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LETTER TO THE EDITOR

Re: Sodium Valproate-Induced Myopathy in a Child

رد: الاعتلال العضلي الذي يسببه دواء صوديوم فالبرويت في طفل

Sir,

We read with interest the article by Ahmed published in the SQUMJ February 2015 issue.[1] The author reports an eight-year-old male weighing 25 kg who developed myopathy with carnitine deficiency after valproate therapy.[1] 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.[2] Upon discontinuation of valproate and the addition of L-carnitine, the clinical manifestations completely resolved.[2]

Ahmed attributes the development of myopathy in his patient to the administration of valproate (1,000 mg/day or 40 mg/kg/day).[1] However, valproate-induced myopathy may not only be due to carnitine deficiency, but also due to the primary mitochondrion-toxic effect of the drug.[3] 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.[4,5] 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.[6] 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.[7] Mitochondrial toxicity of valproate was further documented to induce severe acute liver failure in patients with a mitochondrial depletion syndrome.[8] 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.[9] The mitochondrion-toxic effect of valproate was also confirmed in a patient with MELAS syndrome, in whom valproate aggravated epilepsy.[10] Mitochondrion-toxicity of valproate may be the reason why the compound is often ineffective as an anti-epileptic drug in MID patients.[11]

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.[1]

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.[1] The question as to whether valproate myopathy is a mitochondrial disorder would have to be answered with "yes".

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