

Sodium Valproate-Induced Myopathy in a Child

الاعتلال العضلي الناجم عن صوديوم فالبرويت في طفل

Sir,

An eight-year-old Saudi male child presented to the Department of Paediatric Neurology at King Fahad Military Hospital, Jeddah, Saudi Arabia, in May 2013. He was diagnosed with childhood onset epilepsy with absence seizures on the basis of clinical seizure semiology and classical electroencephalography findings. Baseline haematological and biochemical investigations, including serum lactate and ammonia tests, performed prior to the administration of any medication proved to be normal. The patient was subsequently started on 250 mg of sodium valproate in two divided doses (20 mg/kg). As his response to the treatment was inadequate, the dose of the medication was gradually increased over the following few weeks to the maximum permissible dose of 500 mg twice daily (40 mg/kg/day). At this dose, the absence seizures were controlled.

Six months later, it was observed that the patient had slowly developed progressive weakness of the lower limbs. He found it difficult to rise from a sitting position, climb stairs, run or play games. There was no pain in the legs or any diurnal variation in weakness. There was no difficulty in using the upper limbs. Since the symptoms were progressive, the child's parents sought medical advice. A clinical examination at this time revealed predominant weakness of the proximal limb muscles, particularly in the lower rather than the upper limbs, with retained deep tendon reflexes and a normal sensory examination. There was no weakness of the neck, chest or abdominal muscles and no sensory involvement or calf muscle hypertrophy. He walked with exaggerated lumbar *lordosis* and had a waddling gait.

The findings of this clinical examination were consistent with the diagnosis of a form of myopathy, predominantly proximal. Routine investigations were normal, including tests for serum lactate, creatinine kinase and serum valproate levels. A nerve conduction study was normal, however needle electromyography (EMG) in the lower limb muscles revealed action potentials of short duration and with a low amplitude which were consistent with the myopathic pattern. A muscle biopsy was planned but not performed as the parents did not give consent for the procedure. There was no history of preceding neurological illness and the family history was negative. Additionally, the valproate therapy was determined to have been of sufficient duration. A diagnosis of valproate-induced myopathy was concluded from the available clinical and EMG findings.

Further investigations revealed low serum carnitine levels at 13 micromoles/L (normal range: 25–54 micromoles/L). A diagnosis of secondary carnitine deficiency due to valproate was considered. The patient's medication was changed to lamotrigine at a dose of 50 mg twice daily (5 mg/kg). Oral carnitine was also prescribed at a dose of 500 mg four times daily (100 mg/kg/day). He showed good clinical response to the therapy; in three weeks, he had regained power in the skeletal muscles. Furthermore, his gait improved considerably with limited waddling and no *lordosis*. A repeat EMG was normal after six months, as were his serum carnitine levels. These factors were suggestive of transient secondary valproate-induced myopathy.

The drug of choice for childhood absence seizures is ethosuximide; however, due to its potential haematological side-effects and lack of availability in many countries, sodium valproate has become an equivalent choice because of its efficacy and improved safety profile.¹ Many clinicians prefer sodium valproate as opposed to ethosuximide because of the use of the former in controlling myoclonic and generalised tonic-clonic seizures, although this may not be a cause of concern in childhood absence epilepsy.²

Carnitine synthesis takes place in the liver and kidney from amino acids (lysine and methionine). It functions as a transporter of fatty acids from the mitochondria to the matrix for the purposes of lipid breakdown and generation of metabolic energy. Prolonged valproate therapy can induce transient carnitine deficiency due to either renal loss of carnitine esters or inhibition of plasmalemmal carnitine uptake.^{3,4} Although decreased carnitine levels may not induce major pathological changes in children, cardiac dysfunction, encephalopathy, hepatic toxicity and cerebral oedema have been reported in the literature as complications of long-term valproate therapy.^{5,6} Shapira *et al.* described six patients who presented with hypotonia with low carnitine levels.⁷ Muscle biopsy studies have also showed ultrastructural abnormalities in the muscles with lipid droplet accumulation by electron microscopy.^{7,8}

Beversdorf *et al.* illustrated several risk factors for the development of valproate-induced encephalopathy, including hyperammonaemia, metabolic acidosis and multiple neurological disabilities.⁹ Patients of a younger age (less than two years old) and those who were non-ambulatory, underweight or on multiple anticonvulsants were also considered to be at higher risk.⁹ In addition, valproic acid was also considered to be the cause of myopathy and rhabdomyolysis among patients with lipid storage disorders and carnitine palmitoyltransferase deficiencies.^{10,11}

The current patient presented here was not subject to any of the aforementioned risk factors and a muscle biopsy was not performed. In this case, low serum carnitine levels and the observed clinical recovery following supplementation of oral carnitine were enough to confirm the diagnosis of valproate-induced myopathy. This case clearly illustrates that secondary carnitine deficiency should be considered for children developing muscle weakness while on valproate therapy.

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