

## CLINICAL PRACTICE

## Diagnosis and management of Pompe disease

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Pompe disease (PD) is an autosomal-recessively inherited neuromuscular disease that, if not diagnosed and treated early, can be fatal. It can present from early infancy into adulthood. Due to the lack of acid  $\alpha$ -glucosidase, there is progressive intracellular accumulation of glycogen. The severity of the disease is determined by age of onset, organ involvement including the degree of severity of muscle involvement, as well as rate of progression. PD is classified into two groups: infantile and late-onset, each having two subgroups. The need for two tests performed by separate methods (screening and confirmatory) is outlined. It is imperative to try to reduce the time to diagnosis and to recognise the possibilities of false-positive results. A multidisciplinary team approach to treatment of affected patients is optimum with, as team leader, a physician who has experience in managing this rare disorder. In this article, we present a brief overview of the disease and provide guidelines for diagnosis and management of this condition in South Africa.

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Pompe disease (PD) is a progressive, debilitating multisystemic neuromuscular disease. It is often fatal if not diagnosed and treated early. It is known by several names: acid maltase deficiency; glycogen storage disease type II; and glycogenosis type II. All muscle groups are affected, viz. skeletal, respiratory and, primarily in infants, cardiac muscle.<sup>[1,2]</sup> There is degeneration of muscle due to progressive intracellular accumulation of glycogen as a result of deficiency of lysosomal enzyme, acid  $\alpha$ -glucosidase (GAA).<sup>[1]</sup> It is an autosomal recessive condition with the GAA gene located on chromosome 17q25.<sup>[2]</sup> The worldwide combined incidence is 1/40 000, though the infantile form of the disease tends to be more common among African-Americans and Chinese people.<sup>[2]</sup>

PD can present from early infancy into adulthood; it encompasses a single disease continuum with variable rates of disease progression.<sup>[1,2]</sup> The severity of the disease is determined by age of onset, organ involvement including the degree of severity of muscle involvement (skeletal, respiratory and cardiac), and rate of progression.<sup>[1,2]</sup> In the

infant under a year, who is a floppy baby in cardiac failure, with cardiomegaly, the disease should be suspected.

### Classification

PD is classified into two groups:

- Infantile form:
  - Classic infantile PD is a most severe disease that is rapidly progressive and is characterised by prominent cardiomegaly with cardiomyopathy, hepatomegaly, muscular weakness and hypotonia.<sup>[3,4]</sup> Death results from cardiorespiratory failure in <1 year, if not treated.
  - Infantile variant form (non-classic in the <1-year group that has slower progression and less severe or absent cardiomyopathy).
- Late-onset form:<sup>[5]</sup>
  - Childhood/juvenile or muscular variant (heterogeneous group) presenting later than infancy and typically not including cardiomyopathy.
  - Adult-onset form characterised by slowly progressive myopathy predominantly involving skeletal muscle and presenting as late as the 2nd - 6th decade of life.

### Diagnosis in South Africa

It is imperative to make an early diagnosis to optimise disease management and outcomes. Testing is by way of two *separate* methods performed on the same day and involves: *screening* for the disease via dried blood spot (DBS) sent to Europe; *confirmation*, requiring whole blood samples sent to the National Health Laboratory Service

Please refer to the following article for a more detailed overview of the comprehensive management of Pompe disease: Kishnani PS, Steiner RD, Bali D, *et al.*; ACMG Work Group on Management of Pompe Disease. Pompe disease diagnosis and management guideline. *Genet Med* 2006;8(5):267-288. [<http://dx.doi.org/10.1097/01.gim.0000218152.87434.f3>]

(NHLS) in Johannesburg, South Africa, for GAA enzyme assay in lymphocytes, with absent or markedly reduced GAA enzyme activity offering a conclusive diagnosis.

Fibroblasts obtained from a skin biopsy may also be tested for GAA, but a limiting factor is that the time to diagnosis is 4 - 6 weeks. A muscle biopsy may be confirmatory, but limiting factors are that it requires general anaesthesia, which can have a fatal outcome. Tissue samples must be frozen and shipped to the USA for analysis. Genetic studies may be performed in the USA or Europe, if required.

### Screening

- Whole blood onto four spots on the DBS card – after DBS is dry and all details are provided on the card, it can be sent to Europe for analysis.
- If infantile-onset PD is suspected, urgent testing should be requested.

### Confirmation

- Arrange courier to be available through a local laboratory.
- Draw whole blood (3 - 5 ml into an acid citrate dextrose (ACD) tube), preferably in the early morning. Samples should include blood from:
  - patient
  - control: unrelated donor (e.g. doctor, nurse, lab technician).
- Wrap both tubes in tissue paper and place on an ice-brick in a polystyrene container (**do not freeze**).
- Specimens should be delivered to the NHLS within three hours of the sample being drawn (i.e. before midday).
- It is advisable to inform the NHLS lab technician to expect samples – this will facilitate quicker transit to the lab from the NHLS reception.
- It is *preferable not to test on a Friday* as there is a huge risk of samples being unattended, resulting in higher false-positive results.
- Results are usually available within 7 - 10 working days.

A positive diagnosis of PD is made when both the *screening* and *confirmatory* tests corroborate each other.

### Management

As this is a multisystem disorder, management requires a multidisciplinary team led by a physician with experience in managing this disorder. The team comprises a:

- metabolic disease specialist/biochemical geneticist (to co-ordinate care)
- cardiologist
- pulmonologist/respiratory therapist
- neurologist, neuromuscular specialist, physical therapist, occupational therapist, audiologist and speech therapist
- intensivist
- orthopaedist
- genetic counsellor
- metabolic dietician.

Due to overall hypotonia and respiratory muscle weakness, patients are at high risk for pneumonia, leading to respiratory failure

requiring ventilatory support; there may be ventilator dependence and even death.<sup>[5]</sup> There should be a low threshold to treat infections. Immunisations are required, including: seasonal influenza vaccine for patients and household members; pneumococcal vaccine; palivizumab is recommended during respiratory syncytial virus (RSV) season in infants and young children and older patients who have not received these immunisations (for which special motivation to the medical funders may be required).

General anaesthesia<sup>[5]</sup> must be performed by someone familiar with anaesthesia in PD patients as 'routine' drugs may result in a fatality, and surgical procedures must be grouped for a single anaesthetic where possible.

Since the end of 2012, enzyme replacement therapy (ERT) (as alglucosidase alfa) has been registered with the Medicines Control Council in South Africa for use in PD patients. Patients with infantile-onset PD who receive ERT have significantly prolonged survival, decreased cardiomegaly, and improved cardiac and skeletal muscle function. The cardiac response appears to be good irrespective of the stage of disease at initiation of ERT, while the skeletal muscle response appears more variable than cardiac muscle. The best skeletal muscle response occurs when ERT is administered prior to skeletal muscle damage.<sup>[6,7]</sup>

Treatment with alglucosidase alfa in late-onset PD is associated with improved walking distance and stabilisation of pulmonary function.<sup>[8]</sup>

Alglucosidase alfa is available in 50 mg dried powder vials. There are specific guidelines to ensure proper reconstitution of the solution. The infusions are performed every 2 weeks (dosage 20 mg/kg) in an environment with correct observation of vital signs and equipment available for full resuscitation.

Infusion-associated reactions (IARs) occur in ~50% of patients treated with alglucosidase alfa. IARs occur at any time during, and mostly up to two hours after, the infusion of alglucosidase alfa, and are more likely with higher infusion rates. Patients may be pre-treated with antihistamines, antipyretics and/or steroids. The prescribing information should be consulted before administration. Patients can eventually receive their infusions in a home-based environment.

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