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LETTER TO THE EDITOR

Carbamazepine: There are still unknowns

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Carbamazepine (CBZ) was developed in the late 1950s, with anticonvulsant properties demonstrated in animals in 1963.[1] Carbamazepine is considered a first-generation antiepileptic drug in treatment guidelines that is believed to have a well-established efficacy and side effect profile. Its mechanism of action involves blocking voltage-sensitive sodium channels. Additionally, by inhibiting L-type calcium channels and glutamate release and partly showing moderate anticholinergic effects, it exhibits anticonvulsant activity.[2] It is widely used in the treatment of epilepsy, neuropathic pain, and psychiatric disorders. Carbamazepine is used for seizures with focal onset and those progressing from focal to bilateral tonic-clonic, as well as being a first-choice treatment for seizures with a generalized onset.[3]

However, there is still much that is unknown about the mechanisms of action and seizure-preventive effects of antiepileptic drugs. For instance, although CBZ is reported to increase myoclonic seizures and thus is not preferred for such seizure types, it is used as the first option for myoclonic seizures associated with subacute sclerosing panencephalitis.[4] This study aimed to discuss our clinical experience and outcomes related to the efficacy of CBZ in treating epilepsies we believe to have a primary generalized onset based on clinical and electroencephalogram (EEG) findings.

The first case was of a 66-year-old female patient who presented to the neurology clinic with complaints of dizziness and imbalance. In medical history, the onset of the patient's first epileptic seizure was at the age of 15, which she described as a generalized-onset tonic-clonic seizure. The patient had a history of severe traumas, fractures, and burns related to the seizures and had been using CBZ 400 mg twice daily for 30 years. The patient could not remember the names of the medications she had used before but stated that she did not benefit from them. The patient mentioned that CBZ worked well for her, was very satisfied with the medication, and had not experienced any seizures for the last 10 years. The patient was not under regular follow-up since she had no complaints. The tests showed a CBZ blood level of 13.7 ug/mL, which is above the therapeutic dose. The EEG was consistent with generalized epileptiform anomalies sensitive to light and eye closure (Figures 1, 2). Cranial magnetic resonance imaging was unremarkable. In family history, the patient reported that her mother and daughter had difficulties in opening their eyelids but did not receive any treatment. The patient's antiepileptic treatment was continued with CBZ, and the dose was reduced by 200 mg. In the follow-up, the patient had no clinical complaints for about a year. A written informed consent was obtained from both patients.

The second case was a 50-year-old female patient who was switched to a different brand of medication containing an equivalent molecule after the CBZ 300 mg tablet the patient had been using for an extended period was discontinued from the market. However, the patient was admitted to our

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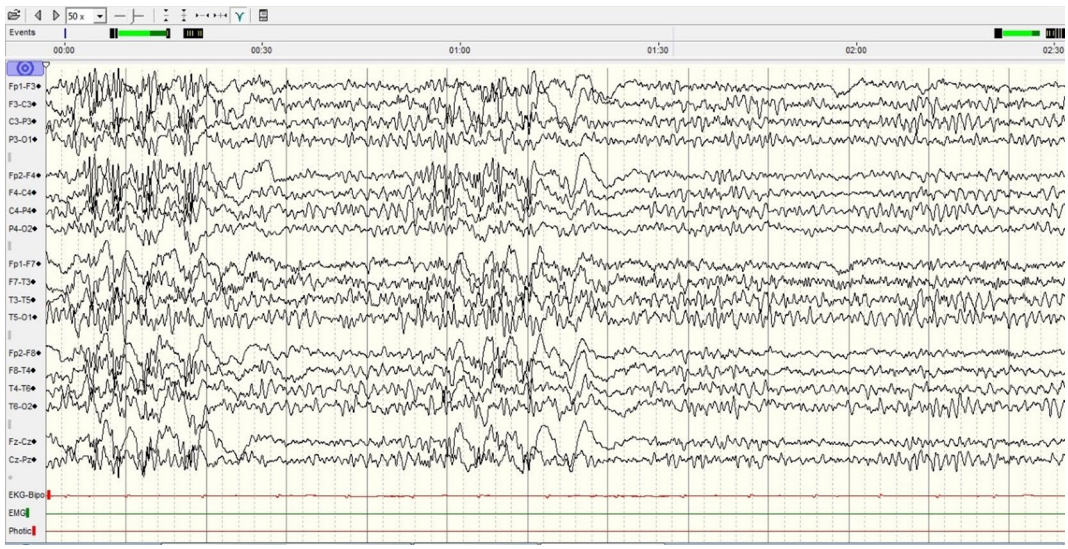

Figure 1. Interictal generalized epileptiform discharge *(Case 1).*

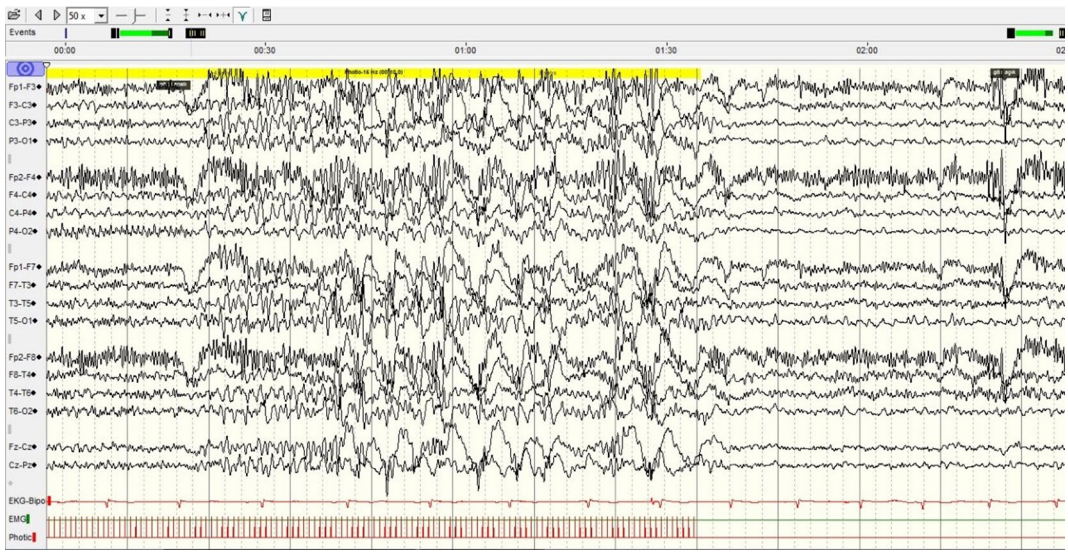

Figure 2. Generalized epileptiform anomalies sensitive to light and eye closure *(Case 1).*

clinic due to the emergence of side effects such as drowsiness, weakness, and dizziness. The patient mentioned that while she had not experienced any seizures for two and a half years, she had two generalized-onset tonic-clonic seizures in the past two months that occurred 15 days apart. In EEG, very active generalized discharges at a frequency of 3 to 3.5 Hz with prolonged discharge durations during hyperventilation were observed (Figures 3, 4). A generalized atypical nonmotor seizure was recorded. Consequently, the CBZ dosage was reduced, and the patient was switched to levetiracetam due to the side effects the patient described related to the medication. However, due to side effects of widespread pain and swelling in the hands and feet, the dosage could not be increased above 1000 mg/day. In the follow-up, the patient experienced generalized-onset tonic-clonic seizures at night once every 7 to 10 days. Since the patient was not reproductive due to her age, treatment with valproic acid was initiated and increased to 1000 mg/day. However, adequate seizure control was not achieved, and CBZ was reintroduced, with a plan to gradually reduce the

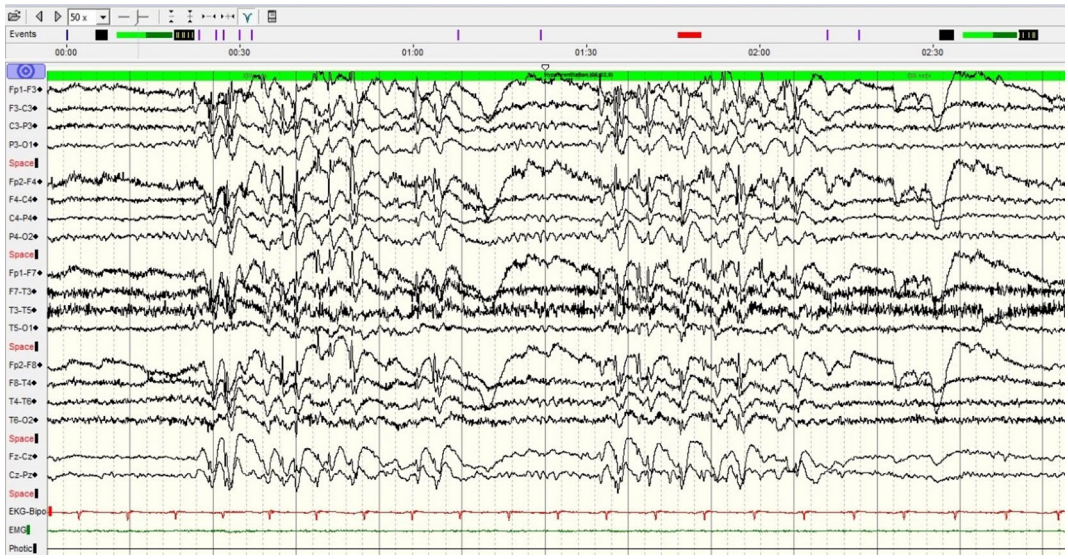

Figure 3. Generalized spike-wave discharges in hyperventilation *(Case 2).*

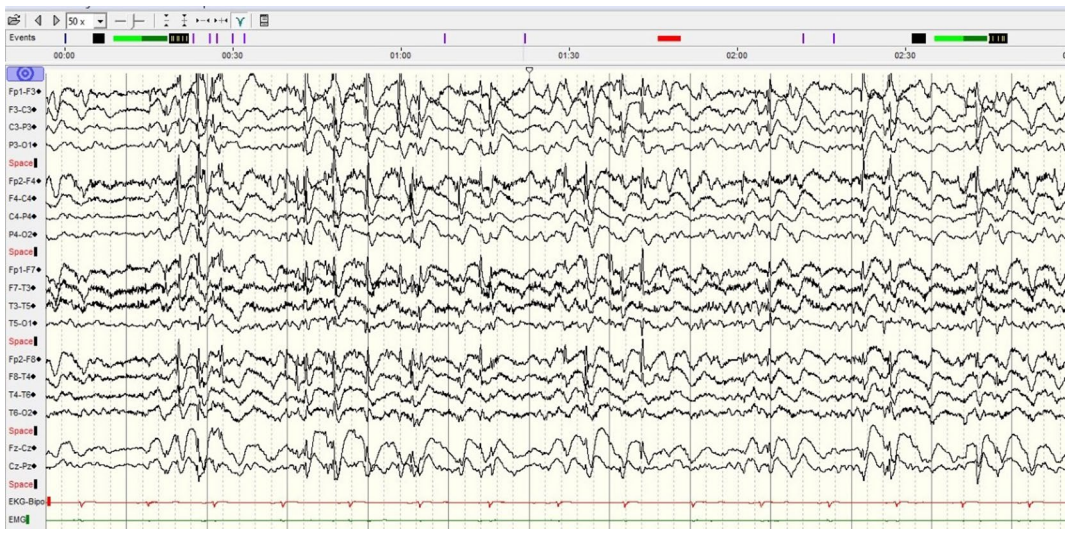

Figure 4. Interictal generalized epileptiform discharge *(Case 2).*

doses of the other medications. After adding CBZ, the seizures were controlled.

These two cases illustrate that the mechanisms of action and seizure-preventive effects of antiepileptic drugs are complex. Although the seizures in these cases were of generalized onset, the efficacy of CBZ was evident.

In a case series presented in the literature, the addition of CBZ to treatment in cases of generalized epilepsy resistant to other antiepileptic drugs resulted in a significant improvement.[5] This improvement was considered to possibly relate to a genetic predisposition in some idiopathic generalized epilepsies, and further studies were suggested. Determining the genetic characteristics in the group of cases we presented would be very valuable. However, we were unable to conduct genetic research in our patients.

Another case report in the literature emphasized that the combination of valproic acid and CBZ was effective in generalized-onset epilepsy, particularly if focal EEG abnormalities were also present.[6]

It was highlighted that CBZ, when added or increased in dosage, provided good seizure control in these patients. In our cases, focal findings did not catch our attention during the 3-h sleep EEG recordings. However, the recordings were not during night sleep.

Antiepileptic drugs can aggravate seizures and lead to status epilepticus when not appropriately used according to the syndrome.[7] Carbamazepine is known to aggravate generalized-onset nonmotor seizures and myoclonus. In the second case, the transition to an equivalent molecule after a long period without seizures led to the emergence of night seizures that had not occurred for a long time. Furthermore, the seizures intensified after the discontinuation of CBZ, which was deemed inappropriate for the patient's type of seizure. The patient and her family were not aware of the generalized nonmotor seizures, which likely occurred even while the patient was on CBZ monotherapy. However, the frequency of nocturnal generalized-onset tonic-clonic seizures increased after the medication was stopped, and the seizures were controlled only after reintroducing CBZ.

Care must be exercised when considering a change in treatment for a patient who has been using CBZ for a long period with seizures under control. If seizure control cannot be achieved in a primary generalized-onset epilepsy syndrome despite using established effective medications at their maximum and effective doses, CBZ treatment should be considered.

The cases presented demonstrate that there are unknowns concerning the mechanisms of antiepileptic drugs, including CBZ, which have been used for a long time, and their relation to epileptogenesis. Further studies into the complex pathways of epileptogenesis and the effects of antiepileptic drugs are needed.

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