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Case report
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Paradoxical effect of sodium valproate that aggravates epilepsy of MELAS in a patient with A3243G mutation of the mitochondrial DNA

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Abstract: Epilepsy is an associated feature of patients with the syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). A substitution at nucleotide position 3243 A>G of the mitochondrial DNA is the most common mutation encountered both in Caucasians and in Chinese/Taiwanese. We herein report a 38-year-old man with A3243G mutation of the mitochondrial DNA whom developed MELAS. The manifestation of his focal motor epilepsy was aggravated by use of sodium valproate (VPA). The mechanism of this paradoxical effect is proposed.

Keywords: Acidosis, epilepsy, MELAS, mitochondrial disease, paradoxical effect, sodium valproate

1 Introduction

Mitochondrial disease (MtD) is a systemic disorder involving multiple organs. The phenotypes and genotypes of MtD are heterogenous [1–4]. A unique clinical syndrome manifested by mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episode, or "MELAS", was reported in 1984 by Pavlakis et al [5]. Genotype-phenotype correlations of MELAS and many other syndromic mitochondrial disorders have been de-

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scribed (see review article) [6]. Nevertheless, the most common mtDNA mutation in Chinese/Taiwanese patients with MELAS is the A3243G transition of mtDNA $tRNA^{UUR(Leu)}$ [6–12]. Multi-organ involvements of MELAS are characterized by diabetes mellitus, hearing loss, cardiac dysfunction, liver dysfunction, myopathy, neuropathy, CNS abnormalities, and so on [1–12]. The heteroplasmy and mutant load determine the clinical phenotypes [2, 6]. Epileptic seizures and myoclonic seizures are common features of MELAS and MERRF. Use of anticonvulsants is a practical issue. We herein describe a patient with MELAS, whose focal seizures were exacerbated by use of anticonvulsant, Sodium Valproate (VPA, 2-propylpentanoate). The mechanism of this paradoxical effect is proposed.

2 Case Report

A 38-year-old man presented to us with continuous focal motor seizures of right limbs. His consciousness remained clear during the ictus. He had diabetes mellitus and his mother had had bilateral blepharoptosis since she was a teenager. The plasma levels of lactate (L) and pyruvate (P) of the patient were remarkably elevated with L/P ratio of $\geq$ 30. Genotyping was performed on the genomic DNA obtained from the peripheral blood leukocytes of the patient and his mother following an informed consent. A point substitution of nucleotide position (np) 3243A>G was confirmed in the index case and his mother. Oral administration of Carbamazepine (Tegretol CR, CBZ) 400mg daily in two divided doses was initiated soon, and seizures were under controlled until about a year later when he developed a stroke with right hemiparesis and Broca's aphasia. Brain magnetic resonance imaging (MRI) showed an acute cerebral infarction involving left temporoparietooccipital lobes. Magnetic resonance angiography (MRA) showed segmental stenosis of the horizontal portion of left MCA (M1 segment). Neurosonogram of the common carotid, internal carotid, and vertebral arteries were unremarkable. Transcranial color-coded duplex showed high pulsaltility index (PI) of 2.1 at the proximal part of left MCA. PI of right MCA remained normal. Oral administration of Aspirin 100mg daily and Coenzyme-Q_{10} 30mg in three divided doses were then added for secondary stroke prevention and for treatment of his mitochondrial cytopathy. The neurological deficits improved and he could walk without assistance in the subsequent 5 months.

In the following 3 years of follow-up, he was hospitalized several times in the internal medicine department for treatment of pneumonia, episodic conscious disturbance, and vomiting. A remarkably increase in the frequency of focal motor seizures during the concurrent medical illness, brought him to a decision on polypharmacy by add-on Sodium Valproate (Depakine-Chrono, VPA). VPA was started at 500mg twice daily, and gradually escalated to 2.0g daily in two divided doses. A week later, the plasma concentrations of carbamazepine was 8.4 ug/mL, and of valproate (VPA) was 87.5ug/mL. However, the frequencies of his focal motor seizures increased with the escalation of VPA dosage. The inter-ictal electroencephalography showed multifocal epileptiform discharges (Figure 1). Followed-up brain MRI revealed multiple small new lesions over bilateral hemispheres.

Serum levels of GOT and GPT were 20 IU/dL and 26 IU/dL, respectively. Plasma level of lactate went up as high as 65.5ug/mL and pyruvate was 1.2ug/mL. Lorazepam 2mg three times daily was added for 2 days, and daily dosage of Carbamazepine (Tegretol CR) was escalated to 1600mg in 2 divided doses. Plasma level of CBZ attained 13.3ug/mL 3 days later. VPA was gradually tapered-off within the subsequent 4 weeks without seizure recurrence. He continued to be seizure-free until last follow-up in Feb 2006.

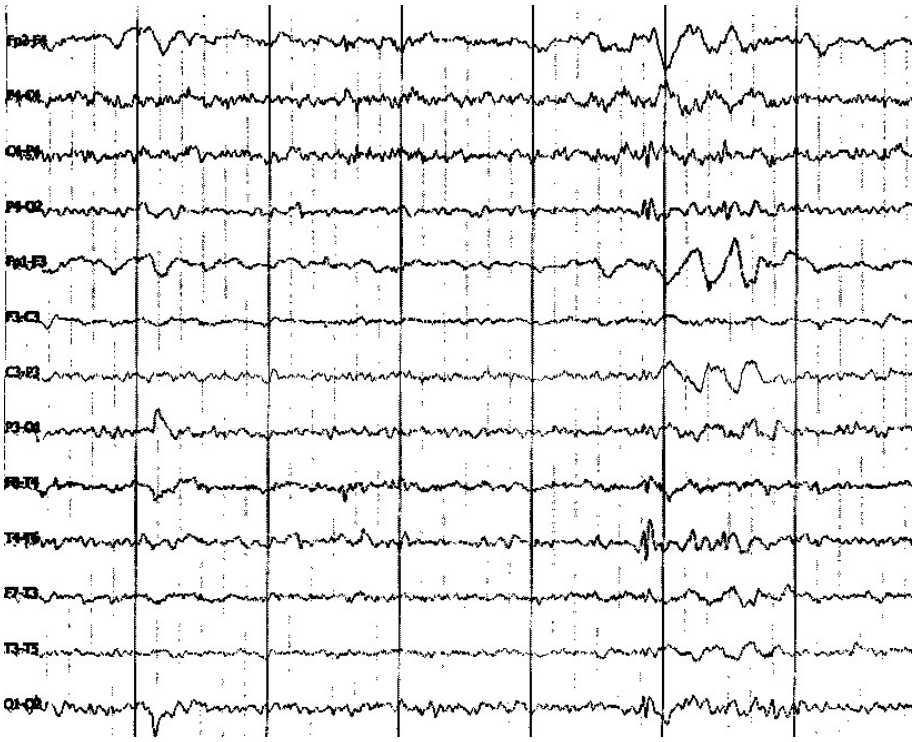

Fig. 1 Interictal electroencephalography (EEG) shows independent focal epileptiform discharges with spikes and sharp waves at the right temporo-parieto-occipital lobe and sharp transients at the left frontal lobe.

3 Discussion

The mechanism of anticonvulsive action of VPA is intriguing. Enhancement of glutamic acid decarboxylation and inhibition of GABA transamination play dual roles. In animal studies, VPA have been reported to cause seizure [13–16]. The mechanism of this paradoxical effect is not known. However, the paradoxical epileptogenic activity of VPA is transient and is dose-dependent [13]. It depends in part on the epileptogenic metabolite of VPA, such as 2-en-VPA, that is 1.3 times more potent than VPA to evoke seizures in animal model. In one report, VPA-induced status epilepticus could be ameliorated by reduction in VPA dosage. Altrup et al [13] reported that VPA changes the structure of the mitochondrial membrane, and Chabrol et al [14] demonstrated that VPA alters the activity of cytochrome c oxidase, a mitochondrial enzyme. Furthermore, measurements of the respiratory enzyme activities in even intact mitochondria of patients with

MELAS, revealed that more than a half have associated with some degree of complex I, or complexes I and IV deficiency [13–17]. Therefore, we propose that in patients with mitochondrial diseases such as MELAS, a defective oxidative and phosphorylation (OXPHOS) due to complex I or complex IV or both might predispose the patient to the unfavorable pharmacological effects of VPA on the mitochondrial machinery toward the paradoxical epileptogenicity. Other supportive evidence gives clue to the explaination of this paradoxical cellular event. First, the papers by Ponchaut et al [15, 16] demonstrated that the activity of complex IV of the respiratory chain is jeopardized by VPA. Second, Lam et al [17] suggested that there is an inborn error of mitochondrial system in patients whose seizures worsen by use of VPA. Third, the action of a potent epileptogenic metabolite, 2-en-VPA, is different from the parent compound VPA, that 2-en-VPA exerts the epileptogenic effect through the action on extra-cellular side of the cell membrane, whereas VPA acts on the intra-cellular site. The "two sides of a sword" make it unique to be prone of the paradoxical effect. A pre-existing hepatic mitochondrial dysfunction in MELAS per se may also contribute to a decrease in the capacity of hepatic elimination of VPA and its metabolite. The toxicity of accumulated VPA and its metabolites in turn accelerates the development of the mitochondrial "encephalopathy", changes of the mitochondrial membrane stability, and thus the paroxysmal depolarization shift (PDS) [13], and the subsequent seizures [12–17]. Finally, the threshold of PDS may be greatly altered and reduced by the regional brain acidic milleau (elevated H^+ concentration) associated with lactic acidosis. Therefore, when the proneness of epileptogenic forces outweighs the membrane stabilization of VPA, the shift of paroxysmal depolarization favors the occurrence of paradoxical effect of VPA.

In conclusion, Sodium Valproate (VPA) may aggravate epilepsy in patients with MELAS in a very paradoxical and unique way, even though it is rare. High plasma level of lactate and regional brain lactic acidosis predispose the cortical neurons to the paradoxical epileptogenic effect of sodium valproate. Therefore, we suggest that sodium valproate must be avoided in patients with MELAS with high level of lactate/pyruvate ratio, and severe lactic acidemia.

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