

Valproic Acid-induced Hyperammonemic Encephalopathy Promoted by Levetiracetam

Case Report

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Encephalopathy resulting from the administration of levetiracetam (LEV) is a rare occurrence. We experienced a patient receiving LEV treated with valproic acid (VPA) for partial seizures with secondary generalization, following which she developed hyperammonemic encephalopathy and showed complete recovery after the drug was withdrawn. LEV is able to promote hyperammonemic encephalopathy when added to VPA. (2014;4:82-84)

Key words: Valproic acid, Hyperammonemic encephalopathy, Levetiracetam

Introduction

Although levetiracetam (LEV) is a relatively well-tolerated anti-epileptic drug (AED) that is used to control partial and generalized seizures, an encephalopathy resulting from LEV administration has been previously reported.^{1,2} Encephalopathy induced by AED has been observed in patients with VPA, however, it is debatable whether the concomitant use of LEV with valproic acid (VPA) causes the encephalopathy or not. We report here on the manifestation of a VPA-induced hyperammonemic encephalopathy promoted by LEV.

Case

A 60-year-old female suffering from frontal lobe epilepsy was presented to our hospital with a mental obtundation.

We have treated the patient for a period of 5 years and have registered an electroencephalogram (EEG) with ictal fast activity in the right frontocentral area. A brain MRI showed a T2 high, T1 low signal intensity of a single lesion without enhancement in the right anterior basal frontal lobe white matter (Fig. 1). She used to have partial seizures with a secondary generalization, and she has been on 1,200 mg/day VPA for the last 4 years. Generalized tonic-clonic seizures (GTCSz) were well controlled, but partial seizures of left head version following left arm clonus occurred one to two times per several months. We added LEV to VPA and increased the daily dosage of LEV to 1,000 mg/day. Her partial motor seizures ceased and her EEG showed normal findings (Fig. 2A).

Eight months later, mental obtundation developed insidiously. The neurologic findings showed no ataxia or nystagmus, and routine hematology and biochemical laboratories presented a normal complete blood count (WBC 6,600/mm³, Hb 13.4 g/dL, platelet 168,000/mm³), electrolyte (Na 138 mmol/L, K 4.1 mmol/L), renal (BUN 11.1 mg/dL, Creatinine 0.72 mg/dL), and thyroid function test (free T4 1.230 ng/dL, TSH 0.779 uIU/mL). Her creatinine clearance was of 75.6 mL/min. However, her liver function test showed a mild impairment (aspartate aminotransferase 46 IU/L, alanine aminotransferase 44 IU/L, γ -glutamyl transferase 656 IU/L), and the serum ammonia level was high (154 μ mol/L, normal: 12 to 47 μ mol/L). An abdomen computed tomography (CT) with a contrast enhancement showed no remarkable finding, except for a 0.6 cm-sized liver cyst. The blood concentrations of VPA was of 82.4 μ g/mL (therapeutic range: 50-100 μ g/mL). The EEG presented an intermittent generalized delta slowing

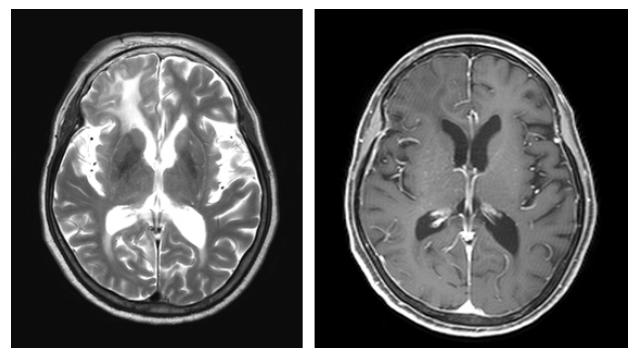


Figure 1. Brain MRI finding showed the T2 high, T1 low signal intensity single lesion without enhancement in the right anterior basal frontal lobe white matter. MRI, magnetic resonance imaging.

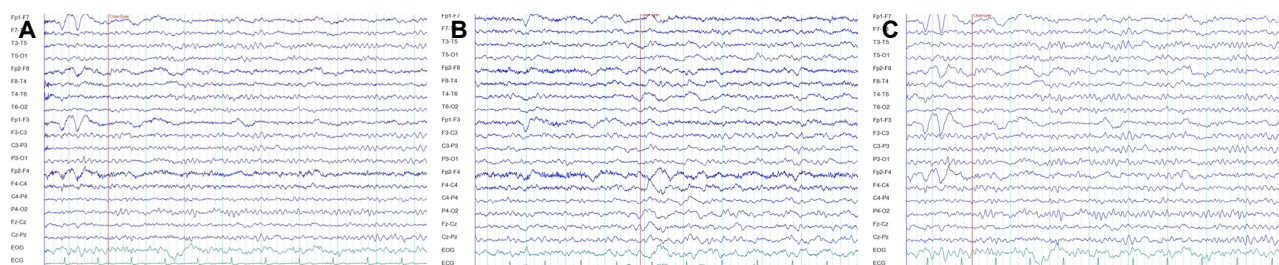


Figure 2. EEG findings. (A) Before LEV add on: normal EEG. (B) After LEV add on: intermittent generalized delta slowing. (C) After LEV stopped: disappeared slowing. EEG, electroencephalography; LEV, levetiracetam.

(Fig. 2B). We suspected the possibility of side effects associated with LEV because she tolerated medication with VPA for 4 years and stopped LEV. Her mental function was gradually restored, with a decrease in the blood ammonia level (56 $\mu\text{mol/L}$), and the generalized slowing disappeared in a follow-up EEG (Fig. 2C). We added carbamazepine to treat for partial seizures, and the patient was asymptomatic until the last visit in July 2014.

Discussion

Our patient showed mental obtundation and hyperammonemia following administration of LEV receiving VPA, and the condition was resolved completely after discontinuation of the drug. We consider the patient to have had VPA-induced hyperammonemic encephalopathy promoted by LEV.

An encephalopathy induced by AED has been described in patients with VPA medication.³ However, the condition has been rarely seen with LEV and only in specific conditions, such as when there is renal failure or when there is concomitant use of VPA.^{1,2} LEV undergoes minimal hepatic metabolism via enzymatic hydrolysis, and it is eliminated entirely by renal excretion.⁴ The clearance of the LEV decreased in subjects with renal impairment, whereas no significant pharmacokinetic changes for LEV were observed in patients with hepatic dysfunction.⁴ Vulliamoz et al. observed that the administration of LEV in a patient with chronic renal failure caused a myoclonic encephalopathy due to the toxic accumulation of LEV.¹

Previous studies indicated that LEV has no clinically relevant interactions with other AEDs due to its minimal protein binding and lack of hepatic metabolism.^{4,5} However, a recent meta-analysis observed that the enzyme inducing AEDs have a modest influence on the kinetics of LEV.^{6,7} Serum concentrations of LEV might be increased or decreased about 20 to 30% as the enzyme inducing or inhibiting AEDs are added.⁶ These results suggest that LEV is metabolized by cytochrome

P450 enzymes to a greater extent than what previously observed data had suggested.

A few reports on the pharmacokinetic influences and of the comedication effects of new AEDs on VPA toxicity have been noted.⁴ Hamer et al.⁸ described that patients receiving topiramate in addition to VPA suffered from an encephalopathy, and topiramate was concluded to have facilitated the toxic effect of VPA and to have contributed to the increase in the ammonia levels through its inhibition of carbonic anhydrase and cerebral glutamine synthetase.⁸

Although the mechanism for VPA-induced hyperammonemia is not fully understood, it is known that a propionate, metabolite of VPA, leads to a carbamyl phosphate synthetase-1 activity deficit, the decrease in hepatic carnitine concentration via VPA induces β -oxidation suppression of fatty acid, and an increase in the mitochondrial glutamine receptors causes the absorption of glutamine in the kidney.⁹ The hyperammonemia resulting from VPA causes encephalopathy mainly by influencing the astrocyte, which has the function of ammonia detoxication and leads to mitochondrial proliferation and cerebral edema through glycogen precipitation in the astrocyte cytoplasm.¹⁰

Previous reports on VPA-induced hyperammonemic encephalopathy have usually observed that patients with a concomitant use of other AEDs, such as phenytoin or phenobarbital, rather than those with single use, experienced β -oxidation suppression in the urea cycle which led to hyperammonemic encephalopathy without hepatic dysfunction.^{3,10} The mechanisms that cause encephalopathy with only LEV itself or with the comedication with VPA are debatable since VPA is usually well tolerated with a concomitant use with other new AEDs, and both increased serum LEV concentration with enzyme inhibiting VPA use and the VPA toxicity may induce an encephalopathy, even when within a therapeutic range.

We cannot explain the complete pathophysiological mechanisms responsible for the observed hyperammonemic encephalopathy. However, the lack of toxicity of VPA when used without LEV for an ex-

tended period of time, the insidious onset of mental obtundation after LEV add on, the generalized EEG slowing, the elevated ammonia level, and the complete recovery of mental symptoms after stopping the drug support the conclusion that a VPA-induced hyperammonemic encephalopathy was promoted by LEV. Our case demonstrates that a LEV provoke a condition of hyperammonemic encephalopathy in a patient receiving VPA, and such cases can be suspect when diagnosing this condition.

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