Agalsidase alfa: specific treatment for Fabry disease

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Fabry disease is a rare genetic lysosomal storage disorder characterized by a deficiency of the enzyme α-galactosidase A. The recent availability of enzyme-replacement therapy with agalsidase alfa offers specific treatment for this serious, progressive condition.

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Fabry disease (also known as Anderson–Fabry disease) was first described in the 1890s by two dermatologists, William Anderson in the UK and Johannes Fabry in Germany, who independently concluded that their patients' symptoms, which included cutaneous lesions and proteinuria, might be the result of a generalized disease.

Fabry disease is now recognized as one of the lysosomal storage disorders. It is an inherited, X-linked, pan-ethnic condition caused by an error of glycophospholipid catabolism resulting from a deficiency of the enzyme α-galactosidase A. The gene encoding α-galactosidase A is located on the X chromosome (locus Xq22). Consequently the majority of patients are hemizygous males carrying a single copy of the defective gene. Females are usually heterozygous, carrying one defective copy and one normal copy of the gene, and have previously been regarded as unaffected carriers. However, more recent studies suggest that in fact a majority of female carriers are symptomatic. The mechanism is unclear but random inactivation of one X chromosome in each cell could explain why most females are clinically affected (Lyon, 1961).

Deficiency of α-galactosidase A results in a progressive accumulation of lipid – mainly globotriaosylceramide (Gb_3) – in cells, especially of the kidney, heart, peripheral nervous system and blood vessels. Accumulation of Gb_3 in the kidney and heart results in early mortality, with a median survival of 50 years for hemizygous males and 70 years for heterozygous females (MacDermot et al, 2001a).

CLINICAL FEATURES

Symptoms of classical Fabry disease (*Table 1*) usually begin in childhood or early adolescence, often with acroparaesthesia in the arms and the legs, and agonising burning pains in the palms and soles that frequently spread to the rest of body (Fabry crisis). The pain can be exacerbated by temperature changes, fever, stress and physical exercise, and prevents patients from full participation at school or work, especially as their reduced ability to sweat (hypohydrosis) means that they cannot tolerate heat and exercise. Fabry disease pain may sometimes not respond to standard analgesics including opiates and anticonvulsants, and in some cases has been so

TABLE 1.
Clinical features of Fabry disease

Classical male	Acroparaesthesia
	Angiokeratoma
	Hypohydrosis
	Fever
	Eye disorders
	Gastrointestinal symptoms
	Renal disease
	Cardiac disease
	Central nervous system disease
	Respiratory disorders
	α-galactosidase A cannot be detected in plasma
Atypical male	Cardiac (ventricular hypertrophy, arrhythmia, valvular involvement)
	Renal disorders (proteinuria in a few patients)
	Acroparaesthesia (seldom)
	5–35% normal level of α-galactosidase A
Heterozygous (female)	Corneal dystrophy (in 70%)
	Angiokeratoma (in 30%)
	Acroparaesthesia (in <10%)
	Hypohydrosis, CNS involvement, renal failure, cardiac involvement (>50%)
	0–100% activity of α-galactosidase A in plasma

Adapted from Peters et al (2001)

excruciating that patients have committed suicide (Grewal, 1993). Angiokeratomas are a frequent early sign of classical Fabry disease. The small, raised, dark red lesions are mainly found on the thighs, buttocks, groin, lower abdomen and genital area, and increase in number as the patient gets older.

Although the degree of involvement may vary between patients, renal disease is perhaps the most significant clinical feature of Fabry disease. Gradual deterioration in renal function usually occurs between the ages of 20 and 40 years, and results in renal failure that may be complicated by cardiac disease. Deposits of Gb_3 in the electrical conduction system of the heart lead to arrhythmias, while there is an increased incidence of structural defects including mitral valve prolapse, interventricular septum thickening and left ventricular hypertrophy.

Ophthalmological abnormalities are also common, but do not affect the patient's sight. A whorl-shaped, cream opacity of the cornea is especially characteristic and may be the only sign in heterozygous females (Sher et al, 1979). Patients may also have distinctive cataracts, and there may be varying degrees of ischaemia in the retinal blood vessels.

Patients report frequent gastrointestinal symptoms, including pain after eating, abdominal cramps, diarrhoea, nausea and vomiting. CNS symptoms include tinnitus, poor concentration, dizziness and headaches. There may also be personality change, cognitive deficits, hearing loss and clinical depression.

Onset of atypical Fabry disease (*Table 1*) is later and the clinical features tend to be confined to the heart. Clinical features also appear later and in a milder form in heterozygous women, although a few experience severe symptoms (*Table 1*). The most common clinical features in women are corneal dystrophy (in 70% of patients) and angiokeratoma (30% of patients) (Peters et al, 2001). Acroparaesthesia is seen in fewer than 10% of heterozygous women, but may begin in childhood (Chowdhury and Holt, 2001).

DIAGNOSIS

The diverse clinical features of Fabry disease make diagnosis difficult, especially as symptoms vary according to the sub-classification of the disease (*Table 1*). More than 150 mutations have been described. There is no clear genotype/phenotype correlation, and phenotypes may vary even within families (Peters et al, 2001).

Diagnostic difficulty is compounded by the rarity of the condition. An incidence of one in 117 000 was found in Australia (Meikle et al, 1999), while an incidence of one in 476 000 has been reported for the Netherlands (Poorthuis et al, 1999). However, even the lower figure may be an underestimation since it may exclude patients with residual enzyme activity in whom Fabry disease may present primarily as a cardiac disorder. Studies suggest a quite high incidence in patients with hypertrophic cardiomyopathy of unknown origin (Kuhn et al, 1982; Nakao et al, 1995; Sachdev et al, 2001).

A positive family history should raise the index of suspicion, although family histories are often sketchy and incomplete, and patients may not know the cause of death of relatives. It is therefore not uncommon for the patient to be referred to a number of specialists over several years before the correct diagnosis is made – a typical patient with Fabry disease will have seen 10 specialists over an average of 10 years (Morgan and Crawfurd, 1988).

The diagnosis can be established by a low activity of α-galactosidase A in plasma, leucocytes or cultured fibroblasts. However, this test is less valuable in heterozygous females because the level of α-galactosidase A may overlap with that in normal individuals at the lower end of the scale. Genetic examination is therefore needed to confirm the diagnosis, although absence of a known mutation does not eliminate Fabry disease because of the large number of genetic variations. In addition, documentation of Gb_3 storage, e.g. in urine sediment, is of value for the diagnosis.

AGALSIDASE ALFA

Until recently there was no specific treatment for Fabry disease and symptoms were treated individually as they occurred; for example, analgesics for pain, dialysis or transplantation for renal failure. However, since Fabry disease is caused by the deficiency of a single enzyme – α-galactosidase A – enzyme replacement therapy is a logical treatment. This approach has been made possible by recent advances in molecular genetic techniques, and has already proved its effectiveness in Gaucher's disease, another lysosomal storage disorder.

Agalsidase alfa (Replagal, TKT Europe-55 AB, Stockholm) is α-galactosidase A derived from a continuous human cell line. This enables large quantities to be produced and ensures the correct post-translational modifications, including authentic human glycosylation – important for correct biodistribution and low immunogenicity. In a pre-clinical study, 10 patients with confirmed Fabry disease received a single intravenous infusion of one of five escalating doses of agalsidase alfa. All infusions were well toler-

ated and nine out of the 10 patients had significantly reduced Gb_3 levels both in the urine sediment and the liver. The authors concluded that the degree of Gb_3 reduction was especially significant given the fact that Gb_3 burden increases gradually over decades in patients with Fabry disease (Schiffmann et al, 2000).

Treatment with agalsidase alfa consists of a 40-minute 0.2 mg/kg infusion every 2 weeks. In a randomized, controlled study (*Table 2*) conducted by the National Institutes of Health investigators (Schiffmann et al, 2001), 6 months' treatment compared to placebo resulted in:

- Consistent, progressive, clinically significant reduction in scores for severe, debilitating pain (P=0.02)
- Decrease in the use of medication for chronic neuropathic pain (four of 11 actively treated patients discontinued analgesics *vs* none in the placebo group; P=0.03)
- Improvement in pain-related quality of life (P=0.05)
- Stabilization of renal function in the treatment arm as measured by creatinine clearance (P=0.02) and inulin clearance (P=0.19)
- Reversal of pathological changes in the kidney indicated by 20% increased fraction of normal glomeruli (P=0.01) and 33% decrease in mesangial widening (P =0.01)
- Improved cardiac conduction (P=0.047)
- Increased body weight (P=0.02)
- Improved Gb_3 clearance: 54% in plasma, 20% in kidney tissue, 28.9% in urine sediment.

Treatment was well tolerated throughout the study and none of the patients withdrew because of infusion-related reactions. Fifty-five per cent of actively treated patients developed antibodies to α-galactosidase A, but this did not affect outcome and titres fell over time.

Agalsidase alfa's beneficial effects on the heart have been further demonstrated in a randomized controlled study (MacDermot et al, 2001b). There was a significant decrease in cardiac mass in the seven patients receiving active treatment compared with an increase in the eight patients in the placebo group.

Agalsidase alfa is infused intravenously over 40 minutes at a dose of 0.2 mg/kg every 2 weeks. The short infusion time has enabled the patients in the above mentioned trials to be transferred to home therapy.

CLINICAL USE

Agalsidase alfa was approved for use in the European Union in August 2001, following a positive opinion in March from the European Agency for the Evaluation of Medicinal Products, and the drug has now been licensed for use in the UK. The cost is likely to be approximately £120 000 per patient (70 kg in weight) per annum. However, agalsidase alfa is classified under recent European Commission regulations as an 'orphan medicinal product' – i.e. a drug that treats life-threatening or chronically debilitating conditions affecting no more than five people per 10 000 in the European Union – and is therefore eligible for incentives to support availability as well as research and development. Although no cost-effectiveness studies are available, the potential costs of specific treatment with agalsidase alfa need to be weighed against the current costs to the NHS of symptomatic treatment, including frequent hospitalization and inappropriate referrals, and the social costs of premature mortality and loss of productivity through disability.

Clinical use of agalsidase alfa should resolve some practical questions that were not addressed in the clinical studies, including the appropriate time to initiate enzyme replacement therapy and the potential benefit of treatment in heterozygous females. Cost-effective use of agalsidase alfa clearly depends on the accurate identification of patients in both primary and secondary care followed by referral to specialist centres. Specialist groups, such as the recently announced collaboration at the Royal Free Hospital in London – including specialists in cardiology, ophthalmology, neurology, dermatology, psychology and nephrology – are able to accurately and cost-effectively confirm diagnosis of the disease and its complications and advise on the treatment and management of the disease. GPs and paediatricians in particular will need to bear in mind the possibility of Fabry disease in 'heartsink' patients presenting repeatedly

TABLE 2.
National Institutes of Health study investigating enzyme replacement therapy with agalsidase alpha

Design	Randomized, placebo-controlled, parallel group study	
Duration	24 weeks randomized	
	24 weeks open label	
Number (mean age)	Active treatment	14 males (34.0 years)
	Placebo group	12 males (34.4 years)
Dosage of agalsidase alfa	0.2 mg/kg, 12 doses over 24 weeks. 20-minute infusion increased to 40 minutes midway into study. No premedication	
Primary outcome measures	Effect on neuropathic pain (assessed by Brief Pain Inventory) while without analgesics	
Secondary outcome measures	Glomerular filtration rate, renal histology, globotriaosylceramide in plasma, kidney tissue, and 24-hour urine sediment	

From Schiffmann et al (2001)

with symptoms of chronic severe pain, angiokeratomas, and gastrointestinal symptoms.

The availability of specific treatment may also increase awareness among patients, especially as the MPS Society (Society for Mucopolysaccharide Diseases) has included Fabry disease in its remit (see *Useful address*). It will also be important to identify patients who will be able to adhere to lifelong treatment, preferably in the community. Home infusions will increase the cost-effectiveness of treatment, and are currently proving successful for certain patients through the auspices of a specialist company.

Agalsidase alfa is not the only specific treatment for Fabry disease following the coincidental approval of agalsidase beta (Fabrazyme; Genzyme, Cambridge, Mass) The two compounds have been not been directly compared in studies and extrapolation from clinical trials is not possible because of the different entry criteria and outcome measures (Eng et al, 2001; Schiffmann et al, 2001). Its longer infusion time (4–6 hours compared to 40 minutes for agalsidase alfa) may make agalsidase beta less suitable for home infusion.

Useful address: The MPS Society

The MPS Society (Society for Mucopolysaccharide Diseases) was established in 1982 and is a voluntary support group for patients with mucopolysaccharide and related disorders, their families, carers and professionals. It aims to act as a support network, increase public awareness of these diseases, and to promote and support research.

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KEY POINTS

- Fabry disease is a rare, X-linked, genetic lysosomal disorder characterized by a deficiency of the enzyme α-galactosidase A.
- The resulting accumulation of globotriaosylceramide progressively damages the kidney, heart, peripheral nervous system, and blood vessels.
- Symptoms of classical Fabry disease usually begin in childhood or early adolescence and include acroparaesthesia in the arms and legs, agonising pain in the palms and soles, angiokeratomas and hypohydrosis.
- Until recently, treatment was symptomatic, but enzyme replacement therapy with agalsidase alfa has recently become available.
- Treatment consists of a 40-minute infusion every 2 weeks, which in clinical studies reduced pain, improved quality of life, stabilized renal function, reversed pathological changes in the kidney, and decreased cardiac mass.
- The development of enzyme replacement therapy for Fabry disease warrants greater awareness of the condition among clinicians.

CONCLUSION

Fabry disease is a debilitating, painful condition and the availability of specific treatment is good news for patients, especially as the results of clinical studies promise not only control but also potential reversal of the disease process (Pastores and Thadhani, 2001). The observed improvements in organ function are, however, small and falls in plasma and tissue Gb_3 mean that a substantial tissue load remains. Clinicians now need greater awareness of lysosomal storage disorders such as Fabry disease and the development of enzyme replacement therapy should encourage early diagnosis, specialist referral and active intervention. HM

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