# From symptoms to causes: progress in the treatment of neurological disease

## Introduction

It is generally acknowledged that treatment of the causes of disease, if possible, is more desirable than treating symptoms, although in neurological practice only the latter is often possible. Identifying the presence of a neurological disorder may nevertheless be the prelude to treatment of the pathogenic disease process, the more so as advances in the understanding of neurological disorders progresses and new treatments become available. This article reports a case which illustrates the change from treatment of symptoms to treatment of causes in neurological disease.

## Discussion

Acid maltase deficiency, also known as glycogen storage disease type II or Pompe disease, is a rare autosomal recessive disorder caused by reduced activity of the lysosomal enzyme acid alpha-glucosidase leading to decreased metabolism of glycogen to glucose within skeletal muscle lysosomes. This results in glycogen accumulation and consequent lysosomal expansion and rupture causing muscle cell damage and death (Larner et al, 2011).

Acid maltase deficiency may be classified by age at onset into infantile and late-onset types, with subtypes of the latter (childhood, juvenile, adult). These are related to the extent of enzyme deficiency and differ in prognosis.

Infantile-onset disease is rapidly progressive, the complete or almost complete lack of acid alpha-glucosidase activity within skeletal muscle resulting in cardiorespiratory failure and death before the age of 2 years (van den Hout et al, 2003; Kishnani et al, 2006).

Late-onset disease caused by partial acid alpha-glucosidase deficiency is milder, with slowly progressive proximal myopathy and respiratory insufficiency secondary to diaphragm and accessory muscle weakness (Laforet et al, 2000; Winkel et al, 2005). The varied presentations of late-onset acid maltase deficiency often cause diagnostic delay, as in this case, with a reported average of 7–9 years (Hagemans et al, 2006).

Although first described by Pompe in 1932, treatment for acid maltase deficiency was limited to physical therapy and high protein diets until enzyme replacement therapy with human recombinant acid alpha-glucosidase became available (van den Hout et al, 2000). A number of trials have shown that enzyme replacement therapy improves motor and respiratory function in late-onset acid maltase deficiency (Winkel et al, 2004; Merk et al, 2009; Strothotte et al, 2010; van der Ploeg et al, 2010). Early commencement of enzyme replacement therapy may limit muscular damage (Bembi et al, 2010).

## Conclusions

Early recognition of acid maltase deficiency is of paramount importance to ensure that treatment of the causal biochemical defect, rather than the symptoms, is initiated early in the disease course. BJHM

**Miss Rebecca AD Sells** *is Final Year Medical Student and* **Dr Andrew J Larner** *is Consultant Neurologist in the Walton Centre for Neurology and Neurosurgery, Fazakerley, Liverpool L9 7LJ*

*Correspondence to: Dr AJ Larner*

### Case Report

A 33-year-old man with no relevant family history was referred to the neurology clinic for assessment of an approximately 10-year history of motor problems not responding to physiotherapy.

He reported being fit and well until a work-related lower back injury. A few weeks later he noticed a tendency to 'waddle' when walking. A plain spinal radiograph was normal and he was advised to rest. However, his difficulties gradually progressed. Two years post-injury the 'waddling' became more noticeable and he developed problems bending to lift things from the floor. A consultation with a specialist in back pain management led to physiotherapy for back strengthening exercises, despite which the patient continued to worsen. By 6 years post-injury he began to have difficulty going up stairs and getting out of a chair. Despite these difficulties he continued to work, until he was only able to walk 100 yards on the flat, and at no time was there ever litigation regarding the original accident. Around 8 years post injury he was still driving but had occasional problems controlling the clutch pedal. He returned to the back pain clinic where further physiotherapy was advised and referral to rehabilitation services was made, following which referral for neurological consultation was recommended.

On neurological examination the patient had a myopathic, waddling type of gait. There was wasting of the right quadriceps with bilateral proximal lower limb weakness (hip flexion MRC grade 4-/5), knee jerks were absent bilaterally and plantar responses were down-going. Sensory examination was normal.

Investigations for a suspected myopathic process were initiated. Creatine kinase was elevated (1048 U/litre, normal range 3–194 U/litre). Magnetic resonance imagining of the whole spine showed no intrinsic cord lesion or compression but was incidentally noted to show striking fatty change in the lower paraspinal muscles and iliopsoas. Electromyography showed changes suggestive of a primary underlying myopathy. Spirometry suggested diaphragmatic involvement (forced vital capacity 2.1 litres upright; 1.3 litres supine).

In light of these findings, the patient proceeded to a muscle biopsy (tibialis anterior) which showed a punctate increase in glycogen in many of the fibres with patches of increased staining for acid phosphatase, but vacuolation was not seen. Definitive diagnosis was established by measurement of white cell enzymes which showed very low levels of alpha-glucosidase thus confirming a diagnosis of acid maltase deficiency.

The patient was referred to a dedicated neuromuscular disease clinic for consideration of enzyme replacement therapy. After 2 years of Myozyme (20 mg/kg body weight intravenously every 2 weeks) his muscle power is stable. He has required nocturnal continuous airway pressure for daytime somnolence with evidence of overnight oxygen desaturation on sleep study.

Bembi B, Pisa FE, Confalonieri M et al (2010) Long-term observational, non-randomized study of enzyme replacement therapy in late-onset glycogenosis type II. *J Inherit Metab Dis* **33**: 727–35
Hagemans ML, Winkel LP, Van Doorn PA et al (2006) Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. *Brain* **128**: 671–7
Kishnani PS, Hwu WL, Mandel H et al (2006) A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. *J Pediatr* **148**: 671–6
Laforet P, Nicolino M, Eymard PB et al (2000) Juvenile and adult onset acid maltase deficiency in France: genotype-phenotype correlation. *Neurology* **55**: 1122–8
Larner AJ, Coles AJ, Scolding NJ, Barker RA (2011) *The A-Z of Neurological Practice. A guide to clinical neurology.* 2nd edn. Springer, London: 580–2
Merk T, Wibmer, Schumann C, Kruger S (2009) Glycogen storage disease type II (Pompe disease) - influence of enzyme replacement therapy in adults. *Eur J Neurol* **16**: 274–7
Strothotte S, Strigl-Pill N, Grunert B et al (2010) Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2: 12-month results of an observational clinical trial. *J Neurol* **257**: 91–7
van den Hout H, Reuser AJ, Vulto AG et al (2000) Recombinant human alpha-glucosidase from rabbit milk in Pompe patients. *Lancet* **356**: 397–8
van den Hout HM, Hop W, van Diggelen OP et al (2003) The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. *Pediatrics* **112**: 332–40
van der Ploeg AT, Clemens PR, Corzo D et al (2010) A randomized study of alglucosidase alfa in late-onset Pompe's disease. *N Engl J Med* **362**: 1396–406
Winkel LP, Van den Hout JM, Kamphoven JH et al (2004) Enzyme replacement therapy in late-onset Pompe's disease: a three-year follow-up. *Ann Neurol* **55**: 495–502
Winkel LPF, Hagemans MLC, van Doorn PA et al (2005) The natural course of non-classic Pompe's disease: a review of 225 published cases. *J Neurol* **252**: 875–84

## LEARNING POINTS

- Late-onset acid maltase deficiency has a variable phenotype, but proximal myopathy and diaphragmatic weakness are common features.
- Diagnosis of late-onset acid maltase deficiency is often delayed.
- Enzyme replacement therapy for acid maltase deficiency is now available, mandating earlier diagnosis of this condition.



# Angelchik prosthesis revisited: radiological appearance mimicking a foreign body

The Angelchik prosthesis, resembling an incomplete doughnut (*Figure 1*), was used in the past to treat patients with hiatus hernia. The prosthesis is tied around the gastro-oesophageal junction, using Dacron straps, to minimize reflux disease. It is outdated (Varshney et al, 2002) but surgeons may still see patients with this prosthesis which were inserted more than a decade ago. Migration, dysphagia, erosion and recurrent reflux are common complications (Stewart et al, 1994; Maxwell-Armstrong et al, 1997; Carbonell and Maher, 2006). Many radiologists are not familiar with the prosthesis and therefore radiologically it may be reported as a foreign body.

*Figure 2* shows the radiological appearance of an Angelchik prosthesis on computed tomography. When there is a complication, the prosthesis can be removed laparoscopically and an anti-reflux procedure may be required at the same time. BJHM

***Figure 1. An Angelchik prosthesis which was removed from a patient with dysphagia.***

**Mr Rajaraman Durai** *is Specialist Registrar,* **Mr Imran Chishti** *is Associate Specialist Surgeon and* **Mr Midhat Siddiqui** *is Consultant Surgeon in the Department of Surgery, Queen Elizabeth Hospital, London SE18 4QH*

*Correspondence to: Mr M Siddiqui*

Carbonell AM, Maher JW (2006) Laparoscopic transgastric removal of an eroded Angelchik prosthesis. *Am Surg* **72**(8): 724–6; discussion 727
Maxwell-Armstrong CA, Steele RJ, Amar SS, Evans D, Morris DL, Foster GE, Hardcastle JD (1997) Long-term results of the Angelchik prosthesis for gastro-oesophageal reflux. *Br J Surg* **84**(6): 862–4
Stewart KC, Urschel JD, Hallgren RA (1994) Reoperation for complications of the Angelchik antireflux prosthesis. *Ann Thorac Surg* **57**(6): 1557–8
Varshney S, Kelly JJ, Branagan G, Somers SS, Kelly JM (2002) Angelchik prosthesis revisited. *World J Surg* **26**(1): 129–33

***Figure 2. A computed tomography scan of a patient with dysphagia demonstrating part of the Angelchik prosthesis (arrow).***