Peripheral edema with Valproate therapy

Sir,

In this letter we describe a 34-year-old male known to have mitochondrial disease and intractable myoclonic seizures. His seizures were managed with Sodium Valproate (VPA) 1800mg orally in divided doses and Lamotrigine, after most other anti-epileptic drugs failed to control his seizures. He developed slowly progressive peripheral edema involving the legs, hands and face, which were becoming quite disturbing to the patient.

On examination, patient was a well-nourished male who had gained 8 kg over 2-years. Bilateral and symmetrical pitting edema was noticed in face, hands and feet. Jugular venous pressure was not raised and rest of the cardiovascular examination was normal with no sign of cardiac failure. Chest examination was normal and for the abdomen, no hepatosplenomegaly or ascites was noted. There were no signs of hepatic dysfunction. Urine dipstick and microscopy revealed no abnormalities. Investigations included complete blood count, blood film, urea and electrolytes; liver function tests, albumin, calcium and phosphate were all normal. Echocardiogram revealed no valvular or structural abnormalities. There was no evidence of systolic or diastolic dysfunction. Patient was started on a low salt diet and trial of Frusemide was given. At the end of a 2-month trial of Frusemide and salt restriction patient complained of occasional incontinence of urine due to inability to hold urine. His weight remained unchanged and no improvement of edema was noticed. At this stage VPA-associated edema was considered and VPA dose was reduced from 1600 mg per day in divided doses to 1000 mg per day in divided doses, maintaining trough levels of 82 µmol/l. This resulted in slight reduction in weight and edema but was associated with episodes of intractable seizures requiring addition of other anti-epileptic drugs in addition to Lamotrigine. As Carnitine deficiency was reported in a patient taking VPA with cerebral edema and normal liver function, Carnitine levels were checked and deficiency as an etiology of his edema was ruled out [Free Carnitine = 71 µmol/l (range 30-50µmol/l), Total Carnitine = 86 µmol/l (range 43-65)]. Sodium Valproate is a well-established anti-epileptic drug (AED) commonly used for most forms of generalized seizures. Gastrointestinal disturbances, alopecia, hirsuitism and weight gain are some of the known common side effects. Hepatotoxicity is a less common side effect but potentially fatal, especially in children. Peripheral edema is rarely reported and a poorly understood side effect of Valproate therapy. Several cases have been reported in the literature from other parts of the world with totally normal hepatic function.[1-3] Cerebral edema has also been described in literature in relation to VPA therapy where it was linked to Carnitine deficiency.[4] This type of edema develops in patients who are on long term VPA therapy (mean period of 3.9 years) on moderate to high doses (>1500mg/day) with trough levels ranging from 36-170 µg/ml.[2] In one series of 7 patients, one patient's edema resolved spontaneously without changing the dose, 4 patients' edema resolved after the VPA dose was reduced, one needed totally withdrawing the drug and in one patient it did not improve at all. On the other hand, other cases have been reported to develop peripheral edema with low doses of VPA and hence no definitive conclusion can be drawn on dose dependency of oedema.[1,3] Although diuretics were not useful in treatment of our case, it has been reported to be useful in some to help reduce the edema when VPA dose could not be reduced.[3] Cerebral edema has been described with VPA in association with Carnitine deficiency and in absence of hepatic failure,[4] but none of the reports above describing peripheral edema included Carnitine levels in their investigation. Valproate is known to cause Carnitine deficiency in children and Carnitine supplements are recommended in such patients.[5] To our knowledge, this is the first case describing a lack of evidence of a link between peripheral edema due to VPA and Carnitine in adults. The mechanism by which VPA causes edema remains unclear. Some relate it to hepatic toxicity, which is missing in most of reported patients including ours. Other described mechanisms include decrease in plasma protein levels or an increase in capillary blood pressure or capillary filtering surface.[2] Further studies are needed to identify the etiology of VPA associated peripheral edema.

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