Fabry Nephropathy

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• Fabry disease is a rare X-linked recessive lysosomal storage disease. Multiple mutations of the GLA gene lead to a deficient or absent activity of the lysosomal enzyme α-galactosidase A, resulting in progressive glycoconjugate accumulation in many organs. Low α-galactosidase A activity and mutations in the GLA gene confirm the diagnosis. Clinical signs are multisystemic, heterogeneous, and progressive. Renal, cardiac, and neurovascular involvements are the main life-threatening complications, highlighting the importance of an early initiation of enzyme replacement therapy improving long-term outcome. Fabry nephropathy lesions are characterized by a cell vacuolization of glomeruli, tubules, interstitium, and arteries and by ultrastructural myelin bodies. The main histlogic differential diagnoses are toxicity of lysosomal inhibitors and other renal lipidoses. Renal biopsies are not necessary for diagnosis but have an important role in the evaluation of disease evolution and treatment efficiency, which is a major challenge for improving outcome and quality of life.

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Fabry disease is a panethnic lipidosis first described in 1898 by Johannes Fabry and William Anderson. It is the second most frequent lysosomal storage disease after Gaucher disease. Its incidence rate is estimated at between 1 in 40 000 and 1 in 117 000 births worldwide by the Fabry Outcome Survey, the biggest European Fabry disease database.

PATHOGENESIS

The GLA gene consists of 7 exons situated in position q22.1 on chromosome X, which code α-galactosidase A. This lysosomal enzyme hydrolyzes the glycoconjugates (Gb3) into galactoses and lactosylceramides. More than 475 mutations of GLA gene have been reported, resulting in a deficiency or a lack in α-galactosidase A, which leads to Gb3 lysosomal accumulation in many tissues. Fabry disease follows a recessive X-linked pattern of inheritance. Classically, it affects hemizygous males with no residual α-galactosidase A activity, displaying all the characteristic signs of the disease. Clinical signs and symptoms vary widely in heterozygous females. This phenotypic heterogeneity is due to lyonization, a process whereby one copy of the X-chromosome is randomly inactivated in all the cells of the female embryo, so that heterozygous females are essentially a “mosaic” of normal and mutant cells in varying proportions. Accumulation of Gb3 occurs within lysosomes throughout the body, leading to progressive organ damage resulting in a heterogeneous and multisystemic disease. The delay in diagnosis is estimated at 12 to 15 years.

CLINICAL FEATURES

Disease manifestations appear in childhood, later for girls than for boys. Pain is a frequent sign characterized by intense episodic burning of the soles and hands. Neuropsychiatric symptoms also include acroparaesthesia, hypohidrosis, hearing loss, tinnitus, and vertigo. Angiokeratoma, purple papules on upper thighs and mucosal areas, is a typical but not specific symptom. Classical ophthalmologic signs are cornea verticillata and Fabry cataract. Gastrointestinal symptoms such as abdominal pain and diarrhea might be found. Osteopenia and osteoporosis are more frequent as compared to the general population. A “quiescent stage” of the disease is described in the second to third decade of life. As the disease progresses, renal, cardiovascular, and cerebrovascular complications appear around the age of 30 years. Renal involvement often begins with proteinuria. It seems to be the most important predictor for renal progression. Glycoconjugate deposits, in all renal cell types, lead to gradual deterioration of renal function progressing to end-stage renal disease, requiring hemodialysis or renal transplant in the fourth or fifth decade of life. Cardiac symptoms include dyspnea, angina, arrhythmia, and conduction disorders responsible for syncope and sudden death. It results from myocardial infarction, terminal cardiac failure, and malignant arrhythmias. Transient ischemic attacks and ischemic strokes are the main cerebrovascular complications.

Atypical male variants have a milder phenotype than the “classical” Fabry disease, which is caused by a residual α-galactosidase A activity that varies between 2% and 20% of normal activity, associated with certain types of GLA mutations. Renal or cardiac variants have disease manifestations confined to the kidneys and the heart, respectively, without other systemic involvement. Heterozygous females generally present an asymptomatic clinical form. However, an equally severe form of the disease can occur in females as in males. Random inactivation of 1 chromosome X in the...
cells of various tissues and organs (lyonization) explains the phenotypic heterogeneity in females.6

The European consensus on laboratory diagnostics of Fabry disease recommends the assessment of \( \alpha \)-galactosidase A activity in plasma and leukocytes in males. However, GLA gene molecular analysis is necessary to confirm the diagnosis in heterozygous females because they express highly variable levels of the enzyme owing to lyonization.7

HISTOPATHOLOGY FINDINGS

On light microscopy, glomeruli show a vacuolization of podocytes, mesangial or endothelial cells, and sometimes, glomerular parietal epithelial cells, due to Gb3 inclusions.8,9 Vacuolization is also present in epithelial cells of distal tubules, Henle loops, and collecting ducts. The involvement of proximal tubular epithelial cells is uncommon. Vascular lesions include depositions in myocytes and endothelial cells, sometimes associated with hyaline deposits in the media of arteries and arterioles (Figure 1, A through C). Glycortiaosylceramide accumulation leads to procoagulant and proinflammatory effects, resulting in focal, segmental, and global glomerulosclerosis, interstitial fibrosis, tubular atrophy, and thickening of vascular walls.10

With progression of the disease, there is fusion of podocyte foot processes in association with increasing proteinuria. A decrease in endothelial fenestration and a duplication of the glomerular basement membrane have been reported.11,12 Characteristic cytoplasmic deposits of Gb3 are removed during routine paraffin processing. On frozen sections, Gb3 can be demonstrated with several approaches, including staining with periodic acid–Schiff, Hale, Luxol fast blue, Oil red O, and Sudan black. On light microscopy, a good morphologic method to demonstrate Fabry deposits is to use tissues fixed in glutaraldehyde, embedded in Epon, and stained with toluidine blue dye, which yields dark blue cytoplasmic inclusions in glomeruli, tubules, and arteries (Figure 2, A through D).

ANCILLARY STUDIES

Immunofluorescence is not contributory, showing no specific deposits. However, this technique is useful to eliminate more common renal diseases causing proteinuria (such as immunoglobulin A nephropathy and type I membranous glomerulonephritis), especially in cases of Fabry disease at early stages presenting an isolated proteinuria. Under polarized light, inclusions exhibit birefringence and orange autofluorescence on tissues stained with hematoxylin-eosin-saffron.

Ultrastructural analysis shows intracellular osmiophilic, lamellated membrane structures with a concentric pattern called myelin bodies or with elongated stripes called zebra bodies. The periodicity of the lamellated membrane structures is estimated to be 4 to 5 nm on routine thin sections and 14 to 15 nm on frozen sections, owing to better tissue preservation. They have the same topography as on light microscopy (Figure 2, A through D).

DIFFERENTIAL DIAGNOSES

The main histologic differential diagnoses are other nephropathies with foamy podocytes, such as lysosomal inhibitor toxicity and other renal lipidoses (GM1 gangliosidosis, 1-cell disease, Hurler syndrome, Niemann-Pick disease, Faber disease, and infantile nephrosialidosis).13,14 Ultrastructural morphology and cellular distribution of

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Figure 1. Fabry nephropathy on light microscopy. A, Cytoplasm of podocytes appears expanded, foamy, pale, and lacy owing to lipid deposits. B, Vacuolization of distal tubular epithelial cells. C, Hyaline deposits (arrow) in the media of an artery (hematoxylin-eosin-saffron, original magnification ×200 [A]; Masson trichrome, original magnification ×400 [B]; periodic acid–Schiff, original magnification ×200 [C]).
lysosomal storage material are the most useful criteria to differentiate Fabry disease from its mimics (Table). Indeed, no other renal lipidosis shows prominent and widespread myelin bodies in podocytes, mesangial cells, endothelial cells, proximal tubules, interstitial cells, and arterial endothelial cells.

For example, curvilinear and granular osmiophilic deposits found in Batten disease and the membrane-bound vacuoles containing fibrillogranular material in Hurler syndrome have a completely different aspect from Fabry myelin bodies. Moreover, Niemann-Pick disease can show myelin-like figures, but they are absent from mesangial cells and arterial cells contrary to Fabry disease.

The main alternative diagnostic consideration is iatrogenic renal lipidosis, which has ultrastructural morphologic features not distinguishable from Fabry myelin bodies. Iatrogenic renal lipidoses have been reported in association with different lysosomal inhibitors (chloroquine, hydroxychloroquine, amiodarone), which inhibit lysosomal enzyme α-galactosidase A. Because of the inability to distinguish genetic and iatrogenic conditions based on morphologic grounds alone, a diagnosis of Fabry disease must be confirmed by the demonstration of decreased α-galactosidase A activity and/or a mutation in the GLA gene. Therefore, myelin-like inclusions are not entirely specific for Fabry disease, although they are highly characteristic. Certain drugs can cause cellular injury indistinguishable from classic Fabry disease. This needs to be kept in mind in the evaluation of typical pathologic lesions in case of history of exposure to lysosomal inhibitors.

**CURRENT TREATMENT**

Since 2001, Fabry disease treatment has been revolutionized by the introduction of an intravenous enzyme replacement therapy (ERT) using recombinant human α-galactosidase A. In Europe, there are currently 2 commercially available enzyme preparations. Agalsidase alpha (Replagal, Shire, Cambridge, Massachusetts) is infused at a dose of 0.2 mg/kg every 2 weeks. Agalsidase beta (Fabrazyme, Genzyme Corporation, Cambridge, Massachusetts) is used at a dose of 1 mg/kg every 2 weeks. The safety and efficiency of both enzymes have been assessed in

Figure 2. Fabry nephropathy on toluidine blue–stained semithin sections and by electron microscopy (frozen tissues). A, Dense, dark blue granules in the cytoplasm of distal tubular epithelial cells. B, Myelin bodies in a distal tubule. C, Glycoglycerophospholipids in the cytoplasm of endothelial cells (red arrow) and myocytes (blue arrow). D, Zebra bodies in an arteriole (toluidine blue, original magnifications ×400 [A] and ×1000 [C]; electron micrograph, original magnifications ×1700 [B] and ×3597 [B]). Courtesy of Viviane Gnemmi, MD (CHRU de Lille, France).
| Pathologic Entity | Podocyte | Mesangial Cell | Endothelial Cell | Proximal Tubule | Distal Tubule | Henle Loop | Interstitium | Artery |
|-------------------|----------|----------------|------------------|----------------|--------------|------------|-------------|--------|
| Fabry disease     | +        | +              | +                | +              | +            | +          |             |        |
| Chloroquine       | +        | +              | +                | +              | +            | +          |             |        |
| toxicity          |          |                |                  |                |              |            |             |        |
| GM1 gangliosidosis| +        | +              | +                | +              | +            |            |             |        |
| I-cell disease    | +        | --/+           |                  | --/+           |             |            |             |        |
| Hurler syndrome   | +        | --/+           |                  | +              | +            |            |             |        |
| Niemann-Pick       | +        | +              | +                | +              | +            |            |             |        |
| disease            |          |                |                  |                |              |            |             |        |
| Farber disease    | +        |                |                  | +              |             |            |             |        |
| Infantile          | +        | +              | +                | +              | +            |            |             |        |
| nephrosialidosis  |          |                |                  |                |              |            |             |        |
| Gaucher disease   |          |                |                  |                | +            |            |             |        |
| LCAT deficiency   | +        | +              | --/+             | --/+           |             |            |             |        |
| Metachromatic      | --/+     | +              | +                |                | +            |            |             |        |
| leukodystrophy    |          |                |                  |                |              |            |             |        |
| Batten disease    | --/+     |                |                  | +              | +            |            |             |        |
| Sandhoff disease  |          |                |                  |                |             |            |             |        |
| Refsum disease    | --/+     |                |                  | +              | +            |            |             |        |
| Wolman disease    |          |                |                  | +              | --/+         |            |             |        |

Electron Microscopy
- Osmiophilic, lamellated membrane structures with a concentric pattern (myelin bodies) or with elongated stripes (zebra bodies); diameter: 0.3–10 μm; lamellar periodicity: 4–15 nm
- Myelin-like lamellated bodies, curvilinear bodies
- Membrane-bound empty vacuoles occasionally containing stacks or concentric lamellar material (periodicity: 25–75 nm)
- Membrane-bound empty vacuoles occasionally containing fibrillogranular or lamellar material (residual membranous structures)
- Osmiophilic granules and bundles of curvilinear structures (periodicity: 12–33 nm)
- Membrane-bound, almost empty vacuoles containing occasional granular and electron-dense material
- Membrane-bound packets of lipid material arranged in microtubules (diameter: 50–80 nm)
- Heterogeneous lipid deposits (partly electron lucent, partly osmiophilic), curvilinear and granular debris in epimembranous, intramembranous, subendothelial, and mesangial locations
- Stacked lamellar disks (6–8 nm) in honeycomb or parallel array
- Membrane-bound, rectilinear, curvilinear, or granular cytoplasmic inclusions, granular osmiophilic deposits
- Electron-dense, finely granular or lamellated bodies arranged in concentric or parallel stacks
- Perinuclear cytoplasmic vacuoles and membrane-bound vesicles (glomerular, tubular epithelial cells), crystalloid, quadrangular, microtubular inclusions (400 Å) (distal tubules, loop of Henle)
- Cholesterol clefts and neutral lipids (dropletlike structures)

Abbreviations: LCAT, lecithin cholesterol acyltransferase; +, presence of stored material; --/+, stored material rarely present.

a Empty entries denote absence of stored material.
randomized, double-blind, placebo-controlled trials. Therapeutic management of Fabry disease is multidisciplinary, including specific treatment with ERT, symptomatic and prophylactic therapy. Histologically, there is a total clearance of Gb3 lysosomal accumulation in endothelial and mesangial cells after 11 months of ERT by agalsidase alpha or beta. Posttherapeutic effects on myocyte inclusions are more moderate. The reduction of Gb3 in podocytes and tubular epithelial cells is milder than in other cells. The podocyte clearance is correlated with the cumulative dose of agalsidase. This observation is another argument for early ERT introduction to improve symptomatology, quality of life, and prognosis.

The International Study Group of Fabry Nephropathy scored histologic changes on light microscopy and toluidine blue–stained semithin sections. The score quantifies Gb3 density deposition (mild, moderate, and severe) in glomeruli, interstitium, and vessels and progressive lesions (glomerulosclerosis, ischemic glomeruli, and tubulointerstitial fibrosis). Some studies have underlined the role of kidney biopsies for the follow-up of the disease evolution to identify the presence of significant histologic changes before the decrease of renal function.

**PROGNOSIS**

Cardiac morbimortality is the primary cause of death in Fabry disease. Average life expectancy is approximately 50 years in males and 70 years in females.

**CONCLUSIONS**

Fabry disease is a lysosomal storage disease involving many organs. Clinical symptoms are heterogeneous and aspecific. The diagnosis is established by a low α-galactosidase A activity and the identification of a mutation in the GLA gene. Histologically, renal involvement is characterized by vacuolization in glomerular cells, tubular epithelial cells, and vascular cells. Toluidine blue is particularly useful to reveal Gb3 deposits and electron microscopy examination shows myelin or zebra bodies. The progression of kidney disease is characterized by segmental and global glomerulosclerosis, tubular atrophy, and interstitial fibrosis. Histologic evidence is not needed for the diagnosis of Fabry disease. However, renal biopsy is an important tool to evaluate the renal progression of the disease and the efficiency of ERT.

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