Sodium valproate as a cause of unilateral pitting lower-limb oedema mimicking lymphoedema in a child

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Key words

Filariasis, oedema, sodium valproate

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Abstract

This case study deals with a 7-year-old boy who developed unilateral, lower-limb pitting oedema that was determined to be a complication of long-term sodium valproate use. The diagnosis was complicated by the fact that the child had previously resided in an area known to harbour the pathogens causing filariasis and by the fact that other vascular anomalies were present, suggesting a possible underlying segmental primary lymphoedema. This case serves as a reminder of the importance of undertaking a full history and examination of the presenting patient, including his or her current pharmacology, as well as carrying out a wide range of tests to ensure accurate differential diagnoses for lymphoedema. This is the first report of unilateral swelling as an adverse affect of valproic acid therapy.

Peripheral oedema affecting the limbs and/or face is an infrequently reported complication of valproate therapy (Ettinger et al, 1990; Shuai-Ting et al, 2009). The oedema occurs in the context of long- or short-term therapy in the absence of hypoalbuminemia, fluid overload, excessively elevated serum valproate levels or hepatic dysfunction, and the pathophysiology of this condition is unknown (Ettinger et al, 1990; Shuai-Ting et al, 2009). Shuai-Ting and colleagues (2009) have postulated that it may be the result of alterations in peripheral vascular resistance through a GABAergic effect, but no specific evidence exists to support this theory.

Case study

DC is a 7-year-old boy with a background history of Sturge–Weber syndrome with bilateral facial haemangiomas, cortical atrophy of the left posterior cerebrum, pial haemangiomatosis, right-sided glaucoma, developmental delay and seizures. He had been on sodium valproate for the management of his seizures since he was 2 years of age and had experienced no seizures since the age of 5 years. DC and his family were refugees from Iraq who settled in Australia when he was 3 years of age after having lived in Turkey for 2 years.

Presentation

DC presented with a 3-month history of swelling of the dorsum of the left foot and lower limb and mild ache in the leg after walking for longer than 10 minutes, but he had no other symptoms. He had mild pitting oedema of the dorsum of the foot and the distal shin, but nowhere else.

Apart from the neurocutaneous stigmata related to his Sturge–Weber syndrome, he had no other significant findings and there was no clinical evidence of haemiplegia. Abdominal examination was normal. The swelling became more marked over a period of 4 months, but DC did not develop any further symptoms. His height was 132 cm and his weight was 31.9 kg at the time of presentation.

Investigations

DC had a number of investigations including a full blood count, liver function tests, albumin, renal function, thyroid function and electrolytes, all of which were normal. A urine analysis and protein:creatinine ratio were normal. Abdominal and lower-limb ultrasound, including Doppler scan, was normal.

Given the pitting oedema with normal serum albumen and a history of having lived in Turkey, possible diagnoses of congenital segmental lower-limb lymphoedema or filariasis were considered. A lymphoscintigram was performed and was normal, with no evidence of delayed lymphatic flow, lymphatic dilatation, dermal backflow or obstruction to the lymph flow. A magnetic resonance imaging scan showed diffuse oedema in the superficial fascia and subcutaneous layer of the skin, but was non-specific.

At this point, after the normal investigations listed above, a review of DC's history and medications raised the possibility that long-term sodium valproate use might explain his peripheral oedema. The drug was ceased and he was commenced on oxcarbazepine as an alternative, resulting in rapid resolution of the pitting oedema over a period of less than 2 weeks. Following the resolution of the swelling, no further investigations, such as filarial serology, were undertaken.

Discussion

This case illustrates two important causes of acquired peripheral oedema and the process of differentiating these from childhood-onset congenital lymphoedema. There are numerous reports of valproate-related oedema in patients on combination anticonvulsant therapies or psychiatric drugs, particularly risperidone (Baldassano and Ghaemi, 1996; Sanders and Lehrer, 1998; Shuai-Ting et al, 2009), quetiapine (Chen et al, 2009) and lamotrigine (Farooqui et al, 2002), but it is also seen in valproate monotherapy (Ettinger et al, 1990; Buchanan and Hayden, 1992; Basel-Vanagaite et al, 1999), as in this patient. In most cases, the swelling improves or resolves completely with cessation of the drug or reduction in the dose (Sanders and Lehrer, 1998; Ettinger et al, 1990; Buchanan and Hayden, 1992; Basel-Vanagaite et al, 1999; Shuai-Ting et al, 2009), which is also demonstrated in this case.

There are only a few reports of this complication of valproic acid therapy in children of 16 years of age or younger (Ettinger et al, 1990), with this being only the fourth in the literature to date. Furthermore, our patient presented with unilateral leg swelling, which is unusual in sodium valproate-related oedema. Despite multiple examinations by experienced clinicians, no pitting oedema was detected in any other areas and the presence of such oedema was denied by the child and his family.

The child had migrated to Australia via Turkey, which is not an endemic area for filariasis. Nonetheless, there have been a significant number of cases of filariasis reported from Turkey (Sipahioglu, 1959; Cengiz et al, 2006), thus this was entertained as a possible cause of DC's unilateral pitting oedema. Filariasis is the most common cause of acquired lymphoedema in the world (Pfarr et al, 2009). It is caused by infestation with the filarial nematodes *Wuchereria bancrofti*, *Brugia malayi* or *Brugia timori*, which invade the lymphatic vessels and lymph nodes, and may cause an inflammatory reaction within these vessels when the nematode dies and degenerates, causing obstruction and obliteration of the lymphatics, resulting in oedema (Sipahioglu, 1959). Patients with oedema as a complication of filariasis will have abnormal lymphoscintigraphy, which was not the case in DC, effectively excluding filariasis as the cause of his oedema.

The other likely case of unilateral pitting oedema of the lower limb in this age group is congenital segmental lymphoedema, which was considered. This is a sporadic condition that may affect one or more body areas including the limbs, face and genitalia. It may present in early childhood and be either uni-segmental or multi-segmental. When uni-segmental, it will usually affect the lower limbs (Connell et al, 2009a; 2009b). Again, this diagnosis was not supported by the lymphoscintigraphy, which was normal in DC's case.

Conclusion

In this case, a patient presented with valproate-induced unilateral lower-limb lymphoedema. The history and presentation raised the possibility of the differential diagnoses of filariasis and uni-segmental congenital lymphoedema, both of which needed to be actively excluded using lymphoscintigraphy. This case demonstrates that asymmetric lower oedema is a possible adverse affect of valproic acid and is the first time this has been reported.

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