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LETTER TO THE EDITOR

Genetic generalized epilepsy with a heterozygous missense variant in the chloride channel protein 2 gene responsive to perampanel

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Herein, we reported a patient with genetic generalized epilepsy (GGE) who exhibited focal electroencephalogram (EEG) and clinical findings and responded well to perampanel. The diagnosis was supported with whole-exome sequencing (WES), which showed a missense variant in the chloride channel protein 2 (CLCN2) gene.

A 29-year-old male patient who had been seizure-free for many years after the age of five but continued to receive antiseizure medication (ASM) due to EEG findings was admitted to our neurology outpatient clinic. The patient did not have a family history of epilepsy. In the patient's EEGs, 3.5 to 4 Hz generalized spike- and slow-wave discharges, occasionally asymmetric in the left hemisphere, were observed (Figure 1). After 2019, the patient started to have seizures once a year, characterized by elevation of the right arm and index finger, speech arrest, and preserved consciousness. The patient was using levetiracetam 3000 mg/day and carbamazepine 800 mg/day. The neurological examination was normal. Brain magnetic resonance imaging and brain positron emission tomography/computed tomography were normal. Neuropsychological testing revealed only mild impairment in the ability to maintain attention. Considering that carbamazepine could worsen generalized epileptiform discharges in EEGs, it was replaced with lamotrigine. Although EEG abnormalities improved, the frequency of the patient's usual seizures increased to five to eight per month. Lacosamide, topiramate, clonazepam, and valproic acid were added successively, but the seizures continued. Seizures characterized by unresponsiveness, such as his phone slipping from his hand, and seizures that started with contraction in the right arm and became bilateral tonic-clonic were recorded in video EEG. Ictal EEG findings were evaluated as generalized epileptiform discharges, predominant in the left frontocentral region in most of the seizures (Figure 2). However, in one of the seizures, a rhythmic sharp wave activity in F7 and T3 electrodes was observed at the beginning of the seizure. Perampanel was added, and WES was planned. The number of seizures decreased significantly after the dose of perampanel was increased to 10 mg/day. The patient has been using perampanel for two years, and after the dose was increased to 10 mg/day, he had three seizures in the last 12 months. The patient suffered from excessive sleepiness six months after the dose was increased to 10 mg/day. This adverse event improved when the patient changed the time he took the medication from 22:00 to 24:00. Clonazepam and valproic acid were tapered and discontinued. In WES, c.1792C>T p.(Arg598Trp) missense variant in the CLCN2 gene was detected as heterozygous. In silico prediction algorithms showed that the variant had a destructive effect at the protein level. Written informed consent was obtained from the patient.

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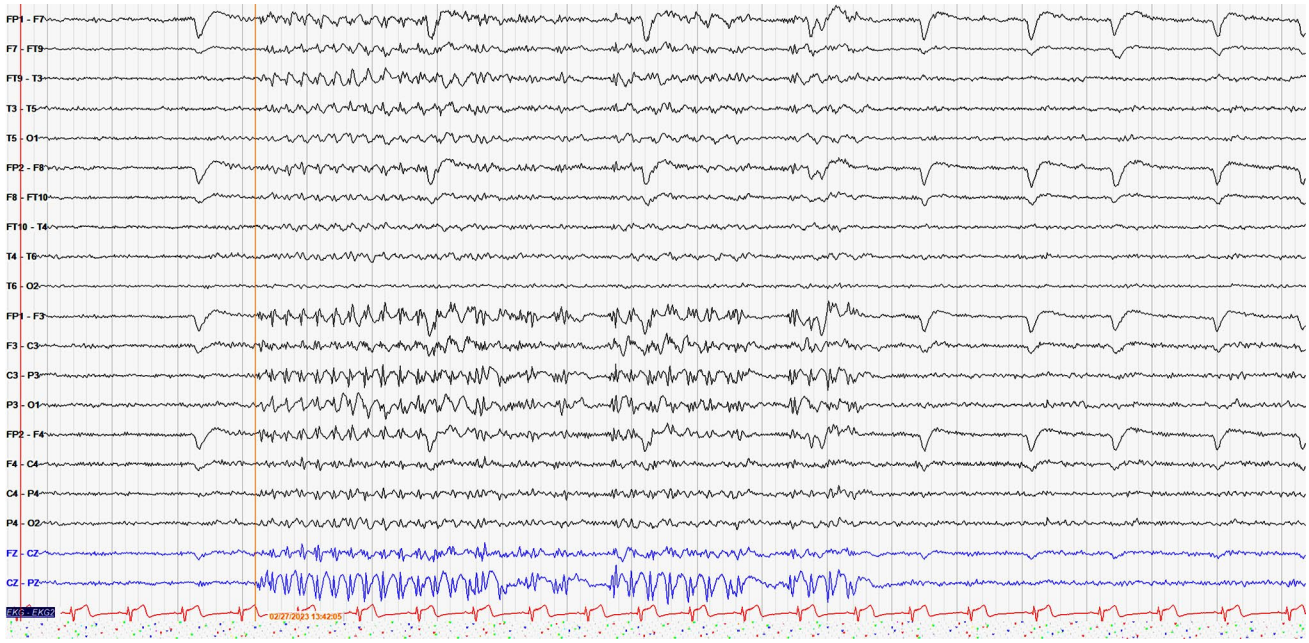

Figure 1. Interictal asymmetric (predominant in the left hemisphere) and generalized 3.5 to 4 Hz spike- and slow-wave discharges.

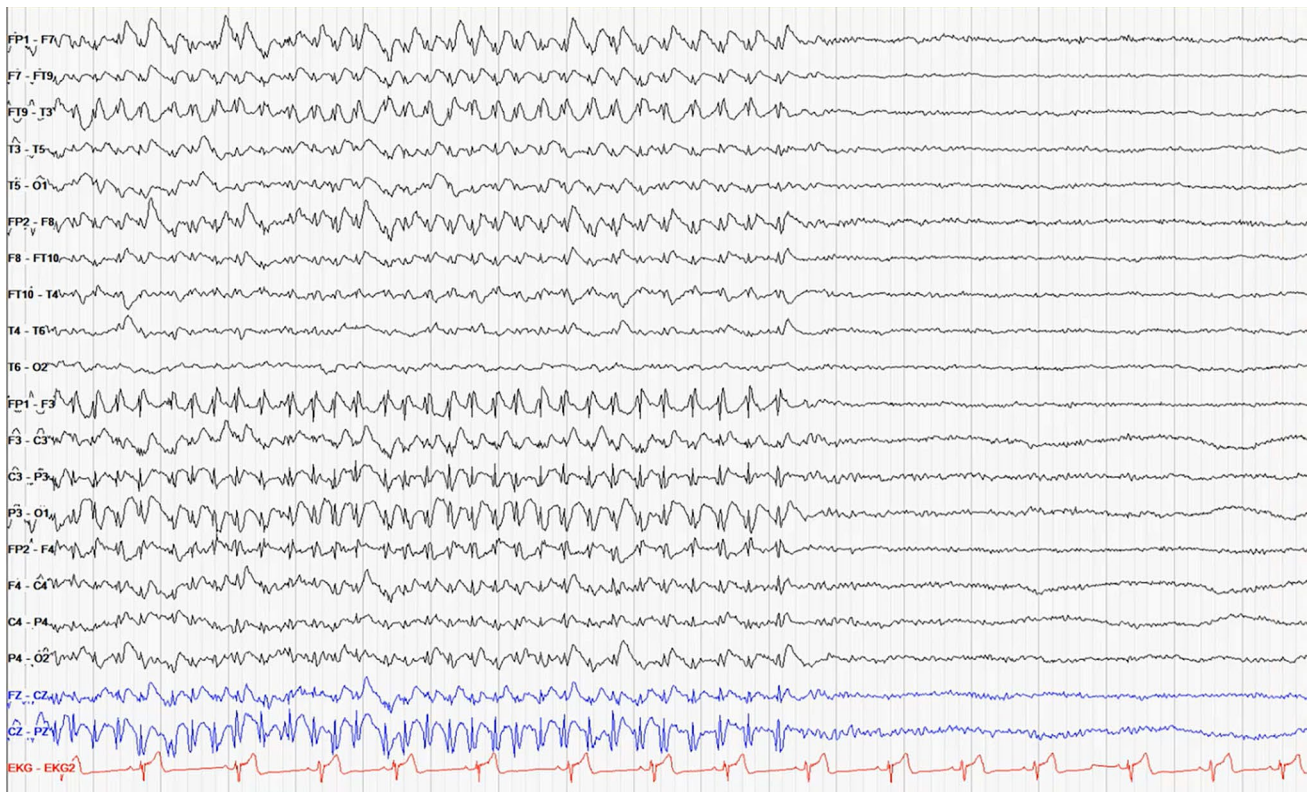

Figure 2. One of the seizures of the patient recorded during video EEG monitoring. Asymmetric (predominant in the left hemisphere) and generalized 3 to 3.5 Hz spike- and slow-wave discharges were recorded during the seizure, in which the patient was unresponsive for a while.

EEG: Electroencephalogram.

Patients with GGE may have focal EEG abnormalities and focal ictal semiological findings, mimicking the diagnosis of focal epilepsy.[1] In a review, focal interictal abnormalities were reported in 14 to 56% of the patients with GGE, and in general, focal ictal findings detected in video EEG of the patients were focal myoclonus, version, figure-of-4 sign, focal clonus, and asymmetric motor symptoms at the end of seizures.[2] Although the patient had some focal EEG and semiological findings, we considered the diagnosis of GGE in our patient.

After reporting the first three mutations in the CLCN2 gene in three families with different clinical forms of idiopathic epilepsy, the authors retracted the original publication after re-examining their findings.[3] They stated that the reported genetic variations might still contribute to the epileptic phenotypes and that rare variants in CLCN2 could represent a susceptibility factor for idiopathic generalized epilepsy. However, the functional results of the study could not be reproduced by others.[4] In a study, two novel missense mutations and one novel variant were identified in three unrelated idiopathic generalized epilepsy families.[5] Their finding of physiological investigations predicted a loss of function that might contribute to intracellular chloride accumulation or neuronal hyperexcitability. Their findings suggested that these CLCN2 mutations alone were not sufficient to induce epilepsy and that they might instead represent susceptibility factors. We found a heterozygous c.1792C>T p.(Arg598Trp) missense variant in our patient, which is a variant of uncertain significance (VUS). We cannot directly associate this VUS in the CLCN2 gene with epilepsy and GGE, but we believe that the VUS we found may be a supporting finding in the patient we considered the diagnosis of GGE based on neuroimaging, electrophysiological, and clinical findings despite the atypical features of the patient.

Perampanel, a selective, noncompetitive AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonist, is a once-daily oral ASM for focal-onset seizures and generalized tonic-clonic seizures. In primary generalized tonic-clonic seizures, perampanel 8 mg resulted in greater reduction in seizure frequency per 28 days (–76.5% *vs.* –38.4%, p<0.0001) and responder rate (64.2% *vs.* 39.5%, p=0.0019) than placebo.[6] In our patient, whose seizures were resistant to many ASMs, perampanel was added, and the number of seizures decreased dramatically.

Detection of mutations and variants by WES, particularly in GGE patients with atypical features, may help diagnosis and increase our knowledge of GGE genetics. However, we must be cautious while associating a VUS with epilepsy. Third-generation ASMs, such as perampanel, should be considered in patients with drug-resistant GGE.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Contributed to the conception and design of the study. Collected the data, drafted and revised the manuscript. Both authors read and approved the final manuscript; M.M.A., C.G.

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