Renal Involvement in Fabry’s Disease

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Fabry’s disease is a sphingolipid storage disorder which is caused by mutations within the gene responsible for the expression of the lysosomal hydrolase, α-galactosidase A (1). The enzyme defect results in the progressive deposition of uncleaved glycosphingolipids within lysosomes of endothelial, peritheatial and smooth muscle cells. The major clinical features may be divided into cutaneous lesions (angiokeratoma), ophthalmological abnormalities (corneal dystrophy), neurological abnormalities, cardiovascular diseases and renal involvement.

A variety of techniques allowed the structural gene responsible for production of mature α-galactosidase A to be localized to the middle of the long arm of the X chromosome, Xq22 (2). Point mutation within the gene, and partial or complete gene deletions, result in the classical phenotypic expression of the disease. No immunologically detectable or catalytically active enzyme protein is found in these patients. Elucidation of the genomic structure of the α-galactosidase A gene and its organization have facilitated the investigation of the molecular lesions producing these defects. Since most of α-galactosidase A gene mutations have been "private" occurring only in single pedigrees, the accurate identification of specific molecular defects in individual families would be impractical and may not be necessary.

The unifying abnormality in all affected tissues is the accumulation of intracellular glycosphingolipid. The most striking renal changes are present in glomeruli, although tubules and blood vessels are also abnormal. Glomerular visceral epithelial cells are enlarged and vacuolated. The vacuoles generally are small and uniform and impart a “honeycomb” appearance to these cells (3—5).

The vacuoles can be rarely identified in parietal epithelial, mesangial or endothelial cells. In early or less severely affected patients, there may be no other glomerular abnormalities. With progressive renal failure, however, segmental and global glomerulosclerosis evolve. The vacuolated cells still can be identified in sclerotic glomeruli and may offer a clue to diagnosis in the patient with advanced renal disease who undergoes renal biopsy. Similar vacuolated cells are also present in tubules, with the distal convoluted segment and the loop of Henle affected most prominently. The cells of proximal tubules are affected infrequently. Arteries and arterioles contain vacuolated cells in abundant quantities. The cells are enlarged and appear as form cells. Smooth muscle cells of the media contain both large and small vacuoles.

Routine immunofluorescence microscopy is typically negative, except in glomeruli with advanced lesions, such as segmental sclerosis. In these instances, IgM, C3 and C1q may be present in capillary walls and mesangial regions in a segmental distribution and granular pattern. Electronically, osmiophilic inclusions are always present in lysosomes and are surrounded by a single membrane, although larger inclusions may be rarely found in the cytoplasm (6). The inclusions which range from 0.3 to 10 μm in diameter, are round and composed of concentric whorls of dense layers, imparting an onion skin appearance, as Shirai and colleagues described (5). This fine structure is considered to be characteristic of stored glycolipids.

Renal dysfunction often presents with mild proteinuria (0.5 to 2.0 g/24h), usually beginning during the third decade of life. Uremia and hypertension develop most commonly in the fourth and fifth decades (7). Renal failure is most common in hemizygotes, but heterozygotes with end-stage renal disease are not rare. Nephrotic range proteinuria is unusual. In the absence of proteinuria, oral fat body on examination with bright field microscopy suggests the possibility of the presence of a lipid storage disease. Mild microhemaeturia has been reported.

The diagnosis of Fabry’s disease may be made on the basis of clinical features of the disease and changes seen on slit-lamp ophthalmoscopy, with confirmation by the demonstration of absent or low residual α-galactosidase A activity in peripheral blood leukocytes or cultured fibroblasts. Most female carriers of the disease are asymptomatic and their identification may be unreliable. The light microscopic lesions of vacuolated glomerular visceral and tubular epithelial cells are nonspecific but suggest a storage process. The finding of urinary myelin bodies or within lysosome in renal tubular cells would be helpful for the diagnosis.

Until dialysis and transplantation became available, there was no specific treatment for this condition and the average age at death caused by uremia was 42 years. With renal replacement therapy mortality from cerebrovascular and cardiovascular involvement is now more common. There are no effective ways to delay the progression of renal or cardiovascular disease, but the early instigation of antihypertensive therapy is advocated. Since deposition of sphingolipid in the vascular endothelium may activate platelets, contributing to embolic or thrombotic cerebrovascular events, the early use of antiplatelet agents such as aspirin would seem rational. Enzyme replace-
ment therapy using human plasma or purified α-galactosidase has been explored (8, 9). Such treatment remains experimental. The large scale production of the enzyme using a genetic method would potentiate the development of trials to evaluate short- and long-term clinical benefits of enzyme replacement therapy.

The main indication for renal transplantation in Fabry's disease is as for renal failure. It has also been undertaken in an attempt to determine whether the transplant could provide sufficient normal enzyme for substrate metabolism, either within the kidney or by release of enzyme into the circulation (10). Symptomatic improvement has been observed. Recurrent deposition of glycosphingolipid within renal allograft has not been reported, although reaccumulation is slow and often minimal (11). Early diagnosis would prevent much personal distress and facilitate referral for genetic counseling.

Seiya Okuda, MD
The Third Department of Internal Medicine,
Kurume University School of Medicine,
Asahi-machi 67, Kurume, Fukuoka 830-0011

References