Anderson–Fabry disease: Clinical manifestations of disease in female heterozygotes

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Summary: Anderson–Fabry disease is a rare, X-chromosomal lipid storage disorder caused by a deficiency of lysosomal α-galactosidase A. Clinical manifestations of Anderson–Fabry disease include excruciating pain in the extremities (acroparaesthesia), skin vessel ectasia (angiokeratoma), corneal and lenticular opacity, cardiovascular disease, stroke and renal failure, only renal failure being a frequent cause of death. Heterozygote female carriers have often been reported as being asymptomatic or having an attenuated form of the disease. To evaluate the spectrum of clinical signs in heterozygotes, a comprehensive clinical examination was performed on 20 carriers of Anderson–Fabry disease. This revealed that, in addition to the skin manifestation, various other clinical manifestations of the disease are present, including acroparaesthesia, kidney dysfunction, cerebrovascular disease, and gastrointestinal and heart problems. It therefore appears that Anderson–Fabry disease affects both hemizygotes and heterozygotes and therefore should be considered to be an X-linked dominant disease.

Anderson–Fabry disease (McKusick 301500) is an X-linked disorder resulting from a deficiency of the lysosomal hydrolase α-galactosidase A (α-D-galactoside galactohydrolase, EC 3.2.1.22; α-Gal A). The enzyme is responsible for the hydrolysis of terminal α-galactosyl residues from glycolipids and glycoproteins. The gene (GALA) encoding α-Gal A maps to Xq22.11 (Vetrie et al 1993). Deficiency
of enzyme activity leads to progressive accumulation of glycosphingolipids (predominantly globotriaosylceramide) in different tissues, particularly in the skin, kidneys, nervous system, eyes and heart. In patients with Anderson–Fabry disease, acroparaesthesia, hypohidrosis, corneal opacity and dysfunction of various organs (kidney, brain, heart) are the leading symptoms. There are few reports describing the clinical manifestations of the disease in carriers. A systematic clinical investigation was therefore performed in 20 heterozygotes in order to evaluate the spectrum of symptoms in carriers of Anderson–Fabry disease.

PATIENTS AND METHODS

Clinical assessment: Clinical manifestations of Anderson–Fabry disease, such as angiookeroma, acroparaesthesia, sweating abnormalities, corneal opacity, kidney dysfunction and cerebrovascular damage were assessed in 20 carriers from 13 families. In addition to general clinical assessments, ophthalmological examination, echocardiography and ECG were carried out. In four probands, magnetic resonance tomography studies of the brain were performed. The ages of probands ranged from 12 to 65 years (mean 38 years).

Molecular genetic studies: In each family, mutation analysis was performed on the index case and on all female relatives for which pedigree analysis did not provide evidence of carrier status. Genomic DNA was extracted from whole blood by a standard method. For polymerase chain reaction amplification and direct sequencing of all exons of the GALA gene, oligonucleotide primers were designed based on the published genomic sequence (Bishop et al 1988; primer sequences are freely available on request). Single-strand conformation polymorphism (SSCP) analysis of all seven exons was performed as described previously (Bunge et al 1996). Each amplified exon was screened under at least two different SSCP conditions, in which the concentration of glycerol (0 or 10% v/v) and the run temperature (4 or 20°C) were varied.

RESULTS

Gene analysis was usually performed on the male patients and revealed a total of 11 different GALA mutations, four of them novel (Table 1). The majority (63%) of the gene alterations identified in the 13 families were point mutations. In four cases, a deletion of one or more nucleotides was detected. Half of the mutations (stop codons, mutations affecting splicing, and small rearrangements) predicted complete loss of enzyme activity due to functional null alleles.

As often seen in affected males, recurrent burning sensations in the extremities were also the first symptoms of Anderson–Fabry disease in carriers. They were reported either as chronic pain or as so-called Fabry crises, characterized by very severe, painful attacks. The excruciating sensation in the hands and feet often leads to misdiagnoses, such as rheumatoid arthritis or multiple sclerosis. The mean age of onset of acroparaesthesia was 10 years (range 4–23 years), whereas, in a group