Anderson-Fabry Disease and Other Lysosomal Storage Disorders

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Lysosomal storage diseases comprise >40 disorders caused by deficient enzymatic activity of lysosomal enzymes that lead to accumulation of substrates in several organs. This review addresses those diseases that involve the cardiovascular system.

Anderson Fabry Disease

This disease is caused by the deficient activity of α-galactosidase A (α-Gal A), which leads to the lysosomal accumulation of globotriaosylceramide. Its inheritance is X-linked and males are usually more frequently and more severely affected than females, and at a younger age. The glycolipid accumulation occurs in several organs including the heart. Thus, the manifestations include cardiac and extra-cardiac findings. The estimated prevalence is ≈1:40000 to 1:60000 males, though a recent study suggests a much higher incidence at 1:3100.2

Genetic Defect

The disease is caused by mutations in the GLA gene which is located at Xq22.1. The gene codes for α-Gal A enzyme with >500 mutations associated with the disease. These include missense and nonsense mutations and splicing defects. For patients with cardiac variant of the disease, GLA mutations are associated with residual enzymatic activity. Prenatal testing is possible and is based on measuring α-Gal A activity or looking for a given pathological GLA mutation in families with known mutations. The latter strategy is also applicable to relatives when patients have a known mutation. Given the location of the GLA gene, an affected male inherits the disease from his mother and can pass it to his daughters only. It is believed that carrier females can develop the disease in part because of random X-chromosome inactivation.3 4

Overall Clinical Presentation

In males with the classic form of the disease, symptoms are noted at a young age and complaints of painful extremities related to peripheral neuropathy and cutaneous lesions often predominate the clinical presentation. The skin lesions (angiokeratoma corporis diffusum) are often in the form of elevated papules (Figure 1) and are usually located in the inguinal, hip, and periumbilical areas. They increase with age, and have a higher prevalence in males. Other findings include reduced sweating, corneal opacities (cornea verticillata), and renal disease.5 Renal involvement is often ushered by proteinuria at a young age with progression to end stage renal disease later in life (after the third decade). However, there are atypical variants of the disease where there is residual α-Gal A activity. These cases present later in life primarily with cardiac involvement, though they can also have renal disease.

Cardiovascular Manifestations

Cardiac Morphology and Function

Cardiac involvement occurs in all forms of the disease: classic and atypical variants. Myocardial biopsies from affected patients show the presence of vacuoles that stain positive for periodic acid-Schiff and Sudan black.6 Concentric lamellar bodies are seen on electron microscopy (Figure 2). Of note, similar deposits have been noted in arterial and capillary endothelial cells. In addition, myocardial fibrosis is present and can be detected by imaging (see below). On a macroscopic level, left ventricular hypertrophy (LVH) is present as well as aortic and mitral valve regurgitation and EKG abnormalities.

Although many patients are asymptomatic, some present with chest pain, dyspnea, or palpitations, as noted in 60% of patients in 1 series.7 This usually occurs in the third decade in males and later on in heterozygous females.7 In patients with the cardiac variant of the disease, cardiac findings are the only manifestations. Importantly, α-Gal A activity is inversely related to the extent of LVH, with age, sex, and renal function also affecting LV mass. The most frequent pattern of LVH is concentric, though there are patients who have asymmetrical septal hypertrophy and rarely dynamic LV outflow tract obstruction.8 9 Some patients have reduced thickness at the basal segment of the inferolateral wall which can be imaged by echocardiography and CMR. In addition, CMR can detect delayed hyperenhancement in that region which appears to be specific for Fabry disease.10 There are LV systolic abnormalities that can be detected by myocardial velocity and strain measurements as well as diastolic dysfunction. Interestingly, some studies have shown that abnormal myocardial function can be detected before the development of LVH using tissue Doppler imaging of the mitral annulus velocities.11 In line with this early report, abnormal longitudinal function was reported using systolic strain rate in patients without LVH, whereas radial strain was impaired in patients with hypertrophy.12 RV involvement...
can occur and is most profound in patients with advanced LV
disease burden and does not appear to improve with enzyme
replacement therapy.13 Valvular thickening has been reported in
some patients along with valvular regurgitation. However, most
lesions are mild and do not necessitate specific intervention.

EKG Abnormalities and Arrhythmias
EKG findings include voltage criteria for LVH and ST-T
changes in younger patients, and first degree atrioventricular
block in older subjects. Pathological Q waves can be present
in the absence of myocardial infarction. Supraventricular and
ventricular arrhythmias occur, including atrial fibrillation and
nonsustained ventricular tachycardia. High grade atrioventric-
ular block is rare and is possibly related to globotriaosylce-
ramide deposition in the conduction system.14,15

Vascular Abnormalities
Hypertension is common (>50% prevalence) in males with
renal disease and is a contributing factor to clinical events in this
patient population. Aortic root dilatation is not uncommon
and aneurysms have been reported in 9.6% of males and 1.9% of
females in a study that included 106 patients from 3 European
countries.16 Small vessel disease of the coronary circulation
has also been reported and was particularly severe in the intra-
mural vessels. It was associated with angina and reversible and
fixed defects on stress perfusion imaging.17 Involvement of the
cerebral circulation with small vessel disease can lead to TIA
and stroke and can be the first manifestation.18

Diagnosis
Careful clinical evaluation of a given patient with cardiac dis-
ease is essential as cutaneous and renal abnormalities along
with family history can lead to a faster diagnosis. On the other
hand, in patients with the cardiac variant of the disease, the
diagnosis can be more challenging because there are few spe-
cific findings that can be detected by cardiac imaging. EKG,
echocardiography, and CMR can all detect the presence of
LVH (though with lower sensitivity for EKG). Likewise, both
echo and CMR can reveal the presence of abnormal cardiac
function which is not specific (Figures 3 and 4 and Movie I
in the online-only Data Supplement). However, replacement
fibrosis by CMR in the basal segment of the inferolateral wall
is a specific finding.10 The presence of thickened hyperecho-
genic endocardium by echocardiography was attributed to
endocardial deposits of globotriaosylceramide in 1 study,19 but
other reports noted low sensitivity20 and thus the absence of
this finding cannot rule out cardiac involvement. With respect
to biomarkers, there is a limited role for measuring serum tro-
ponin or NT-proBNP levels. In general, NT-proBNP levels are
related to disease burden and LV filling pressures.21 A recent
study showed a promising role for the degradation product of
globotriaosylceramide in evaluating the clinical relevance of
potential mutations that can lead to the disease.22

For most males with Fabry disease, the diagnosis can be
established by measuring leukocyte and plasma α-Gal A activ-
ity. With low enzyme (cardiac variant) or undetectable (classic
disease) activity, there is no need for molecular genetic testing
from a diagnostic perspective, though genetic testing is valuable
in males with low normal levels of enzyme activity. It is also use-
ful in identifying carriers in the presence of a known GLA muta-
tion in the family. Enzymatic assay is less useful in females and
when α-Gal A enzyme activity is in the normal range. Molecular
genetic testing is essential in the above scenarios. In addition,
endomyocardial biopsy can identify the combination of sarco-
meric and GLA gene mutations in males and females by show-
ing the coexistence of accumulation of the degradation product
of globotriaosylceramide with myocytes’ disarray.

Differential Diagnosis
Fabry disease should be considered in patients with unex-
plained LVH. Thus, it is usually considered in the differential
diagnosis of hypertrophic cardiomyopathy (HCM), and
2% to 5% of the patients referred with HCM diagnosis have
Fabry disease. Family history plays an important role in the
evaluation of patients with possible Fabry disease (excluding patients with de novo mutations) because male to male transmission does not occur. Asymmetrical LVH and severe dynamic LV outflow tract obstruction in particular, are more common in HCM, though they can be seen in patients with Fabry disease. Glycogen storage diseases are among the other phenocopies of HCM (see below and Table 1). It is currently the usual practice to screen patients with unexplained LVH for these storage diseases (including GLA mutations) before looking for sarcomeric protein mutations that cause HCM.

The disease should also be considered in patients presenting with restrictive cardiomyopathy, including those that might raise the possibility of cardiac amyloidosis. Of note, while cardiac amyloidosis causes increased LV wall thickness, EKG findings and relatively preserved apical strain are helpful in identifying patients with amyloid infiltration. Management

**Treatment of Cardiac Symptoms**

Management of patients with cardiac disease depends on the clinical presentation. In the presence of angina, the presence of epicardial coronary artery disease should be excluded first and standard antianginal therapy including nitrates, β-blockers, calcium channel blockers, and antiplatelet drugs can be offered. Antiplatelet drugs are also considered in patients with TIA or stroke. Antiarrhythmic drugs can be used to convert patients in atrial fibrillation to sinus rhythm, though there is limited experience about the safety of these drugs in Fabry disease. Pacemakers are implanted in patients with symptomatic bradycardia.

In the presence of heart failure symptoms and normal LV ejection fraction (EF), diuretics are administered. In addition, when hypertension occurs in the setting of renal disease, ACE inhibitors should be considered. The latter drugs are also indicated in patients with depressed EF. Importantly, cardiac transplantation in patients with advanced heart failure has been performed without disease recurrence as a result of normal enzyme activity in the donor’s heart.

For symptomatic patients with severe dynamic obstruction despite medical therapy, surgical myectomy and alcohol septal ablation can result in successful relief of symptoms, though there are few cases who have received septal reduction therapy.

**Enzyme Replacement Therapy**

There are 2 galactosidase A enzyme preparations that have been tested in clinical trials. They are alglucosidase-α and alglucosidase-β. An important double-blind study showed that alglucosidase-β was successful in clearing the microvascular endothelial deposits of
globotriaosylceramide from the skin, heart, and kidneys in 20 of 29 patients with Fabry disease. Furthermore, in the open label phase of the study, all patients in the placebo group and 98% of patients in the treatment arm who had biopsies showed clearance of endothelial deposits (after 6 months of therapy). Although 88% of the patients developed IgG antibodies to the enzyme, this was not associated with a reduced response to treatment. With respect to cardiac function, there are few studies showing that enzyme replacement therapy (ERT) can result in an improvement in myocardial strain, but there may be little benefit in patients with replacement fibrosis. From a treatment perspective, CMR can play an important role in identifying patients with fibrosis as well as those without hypertrophy but with increased extracellular volume. There are recent reports showing ERT has no apparent effect on the rate of sudden cardiac death in patients with advanced disease. Notwithstanding, ERT should be considered in patients with cardiac disease and started as early as possible when the benefit may be the most. In addition, one can argue that increasing ERT dose could still be beneficial in patients with advanced disease because the accumulation of degradation products of globotriaosylceramide and interstitial fibrosis can interfere with ERT entrance into the myocytes, which could be overcome with a larger enzyme dose.

Other Treatment Options

There has been a case report of a patient with LVEF of 32% attributable to Fabry disease who was treated with intravenous galactose. Galactose acted as a chaperone that helped the residual lysosomal α-Gal A break down globotriaosylceramide, thus leading to symptomatic improvement and an increase in LVEF to 55% after 2 years of therapy. This case report provides an encouraging alternative to ERT, and there is interest in the clinical utility of pharmacological agents performing the chaperone role.

Glycogen Storage Diseases

Danon Disease

This is a rare lysosomal storage disease caused by deficiency of lysosome-associated membrane protein 2 (LAMP 2). Cardiac manifestations are an important part of the clinical presentation and cardiac disease is the cause of death, be it progressive heart failure or sudden cardiac death.
Genetic Defect
The gene is located at Xq24, and >60 mutations have been reported.\textsuperscript{35} It is an X-linked dominant disease. Once glucose enters the cell, it is either used for energy production or stored as glycogen. Excess glycogen is broken down in lysosomes, but with LAMP2 defects glycogen accumulates in cardiac myocytes leading to the appearance of vacuoles that stain positive with periodic Acid Schiff (Figure 5).

Figure 6. The EKG is from a 22-year-old male with Danon disease who presented with fatigue, palpitations, and dyspnea. Findings are consistent with Wolf-Parkinson-White syndrome.

Figure 7. The echocardiographic images were obtained from the same patient in Figure 6. Although left ventricular wall thickness is increased in all segments, the pattern of hypertrophy is asymmetrical with the highest wall thickness present in the anterolateral wall. There is also posterolateral pericardial effusion (upper left). Myocardial strain measured with speckle tracking shows profound abnormalities in all myocardial segments and is most notable in the basal anteroseptal and inferolateral regions (upper right). Mitral inflow (lower left) shows restrictive LV filling, consistent with markedly elevated LV filling pressures (E refers to mitral early diastolic velocity and A to mitral late diastolic velocity). Tissue Doppler at lateral mitral annulus (lower right) shows markedly reduced systolic (s'), early diastolic (e'), and late diastolic (a') velocities.
Overall Presentation

The usual clinical presentation is the result of disease in skeletal and cardiac muscle and mental changes. Males are more severely affected and present at a younger age than females. Females usually have a more benign course but there are reports of sudden cardiac death in women.36 As to mental changes, these may not be severe enough to be easily recognized because they present in the form of cognitive disabilities with mild to moderate but usually not severe mental retardation.37,38 Nevertheless, they occur with a very high frequency in men and can occur in up to 50% of women.38 Other less frequent findings include neuropathy and peripheral pigmentary retinopathy.38 Skeletal muscle biopsy reveals the presence of vacuoles that contain acid phosphatase positive content39 and serum creatine kinase and alanine aminotransferase levels are usually elevated.

Cardiac Manifestations

The usual findings include LVH in males (HCM phenocopy) with extreme hypertrophy noted in some cases (maximum wall thickness as high as 65 mm). Follow-up of these cases showed the subsequent development of LV dilatation and depression of LVEF.40 In 1 series, there was evidence of scarring and myocyte disarray at autopsy. Some patients can also present with a dilated cardiomyopathy,41 including females who appear to have an equal incidence of hypertrophic and dilated cardiomyopathy. In some patients, vacuolization was not present in the cardiac biopsy but the disease was suspected based on clinical findings of skeletal muscle disease and confirmed by analysis of LAMP2 gene.41 EKG findings of increased QRS voltage and T wave abnormalities have been noticed as well. Wolf-Parkinson-White syndrome occurs in both males and females, though with a much higher frequency in males.38 Figures 6 through 8 show EKG and imaging findings from a patient with Danon disease.

Diagnosis

It is important to consider Danon disease in patients with unexplained LVH. In 1 study, the disease was present in 6% of patients with LVH who underwent myocardial biopsy.42 In another study, 4% of children believed to have HCM had LAMP2 mutations.43 The presence of Wolf-Parkinson-White syndrome, mental changes, and skeletal myopathy can be helpful in raising suspicion of this diagnosis. The disease is most reliably confirmed by analysis of LAMP2 gene.

Management

There is no specific treatment. For patients with Wolf-Parkinson-White syndrome, catheter ablation is usually effective. Implantable cardiac defibrillator can be life-saving because of the danger of sudden cardiac death. With progressive LV dysfunction, cardiac transplantation should be considered.

Figure 8. Short-axis view by CMR shows multiple areas of delayed hyperenhancement (arrows) from the same patient with Danon disease. This is most extensive in the midmyocardial region of the anterolateral and lateral segments of the left ventricle (LV). There is also involvement in the inferolateral segment (epicardial and identified by the black arrow) as well as the septum at LV and (right ventricle)RV junctions. Pericardial effusion is seen as the white space surrounding the heart (courtesy of Dr Dipan Shah).

Figure 9. Images were obtained from deltoid muscle biopsy from a patient with a PRK AG2 mutation that caused conduction system disease, left ventricular (LV) hypertrophy, and glycogen accumulation in skeletal muscles. A, Presence of subsarcolemmal vacuoles (arrows) in a hematoxilin and eosin stained section. B, Positive staining of the vacuoles by periodic acid-Schiff. Panel There is no staining after diastase digestion (C), whereas the electron microscopy image (D) shows the presence of granular nonmembrane bound dense material. Reproduced from Laforêt et al47 with permission of the publisher. Copyright ©2006, Elsevier.
PRKAG2 Deficiency
This is a rare autosomal dominant disease with glycogen storage and is characterized by cardiac hypertrophy, arrhythmias, and conduction defects. The disease is characterized by glycogen accumulation, due to increased cellular uptake of glucose, as opposed to a defect in glycogen degradation. While the disease is not due to lysosomal enzyme defect, it is included in this article as it is important to consider in the differential diagnosis of unexplained LV hypertrophy.

Genetic Defect
Disease-causing mutations in the gene for gamma 2 regulatory subunit of AMP-activated protein kinase (PRKAG2) cause glycogen accumulation (Figure 9). Patients have LVH, but unlike HCM there is no disarray. This gene codes for the γ-2 regulatory subunit of AMP-activated protein kinase, an enzyme that plays an important role in the cellular response to energy demands. Transgenic animal have increased activity of AMP-activated protein kinase along with increased glucose uptake, possibly via upregulation of a sodium-dependent glucose transporter.44 However, a recent study in 6 adult humans with PET showed reduced glucose uptake in comparison with controls.45 This may be the situation in patients with late disease as opposed to early findings.

Clinical Presentation
Patients present at a young age with arrhythmias related to Wolf-Parkinson-White syndrome, cardiac hypertrophy, and skeletal myopathy. Later on, LV systolic dysfunction can develop and high grade atrioventricular block can necessitate pacemaker implantation.46–48

Diagnosis
The disease should be considered in children with features suggestive of HCM, particularly when accessory pathways may be present as inferred from EKG findings. The same findings in adults should trigger molecular analysis for the PRKAG2 gene.

Management
Ablation of the accessory (fasciculoventricular or atrioventricular) pathways is an effective treatment for patients presenting with supraventricular tachycardia. In a transgenic animal model, early postnatal transgene suppression resulted in absent accessory pathways but not cardiomyopathy or conduction system disease.49 This suggests that it is possible to limit ventricular preexcitation by reducing intracellular glycogen content.

### Table 2. Mucopolysaccharidosis

<table>
<thead>
<tr>
<th>Type</th>
<th>Mucopolysaccharidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Hurler, Scheie)</td>
<td>Type II (Hunter)</td>
</tr>
<tr>
<td>Deficient enzyme</td>
<td>Alpha L-iduronidase</td>
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<td>Gene locus</td>
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<td>Hydrocephalus</td>
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<tr>
<td>Ophthalmologic</td>
<td>Corneal clouding</td>
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<tr>
<td>Hepatoplenomegaly</td>
<td>Hepatoplenomegaly</td>
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<tr>
<td>Skeletal involvement</td>
<td>Bone and joints</td>
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<tr>
<td>Cardiovascular</td>
<td>AR, AS, MR, MS, CAD</td>
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<tr>
<td>Gastrointestinal</td>
<td>Hernia, diarrhea</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Reduced FVC</td>
</tr>
<tr>
<td>Treatment</td>
<td>SCT, ERT</td>
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</tbody>
</table>

AR indicates aortic regurgitation; AS, aortic stenosis; CAD, coronary artery disease; ERT, enzyme replacement therapy; FVC, forced vital capacity; MR, mitral regurgitation; MS, mitral stenosis; PR, pulmonary regurgitation; and SCT, stem cell transplantation.

### Table 3. Mucolipidosis

<table>
<thead>
<tr>
<th>Type II</th>
<th>Type III α/β</th>
<th>Type III γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzymatic problem</td>
<td>UPDGlcNAc 1-P-transferase</td>
<td>UPDGlcNAc 1-P-transferase</td>
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<td>Mode of inheritance</td>
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<td>Autosomal recessive</td>
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<td>Delayed development</td>
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<td>Ophthalmologic</td>
<td>Epicanthal folds</td>
<td>Epicanthal folds</td>
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<tr>
<td>Hepatoplenomegaly</td>
<td>Rare splenomegaly</td>
<td>Absent</td>
</tr>
<tr>
<td>Skeletal involvement</td>
<td>Bone deformity, hip dislocation</td>
<td>Joint stiffness</td>
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<tr>
<td>Cardiovascular</td>
<td>MR, AR, LVH, RVH, PH</td>
<td>MR, AR, LVH, RVH</td>
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<tr>
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<td>Umbilical hernia</td>
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<tr>
<td>Respiratory</td>
<td>Hoarseness, ILD</td>
<td>Hoarseness, bronchitis</td>
</tr>
<tr>
<td>Treatment</td>
<td>Supportive</td>
<td>Supportive, pamidronate</td>
</tr>
</tbody>
</table>

AR indicates aortic regurgitation; ILD, interstitial lung disease; LVH, left ventricular hypertrophy; MR, mitral regurgitation; PH, pulmonary hypertension; and RVH, right ventricular hypertrophy.
Pompe Disease (Glycogen Storage Disease–Type II)
This is an autosomal recessive disease, and both parents are usually heterozygous with a 25% chance of disease in their offspring. Presentation spans from in utero to late onset disease in adults. The disease can be fatal in neonates because of cardiac involvement if undiagnosed.

Genetic Defect
The defect is attributable to deficiency of the lysosomal enzyme acid alpha glucosidase. The gene (GAA) is located at 17q25.3. There are >150 mutations including nonsense, gene rearrangements, and splicing defects.50 Complete absence of enzyme activity results in early onset of severe disease, whereas residual enzyme activity is seen in patients with adult onset disease.

Overall Presentation
Infants present with muscle weakness, hypotonia, and hepatomegaly. Muscle weakness includes the diaphragm, which can lead to respiratory problems and recurrent pulmonary infections. Creatine kinase levels are elevated. Urinary levels of tetrasaccharides can be used to monitor patients with the infantile onset of disease.51 Proximal muscle weakness is the main presentation in patients with late onset disease.

Cardiac Manifestations
Cardiac involvement is present in neonates and juvenile forms of the disease. It is characterized by cardiomegaly, LVH, and LV outflow tract obstruction. EKG findings include increased QRS voltage and short PR interval. Echocardiographic imaging of affected neonates reveals LVH with or without dynamic obstruction. LV systolic dysfunction with dilated LV and depressed EF can be seen later on.50

Diagnosis
For children, the diagnosis should be considered in the presence of features suggestive of HCM. The presence of severe skeletal muscle abnormalities should raise strong clinical suspicion of the diagnosis. The diagnosis can be reached by measuring acid α-glucosidase activity from blood and confirmed by enzyme activity in cultured fibroblasts and molecular genetic analysis.

Management
For patients who present with infections, antibiotics are administered. ERT is available and can be successfully given to patients with the infantile form of the disease. On long-term follow-up, it is possible to observe regression of LVH in some patients, though ERT does not appear as effective against arrhythmias.52

Mucopolysaccharidosis
This is a group of lysosomal storage diseases that affect children and adolescents and involve several body organs.53–56 Cardiovascular abnormalities are most frequently seen in mucopolysaccharidosis types I, II, and VI (up to 88% in some series). Table 2 presents a summary for these 3 types. In general, urinary levels of glycosaminoglycans (dermatan sulfate, heparan sulfate, keratan sulfate) are elevated and can be used for initial evaluation and follow up of the response to treatment with ERT or stem cell transplantation.57–59

Mucolipidosis
Cardiac disease is present in patients with mucolipidosis types II, IIIα/β, and IIIγ (Table 3). These diseases manifest in childhood.60–62 In general, lysosomal hydrolases are elevated in plasma but their cellular activity is defective. This happens as a result of deficiency of a phosphotransferase enzyme, which is needed to phosphorylate glycoproteins so they can be targeted to the lysosomes for subsequent breakdown.

Gaucher Disease
This is an autosomal recessive disease attributable to deficiency of β-glucocerebrosidase. There are 3 forms of the disease and in types 2 and 3, neurological manifestations are present. In type 1, hepatosplenomegaly, bone marrow disease, and skeletal abnormalities are present. Cardiac manifestations are rare, except in a rare homozygous D409H mutation. In a case report of the latter mutation, calcification was present in the aorta and aortic and mitral valves in 3 siblings, and 2 of the 3 died after aortic valve replacement.63

Conclusion
There are several lysosomal storage diseases that affect the cardiovascular system. They should be considered in the differential diagnosis of children and adults presenting with cardiac hypertrophy. Diagnosis is confirmed based on enzymatic and molecular genetic analysis and if needed skeletal muscle or endomyocardial biopsy. The identification of these disorders is important because of the availability of ERT for some diseases, the need for family screening, as well as appropriate patient management and counseling given the particularly dismal prognosis of some cases in the absence of life-saving measures as implantable cardiac defibrillator implantation and early cardiac transplantation, particularly in patients with Danon disease.

Disclosures
None.

References

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