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 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. The two clinicians coined the term “angiokeratoma corporis diffusum”. In time, the generalized nature of this disease was more clearly recognized. Sweeley and Kliosky initially and then later Roscoe Brady 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 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. 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.

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

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.

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

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.

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. 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

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.

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.
sweating may be because of central autonomic dysfunction, peripheral dysautonomia or due to primary sweat gland disorder. 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. In fact, the eccrine sweat glands and the surrounding blood vessels had abnormal deposition of glycolipids.

- 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. In 50% of FD cases, there were impaired pupillary constriction to pilocarpine, reduced salivation and lacrimation. In all cases, the cutaneous flare response to scratch and intradermal histamine was diminished. Puritus was not experienced.

- Other types of peripheral neuropathy: symptomatic auditory nerve impairments do occur, although rare. However, investigations frequently showed peripheral auditory and vestibular dysfunctions.

- Cerebrovascular manifestations: cerebral infarcts are common complications in FD. The glycolipid is stored in vascular endothelial, perithelial and smooth muscle

Figure 1. Typical cutaneous angiokeratoma in a patient of Fabry disease.
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 fi-bromuscular blood vessels in FD. Instead it was likely that functional abnormality in the downstream conductance vessels was the cause for Fabry vasculopathy\(^{25}\).

- 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 subcortical N-acetylaspartate reduction signifying subclinical diffuse neuronal dysfunction in FD\(^{26}\).

**Investigations**

To establish the diagnosis of FD, diminished enzymatic activity of \(\alpha\)-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 \(\alpha\)-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 ceramide trihexoside 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 dis-
covered, Dr Roscoe Brady of N.I.H. pro-
posed “Enzyme Replacement Therapy” as a
therapeutic option. During that time, gluco-
cerebrosidase, the enzyme deficient in
Gaucher disease, was purified from placental
extract and infused in this above disorder;
this resulted in reduction of abnormally ac-
mulated hepatic glucocerebrosidase but the
result was inconsistent. Subsequently it was
learnt that macrophages have a lectin on the
surface that has a high affinity for mannose-
terminated glycoconjugates. The glucocere-
broside 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. Consequently, in
non-neuropathic Gaucher disease or Gaucher
disease type 1, this mannose-terminated glu-
cocerebrosidase infusion lead to a dramatic
improvement in clinical deficits. The suc-
cess in the above therapy paved the path for
pursuing enzyme replacement in the treat-
ment of the other lysosomal disorders, name-
ly, 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. This therapeutic ap-
proach 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 globotriaosyle-
ceramide and in normalizing many of the de-
bulitating manifestations of the disorder. A
double-blind placebo-controlled trial in 26 hem-
izygous male patients showed that agalsidase
alfa (human α-Gal A) significantly reduced
neuropathic pain (p = 0.02), increased creati-
nine clearance (p = 0.02), improved glomeru-
lar histology, reduced the QRS interval on
ECG and increased weight gain. Positron
emission tomography also revealed normaliza-
tion 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 func-
tion stabilized in those with renal insufficiency
at the beginning of treatment. There were nor-
malizations of sweating and improvement in
the level of energy and sense of well-being.
Enzyme replacement therapy is now an ac-
cepted mode of treatment in many western
countries. Currently, two types of α-Gal A are
commercially available for treatment of FD,
namely, Fabrazyme (agalasidase beta) and
Replagal (agalasidase alpha).

The future prospects

Enzyme replacement therapy is now the ac-
cepted definitive treatment for Lysosomal
Storage disease. But the enormous expense of
this therapy for Gaucher disease and Fabry dis-
ease – several hundred thousand dollars per pa-
tient per year – prompted a task force to con-
dude, “despite the success of enzyme therapy,
treatment is limited by the cost of the agent”.

Therefore alternative therapeutic strate-
gies 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-deoxy-
galactonojirimycin 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 chaper-
one” 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, re-
duction of ventricular wall thickness and
also reduction of cardiac mass after three
months of treatment.

2. Administration of selective glucosyle-
ceramide synthase inhibitors, 4′-hydroxy-P4
and etheledoxy-P4, are highly effective
in the depletion of the substrate globoto-
riaosylceramide from Fabry cell lines and
these compounds have the potential thera-
petic utility in FD.

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The enzyme may be delivered by genes, as in vector-mediated gene therapy. 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. 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. 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.

References

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