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LETTER TO THE EDITOR

A case with hyperammonemic encephalopathy triggered by single dose valproate

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Dear Editor,

Hyperammonemic encephalopathy rarely occurs when valproate is used alone. Underlying urea cycle enzyme deficiencies, concomitant drugs like salicylates, topiramate, underlying liver disease, high initial dose and long-term valproate therapy are the main known risk factors [1]. Here, we present a case of hyperammonemic encephalopathy which is triggered by single dose of valproic acid.

A 19-year-old girl was admitted to our clinic with sudden episode of altered state of consciousness. She had learning difficulties and diagnosed as attention deficit hyperactivity disorder when she was 7 years old. Because of her aggressive and inappropriate behaviors, she had been using sertraline 50 mg/day for the last 2 years. One day before her new symptom, sertraline was changed to valproate 1000 mg/day. She was confused, uncooperative and there was no any motor deficits, neck stiffness on neurological examination. Biochemical tests (liver function tests, renal function tests, serum electrolytes) and complete blood count were normal but serum ammonia level was elevated (588 mcg/dl, normal range 5–40 mcg/dL). Serum concentration of total valproic acid was lower than therapeutic range (44 mg/L, therapeutic range 50–100 mg/L). Brain MR showed bilateral cortical and subcortical diffusion restriction with corresponding ADC hypointensity and Flair hyperintensity on the same localizations (Fig. 1). Electroencephalography (EEG) revealed diffuse slowing with delta activity. During clinical follow-up, serum ammonia level also progressively increased to 900 mcg/dL. With hemodialysis, it regressed to 300 mcg/dL; so patient underwent eight-session hemodialysis. On the 13th day of the treatment, serum ammonia level was normal and her neurologic findings were also resolved. She was discharged from hospital without any neurological sequelae. Serum amino acid levels showed that low citrulline (9 μmol/L, normal range 12–55 μmol/L) with normal arginine, alanine and ornithine concentrations. Urine orotic acid level was also low (0.37 mmol normal range 0.4–1.2 mmol). In the light of these findings, carbamoyl phosphate synthetase 1 deficiency was suspected and genetic test revealed that there was heterozygous mutations on chromosome 2q35, exon 19 c.2339G > A (p.Arg780His) and exon 27 c3402G > C (p.Leu1134Phe).

'Valproate sensitivity' has been observed with ornithine transcarbamylase (OTC) and carbamoyl phosphate synthetase 1 deficiency (CPS1) in urea cycle disorders. In fact without any metabolic defects, valproate itself can cause hyperammonemia by inhibiting the activity of carbamoyl phosphate synthetase 1 [2] and if patients have also undiagnosed urea cycle disorder, hyperammonemia can cause deleterious results. OTC is the most common inherited cause of hyperammonemia; so screening for this enzyme deficiency is usually recommended [3]. In the literature, only three cases were reported as valproate induced hyperammonemia related to CPS-1 deficiency. CPS1 catalyzes the first step of the urea cycle and metabolic tests in CPS1 deficiency show low serum citrulline and also low urine orotic acid levels. This findings help clinician in the differentiation CPS1 deficiency from OTC because in OTC deficiency, with low serum citrulline level, urine orotic acid level increases. CPS1 deficiency is a rare, autosomal-recessive inborn error of the urea cycle characterized by episodes of life-

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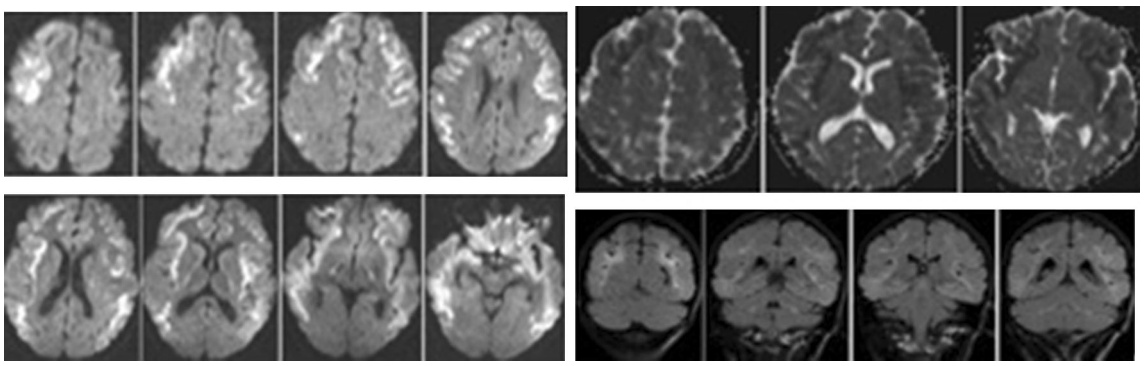

Fig. 1 Bilateral cortical, subcortical hemispheric diffusion restriction corresponding ADC hypointensity. On flair MRI, hyperintensity is seen in the same localization

threatening hyperammonemia [4]. Most patients have learning difficulties and mild intellectual impairment. The human CPS1 gene is located on chromosome 2q34-35 and comprises 38 exons [5]. In our patient, low serum citrulline and low urine orotic acid level supported our suspicion about CPS-1 insufficiency and we have proved the diagnosis with genetic analysis. As a result, if low dose and short duration valproate treatment causes hyperammonemic encephalopathy with very high serum ammonium level, urea cycle disorders must be considered.

Compliance with ethical standards

Conflict of interest There is no conflict of interest.

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