Eponyms in medicine revisited

Fabry’s disease: a multidisciplinary disorder

FPJ Peters, A Sommer, A Vermeulen, EC Cherieux, TL Kho

Summary
Fabry’s disease is an X-linked hereditary disorder resulting in accumulation of a glycolipid (galactosylgalactosyl glucosylceramide) due to deficiency of α-galactosidase A. The diagnosis can be made by histopathologic examination of skin biopsy, low activity of α-galactosidase in leukocytes and genetic examination. Treatment is symptomatic. We want to stress the multidisciplinary collaboration necessary to deal with this condition, in order to prevent acceleration of symptoms.

Keywords: Fabry’s disease, corneal opacities, angiokeratoma corporis diffusum, symptomatic treatment

Clinical manifestations of Fabry’s disease

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>cutaneous lesions (telangiectasias)</td>
<td>located at the umbilicus, penis, scrotum, buttocks, hips and thighs</td>
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<tr>
<td>decreased sweating</td>
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<tr>
<td>paresthesias of hands and feet</td>
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<td>burning pain in the extremities</td>
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<tr>
<td>fever</td>
<td></td>
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<tr>
<td>gastrointestinal symptoms</td>
<td>diarrhoea, abdominal pain</td>
</tr>
<tr>
<td>ocular disorders</td>
<td>cornea, retina, lens and conjunctiva</td>
</tr>
<tr>
<td>renal involvement</td>
<td>hypertension, proteinuria</td>
</tr>
<tr>
<td>cardiac symptoms</td>
<td>ischaemia, infarction</td>
</tr>
<tr>
<td>cerebral symptoms</td>
<td>seizures, hemiplegia, aphasia</td>
</tr>
</tbody>
</table>

Box 1

Fabry’s disease was first described independently by two dermatologists, Anderson in England and Fabry in Germany in 1896.1 It is a rare (incidence about 1:40 000) hereditary disorder of glycolipid catabolism resulting from a genetic defect of lysosomal α-galactosidase.4 The disease is X-linked (locus Xq22) and males exhibit the full-blown disorder. Females are asymptomatic carriers or develop mild forms of the disease.

The enzymatic defect results in the systemic accumulation of major glycolipid, trihexosylceramide (galactosylgalactosyl-glucosylceramide) in various tissues including endothelial cells, smooth muscle cells, leucocytes, fibrocytes, nervous system, kidneys and heart. The lipid deposits can result in multiple clinical manifestations such as acroparesthesia, angiokeratoma, corneal opacities, renal involvement and systemic vascular diseases.

Clinical symptoms and signs

Fabry’s disease occurs in childhood or in early adolescence. Clinical onset may be delayed until the second or third decade. In childhood, the diagnosis is suggested before onset of cutaneous lesions when the patient suffers from recurrent fever with pain of the hands and feet (not responding to common pain medication), sometimes misdiagnosed as rheumatic fever or erythromelalgia. The disorder is frequently characterised by pain crises in palms and soles, burning paresthesias, low-grade fever, gastrointestinal complaints, skin lesions, ocular disorders (cornea, lens, retina and conjunctiva) and, with increasing age, cardiac (myocardial ischaemia, myocardial infarction, heart failure, valvular lesions, arrhythmias), cerebral (thrombosis, seizures, hemiplegia, aphasia) and renal involvement (proteinuria, hypertension, elevation of creatinine concentration, disturbances in tubular reabsorption and secretion). The systemic accumulation of lipids can result in signs and symptoms in many other organs.

Diagnosis

The clinical diagnosis is most readily made by observation of the cutaneous lesions and corneal dystrophy. Corneal involvement has been reported in 80% of heterozygotic patients and is often the sole location of the disease.1 The diagnosis can be confirmed by ophthalmologic examination (demonstrating corneal dystrophy by slit lamp microscopy), skin examination (biopsy showing lipid inclusions and capillary dilatation), urine examination (birefringent lipid molecules showing ‘Maltese crosses’), and/or bone marrow aspiration (revealing lipid-containing macrophages). The diagnosis can also be made biochemically by demonstrating a deficiency of α-galactosidase A activity in leucocytes or cultured fibroblasts.5,6

The enzyme assay does not always distinguish between heterozygotes with high residual enzyme activity and normal persons with low enzyme activity. The solution for this problem is a monoclonal antibody against trihexosylceramide, which has recently become available.1,6 Recently, it has also been possible to find a specific mutation in the α-galactosidase gene.6

Pathogenesis

The target lesion in Fabry’s disease is a glycolipid which is deposited in endothelial cells and smooth muscle of blood vessels, arterioles pilorum muscles and heart muscle. The symptoms and signs of the disease are usually induced by narrowing and dilatation of blood vessels causing peripheral ischaemia and/or infarction. Swollen and proliferating endothelial cells cause endothelial instability and angiectasias.

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**Diagnosis of Fabry’s disease**

- biochemically by demonstrating a deficiency of α-galactosidase A activity in leucocytes or cultured fibroblast
- histopathologic examination of skin, bone marrow, showing lipid inclusions and capillary dilatation
- genetically by detecting mutations in the α-galactosidase gene

**Pathogenesis of Fabry’s disease**

- genetic defect of lysosomal enzyme α-galactosidase, leading to deposition of glycolipid in various tissues, leading to clinical manifestations (box 1)

**Treatment of Fabry’s disease: symptomatic**

- multidisciplinary treatment (nephrologist, neurologist, dermatologist, ophthalmologist, cardiologist)
- pain treatment: carbamazepine, phenytoin, low dose morphine
- renal failure: dialysis, renal transplantation
- cutaneous lesions: pulsed dye laser therapy

**Expected outcome**

The treatment of Fabry’s disease is symptomatic. The pain in hands and feet can be treated by carbamazepine, phenytoin or low-dose morphine. Renal failure is treated by dialysis or renal transplantation, with variable success. The

**Case report**

A 25-year-old man, with no other medical history, presented to the dermatologist with a 10-year history of progressive skin lesions located between the umbilicus and knees (hips, back, thighs, buttocks, penis and scrotum) (figure 1). He complained of episodic onset of pain crisis in the extremities which had decreased during the last few years. *Dermatologic examination* revealed a great number of angiectasias. The lesions were slightly raised and did not blanch with diascopy. *Internal examination* showed no abnormalities; there was no hypertension.

*Ophthalmologic examination*, by slit lamp, showed corneal dystrophy (slight corneal opacities, so-called verticillata). *Cardiac examination*: electrocardiography was unremarkable. Echocardiography showed normal systolic function with increased left ventricular mass (129 g/m², normal: 92 g/m²) without asynergy. *Laboratory results*: normal electrolytes, haematologic, liver and kidney functions. Urine sedimentation revealed no leuco- or erythrocyturia. There was no proteinuria. Examination of the urine with polarisation microscopy showed ‘Maltese cross’ material (figure 2).

*Histopathologic examination*: in frozen sections of skin biopsy, dilatation of some superficial capillaries was observed, with slight hyperplasia of the epidermis. On PAS staining, even after exposure to diastase, lipid deposition could be seen in capillary and venous endothelium, in smooth muscles of small vascular walls, in the arrector pilorum muscles and in the epithelium of eccrine glands (figure 3).

*Enzyme examination*: α-galactosidase A activity in leucocytes was 1.7 nmol/mg protein/h (normal 50-150).

The diagnosis morbus Fabry with cutaneous, ophthalmic, and probably heart and renal involvement was made. The cutaneous lesions were treated by pulsed-dye laser therapy. The patient will be followed by the nephrologist, dermatologist, cardiologist and ophthalmologist. He did not show any neurological symptoms and therefore he was not further examined by the neurologist.

**Figure 1** Skin lesion

**Figure 2** Polarisation microscopy of the urine showing ‘Maltese cross’ material

**Figure 3** Skin biopsy. Dilatation of superficial capillary and slight epidermal hyperplasia. Lipid deposition in endothelium and arrector pilorum muscle (frozen section, PAS diastase, ×200)
cutaneous angiectasias can be treated by pulsed-dye laser therapy. The disease is slowly progressive in males, who usually die of renal failure complicated by cardiovascular disease in the fourth or fifth decade. In the future, enzyme substitution and gene therapy may be a therapeutic option.2,4

Usually, as in our patient, the diagnosis can be made by ophthalmologic or cutaneous signs. When the diagnosis is made, it is important to examine for the involvement of other organ systems, as Fabry’s disease is an ophthalmo-neuro-dermato-cardio-nephrologic problem.5 However, recently several cases of an atypical variant of the disease with manifestations limited to the heart have been reported.9

In conclusion, Fabry’s disease is a rare disorder which can be diagnosed histologically, biochemically and genetically. When the diagnosis is made, other organs of the patient should be screened by several specialists to prevent acceleration of symptoms.

Fabry's disease: a multidisciplinary disorder.

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