Sir,

We read with interest the article by Ahmed published in the SQUMJ February 2015 issue. The author reports an eight-year-old male weighing 25 kg who developed myopathy with carnitine deficiency after valproate therapy. This case is not the only one of its kind; Kasturi et al. reported a similar case in 2005 of a four-year-old boy developing neurocysticercosis proximal muscle weakness and carnitine deficiency after long-term valproate therapy due to symptomatic epilepsy. Upon discontinuation of valproate and the addition of L-carnitine, the clinical manifestations completely resolved.

Ahmed attributes the development of myopathy in his patient to the administration of valproate (1,000 mg/day or 40 mg/kg/day). However, valproate-induced myopathy may not only be due to carnitine deficiency, but also due to the primary mitochondrion-toxic effect of the drug. Valproate not only inhibits complexes I and IV of the respiratory chain, but also restricts oxidative phosphorylation and thus adenosine triphosphate synthesis and β-oxidation. As a consequence, oxygen consumption is reduced, coenzyme A (CoA) and cytochrome c are sequestered, the structure of the inner mitochondrial membrane is impaired and there is vacuolar fragmentation of mitochondria.

Additionally, valproate has been reported to unmask mitochondrial disorders (MIDs). Chaudhry et al. reported a patient with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome, in whom the MID became evident after the administration of valproate. Valproate has also been shown to cause myopathy in patients with acyl-CoA dehydrogenase deficiency, rhabdomyolysis in neonates with chromosomal defects and rhabdomyolysis in patients with carnitine palmitoyltransferase II deficiency. Mitochondrial toxicity of valproate was further documented to induce severe acute liver failure in patients with a mitochondrial depletion syndrome. Valproate-induced myopathy has additionally been observed in a patient with schizoaffective disorder, although this patient was also taking quetiapine, nifedipine, torsemide, levothyroxine and acetylsalicylic acid.

The mitochondrion-toxic effect of valproate was also confirmed in a patient with MELAS syndrome, in whom valproate aggravated epilepsy. Mitochondrion-toxicity of valproate may be the reason why the compound is often ineffective as an anti-epileptic drug in MID patients.

Concerning the case presented by Ahmed, it would be helpful to know: if there was consanguinity between the parents; if the family history was positive for epilepsy; if myopathy developed in any first-degree relative; if muscle cramps, easy fatigability, double vision, exercise intolerance, muscle weakness or myalgia were reported by the parents, grandparents or siblings; if there were complications during general anaesthesia in the individual or his family; the results of neurological investigations by specialists familiar with metabolic myopathies; and if there were elevated creatine kinase or lactate levels or myoglobinuria in any of the relatives.

Overall, there is evidence that valproate may cause mitochondrial myopathy due to its mitochondrion-toxic effect. However, this seems to predominantly affect patients with subclinical or clinical manifestations of MID. The interesting case reported by Ahmed would thus profit from an extensive work-up for MID or a β-oxidation defect. The question as to whether valproate myopathy is a mitochondrial disorder would have to be answered with "yes".

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References


