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LETTER TO THE EDITOR

A case of stroke with epilepsy, drug-induced encephalopathy, and movement disorder

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Herein, we reported a case involving thalamic lesions associated with epileptic seizures, encephalopathy due to a combination of valproic acid (VPA) and topiramate (TPM), and rubral tremor developing three years after stroke.

A 39-year-old male patient was admitted with ischemic stroke involving the right cerebellum, right medulla oblongata, midline of mesencephalon, and bilateral thalami (Figure 1). The medical history revealed childhood absence epilepsy that had been treated with 500 mg/day of VPA until the patient was admitted for stroke, despite having remained seizure-free for years. The patient developed generalized tonic-clonic seizures (GTCS) two days after hospitalization. Valproic acid was discontinued. Initially, levetiracetam (LEV) was added, and when seizures continued, carbamazepine (CBZ) was added. In addition to generalized epileptiform discharges (GEDs), focal epileptic focus was detected in the electroencephalogram (EEG) (Figure 2). At the end of two months, the patient was discharged with LEV 3000 mg/day, CBZ 1200 mg/day, and acetylsalicylic acid 100 mg/day.

Topiramate 100 mg/day was added to the treatment, as seizures recurred every one to two months after discharge. In the control EEG, focal findings disappeared, and only GEDs were detected. Serum LEV level was not measured, and serum CBZ level was 12.6 mg/L (normal range: 4-10). Considering that CBZ might worsen GEDs, CBZ 1200 mg/day was changed to lacosamide (LCM) 600 mg/day. The frequency of GTCS decreased, but the patient started to have confusion attacks lasting one to two days, recurring approximately once a month, six months after the switch from CBZ to LCM. In one of these attacks, the patient was hospitalized, and nonconvulsive status epilepticus (NCSE) consisting of continuous GEDs was detected in the EEG. The hospitalized patient was treated with intravenous VPA at a loading

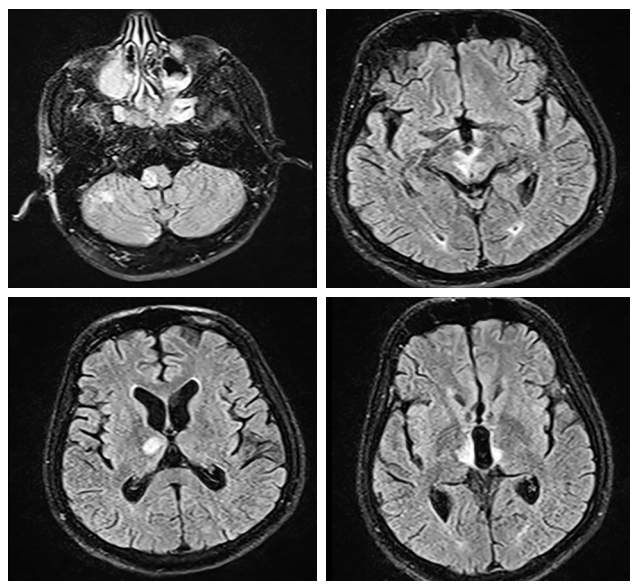

Figure 1. Fluid-attenuated inversion recovery sequences in the subacute period of stroke show hyperintense infarct areas in the right halves of the cerebellum and medulla oblongata (supplied by the right posterior inferior cerebellar artery), mesencephalon, and bilateral thalami (supplied by the Percheron artery).

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dose of 20 mg/kg, followed by oral VPA at a maintenance dose of 500 mg twice daily. The next day, the patient's neurologic status improved and NCSE ceased in the control EEG (Figure 3). Ten days after discharge, the patient was readmitted due to another deterioration that developed over the days. Blood tests and neuroimaging were normal. An EEG revealed widespread slowing suggestive of encephalopathy. Serum VPA level was 68.2 µg/mL (normal range: 50-100). Serum TPM and ammonia levels were not measured. Considering metabolic encephalopathy due to the interaction between VPA and TPM, TPM was discontinued, and the patient was discharged at his wife's request. At the follow-up visit two weeks later, it was observed that the patient returned to his previous clinical state, and the EEG findings improved (Figure 4).

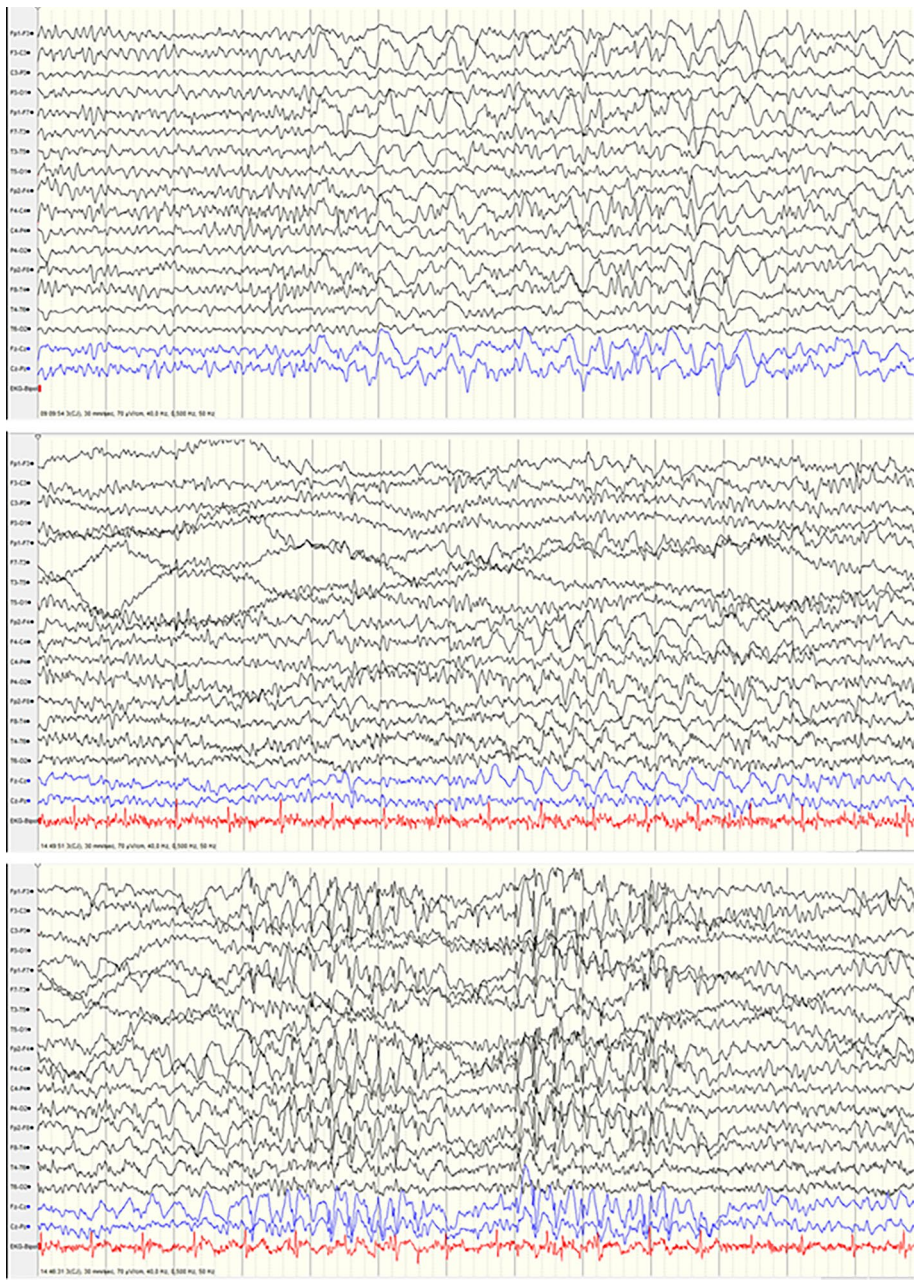

Figure 2. (Above) Epileptic focus in the right centrotemporal region as equipotential at F7-T3 electrodes; (middle) frontal intermittent rhythmic delta activity predominantly on the right; (below) 3 to 3.5 Hz generalized spike-wave discharges.

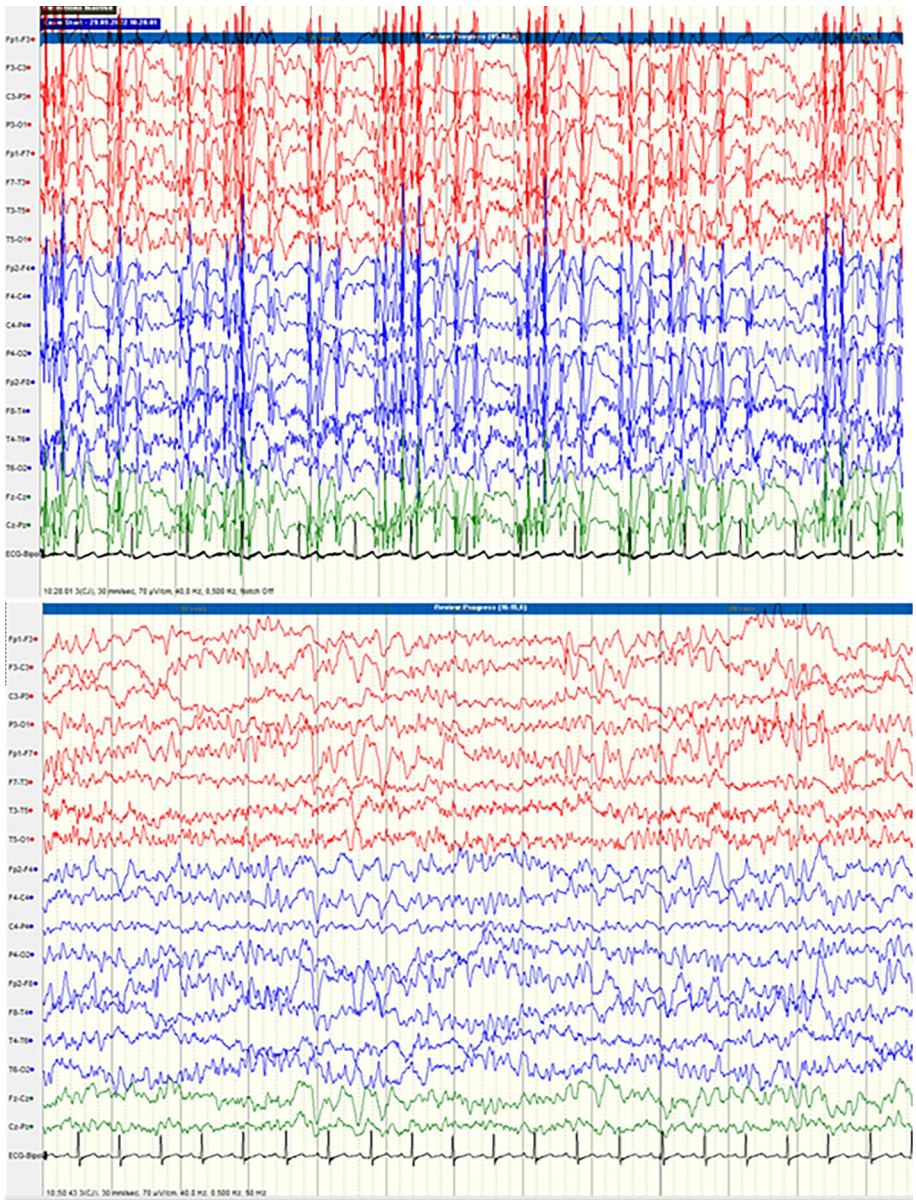

Figure 3. (Above) Continuous 3 to 3.5 Hz generalized spike-wave discharges suggesting NCSE; (below) EEG recorded one day after the treatment with intravenous diazepam and valproic acid shows that status epilepticus has ended.

The patient developed dystonic tremor in the left hand, which occurred with rest, posture, and movement, six months after starting VPA and three years after the stroke. It was evaluated as rubral tremor. When there was no response to levodopa+benserazide 375 mg/day, clonazepam was started. Written informed consent was obtained from the patient.

In the literature, patients who were clinically and electrophysiologically suggestive of genetic generalized epilepsy (GGE) but were found to have a thalamic lesion on brain magnetic resonance imaging were reported.[1,2] A study showed that the medial thalamus played a role in the formation of epileptiform discharges in symptomatic epilepsy, as well as in GGE.[3] We believe that seizures and GEDs in our patient might be related to the thalamic lesions, potentially facilitated by the patient's previous history.

Metabolic encephalopathy is a rare complication of VPA therapy, which is aggravated when combined with TPM. A pharmacokinetic

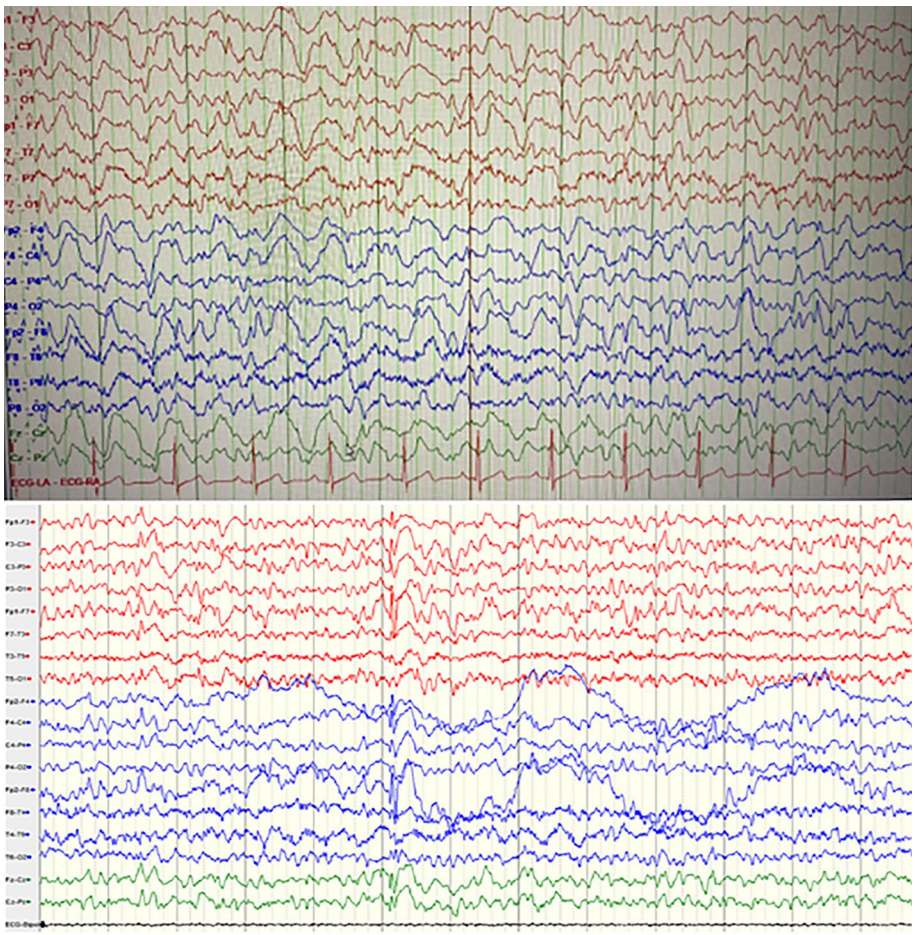

Figure 4. (Above) Generalized slowing compatible with encephalopathy; (below) control EEG performed two weeks after topiramate was discontinued shows that the generalized slowing improved. Generalized 3 to 3.5 Hz spike-wave discharges, which were also found in the patient's previous EEGs, can be observed.

EEG: Electroencephalogram.

interaction between VPA and TPM, leading to hyperammonemia, and a pharmacodynamic mechanism due to direct toxicity of TPM in at-risk epileptic patients are two distinct mechanisms suggested to explain this complication.[4] In a study, the incidence of VPA-induced encephalopathy was found to be higher when TPM was added.[5] In our patient using TPM, encephalopathy developed after the addition of VPA, and two weeks after discontinuing TPM, both the patient's clinical and EEG findings improved.

Carbamazepine may exacerbate absence and myoclonic seizures due to a paradoxical reaction in patients with GGE.[6] Therefore, CBZ was switched to LCM, which resulted in a reduction in GTCS frequency but led to the emergence of NCSE attacks.

Rubral tremor is characterized by flexion-extension oscillations at a frequency of 3 to 4 Hz. Thalamus and brainstem lesions can cause rubral tremor. Vascular etiology is frequently found. It occurs one to 24 months after central nervous system damage. This delayed onset might be due to neuronal plastic changes.[7] Although the tremor in our patient appeared three years after the stroke, we believe that the semiological features of the tremor are compatible with rubral tremor.

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

Author Contributions: Surgical and medical practices, data collection or processing, literature search, writing: M.M.A.; Concept, design: C.G., M.M.A.; Analysis or Interpretation: C.G.; Both authors read and approved the final manuscript.

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