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Case Report

Fabry's Disease: A Rare Cause of Rash and Arthralgia in an Adult Rheumatology Clinic

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Abstract

Fabry's disease is a rare X-linked lysosomal storage disorder associated with potential multiorgan dysfunction. We describe Fabry's disease in an adult patient presenting to the Rheumatology clinic, St John's Hospital, West Lothian, Scotland with "Raynaud's- like" phenomenon, rash and renal impairment.

Introduction

Fabry's Disease is an X- linked lysosomal storage disorder initially described in 1898, caused by α galactosidase A deficiency, usually first manifest with symptoms in childhood. The consequent abnormal accumulation of glycosphingolipids results in several clinical signs and symptoms, and substantial morbidity and mortality. Early treatment with enzyme replacement therapy is key for improvement in major affected organs, and other disabling symptoms.

Case Report

A 35 year old male is referred to the Rheumatology clinic with a 5 year history of episodes of arthralgia affecting hands, feet, and knees, with a "burning" sensation of hands and feet with extension to his groins. Symptoms are triggered by hot or cold weather. There is a long history of diarrhea and skin rash on periumbilical skin (Figure 1), genitalia, and groins. The lesions are occasionally painful and sometimes bleed. His mother and two cousins experience similar symptoms. He is married, a parent, a security guard, smokes 15 cigarettes a day and rarely drinks alcohol.

Examination revealed a petechial rash around the umbilicus, on buttocks, extensor surfaces of legs, digits, genitals, and flanks. No digital ulcers/vasculitic lesions were seen, and rest of system exam was normal.

Haematology and inflammatory markers were normal. Routine biochemistry was normal apart from mild renal impairment (creatinine 132 mmol/l, eGFR 53ml/min). Urinalysis revealed a trace of protein, renal ultrasound was normal and urine protein creatinine ratio 44mg/mmol. Myeloma screen, immunology, Hepatitis B, C, EBV, parvovirus serology and cryoglobulins were negative. Chest X Ray was clear and echocardiogram revealed mild left ventricular hypertrophy.

Skin biopsy was consistent with angiokeratoma and early corneal verticillata were noted on ophthalmology screening. The diagnosis was confirmed by low α galactosidase levels checked at the outset on three occasions: 0.25 nmol/min/mgP, 0 nmol/min/mgP, and 0.17nmol/min/mgP (normal 0.3-1.3 nmol/min/mgP), and a Galactosidase A (GLA) gene mutation. The diagnosis, treatment, and screening for other potential organ complications were discussed with the patient.

Treatment with recombinant human α-GalA infusions fortnightly was commenced in 2011, and is currently congoing with the aim to reduce progression of renal and cardiac disease, and frequency of pain crises. Unfortunately his acroparaesthesia and pain crises persist, however renal and cardiac function remain stable.

Symptomatic management includes analgesia, and anti-diarrhoeal agents. Monitoring includes biochemistry, haematology, urinalysis, echocardiography, audiometry, and ophthalmology review. Family genetic screening was discussed and offered however family members did not engage with this service.

Discussion

Fabry's Disease is an X- linked lysosomal storage disorder initially described in 1898, caused by α galactosidase A deficiency, usually first manifest with symptoms in childhood1. The incidence is estimated at 1/40 000 - 1/117 000 worldwide. Point mutations in the GLA gene are the commonest cause of α galactosidase A deficiency.

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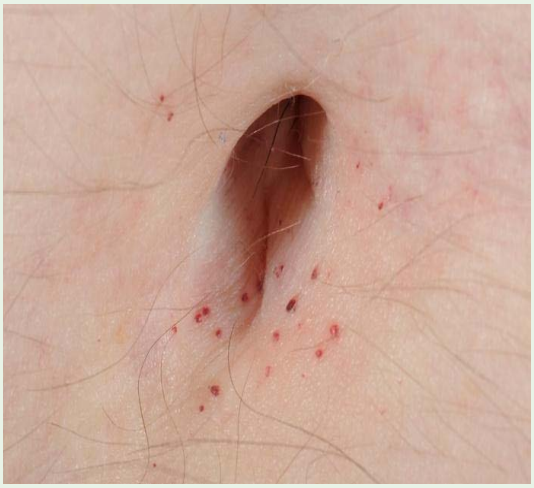

Figure 1: Petechial periumbilical skin lesions.

α galactosidase A deficiency leads to storage of neutral glycosphingolipids, particularly globotriaosylceramide (Gb3) and galactosylceramide, in many tissues and cell types associated with inflammation or fibrosis, or both. The mechanism of tissue damage is possibly due to poor perfusion caused by glycosphingolipids in the vascular endothelium of kidneys, heart, nervous system, and skin [2].

Early symptoms in childhood include burning pain in the hands, and feet, hypohydrosis, nausea, abdominal pain, postprandial diarrhea, poor growth and school difficulties. Average age of onset is 5-6 years in boys, and 9 years in girls. Of note for the Rheumatologist acroparaesthesia is the earliest and most disabling manifestation, typically starting in the hands and feet, triggered by heat, stress, illness, fatigue and exercise.

Renal disease is a major complication and proteinuria is a poor prognostic sign for outcome [3]. Hypertrophic cardiomyopathy is the classic cardiac manifestation as mild diastolic dysfunction in an early stage progressing to systolic and diastolic ventricular dysfunction later [4]. Valve regurgitation and uncontrolled hypertension have also been described.

Strokes and transient ischaemic attacks have been seen with lesions in the white matter, grey matter and posterior circulation [5]. Altered temperature, pinprick, light touch sensation, and neurological hearing loss or tinnitus, may occur. Pulmonary involvement with chronic cough, exertional dyspnoea, wheeze and gastrointestinal disturbance with nausea, vomiting, abdominal pain and diarrhea may occur.

Angiokeratomas are commonly seen at presentation as was the case with our patient (Figure 1). They tend to increase in number and size with age and cluster around the umbilicus and swimming trunk regions. They can be cosmetically disfiguring and bleed with trauma.

Autonomic dysfunction is suggested by hypo/ hyperhydrosis typically affecting the palms of the hands and soles of the feet. Distinctive corneal opacities (cornea verticillata) are seen in most patients, but usually do not interfere with visual acuity.

The diagnosis is made by measuring reduced α-galactosidase A activity in peripheral leucocytes and GLA gene sequencing [6]. Genetic testing for family members is available, and should be pursued. Disease modifying management includes enzyme replacement therapy which has been reported to reduce cardiac mass, frequency of pain crises, and clearance of storage of the protein glycosphingolipids in skin and kidneys [7]. This treatment might not be symptomatically beneficial for all patients. Studies have shown the greatest benefit when treatment is started at an early stage before extensive fibrosis or irreversible tissue damage has occurred. More data are needed to document long term treatment outcomes. As with systemic autoimmune conditions, monitoring and treatment of organ dysfunction is crucial [8].

The prognosis is poor in untreated patients with life threatening complications developing by middle age. The life expectancy in untreated males is reduced by 20yrs from that of the general population of 50yrs with a steep decline in survival after 35yrs [9]. Symptom onset in females is later and life expectancy is reduced by 15yrs [10].

This patient was referred to the Rheumatology service because of suspected Raynaud's phenomenon. A careful history and examination identified atypical musculoskeletal pain, cold painful extremities, poor peripheral circulation, and the unusual rash thought to be of some significance. The unexplained renal impairment in concert with the clinical findings prompted a more extensive search for the aetiology, involving referral to dermatology and renal physicians, thus emphasizing the need for a multidisciplinary approach to diagnosis and subsequent management.

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