SHORT REPORT

Erythromelalgia: an endothelial disorder responsive to sodium nitroprusside

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Erythromelalgia is an unusual syndrome of painful vasodilatation. Aetiopathology is probably different in children and adults. Presentation can be severe and associated with hypertension. Dramatic benefit from infused nitroprusside suggests the disorder could represent a dysfunctional endothelium.

Erythromelalgia (EM) is a rare episodic painful condition. Mitchell coined the term in 1878.[1] It is characterised by episodic erythema and warmth of extremities with severe burning pain. It is precipitated by heat, exercise, and dependency, and relieved by cold exposure, rest, and elevation.[2]

Some adult patients have cyclo-oxygenase related platelet activation and vessel thrombosis,[3] often in association with myeloproliferative disorders.[2] EM is associated occasionally with diabetes mellitus, multiple sclerosis, and pregnancy.[4]

In childhood, a different clinicopathological picture is seen, with often no underlying cause. Two patients with EM are presented, illustrating the clinical manifestations in childhood, and emphasising the association with hypertension and the benefit from sodium nitroprusside (SNP) treatment.

CASE 1

An 11 year old boy of Italian descent presented with sudden onset of burning pain in hands and feet with vasodilatation and increased skin temperature. Warmth, exercise, and stress provoked attacks with pain relief from rest and cold. Despite morphine, nifedipine, propranolol, and aspirin he was spending 24 hours a day with hands and feet in ice cold water to obtain relief.

Examination revealed a distressed boy with hands and feet in ice cold water. Systolic blood pressure was 130 mm Hg and his extremities were dark red with hyperkeratosis, maceration, and superficial ulceration. Peripheral pulses were palpable, tendon reflexes were symmetrically present, and sensation testing normal. A diagnosis of EM was made.

Investigations were negative for immunologically determined disease, Fabry's disease, porphyria, and mercury intoxication. Nerve conduction studies showed a sensory motor neuropathy of axonal type. Thermography showed symmetrically hot and vasodilated hands. Vasomotor responses to mild cold stress, and finger nailfold capillaroscopy revealing reduced capillary numbers, apical microhaemorrhages, and capillary morphological changes supported a diagnosis of EM.

He commenced intravenous SNP up to 2 μg/kg/min but developed hypotension with little clinical improvement. Prostacyclin infusion at 2–3 ng/kg/min was substituted for three days with little effect. SNP was subsequently tolerated at 3 μg/kg/min for 10 days with good clinical response. He was gradually weaned on to oral propranolol.

Psychological intervention reduced his conditioned anxiety response to pain and a cognitive behavioural programme reduced the time of cold water immersion. He has subsequently remained pain free and normotensive.

CASE 2

A 5½ year old Asian boy had three years of paroxysmal hot painful feet, requiring almost constant cold water immersion. The diagnosis of EM was made locally, but various therapies failed including aspirin, propranolol, clonidine, cyproheptadine, trimeprazine, amitriptyline, carbamazepine, analgesics, and epidural analgesia.

Red, sweaty skin had been noted at a few weeks of life. At the age of 1 year, episodic loss of consciousness and apnoea was treated with anticonvulsants. He walked late (3 years), possibly because of painful feet, and never wore socks or shoes.

On examination he was unhappy, with feet in cold water that were swollen and ulcerated as a result of chronic immersion. Hands were relatively spared. Systolic blood pressure was raised for age (120–130 mm Hg).

Capillaroscopy showed large, loosely coiled vessels typical of EM. Nerve conduction was normal but electromyography showed changes consistent with myopathy.

He commenced SNP, increasing to a maximum dose of 4 μg/kg/min. There was benefit within hours. This was maintained for five days. He became pain free with no need for cold water for five weeks. Recurrence despite minoxidil and topical glycerol trinitrate resulted in further SNP with impressive response. Six months later he remains symptom free and normotensive.

DISCUSSION

It appears that EM can be subdivided into four distinct entities: two predominantly affecting adults and two usually found in children.

Adult EM with thrombocythaemia/platelet activation linked to myelofibrosis,[2] generally responds to aspirin, and EM linked to other disorders such as vasculitis, neurological disease, and vasoactive drugs is managed by treating the cause.[4]

Paediatric EM appears to be idiopathic. In so called "primary" EM, recurrent episodes date back to early childhood and are resistant to treatment,[2] sometimes with a family history.[5] A second childhood form, "secondary" erythermalgia (another name for EM) associated with hypertension, is not familial with no recurrences after successful treatment.[6] Aspirin is ineffective but SNP offers benefit.[6]

Case 1 fits the category of "acute secondary" EM, with benefit from SNP. Case 2 could be classified as "primary" EM, although hypertension and benefit from SNP is atypical.

The electrophysiologically demonstrated neuropathy and myopathy are unexplained, although a skin biopsy from a diabetic with EM showed virtually no large diameter axons.[7] A contribution from chronic water immersion is possible.

Abbreviations: EM, erythromelalgia; SNP, sodium nitroprusside

The hypertension in a condition characterised by peripheral vasodilatation suggests non-apparent vasoconstriction of resistance vessels. Evidence suggests that despite hyperperfusion, tissue ischaemia exists, possibly because of increased arteriovenous shunting in the microcirculatory bed.[8] Recently, using laser Doppler fluxmetry to measure skin blood flow, a vasoconstrictor tendency in EM has been shown.[9]

The remarkable response to SNP, an endothelium independent NO donor, gives some insight into the pathophysiology. Dysfunction of endothelial dependent NO pathways would cause vasoconstriction and hypertension. Five of nine patients with the "acute secondary" form responded to SNP.

In conclusion, childhood EM is rare and almost always idiopathic. It can be severe with associated hypertension. Demarcation between primary and secondary forms in children based on current nomenclature is not clear cut. SNP is probably the treatment of choice.

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ARCHIVIST

Breath nitric oxide concentrations

Exhaled nitric oxide (eNO) concentrations are increased in both children and adults with asthma but whether eNO is a marker of airway inflammation or simply of atopy is debated. Two recent reports suggest the former.

In Belfast (TJ Warke and colleagues. *Thorax* 2002;**57**:383–7) 71 children (median age 9.4 years) were studied during admission for elective surgery. Twenty-nine had asthma, 15 were atopic but did not have asthma, and 27 had neither atopy nor asthma. Exhaled NO was measured using two techniques (tidal breathing and restricted breath) and nonbronchoscopic bronchoalveolar lavage fluid was obtained immediately after induction of anaesthesia. Concentrations of eNO were significantly raised in asthmatic children compared with both control groups combined (24.3 *v* 9.7 parts per billion). The atopic, nonasthmatic group had intermediate concentrations not significantly different from either the asthmatic or the nonasthmatic, nonatopic group. There were significant correlations between eNO concentration and both eosinophil percentage and eosinophilic cationic protein concentration in bronchoalveolar lavage fluid.

In rural new South Wales, Australia (JD Leuppi and colleagues. Ibid: 518–23) eNO and airway responsiveness to histamine were measured in winter and summer in 235 atopic children aged 8–14 years. Raised eNO concentrations were associated with sensitisation to perennial allergens such as house dust mite and *Cladosporium* but not to seasonal allergens such as grass pollen. They also correlated with airway hyperresponsiveness to histamine especially in children with current wheeze. Persistent dry cough was not associated with raised eNO.

Raised eNO concentrations are probably a marker of airway inflammation.