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Letters to the Editor

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Paediatric hypertension-associated erythromelalgia responds to corticosteroids and is not associated with *SCN9A* mutations

SIR, we report the case of a 9-year-old boy admitted to our Pediatrics Service in May 2010 with severe burning pain of his hands and feet. The pain became progressively more intense, leading to gait alterations and severe sleep disturbance. He developed erythema, increased warmth and mild oedema with socks and gloves distribution, but had no vascular changes compatible with Raynaud's syndrome. Distal pulses were normal. In addition, he had severe arterial hypertension up to 150/96 mmHg (>99th percentile), with poor correlation of blood pressure to pain crises. There was no history of heavy metal ingestion. Family history was negative for autoimmune, neurological and metabolic diseases.

The boy reported that the pain was alleviated only with cold water, so he persistently kept his hands and feet in cold water basins. He began treatment with intravenous NSAIDs with no response. He was progressively treated with increasing strength of analgesic agents, showing a poor response to methadone, gabapentin, amitriptyline, lidocaine patches and lidocaine intravenous infusions. Arterial hypertension was initially treated with nifedipine with poor control, subsequently being switched to doxazosin and atenolol. This combination was successful in achieving normotension but not pain control.

Laboratory studies included normal complete blood counts, ESR and blood biochemistry. Normal α-galactosidase levels ruled out Fabry disease. Electromyography and spine and brain MRI were completely normal, ruling out demyelinization, large-fibre polyneuropathy and myelopathy. The patient did not have symptoms or signs suggestive of small-vessel vasculitis, had negative ANCA and normal von Willebrand factor antigen. Lesional skin biopsy was normal with no signs of small-vessel vasculitis. Abdomen CT and I131-labelled MIBG scintigraphy ruled out pheochromocytoma.

After 14 days of hospitalization, the patient continued to have incapacitating pain and poor response to analgesia. Hypertension-associated erythromelalgia (HAE) was suspected. Based on the reports of a possible autoimmune aetiology of this condition and effective treatment with corticosteroids [1, 2], methylprednisolone pulses (30 mg/kg/dose) were administered on three consecutive days with rapid reduction of pain severity from 10/10 to 3/10. A gradual taper of prednisone was prescribed over 3 months, quickly achieving complete remission of symptoms. Antihypertensive drugs were weaned over 2 months and discontinued, after which the patient remained normotensive. Genotyping studies of *SCN9A*, encoding the sodium channel α subunit protein $NA_V1.7$, which has been associated with familial erythromelalgia [3, 4], were normal in our patient. During prednisone treatment, the patient also received oral mexiletine, which was discontinued once genetic studies were received. He was discharged from the hospital without pain and achieved prolonged remission off corticosteroids at 18-month follow-up.

Erythromelalgia is a rare disease characterized by erythema, increased warmth and severe pain of the hands and feet. Pain is usually precipitated by increased temperature and exercise, and alleviated with cold water. It has been described in primary and secondary forms: the latter is usually present in adults and is associated with myeloproliferative disease or autoimmune diseases such as lupus [5]. A few cases of HAE have been described in children with transient non-relapsing severe attacks of erythromelalgia with variable elevations in blood pressure [1, 2, 6–8].

The pathogenesis of HAE in children is yet unclear. Pathogenic mutations in the *SCN9A* gene have been described in cases of primary EM with autosomal dominant inheritance, but this gene has not been previously studied in cases of HAE [3, 4]. Electrophysiological alterations of motor and sensory nerves, as well as a decrease in small-fibre nerve density have been described in HAE patients [1, 7], similar to other types of erythromelalgia [9]. An autoimmune aetiology of HAE has been postulated due to the findings suggestive of a small-fibre axonopathy and an exquisite response to corticosteroids [1, 2].

Optimal treatment of erythromelalgia in children is yet unclear. A targeted therapeutic approach of erythromelalgia attacks ideally requires unraveling its pathogenesis through ancillary studies. However, excepting the cases of familial erythromelalgia, likely to be associated with *SCN9A* mutations, this is a slow and difficult process. Genotyping studies and pathological confirmation of a small-fibre axonopathy are cumbersome and not commonly available to rheumatologists and other clinicians. Thus the choice of treatment is generally based on clinical judgement and usually left to trial and error. Sodium nitroprusside has been effective in controlling hypertension and pain in HAE [6, 7]. This was not tried in our patient, because normotension was achieved with oral antihypertensive drugs, but without pain control. Lidocaine and mexiletine, sodium channel blockers, have been effective in treating erythromelalgia due to *SCN9A* mutations [10], but have not induced remission in HAE [1]. As seen in our patient, HAE appears to be unrelated to *SCN9A* mutations, and thus treatment with sodium channel blockers may not be effective. In fact, the exquisite responsiveness to corticosteroids suggests that this entity may be due to an inflammatory, possibly

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autoimmune, small-fibre neuropathy. Aggressive treatment with corticosteroids led to remission in our patient, and may be an effective option for other cases of HAE.

Rheumatology key message

- Corticosteroid response and the absence of *SCN9A* mutations suggest an autoimmune pathogenesis in paediatric HAE.

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References

1 Paticoff J, Valovska A, Nedeljkovic SS, Oaklander AL. Defining a treatable cause of erythromelalgia: acute adolescent autoimmune small-fiber axonopathy. Anesth Analg 2007;104:438–41.

2 Pfund Z, Stankovics J, Decsi T, Illes Z. Childhood steroid-responsive acute erythromelalgia with axonal neuropathy of large myelinated fibers: a dysimmune neuropathy? Neuromuscul Disord 2009;19:49–52.

3 Drenth JP, te Morsche RH, Guillet G *et al*. SCN9A mutations define primary erythermalgia as a neuropathic disorder of voltage gated sodium channels. J Invest Dermatol 2005;124:1333–8.

4 Yang Y, Wang Y, Li S *et al*. Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. J Med Genet 2004;41:171–4.

5 Davis MD, O'Fallon WM, Rogers RS III, Rooke TW. Natural history of erythromelalgia: presentation and outcome in 168 patients. Arch Dermatol 2000;136:330–6.

6 Drenth JP, Michiels JJ, Ozsoylu S. Acute secondary erythermalgia and hypertension in children. Erythermalgia multidisciplinary study group. Eur J Pediatr 1995;154:882–5.

7 Chan MK, Tucker AT, Madden S *et al*. Erythromelalgia: an endothelial disorder responsive to sodium nitroprusside. Arch Dis Child 2002;87:229–30.

8 Cook-Norris RH, Tollefson MM, Cruz-Inigo AE *et al*. Pediatric erythromelalgia: a retrospective review of 32 cases evaluated at mayo clinic over a 37-year period. J Am Acad Dermatol 2011, Advance Access published 26 July 2011, doi: 10.1016/j.jaad.2011.01.010.

9 Sandroni P, Davis MD, Harper CM *et al*. Neurophysiologic and vascular studies in erythromelalgia: a retrospective analysis. J Clin Neuromuscul Dis 1999;1:57–63.

10 Nathan A, Rose JB, Guite JW, Hehir D, Milovcich K. Primary erythromelalgia in a child responding to intravenous lidocaine and oral mexiletine treatment. Pediatrics 2005;115:e504–7.

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Sustained improvement of diffuse systemic sclerosis following human cytomegalovirus infection offers insight into pathogenesis and therapy

SIR, SSc remains an enigmatic disease of unknown aetiology, although genetic predisposition, environmental triggers and infectious agents have all been postulated. Here we report a case of severe diffuse SSc that demonstrated rapid and sustained improvement following severe intercurrent human CMV infection that occurred in the context of systemic immunosuppression with MMF. The patient had previously relapsed after withdrawal of MMF, but has not required any additional disease-modifying therapy after recovery from her CMV-related illness. The striking improvement suggests that CMV infection may have had a disease-modifying effect in this case.

We report the case of a 54-year-old female patient with diffuse SSc who improved dramatically after a severe CMV infection. Initially in 2004, she noted the development of characteristic RP, associated with puffy fingers and rapidly progressive skin thickening according to the diffuse subtype of SSc. Testing for ANAs (titre >1:1000) revealed anti-RNA polymerase (RNAP) autoantibodies with a fine speckled pattern (ENA−). It is noteworthy that in 1988 she had suffered from severe post-infectious polyneuropathy (Guillain–Barré syndrome) that had been treated with plasma exchange and from which she made a full recovery following a prolonged hospital admission including ventilatory support. Due to the very progressive course of skin involvement from dcSSc with discolouration, itchiness and swelling involving the forearms, neck, face, back and the medial parts of the lower limbs, she commenced MMF 1 g twice daily in 2005, which stabilized her skin involvement and symptoms. However, an attempt to reduce and stop this treatment in May 2009 was associated with significant worsening of skin thickening and constitutional symptoms, strongly suggesting that she had previously responded well to MMF therapy. MMF was therefore re-instituted at the same dose in September 2009. Nine months later, in June 2010, she developed abrupt onset of severe bloody diarrhoea and was diagnosed with a CMV viraemia (CMV DNA detected in citrated blood); results were consistent with a primary CMV infection, confirmed by a

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