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Weekly methotrexate may reduce valproate levels causing relapse of genetic generalized epilepsy

To the Editor

We wish to report a patient with genetic generalized epilepsy on weekly methotrexate (Mtx) therapy who developed a breakthrough seizure due to a reduced level of valproic acid (VPA). Awareness about pharmacological interactions, of antiseizure medication (ASM) is essential in the management of patients with epilepsy and other coexisting medical diseases. ASM can affect the serum levels of co-administered medicines and vice versa. This could result in loss of efficacy or toxicity of either drug. Mtx is a commonly used immunomodulator in various autoimmune diseases, and an antineoplastic agent at high doses. Acute neurologic dysfunction like leukoencephalopathy and stroke like episodes have been reported with Mtx especially when large doses are administered intrathecally as in leukemias. To date only a single case report of high dose Mtx infusion (5 g/m^2) associated with reduction in VPA levels and seizure relapse has been documented [1]. However impact of prolonged low dose weekly Mtx exposure on VPA levels and its impact on epilepsy has not been described.

A 21-year-old boy with normal birth and development presented with absence seizures and occasional generalized tonic-clonic seizures (GTCS) since 13 years of age. A diagnosis of Juvenile Absence Epilepsy was made. His electroencephalogram (EEG) showed normal background activity and frontally dominant generalized 3 Hz spike- and polyspike-and-wave discharges, activated during hyperventilation and drowsiness (Fig. 1 a,b) consistent with the diagnosis. He was in remission for five years and taking VPA 600 mg/day. Later he developed psoriasis for which he was placed on steroids initially, and subsequently started on Mtx 15 mg/week taken one day of the week. His absence seizures relapsed after Mtx introduction. He noticed a tendency to have brief absence seizures (but no GTCS) either on the day of his weekly exposure to Mtx or on the day thereafter.

His serum total VPA levels checked in the fasting state before administration of Mtx was 92 mcg/mL and it dropped to 18 mcg/mL the following day (therapeutic range for valproic acid is 50–100 mcg/mL) despite continued administration. We do not check ASM levels routinely but do so when seizure relapse occurs despite adequate drug compliance. In our patient, estimation of ASM levels proved that drug level fell despite uninterrupted administration of VPA. After reviewing with the dermatologist Mtx was stopped. He was subsequently begun on cyclosporine, which brought his epilepsy back under control again. The metabolism of VPA can be increased when combined with prednisone, and due to this steroid-VPA interaction it was avoided [2].

Mtx induced neurotoxicity includes leukoencephalopathy (especially necrotic leukoencephalopathy), aseptic meningitis, paraplegia, cerebellar dysfunction and seizures [3]. Seizures occurring during Mtx therapy have been observed in patients receiving high intravenous doses or intrathecal therapy for the treatment of leukemias. In the only case reported to date, seizures occurred 8 hours after completion of Mtx infusion, at a time when the serum VPA concentration was reduced to one-fourth of the patient's baseline level [1]. Co-admininstration of Mtx with VPA can affect VPA concentrations and decrease it to one-quarter of the baseline level as seen in our case. Alteration in the metabolism of VPA was probably responsible for the acute decline in its serum concentration. 90% of VPA is bound to albumin. Mtx is a weak acid and 75% is bound to albumin suggesting possible displacement of VPA. It is known that alterations in plasma protein binding may be seen with highly protein bound drugs and weak organic acids (eg. salicylates) [4]. Mtx competes with VPA for binding to albumin as a result of which a larger proportion of VPA becomes unbound and is rapidly metabolized by the liver. Competitive binding, protein displacement, and quick metabolization are possible causes of decline in VPA levels.

Patients with genetic generalized epilepsies may not have seizures even if they are noncompliant for a few days. Mtx by itself may cause seizures secondary to impaired astrocytic glutamate uptake which can lead to excitation and potentially to seizures. Impaired astrocytic function disturbs glutamatergic synapses and damages neurons [5]. In the mouse model, to investigate putative mechanisms of Mtx involving epileptogenesis, tonic–clonic seizures were induced by intravenous injection and animals were later subjected to autopsy for determination of the intracellular content of glutamate by scintillation counts [6]. It was demonstrated that Mtx decreased glutamate uptake by 20%–30% in the cortex. The chemical 6,7-dinitroquinnoxaline-2,3-dione, a competitive antagonist of the glutamate receptors prevented the seizures in 94 %, demonstrating the involvement of ionotropic glutamatergic receptors in the pathogenesis of Mtx induced seizures in mice. Adenosine, known as a neuromodulator of the glutaminergic system via presynaptic inhibition of glutamate release by A1 receptor activation, prevented 50% of Mtx-induced seizures [6].

Our patient's three EEGs taken over a 5-year period showed epileptiform abnormalities in all three, suggesting that there was an active potential for breakthrough seizures despite clinical seizure freedom. In our patient, Mtx may have resulted in breakthrough seizures by reducing VPA levels to subtherapeutic range and by its own epileptogenic potential.and by its own epileptogenic potential.

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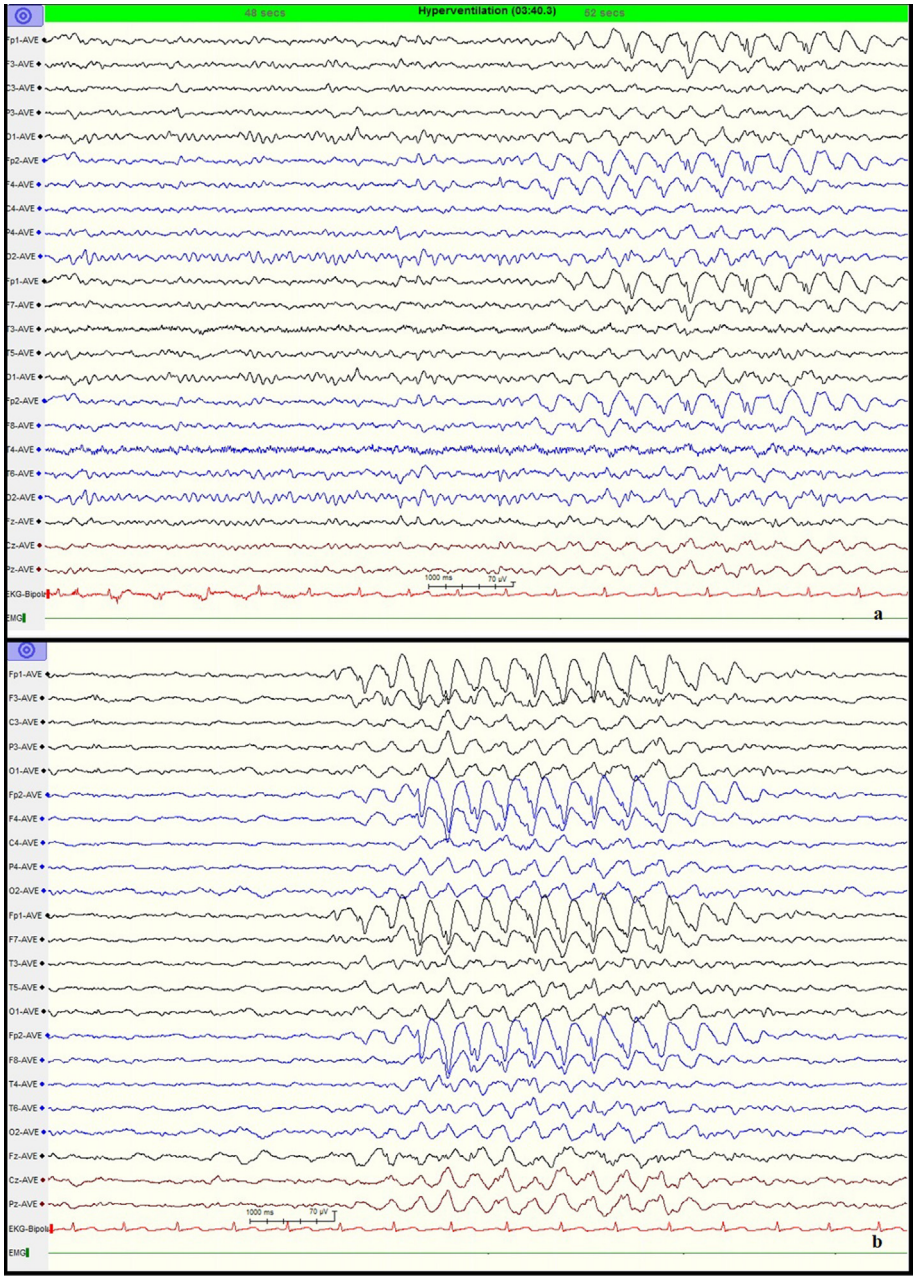

Fig. 1. EEG showing frontal intermittent rhythmic delta activity with intermixed bifrontally dominant spikes activated during hyperventilation (a) and drowsiness (b) consistent with a clinical diagnosis of genetic generalized epilepsy.

To our knowledge, this is the first report of low dose prolonged intermittent therapy with Mtx reducing VPA total serum concentrations. Our findings support acute administration of low dose maintenance Mtx given on a weekly basis can lead to seizure relapse. Since both these drugs may be used together in clinical practice we suggest that monitoring VPA concentration during Mtx therapy may be beneficial. ASM dose adjustment or switch to a noninterfering immunomodulator is recommended in such a scenario.

Disclosures

None.

Compliance with ethical standards

Ethical approval from the institutional review board was not required for this study.

Informed consent

Formal consent was taken from the patient.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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