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Fabry disease with special reference to neurological manifestations

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Abstract: Fabry's disease is an X-linked recessive Lysosomal Storage disease. The underlying metabolic defect is deficiency of lysosomal enzyme ceramidetrihexosidase. The disease has multisystem involvement. Neurological manifestations include small-fiber polyneuropathy manifested as painful distal extremities and anhidrosis. Fabry's disease also presents with both small-vessel and cortical multiple cerebral infarcts. Enzyme-replacement therapy has been found effective but expensive. Gene therapy could evolve as the ultimate therapeutic strategy.

Key Words:
Fabry's disease, Polyneuropathy, Stroke, Therapy.

Preamble

Fabry Disease (FD) is a rare inherited metabolic disorder with involvement of skin, kidney, heart, blood vessels and nervous system. The original[1] description of this disease was given by W. Anderson, a dermatologist in 1898 on a patient with unusual cutaneous abnormality and concomitant proteinuria. Around the same time, J. Fabry reported a similar case[2]. The two clinicians coined the term "angiokeratoma corporis diffusum". In time, the generalized nature of this disease was more clearly recognized[3]. Sweeley and Kliosky[4] initially and then later Roscoe Brady[5] elucidated the pathophysiology and nature of the underlying metabolic lesion. Fabry disease falls under the rubric of "Lysosomal Storage disease".

What is a Lysosomal Storage disease?

In health, a wide range of complex intracellular and extracellular substances, namely lipids, glycoproteins, mucopolysaccharides and glycogen, undergo intracellular degradation into simpler substances in order to be reutilized by cells. This degradation occurs in the subcellular membrane bound particles called "lysosomes" with the help of enzymes, the acid hydrolases. In those disorders called Lysosomal Storage diseases, there are deficiencies of the above enzymatic activities leading to abnormal substrate accumulation in lysosomes with consequent cell damage. According to the nature of substrate accumulated, the Lysosomal Storage diseases[6] are classified (Table I).

Pathology and biochemistry

In FD, ceramidetrihexoside (globotriaosylceramide) is the abnormal lysosomal lipid accumulated; the underlying deficient enzyme is ceramidetrihexosidase (α-galactosidase A), which is required to cleave the terminal galactose from the accumulated ceramidetrihexoside[5]. The principal source of ceramidetrihexoside is globoside present in the erythrocytic stroma. When red cells become senescent, reticuloendothelial cells in liver and spleen phagocytose the cells and degrade the globoside to yield ceramidetrihexoside. When ceramidetrihexosidase is deficient, the lipid ceramidetrihexoside is deposited excessively and being soluble is transported via blood stream from liver and spleen to be deposited in the various organs of the body.

Table I. Classification of Lysosomal Storage diseases.

	Types	Substrate	Examples
I.	Sphingolipidoses	Sphingolipid	Tay-Sachs, Gaucher, Fabry, Sandhoff, Niemann-Pick, Krabbe, Metachromatic Leucodystrophy
II.	Lipogranulomatosis	Lipoglycoprotein	Farber disease
III.	Mucopolysaccharidoses	Mucopolysaccharide	Hurler, Hunter, Scheie, Sanfilipo, Morquio, Maroteaux-Lamy
IV.	Mucolipidoses	Acidmucopolysaccharide	Mucolipidosis I, II, III, IV
V.	Glycoproteinoses	Oligosaccharide Glycoprotein	Fucosidosis, mannosidosis Sialidosis

Ceramidetrihexoside is found mainly in the vascular elements, particularly in the endothelial, perithelial and smooth muscle cells of the arterial system. Also the histiocytes of reticuloendothelial system and the cells of cardiac muscle, renal tubules and sweat glands have excess accumulation of the glycolipid. Abnormal storage of glycolipid is also noted in the neurons and ganglion cells of central nervous system and in the ganglion cells of the peripheral somatic and the sympathetic nerves.

Clinical manifestations

FD is a multisystem disorder. Being X-linked recessive, the mother needs to be the carrier for the affected hemizygous male child. Fabry heterozygous female may also have manifestation of the disease to a varying degree.

Cutaneous manifestations

Widespread cutaneous angiokeratoma is the hallmark of the disease (Figure 1), and hence other name for this disorder is angiokeratoma corporis diffusum. Angiokeratoma are telangiectasia of the epidermis associated with proliferation of keratin and epidermal cells. These lesions are located over the lower trunk, buttocks, perineum, scrotum and upper thighs[7,8].

Renal manifestations

Initially there is albuminuria and inability to concentrate urine. Later in the course of the illness chronic renal failure prevails. Nephropathy is the major cause of mortality and death usually occurs in the mid to late forties.

Cardiac manifestations

Myocardial infarction at an early age and hypertension are also the principal complications of FD. In addition, there may be progressive hypertrophic/ infiltrative cardiomyopathy, valvular abnormalities, arrhythmias and conduction disturbances[9].

Chronic airway obstruction

Chronic airway obstruction may occur because of lipid accumulation in the alveolar lining cell of lung parenchyma[10].

Ocular manifestations

The ocular changes typically do not impair vision, but are unique and diagnostic. Whorl-like corneal deposits are seen in almost all patients. The lens shows cream-colored anterior capsular deposits, sometimes in striking "propeller" distribution. A faint but unique posterior capsular opacity with a branching radial pattern, aneurismal dilations of conjunctival vessel and retinal vascular tortuosity are seen. Unilateral blindness may rarely occur as a result of central retinal artery occlusion[11].

Neurological manifestations

A wide range of neurological disturbances is seen in FD.

– Pain and burning sensation of hands and feet in children and young adults is one of the cardinal features of this disease[6]. The pain aggravates with change in temperature and exertion and may become intense at times making the patient wheel chair bound. This phenomenon is called "Fabry crisis". Clinically, reduced pinprick

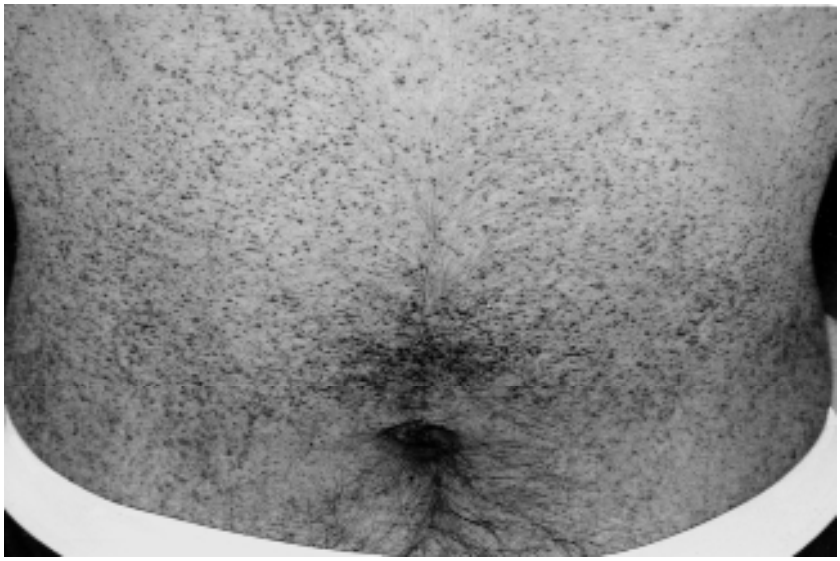

Figure 1. Typical cutaneous angiokeratoma in a patient of Fabry disease.

sensation in stocking distribution is noted but the strength of the distal extremities, deep tendon reflexes and the other modalities of sensations are intact with absence of tactile allodynia. The conventional nerve conduction studies are usually normal. Quantitative sensory testing (QST) performed on FD patients showed intact vibration threshold, but impaired thermal threshold in distal extremities[12]. The cold sensory threshold was more abnormal than warm detection threshold[12,13]. The result signified "length-dependant small fiber polyneuropathy" affecting principally the small myelinated A-delta fibers and to some extent the unmyelinated C-fibers[14]. This preferential involvement of small fibers with intact large myelinated nerve fibers, confirmed by sural nerve biopsy and also by means of nerve quantification in skin biopsy specimens[15], is an unique feature of FD. The exact mechanism is still unknown[6]. Although the exact mechanism for neuropathy in FD is still unknown[6], deposition of abnormal glycolipid in dorsal root ganglia is probably the cause. Large fiber neuropathy is encountered in FD when there is complicated renal failure with additional uremic polyneuropathy. Increased incidence of carpal tunnel syndrome is also noted in FD[13].

– Hypohidrosis/anhidrosis is a universal complaint in patients with FD. Lack of sweating may be because of central autonomic dysfunction[16], peripheral dysautonomia[17] or due to primary sweat gland disorder[17]. Preservation of sympathetic skin response (SSR) in the majority of patients suggested that the sudomotor sympathetic fibers were largely intact and hyperhidrosis was due to primary sweat gland disorder[13]. In fact, the eccrine sweat glands and the surrounding blood vessels had abnormal deposition of glycolipids[18].
– Autonomic dysfunction is evident in FD not only by impaired sweating mentioned above, but also by gastrointestinal symptoms. Gastric stasis manifested as easy satiety and intestinal stasis with bacterial overgrowth manifested as diarrhea were demonstrated[19]. In 50% of FD cases, there were impaired pupillary constriction to pilocarpine, reduced salivation and lacrimation[16]. In all cases, the cutaneous flare response to scratch and intradermal histamine was diminished. Pruritus was not experienced[16].
– Other types of peripheral neuropathy: symptomatic auditory nerve impairments do occur, although rare. However, investigations frequently showed peripheral auditory and vestibular dysfunctions[20].
– Cerebrovascular manifestations: cerebral infarcts are common complications in FD. The glycolipid is stored in vascular endothelial, perithelial and smooth muscle

cells. This results in vasculopathy and leads to ischemic stroke typically occurring in the late fourth through early sixth decades of life[21,22] (Figure 2).

A careful study of 50 hemizygous Fabry cases with serial cerebral MRI showed that there was progressively increasing burden of cerebrovascular ischemic changes with age[23]. On T2-weighted MRI, 32% had no lesion (mean age, 33 years); 16% had gray matter ischemic lesions only (mean age, 36 years); 26% had lesions in white matter only (mean age, 43 years) and 26% had lesions in both gray and white matter (mean age, 47 years). No patient younger than 26 years had ischemic lesions on MRI whereas all patients over the age of 54 years had cerebrovascular involvement. Typically, the small vessels were involved first, but at a later age the large vessels also got affected and cortical infarcts set in[23]. The cortical lesions usually occurred in the vertebrobasilar territory and this could be explained by thromboembolism from ecstatic vertebrobasilar arteries[24]. Recent investigations revealed that there was no structural narrowing of fibromuscular blood vessels in FD. Instead it was likely that functional abnormality in the downstream conductance vessels was the cause for Fabry vasculopathy[25].

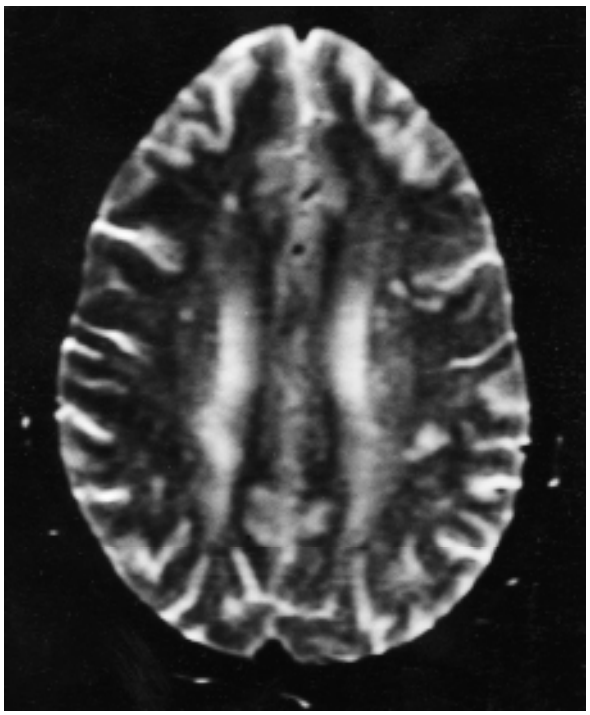

Figure 2. Cerebral MRI of a young Fabry patient showing multiple sub cortical small vessel infarcts.

– Cognitive decline and epilepsy may be seen in the older FD cases, directly related to cerebrovascular disease. Glycolipid accumulation, however, takes place in the selected neuronal cells of spinal cord, brainstem, amygdala, hypothalamus and cerebral cortex, but neuronal glycolipid storage is asymptomatic. Nevertheless, cerebral proton magnetic resonance spectroscopy demonstrated widespread cortical and sub cortical N-acetylaspartate reduction signifying sub clinical diffuse neuronal dysfunction in FD[26].

Investigations

To establish the diagnosis of FD, diminished enzymatic activity of α-galactosidase A in washed leukocyte preparation or in cultured fibroblast is to be demonstrated[27,28]. Determination of reduced enzymatic activity in the above tissue samples is also helpful to diagnose heterozygous females; but if this result is equivocal, hair follicles may be used instead as the tissue source[29]. FD can be diagnosed prenatally by assaying α-galactosidase activity in the cultured amniotic cells[27].

Treatment

Phenytoin and carbamazepine are useful to obtain some relief from peripheral neuropathic pain and paresthesia, but this response has not been universal. Most of the FD patients require repeated hemodialysis because of renal dysfunction as they reach their forties. Renal transplantation helped in several patients in renal failure[30]. Also, many of the FD cases had relief from neuropathic pain with partial restoration of sweating while the implanted kidney was functioning. The underlying mechanism is unclear. It appears that there is reduction in ceramidetrihexoside in the circulation soon after operation, but this usually returns to the preoperative state.

Enzyme replacement therapy for Lysosomal Storage diseases – the new frontier in therapeutics

Way back in the sixties when the various enzyme deficiencies as causes of different Lysosomal Storage diseases were being discovered, Dr Roscoe Brady of N.I.H. proposed "Enzyme Replacement Therapy" as a therapeutic option[31]. During that time, glucocerebrosidase, the enzyme deficient in Gaucher disease, was purified from placental extract and infused in this above disorder; this resulted in reduction of abnormally accumulated hepatic glucocerebroside but the result was inconsistent[32]. Subsequently it was learnt that macrophages have a lectin on the surface that has a high affinity for mannose-terminated glycoconjugates[33]. The glucocerebroside enzyme of Gaucher disease was later modified into a mannose-terminated one to make it more effectively targeted to macrophages than had been possible with the previous native enzyme[34]. Consequently, in non-neuropathic Gaucher disease or Gaucher disease type 1, this mannose-terminated glucocerebrosidase infusion lead to a dramatic improvement in clinical deficits[35,36]. The success in the above therapy paved the path for pursuing enzyme replacement in the treatment of the other lysosomal disorders, namely, Fabry disease, Pompe disease, Morquio disease and Hunter disease.

A spate of clinical trials demonstrated that enzyme replacement with alpha-galactosidase A (α-Gal A) offered promise as an effective treatment for FD[37,38]. This therapeutic approach with α-Gal A at a dosage of 0.2 mg/kg administered intravenously every other week showed to be well tolerated and effective in reducing levels of the stored globotriaosylceramide and in normalizing many of the debilitating manifestations of the disorder. A double-blind placebo-controlled trial in 26 hemizygous male patients showed that agalsidase alfa (human α-Gal A) significantly reduced neuropathic pain (p = 0.02), increased creatinine clearance (p = 0.02), improved glomerular histology, reduced the QRS interval on ECG and increased weight gain. Positron emission tomography also revealed normalization of the cerebrovascular flow. After the 6-month controlled period, all patients had a reduction in neuropathic pain, and there was a significant improvement in their ability to sense heat and cold. Besides, the renal function stabilized in those with renal insufficiency at the beginning of treatment. There were normalizations of sweating and improvement in the level of energy and sense of well-being. Enzyme replacement therapy is now an accepted mode of treatment in many western countries. Currently, two types of α-Gal A are commercially available for treatment of FD, namely, Fabrazyme (agalsidase beta) and Replagal (agalsidase alpha)[39].

The future prospects

Enzyme replacement therapy is now the accepted definitive treatment for Lysosomal Storage disease. But the enormous expense of this therapy for Gaucher disease and Fabry disease – several hundred thousand dollars per patient per year – prompted a task force to conclude, "despite the success of enzyme therapy, treatment is limited by the cost of the agent"[40].

Therefore alternative therapeutic strategies are now being seriously considered and these are as follows:

1. The deficient enzymatic activity of FD is enhanced by increasing its stability with "chemical chaperones", namely, l-deoxygalactonojirimycin and galactose that bind to the active sites. For example, the cardiac variant of FD has only cardiac dysfunction but the other systems are spared. This has mutation in the α-galactosidase A gene that encoded sufficient residual enzymatic activity to preclude the classic phenotype. Here galactose acts as a "chemical chaperone" to enhance the stability of the mutant enzyme. A study showed that patients with cardiac variant of FD received galactose infusions alternate day for two years. The infusion was well tolerated and there was improvement in cardiac contractility, reduction of ventricular wall thickness and also reduction of cardiac mass after three months of treatment[40].
2. Administration of selective glucosylceramide synthase inhibitors, 4′-hydroxy-P4 and ethelenedioxy-P4, are highly effective in the depletion of the substrate globotriaosylceramide from Fabry cell lines and these compounds have the potential therapeutic utility in FD[41,42].

3. The enzyme may be delivered by genes, as in vector-mediated gene therapy[40]. Gene therapy has a strong potential to be the principal therapy in FD in future. By gene targeting, α-Gal A deficient mice (knock-out Fabry mice) were generated that displayed a complete lack of alpha-Gal A activity[43]. A recombinant adeno-associated viral vector encoding human α-Gal A (rAAV-AGA) was constructed and injected into the hepatic portal vein of Fabry mice. Two weeks post injection, α-Gal A activity in the livers of rAAV-AGA-injected Fabry mice was 20-35% of that of the normal mice. The transduced animals continued to show higher alpha-Gal A levels in liver and in other tissues compared with those in the untouched Fabry controls for as long as 6 months after treatment was completed. This finding suggested that AAV-mediated gene transfer may be useful for the treatment of FD[44]. It seems now that in future gene therapy will be the ultimate treatment strategy for FD as well as for many other Lysosomal Storage disorders.

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