A man with proteinuria, familial history of kidney disease, painful extremities and cutaneous lesions

A 43-year-old man was referred because of mild proteinuria. Proteinuria was first discovered by systematic urine examination at 17 years of age. During childhood and until age 35, the patient experienced recurrent excruciating pain episodes involving the four extremities, especially after exposure to heat or exercise. His two brothers had the same painful episodes, glomerular proteinuria, and reached end-stage renal disease at 34 and 35 years of age. Both subsequently received a kidney transplant but died of infectious and surgical complications at age 45 and 37 respectively. Their mother, aged 70, suffered intermittent proteinuria without renal failure. Pedigree is shown Figure 1.

On admission, the patient was normotensive. His body weight was 45 kg. He had bilateral inferior leg oedema. Cutaneous lesions mainly located at the bottom area are shown below (Figure 2). These lesions were first noticed during teen age, and progressively increased in number with time. Serum creatinine was 76 μmol/l and creatinine clearance estimated by Cockcroft was 71 ml/min. Proteinuria was 0.63 g/24 h. Urinary sediment showed no erythrocyte casts. His electrocardiogram is shown below (Figure 3).

Questions:

(a) What is your diagnosis?
(b) How do you confirm it?
(c) What are the other early and frequent features of this disease?
(d) What are the main complications that may arise in the future?

Fig. 2. Cutaneous lesions on the patient’s back.

Fig. 3. The patient’s electrocardiogram.

Fig. 1. Pedigree of the family.
Answers to questions on the preceding page

(a) Our patient’s proteinuria was very likely to be related to a familial glomerular disease. The above genealogic tree is compatible with two modes of inheritance of this renal disease: autosomal dominant or recessive X-linked. The moderate renal anomalies in the mother are consistent with both hypotheses, with variable penetrance or anticipation phenomenon in the first case, and heterozygote mild expression due to random X chromosome inactivation in the second case. The main hereditary diseases with glomerular involvement are summarized in Table 1.

The painful episodes are highly suggestive of acroparesthesia. The aspect of the cutaneous lesions and their ‘swimsuit’ location evoke the diagnosis of angio-keratoma. Electrocardiogram suggests left ventricular hypertrophy (Sokolow index = 37 mm) and shows a short PR interval (0.10 msec) without pre-excitation wave. Altogether, the association in this male patient of familial glomerular kidney disease with acroparesthesia, angio-keratoma and left ventricular hypertrophy (LVH) without hypertension is highly suggestive of Fabry disease.

Fabry disease, which was jointly described in 1898 by Anderson and Fabry, is an inborn error of glycosphingolipid catabolism resulting from a deficient activity of the hydrolase β-galactosidase A in tissues and fluids of affected patients. The disorder is transmitted by the X-linked gene encoding β-galactosidase A, localized to the X-chromosomal region Xq22. The enzymatic defect leads to the systemic deposition of glycosphingolipids, predominantly globotriaosylceramide or ceramidetrihexoside. Hemizygous males show symptoms of Fabry disease because of extensive deposition of these glycosphingolipids in body fluids and in the lysosomes of endothelial, perithelial and smooth-muscle cells of blood vessels, while heterozygous women are usually healthy carriers even if in some cases signs and symptoms may appear late in life.

(b) Once suspected, the diagnosis of Fabry disease should be confirmed by a β-galactosidase A determination in leukocytes, which is typically below 10% of normal values in affected males. Searching the molecular lesion may be helpful for genetic counselling, i.e. detection of heterozygous women and prenatal diagnosis. Human β-galactosidase A gene rearrangements, splice-junction defects, and point mutations have been identified, which emphasize the heterogeneity of the molecular lesions causing the disease, which can variably affect the enzyme and support the existence of different phenotypes. When performed (usually in unsuspected or atypical cases) renal biopsy shows typical lesions resulting from glycosphingolipid deposition in the endothelial and epithelial cells of the glomerulus and of Bowman’s space and in the epithelium of Henle’s loop and distal tubule, with a concentric lamellar inclusion pattern on ultrastructural examination.

(c) Many clinical manifestations in hemizygous males with no or low detectable β-galactosidase A activity occur during childhood or adolescence: acroparesthesia (often decreasing with time and responsive to carbamazepine or diphenylhydantoin), angio-keratoma with typical swimsuit distribution, corneal opacities termed ‘cornea verticillata’ (shown in Figure 4), and hypohidrosis. Cornea verticillata does not alter vision. It is highly suggestive of Fabry disease, but may be seen after chronic exposure to chloroquine or amiodarone. Of interest, its frequency is equal in hemizygotes or heterozygotes and is about 70%. Hypohidrosis or anhidrosis often explain intolerance to sportive exercises or fever. In Fabry disease, inferior leg oedema is more often due to lymph node infiltration by glycosphingolipids than proteinuria, which is only infrequently nephrotic, as in our case.

(d) The natural history of kidney involvement in Fabry disease is well known, even if some intrafamilial

Table 1. Main hereditary diseases with glomerular involvement

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance</th>
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<tbody>
<tr>
<td>Alport syndrome (X, AR, AD)</td>
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<tr>
<td>Congenital nephrotic syndrome of Finnish type (AR)</td>
<td></td>
</tr>
<tr>
<td>Nail-patella syndrome (AD)</td>
<td></td>
</tr>
<tr>
<td>Charcot-Marie Tooth syndrome (AD)</td>
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<tr>
<td>Metabolic disorders</td>
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<tr>
<td>Fabry disease (X)</td>
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<tr>
<td>lecithin-cholesterol acyltransferase (LCAT) deficiency (AR)</td>
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<tr>
<td>glycogenosis, type I (AD)</td>
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<tr>
<td>hereditary amyloidosis (AD)</td>
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<tr>
<td>diabetes</td>
<td></td>
</tr>
<tr>
<td>Primitive glomerulopathies, sometimes familial (IgA, collagen III, fibronectin, focal and segmental glomerulosclerosis)</td>
<td></td>
</tr>
</tbody>
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Mode of inheritance is indicated in brackets (X = X-linked, AR = autosomic recessive, AD = autosomic dominant).
Familial history of kidney disease exists, with regards to the age at end-stage renal disease. Proteinuria often appears during adolescence or later; end-stage renal failure is typically reached after the fourth decade. Environmental factors or modifying genes probably explain why, as in the family presented here, patients with the same mutation do not reach end-stage renal disease at the same age.

Cardiac involvement is frequent in Fabry disease, with short PR interval and LVH; extensive glycosphingolipid deposition may explain more severe complications, such as angina pectoris (due to specific endotheliopathy and/or LVH), atrioventricular block, and mitral valve prolapse with valvular insufficiency.

Apart from acroparaesthesia, severe neurological complications may occur. There is an unpredictable risk of stroke in young men, predominantly in the vertebrobasilar territory, often leading to deafness and chronic vertigo. Some patients with Fabry disease suffer from psychiatric disorders. Vascular dementia may occur after multiple stroke episodes. Substitutive enzymatic therapy with 2-galactosidase A may be available in the future to prevent organ damage and complications associated with Fabry disease.

Suggested reading


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