatment response, and genetic data. In this integrated framework, we believe that GGE with focal electroclinical features remains a reasonable and clinically relevant interpretation, while focal epilepsy with rapid bilateral synchrony cannot be completely excluded.

We thank the authors again for their valuable comments and for contributing to a nuanced discussion of this diagnostically challenging case.

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