Pompe disease, a storage cardiomyopathy

Tiziana Felice
Cardiology Department, Mater Dei Hospital, Msida, Malta

Abstract

Pompe disease also known as glycogen storage disease type II, is a rare and progressive lysosomal storage disorder caused by the deficiency of the enzyme acid α-glucosidase. This results in the accumulation of glycogen in various tissues particularly involving the heart, skeletal muscle and liver. It is inherited in an autosomal recessive manner due to mutations in the GAA gene. There are several known pathogenic variants, some of which are particularly common in certain geographical regions. Pompe disease is a single disease exhibiting a heterogeneous clinical spectrum depending on the extent of enzyme deficiency, the age of onset, the progression of the disease and the degree of organ involvement. It may lead to muscle weakness, hypotonia, respiratory compromise and premature death. Pompe disease is classically divided into two forms, infantile and late-onset disease. The infantile form is further subdivided into classical and non-classical subtypes. Cardiac involvement is particularly seen in the infantile phenotype of the condition, presenting as severe cardiomyopathy associated with conduction abnormalities. Enzyme replacement therapy with recombinant human acid α-glucosidase is the approved treatment option for patients with this metabolic condition. Further research is currently being done to explore more treatment options. One must keep in mind other metabolic and mitochondrial conditions, which may give a similar cardiac and neurological clinical picture.

Pathology

The enzyme deficiency in PD results in the accumulation of glycogen in various tissues. Lysosomal disruption occurs and excess autophagic vesicle build up is seen inside the myofibres causing progressive cardiac, motor and respiratory failure. The clinical outcome correlates with the degree of enzyme deficiency. Histochemistry in PD shows glycogen accumulation in membrane-bound vesicles known as lysosomes. These changes are widespread occurring in many organs and tissues; skeletal muscle often being the most studied tissue. Microscopically muscle fibre degeneration is characterised by the presence of shrunken nuclei with condensed chromatin. Haematoxylin and eosin staining help to show areas of vacuolization within the myocyte whilst periodic acid Schiff staining highlights the abundance of glycogen. The increased lysosomal abundance is demonstrated by acid phosphatase staining. The histological and ultrastructural changes described occur in both skeletal and cardiac muscle.

Clinical classification

PD may be classified into two subtypes: infantile and late onset forms.

Infantile onset Pompe disease

Infantile onset Pompe disease (IOPD) is the classic sub-type of the condition, which was first described in 1934 and is associated with severe hypertrophic cardiomyopathy in 88-100% of patients. Severe mutations in the GAA gene cause complete or near-complete enzyme deficiency resulting in a severe clinical phenotype characterised by cardiac involvement, respiratory distress, feeding problems, macroglorisa, motor delay, failure to thrive, muscle weakness, hypotonia (floppy baby) and organomegaly. Symptoms usually commence at approximately 1.6 months if untreated, causing cardiomegaly (92-96%) and congestive heart failure (50%), besides respiratory distress (78%), muscle weakness (63-96%), and feeding difficulties (57%). Without treatment, the disease progresses rapidly with 92% of patients reported to die before reaching 1 year of age secondary to respiratory insufficiency. Individuals affected by IOPD may be apparent in utero but more typically the clinical onset is during the first few months of life. There is a less severe form of IOPD (non-classic IOPD) which still presents in the first year of life but it exhibits a slower clinical progression and the cardiac involvement is less severe. Affected patients still develop peripheral muscle weakness, cardiomyopathy and occasionally macroglorisa and organomegaly, but in milder forms.

Late onset Pompe disease

Late-onset Pompe disease (LOPD) includes a childhood, juvenile or muscular variant of the condition. It is a heterogeneous group usually presenting after one year of age and typically does not including severe cardiac involvement. LOPD also encompasses the adult-onset form of the condition, which presents with a slow pro...
Cardiovascular involvement

Myocardial involvement

PD is one of the commonest causes of familial (idiopathic) hypertrophic cardiomyopathy in neonatal and paediatric age. Glycogen accumulates within the cardiac myocytes causing a severe form of hypertrophic cardiomyopathy with significant asymmetrical thickening of the septum. In infants affected by the condition, severe concentric hypertrophy is seen also affecting the septum and the free walls of both the right and the left ventricles resulting in biventricular hypertrophy (Figure 1). In 30% of cases, systolic anterior motion of the anterior mitral valve leaflet is present which may contribute to a worse prognosis. Diastolic and systolic dysfunction may also be observed. The dysfunctional left ventricle may become dilated as well as hypertrophied, and there can be underlying myocardial fibrosis detected by cardiac magnetic resonance imaging. In a study of 40 patients with IOPD, the development of systolic dysfunction, defined as a left ventricular ejection fraction of less than 40%, developed after 5 months of age.

In non-classic IOPD, cardiac involvement as conduction abnormalities and electrocardiogram (ECG) signs of ventricular hypertrophy are generally part of the disease spectrum. On echocardiography, cardiac hypertrophy is less severe and progressive and lacks the left ventricular obstruction and systolic dysfunction that significantly worsens the classic phenotype. Suzuki et al. have reported that the clinical spectrum in this form of PD may be varied.

Conduction system involvement

In PD, glycogen not only accumulates in the heart muscle but also in the conducting tissue of the heart, explaining the classic electrocardiographic abnormalities observed in this systemic condition (Figure 2). Electrocardiographic features of PD include a short PR interval, delta waves, pre-excitation patterns particularly of Wolff-Parkinson-White (WPW) morphology, left axis deviation, left ventricular hypertrophy by voltage criteria with repolarisation changes, atrioventricular blocks, and bundle branch block abnormalities. In this disease, the pre-excitation pattern on the ECG does not signify the presence of an accessory pathway. It is thought that this ECG pattern occurs either due to the direct insulating effect of glycogen on the conducting system or by the anatomical interruption of the annulus fibrosus, giving rise to an indirect insulating effect between the atria and the ventricles.

Arrhythmias

Different types of cardiac arrhythmias have been observed in patients with PD. The arrhythmias described are common unspecified sinus arrhythmias, supraventricular tachycardia (SVT), sick sinus syndrome, Lown IVb ventricular arrhythmia and WPW syndrome. Furthermore, WPW is also associated with supraventricular tachycardia. One study reported that several patients suffering from PD with WPW syndrome, experienced recurrent SVT episodes requiring hospital admission. In a French registry, complete heart block was observed in approximately 3% of LOPD patients. Supraventricular and ventricular tachyarrhythmias are also relatively common affecting up to 29% of patients with LOPD. The electrocardiogram of some patients with PD may suggest ventricular pre-excitation, but pathology studies of mouse models show generalized disruption of the annulus fibrosus associated with glycogen storage disease rather than the presence of a myocardial bypass tract. An insulating effect on the cardiac conduction system by the glycogen within the myocytes, disrupts the normal conduction barriers between the atria and the ventricles thus enhancing electrical conduction. This phenomenon has implications in the treatment of supraventricular tachycardia due to its poor amenability to radiofrequency catheter ablation.

Cardiovascular involvement in IOPD versus LOPD

Cardiac involvement in PD was previously recognized only in infantile cases, but cardiac hypertrophy, heart rhythm disturbances and aortic abnormalities are now also recognized in LOPD (Table 1). In infantile PD, the deficit of lysosomal GAA is often complete. Accordingly, in IOPD the

Table 1. The various features of cardiac involvement in IOPD and LOPD.

<table>
<thead>
<tr>
<th>Cardiovascular findings</th>
<th>IOPD</th>
<th>LOPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>Short PR interval, delta waves, pre-excitation patterns, WPW morphology, left axis deviation, left ventricular hypertrophy by voltage criteria with repolarisation changes, atrioventricular conduction and bundle branch block abnormalities</td>
<td>***</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Biventricular hypertrophy, asymmetrical septal hypertrophy, systolic anterior motion of the anterior mitral valve leaflet, left ventricular outflow tract obstruction, systolic and diastolic dysfunction</td>
<td>***</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Sinus arrhythmias, supraventricular tachycardia, sick sinus syndrome, Lown IVb ventricular arrhythmia, WPW</td>
<td>***</td>
</tr>
<tr>
<td>Vascular</td>
<td>Dilated aortopathy, aneurysm formation and dissection</td>
<td>*</td>
</tr>
</tbody>
</table>

*Shows the increased frequency and severity in both categories.
storage of glycogen in the heart is of considerable magnitude with consequent increase in mass and functional alterations of the heart. In contrast in LOPD, there is partial GAA enzyme deficiency (2-40% of normal activity) and consequently structural and functional cardiac alterations are absent or mild, despite severe musculoskeletal changes. The metabolism and storage of glycogen is also different in the two groups, with less glycogen accumulation in cardiac muscle in the LOPD subgroup of patients. The residual activity of the GAA enzyme would be just sufficient to eliminate the accumulation of glycogen in cardiac but not in skeletal muscle.

Controversy exists on the prevalence of cardiac involvement in LOPD patients. Soliman and colleagues assessed 46 patients with LOPD and found that there were no major cardiac abnormalities. The cardiac pathology seen in this group included isolated low systolic mitral annular velocities and mild left ventricular diastolic dysfunction, which could have been explained by a history of hypertension and/or advanced age rather than by LOPD. Forshä et al., reported limited cardiac involvement in 87 patients with LOPD. These changes included left ventricular hypertrophy, short PR interval on ECG, and a decreased ejection fraction on echocardiogram. Morris and colleagues, on the other hand, demonstrated that individuals with LOPD, had no myocardial features of the disease when compared to healthy subjects. A recent study was performed analyzing comprehensively the heart with modern and sensitive myocardial techniques. No evidence of structural or functional alterations in adults with LOPD was seen. Both structural and functional cardiac features were normal in these patients.

Gangor et al. described the survival of 268 patients with LOPD, collected in a prospective international observational study conducted between 2002 and 2009. Out of 34 deaths reported, the cause of death was recognized in 9 patients, including 1 patient who died of aortic dissection. In a German study of LOPD patients, dilated aortopathy, aneurysm formation and dissection, was seen in up to 12.5% of patients. Smooth muscle involvement occurs in LOPD patients as shown by the presence of increased aortic stiffness, secondary to glycogen accumulation in the vessel wall, reducing vascular elasticity. Severe vacuolization of vascular smooth muscle with accumulation of glycogen, particularly involving large and small cerebral arteries with aneurysm formation have previously been reported, reinforcing the need of cardiovascular follow-up in this cohort of patients.

The latest guidelines on PD highlighted that cardiac involvement in adult PD remains inconclusive. Although the current evidence suggests that there is minimal cardiac involvement in LOPD, there are reported cases of individuals with LOPD and cardiomyopathy alone. Therefore cardiomyopathy and arrhythmias should be recognized as possible LOPD clinical features, although not as common as in IOPD. Clinical screening for patients with LOPD, by performing yearly ECGs, echocardiograms and ambulatory ECG monitoring is highly recommended. Pathological changes in skeletal muscle, on the other hand, are prominent throughout the entire spectrum.

**Differential diagnoses**

Hypertrophic cardiomyopathy is an umbrella term, which encompasses various conditions. The commonest form of hypertrophic cardiomyopathy is the sarcomeric type, secondary to mutations occurring in the genes encoding for sarcomeric proteins. A similar cardiac phenotype is seen in a number of conditions including syndromic, mitochondrial and metabolic pathologies. Ventricular pre-excitation or tall R waves on the ECG and the presence of idiopathic left ventricular hypertrophy in children are a common feature of storage diseases (AMP-kinase disease, Danon disease), and mitochondrial disorders (MELAS, MERRF). Danon disease is an X-linked dominant glycogen storage disorder due to the absence of the lysosomal–associated membrane protein 2 (LAMP-2) which may be diagnosed by immunohistochemistry or by genetic sequencing. Compared with PD, cognitive impairment and retinitis pigmentosa may be distinctive features of this condition. AMP-kinase disease may result in a similar phenotype but is inherited in an autosomal dominant manner.

Mitochondrial disorders may cause left ventricular hypertrophy and are associated with a number of extra cardiac features. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke are seen in MELAS syndrome. Myoclonic epilepsy with ragged red fibres is a multisystem disorder causing generalised seizures, ataxia and later on dementia. Optic atrophy and hearing loss may be present. A family pedigree indicating maternal inheritance may point to the diagnosis.

**Investigations**

The diagnosis of PD is established by demonstrating a deficiency in acid α-glucosidase enzyme activity, combined with finding disease-causing mutations using DNA analysis of the GAA gene. Rapid and sensitive analysis of the GAA enzyme activity can be performed on dried blood spots when using standard conditions. Dried blood spot enzyme analysis is convenient as well as time- and cost-effective, but may give false-positive results and thus requires confirmatory DNA testing to make a diagnosis of PD.

DNA analysis may be performed using traditional targeted Sanger sequencing, once the enzyme deficiency is obtained. Now newer methods of DNA analysis are available involving, massive parallel sequencing which may be used as the initial test for analysis of the GAA gene. PD is inherited in an autosomal recessive manner. Hence if a patient is homozygous for the pathogenic mutations (present in both alleles), the diagnosis is confirmed. On the other hand, the presence of one known mutation and a sequence variant (with unproven pathogenicity), requires confirmation using an enzymatic assay from such sources as a dried blood spot, a skin fibroblast culture, a peripheral blood lymphocyte culture, or histological evidence from a muscle biopsy.

A number of biomarkers may be elevated in this condition. Serum creatinine kinase concentration is elevated (as high as 2000 IU/L; normal range: 60-305 IU/L) in all individuals with IOPD and in some subjects with LOPD. Another biomarker which may be elevated in PD is glucose tetrasaccharide, which is a tetramer identified in the urine and recently applied in GSD type II. It is a biomarker associated with skeletal muscle glycogen content, and raised levels are found in 94% of patients with PD. It is not specific for this condition as it may rise in other inherited neuromuscular diseases, trauma, acute pancreatitis and certain malignancies.

**Recommended cardiac investigations**

In the infantile form, a chest X-ray will convey gross cardiomegaly, which may be done during the first evaluation (Figure 3). The assessment of cardiac function by echocardiography is an essential part of the ongoing management of Pompe patients. Hypertrophy, predominantly affecting the left ventricular posterior wall and the interventricular septum is typically seen in infants at diagnosis and may also be identified prenatally. Left ventricular outflow tract obstruction may be present. The hypertrophic cardiomyopathy results in systolic and diastolic dysfunction that may progress to congestive heart failure. Dilatation of the
left ventricle with a low ejection fraction may develop. Initial findings of increased wall thickness and left ventricular (LV) mass need to be evaluated on a regular basis by a standardized approach since establishing the stage of the cardiomyopathy is useful in determining treatment. This imaging modality may help with following disease progression and response to intervention. The LV mass should be evaluated by two dimensional measurements using the length-area relationship.\(^2^7\) The absolute mass value (not indexed for BSA) is compared to a normal control population to yield a z-score which is an indicator of how far the patient exceeds the mean left ventricular mass in normal subjects. This is particularly useful in the paediatric population. Functional measurements including 2-D ejection fraction and the myocardial performance index are helpful in longitudinal follow-up. In IOPD echocardiography should be performed at baseline then at 6 monthly intervals. Once enzyme replacement therapy is commenced closer echocardiographic monitoring is required as the ejection fraction may deteriorate in the first 12-24 weeks of therapy. In LOPD patients, yearly echocardiography is recommended.\(^2^7\)

Cardiac magnetic resonance imaging may be recommended to assess cardiac morphology, enhanced with gadolinium analysis for cardiac tissue characterization. Ambulatory ECG monitoring is recommended to assess for cardiac arrhythmias, at least 6 monthly in IOPD and yearly in LOPD patients.

**Genetics**

PD is inherited in an autosomal recessive manner due to mutations of the \(GAA\) gene located on the long arm of chromosome 17. Biallelic \(GAA\) pathogenic variants may produce essentially no enzyme activity, resulting in IOPD.\(^4^0\) Several combinations of other pathogenic variants result in some residual enzyme activity, causing milder forms of this disease. The age of onset and progression of PD, are most likely directly proportional to the residual GAA activity.

Genotype-phenotype correlations have been made depending on the type of GAA pathogenic variant present. Variants that cause mRNA instability such as nonsense mutations are more commonly seen in IOPD since they result in near complete absence of GAA enzyme activity. On the other hand, GAA missense and splicing site pathogenic variants may result in either complete or partial absence of GAA enzyme activity and therefore may cause both IOPD and LOPD.\(^4^1\)

Several genotype-phenotype correlations have been observed with other specific pathogenic variants, sometimes endemic in certain populations. The pathological variant \(p.Glu76ArgfsTer45\) (c.525delT) is especially common among the Dutch population.\(^4^1\) It results in negligible GAA enzyme activity and is classified with the more severe alterations. Deletion of exon 18 (p.Gly828\_Asn882del;c.2482\_2646del) is also a common pathogenic variant again particularly among the Dutch. It results in negligible GAA enzyme activity and is considered as one of the more severe disease-causing variants.\(^4^2\) The mutation \(c.336\_13T>G\) is seen in 36% to 90% of late onset GSD II and is not associated with IOPD.\(^4^3\) This pathogenetic mutation leads to a leaky splice site resulting in greatly diminished, but not absent, GAA enzyme activity. Another pathogenic variant \(p.Asp645Glu\), is seen in a high proportion (80%) of IOPD patients in Taiwan and China and is associated with a haplotype suggesting a founder effect.\(^4^4\) Another disease-causing variant \(p.Arg854Ter\), is frequently associated with IOPD. This pathogenic variant has been observed in up to 60% of individuals of African descent who had a common haplotype, suggesting a founder effect.\(^4^5\)

**Management of Pompe disease cardiomyopathy**

Treatment of Pompe cardiomyopathy is directed by the patients’ symptoms. A consultation with a cardiologist is required to outline the treatment and management of the affected patient. PD patients with severe ventricular hypertrophy and left ventricular outflow tract obstruction are managed with \(\beta\)-blockade and careful monitoring of fluid status. Regular assessment of atrio-ventricular conduction is required with ECG and 24 h ambulatory ECG monitoring, to prevent complete heart block. If this occurs, permanent pacing may be required. Avoidance of dehydration or hypotension is important, as this may precipitate ventricular arrhythmia and cardiovascular collapse.

![Figure 2. Electrocardiogram in a patient with Pompe disease. Prominent R waves, features of left ventricular hypertrophy by voltage criteria with repolarization abnormalities are seen. [Reproduced with permission from: Poon GWK, et al. Variable response to enzyme replacement therapy in two Chinese children with infantile-onset Pompe disease in Hong Kong. HK J Paediatr (New Series) 2009;14:243-51. Medcom Ltd.]](image)

Enzyme replacement therapy

Enzyme replacement therapy (ERT) has been found to reverse the cardiomyopathy, improve the clinical course and the expected outcome of PD patients. Significant regression of left ventricular hypertrophy occurs as early as two months after initiation of ERT but may not resolve completely in infants started on treatment after five months of age, or in those subjects with a marked increase in the left ventricular mass index. The normalization of left ventricular mass index has been shown to persist in long-term survivors on ERT. In the first two months of treatment a transient decrease in left ventricular ejection fraction is often noted, which typically returns to baseline by six months of therapy. Similarly the ECG changes associated with PD such as the short PR interval, and elevated QRS voltages, resolve in patients undergoing ERT. In a study by Chen et al., four patients with left ventricular outflow tract obstruction on beta-blockers were noted to have no gradient across the left ventricular outflow tract following one month of ERT. Despite the improvement in cardiac hypertrophy, PD patients undergoing ERT still have an increased risk of long-term conduction abnormalities and tachyarrhythmias.

In general, the monitoring of patients with PD requires a coordinated multi-disciplinary approach by a specialist and individuals who have expertise in the care of these patients. ERT is the only established drug therapy for patients with PD as it targets the enzyme deficiency. Recombinant human acid α-glucosidase (RhGAA) is the only approved ERT currently available and is administered as an intravenous infusion every two weeks. The bioavailability of the recombinant enzyme may be influenced by the development of anti-GAA neutralizing antibodies, which occur at the start of treatment. In cases of IOPD, the probability of developing high titres of anti-GAA antibodies is primarily affected by their cross-reactive immunologic material (CRIM) status.

Patients with IOPD should be offered ERT at a dose of 20 mg/kg every other week. As regards to LOPD, a randomized, placebo-controlled prospective trial of rhGAA was performed in which 90 patients aged ≥8 years of age were randomly assigned to receive treatment either with rhGAA or placebo. Subjects on the active treatment showed significant improvement in the forced vital capacity (FVC) and the six minute walk test.

Although ERT should be initiated as soon as the diagnosis of IOPD or symptomatic PD is established, it may be appropriate to determine the patients' CRIM status prior to initiating treatment, as individuals who do not produce CRIM, may develop higher anti-rhGAA antibodies during ERT and may require modified therapy protocols using immunomodulation, ideally prior to the first infusion. New therapeutic approaches are being tested, one being the development of an antibody-enzyme protein infusion aimed to target both the glycogen within the lysosomes but also within the cytoplasm.

Conclusions

PD is a complex metabolic disease with a heterogeneous clinical spectrum. The severity is related to the varying levels of residual enzyme activity as dictated by the individual's genetic background. The PD cardiomyopathy is often seen in the infantile form of this condition, but cardiac involvement may still be present but less aggressive, in the late-onset sub-type. A multidisciplinary approach is required for the holistic care and management of PD patients. Regular cardiac consultation together with ECG, echocardiography and 24-hour arrhythmia monitoring is necessary. Early commencement of ERT is recommended. Considering the overall limitations of ERT with its high costs, innovative therapeutic approaches are now under development, to reduce the development of anti-rhGAA antibodies as well as to target both lysosomal and cytoplasmic glycogen.

References

15. Limongelli G, Fratta F. Cardiovascular