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Treatment of lysosomal storage disorders

Increased awareness and diagnosis are important as treatment is now feasible

The lysosomal storage disorders have hitherto justifiably been consigned to the small print sections of textbooks of biochemistry and internal medicine and optional modules of the undergraduate medical curriculum. However, new treatments may halt—or even reverse—progressive organ damage. The substantial morbidity and premature mortality of these disorders may be preventable.

The lysosomal storage disorders are a group of 40 or so rare disorders, due to inherited deficiency of individual enzymes. Organ damage arises from progressive accumulation of the substrates for the missing enzyme. The commonest lysosomal storage disorders, with an incidence of 1 in 60 000-120 000,[1–3] are Gaucher's disease (glucocerebrosidase deficiency), Anderson-Fabry disease (α galactosidase deficiency), and mucopolysaccharidosis I (α L-iduronidase deficiency). Enzyme replacement therapy for each of these three conditions is licensed and available in Europe.

The rarity of these disorders makes the potential market for therapeutic products very small while the costs of research, development, clinical trials, and marketing are comparable to those for drugs with a much larger potential market. Furthermore, it is not enough simply to treat patients with recombinant enzymes—modifications must be made so that the infused enzyme is targeted to lysosomes in relevant cells and tissues.

Glucocerebrosidase (Cerezyme, Genzyme Corporation, Massachusetts, United States) has been available for over 10 years and has brought hope to sufferers and carers, with an expectation that the spectacular benefits of enzyme replacement for Gaucher's disease will be realised for other lysosomal storage disorders. Whereas Cerezyme was licensed on the basis of modest safety and efficacy data, the mantra of evidenced based medicine demands that new enzyme replacement therapies (for example, for Anderson-Fabry disease and mucopolysaccharidosis I) have to undergo rigorous appraisal before licensing, including randomised double blind control trials. Two such trials have already been published for enzyme replacement therapy of Anderson-Fabry disease.[4 5] They show that both Replagal (α agalsidase, Transkaryotic Therapies, Massachusetts, United States) and Fabrazyme (β agalsidase, Genzyme) are safe and effective,[6] prompting the European authorities to license both products in August 2001. The US Food and Drug Administration approved Fabrazyme in April 2003.

Heightened awareness by healthcare professionals, which may lead to early diagnosis and referral to specialist centres, is becoming increasingly important. Many lysosomal storage disorders present early in life to paediatricians and metabolic doctors, but many do not. Gaucher's disease typically presents in adult life, and the diagnosis of Anderson-Fabry disease in symptomatic children is often delayed until well into adulthood.

Type 1 Gaucher's disease is the non-neuronopathic adult form of the disease that is particularly common among Ashkenazi Jews, among whom the incidence is reported to be as high as 1 in 850.[1] The United Kingdom has a population of about 300 000 Ashkenazi Jews, which means an estimated 1000-1500 patients. The best prevalence data in the United Kingdom are those held by the Gauchers Association, which knows of about 250 patients, of whom 180 or so are receiving enzyme replacement. Why the discrepancy? Certainly many patients with Gaucher's disease type I (for example, those who have high residual enzyme activity) are asymptomatic during childhood and early adult life, and some may present—with anaemia, thrombocytopenia, hepatosplenomegaly or bone disease, the clinical hallmarks of this condition—only in late adult life, often in their sixth or seventh decade. Many may never show symptoms. The benefits of enzyme replacement are not established for patients with very late onset disease or without symptoms. A worrying alternative possibility is that there are many patients "out there" who have never been assessed for suitability for enzyme replacement. "'Out there" could be in the community, in general practice surgeries, or undiagnosed in hospital outpatient clinics—haematology, orthopaedics, general medicine, and hepatology.

For Anderson-Fabry disease the estimated prevalence means that there are perhaps 500 patients in the United Kingdom; but only about 150 are currently known to the Society for Mucopolysaccharide Diseases, which is the association for Anderson-Fabry disease. Furthermore as many as 3-5% of male patients with hypertrophic cardiomyopathy may have a milder variant form of Anderson-Fabry disease,[7] and heterozygous female patients in this X linked disorder are usually affected, although less so than male ones. "Out there" for Anderson-Fabry disease could be just about anywhere—presenting symptoms could be due to neuropathy (pain in limbs, acroparaesthesia, abdominal pain and diarrhoea, lack of sweating), cardiomyopathy,

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nephropathy, deafness, ophthalmic changes, stroke, or epilepsy. A previous editorial in the *BMJ* emphasised that the diagnosis is often missed.[8]

For commissioners the challenge is how to fund treatment. At a cost of £30 000-100 000 ($50 000-165 000; €42 000-140 000) per patient per year, these are among the most expensive licensed treatments available. If our society is committed to giving patients with rare diseases a fair deal, primary care trusts must make funds available for treatment. At present primary care trusts do not receive any "top sliced" central funding—yet the familial nature of lysosomal storage disorders means that a substantial financial burden can fall on an individual primary care trust. For Gaucher's disease the Department of Health has designated four centres in the United Kingdom, via the National Specialist Commissioning Agency, for assessment and management in a shared care arrangement with patients' local doctors and thereby put out a clear message to primary care trusts that enzyme replacement should be funded if thought appropriate by specialists familiar with the disease. The Gauchers Association has publicly stated that the service is effective and efficient in quickening the process of diagnosis and potential treatment and represents the NHS at is best. There is a strong argument that similar specialist centres should be designated for other lysosomal storage disorders. Primary care trusts need clear central guidance if we are to avoid postcode prescribing. A wider use of consortia funding arrangements would allow individual primary care trusts to negotiate the budgetary hazards of having to fund enzyme replacement therapy.

The challenge for the pharmaceutical industry is to improve treatments while extending them to other enzyme deficiency disorders. An oral treatment for Gaucher's disease (Zavesca, Miglustat, Actelion, UK) was licensed by the European authorities in April 2003 for those patients deemed unsuitable for enzyme replacement.[9] Clinical trials of this treatment are also being conducted for other lysosomal diseases. Gene therapy is feasible, and some preliminary studies have already been carried out in Gaucher's disease. The prospects for patients with rare diseases have never been brighter—let us hope that scientific advances can be translated rapidly into improved patient care.

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The increasing number of older patients with renal disease

Trainees in nephrology should enhance their skills in geriatrics

"Are my kidneys going to wear out before the rest of me?" is a valid question for older patients with hypertension and a raised serum creatinine concentration. The extent of the problem is illustrated by a study in an inner London primary healthcare setting.[1] In the age group 50-75 years, the prevalence of renal impairment (serum creatinine higher than 120 μmol/l) was 6.1% in patients known to have hypertension, 12.6% in those known to have diabetes, and 16.9% in those with both.[1] Many of these patients will progress to end stage renal failure. Of the one million patients who need chronic dialysis worldwide, more than half are over 65 years, as are approximately 10% of patients waiting for cadaveric transplants. (www.uktransplant.org.uk) The renal registry report for the United Kingdom for 2002 indicates the acceptance rate for dialysis for patients over 65 is approaching 300 patients per 1 000 000 population, compared with 72 per 1 000 000 population in those aged 18-64 years.[2]

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