almost always to loss of autonomous walking and forces the patients to use the wheelchair. Lung function becomes increasingly compromised with the duration of the illness and assisted ventilation is required by non-invasive methods or by tracheostomy. Dependence on a wheelchair usually starts a decade after the diagnosis while that on assisted ventilation may start earlier. Respiratory failure is almost always the cause of death in these patients. Today it seems possible to stop this tragic sequence of events by ERT, but for this purpose it is necessary to diagnose the disease at its early stages.

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S1.4 Cardiovascular involvement in Pompe disease

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The heart is part of the clinical phenotype of Glycogen storage disease type II (GDS II; Pompe disease; or acid maltase deficiency) since its original description. In 1932, Johannes Pompe, a Dutch pathologist, described the case of a 7-month old infant who died suddenly for a severe idiopathic hypertrophy of the heart (1). Although other cases of massive hypertrophy of the heart have previously been described, Dr. Pompe first demonstrated that not only the heart was involved, but also other organs showed a vacuolar storage of glycogen ("cardiomegalia glycogenica") (1). From a cardiologist's point of view, Pompe disease is one of the leading cause of familial (idiopathic) hypertrophic cardiomyopathy in neonatal and paediatric age (2). GSD II is broadly divided into two onset forms based on the age symptoms occur.

Infantile onset ("Classic" Form)

In the classic infantile form (Pompe disease), cardiomyopathy and conduction disorders, along with muscular hypotonia ("floppy baby"), macroglossia, and organomegalia, are the cardinal features.

Cardiomyopathy is generally of the hypertrophic type, demonstrating a severe thickening of the septum ("asymmetric" hypertrophy), or frequently of both the septum and free walls of the left and right heart ("concentric" hypertrophy). When the septal hypertrophy is very pronounced, a left outflow tract obstruction (favoured by a systolic anterior motion of the anterior mitral leaflet) may be present to worsen the disease (about 30% of the cases). Both diastolic and systolic dysfunction can be observed. Levine JC et al. showed a rapid regression of left ventricular hypertrophy in response to enzyme replacement therapy (ERT) in most of the patients, and systolic ventricular function was preserved despite rapid changes in ventricular mass and size (3).

Glycogen storage involves not only cardiac myocytes, but also the special cells of the conduction system (particularly, the A-V node and the His-bundle cells), representing the hystological background of classical electrocardiographic abnormalities in Pompe disease: pre-excitation patterns (short PR, delta waves), atrio-ventricular blocks and bundle branch abnormalities. The pathogenesis of ventricular pre-excitation (Wolf Parkinson White syndrome, WPW, when symptomatic) is unknown, though is clear that the pattern does not reflect the presence of an accessory pathway (as in the classic WPW) (4). The suggested hypothesis are: a) a "direct insulating effect" of the glycogen on the conduction system; b) an "indirect insulating effect" of the glycogen on the conduction system, by the anatomic interruption of the annulus fibrosus (which acts as an "electric insulate" between the atria and the ventricles (4).

Differential diagnosis

A metabolic or mitochondrial cardiomyopathy may mimic the presentation of GDSII cardiomyopathy (5). The presence of encephalomyopathy, metabolic acidosis (with or without hypoglycemia), the increase of lactate and lactate/piruvate ratio (normal: < 15:1; abnormal: 25:1) may suggest a mitochondrial cardiomyopathy. Hypoglycemia, with or without variation of plasma ketones, insulin, free fatty acids or carnitine may represent an hallmark of metabolic cardiomyopathies (i.e. beta oxidation deficits).

Infantile onset ("Non Classic" Form)

Compared to the classic form, the onset of the "non classic form" of Pompe disease is generally after the first year of age, with a less severe picture, including muscle weakness, cardiomyopathy, and sometimes macroglossia and organomegalia.

Conduction abnormalities and ECG signs of ventricular hypertrophy are generally part of the disease spectrum. Echocardiographic appearance of cardiac hypertrophy is generally less severe and progressive, lacking the left ventricular obstruction and the systolic dysfunction that significantly worsen the classic phenotype. However, the clinical presentation may be extremely various, as demonstrated by Suzuki et al. (6), which reported on a male who developed cardiomyopathy at 12 years of age and died of heart failure at age 15 years without any clinical and/or histological sign of skeletal myopathy.

Differential diagnosis

On the cardiology point of view, the differential diagnosis is with overlapping phenotypes, including syndromic, mitochondrial or metabolic cardiomyopathies (5). Ventricular pre-excitation on the ECG and the presence of idiopathic left ventricular hypertrophy in children are common feature of storage diseases (AMP-kinase disease, Danon disease), and mitochondrial disorders (MELAS, MERFF). Particularly, Danon disease is an X-linked glycogen storage disorder due to the absence of the LAMP-2, lysosome-associated membrane protein 2 (evidenced by Immuno-

histochemistry or by genetic sequencing). Compared with Pompe disease, cognitive impairment and retinitis pigmentosa may be distinctive features of the diseases.

Adult Onset

Adult-onset acid maltase deficiency may simulate limb-girdle dystrophy and the heart may represent a rare finding. Nevertheless, the cardiac phenotype of adults with GDSII is poorly characterized, so far.

Descriptions of heart abnormalities in adults with Pompe disease are sparse. Recently, a relatively large cohort of adults (87 patients, median age 44 years old, 51% males) with Pompe disease have been evaluated (7). A short PR interval was present in 10%, 7% showed a decreased left ventricular systolic function, and 5% had elevated left ventricular mass on echocardiogram. No change in cardiovascular status associated with enzyme replacement therapy (ERT) was observed.

Severe vacuolization of vascular smooth muscle with accumulation of glycogen, particularly involving large and small cerebral arteries with aneurysm formation, have previously been reported (8, 9). Gungor D et al. (10) described survival of 268 patients with Pompe diseases, 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 for aortic dissection. The evidence of smooth muscle involvement seem to be confirmed by the finding of an increased aortic stiffness in adults with Pompe disease (11), which may be due to glycogen storage in the vessel wall, causing reduced vascular elasticity. These findings deserve future investigations.

SUMMARY CLINICAL SYNOPSIS

Principal investigations:

- ECG: short PR (WPW syndrome), signs of left ventricular hypertrophy with repolarization abnormalities, Atrioventricular and/or intraventricular conduction delays.
- Echo: left ventricular hypertrophy (or, biventricular hypertrophy), with or without: a) left ventricular outflow tract obstruction (about 30%); b) systolic dysfunction; c) diastolic dysfunction (generally, present).

Other investigations:

- 24 hours ECG Holter: intermittent WPW and/or conduction delays.
- Functional capacity study: by six minute walking test and/or cardiopulmonary exercise test.
- Cardiac Magnetic Resonance Imaging (CMRI), with late gadolinueum analysis: to study cardiac morphology and function, and to determinate a non invasive, "texture characterization" of the cardiac muscle.

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S1.5 Role of the pulmonologist in the late-onset Pompe disease

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Pompe disease is a single disease continuum that includes variable neuromuscular symptoms and rates of progression. However, specific clinical features, such as an early onset of respiratory problems preceding limb muscular weakness, distinguish Pompe disease from other neuromuscular diseases in which respiratory insufficiency occurs after loss of ambulation.

The management of Pompe disease also differs from other neuromuscular diseases in that specific treatment is now available, making early recognition of the disease a priority. Late-onset form of Pompe disease, that may occur at any age after the first year of life, is characterized by slow and progressive loss of function of skeletal muscles. Respiratory failure is the major cause of morbidity and mortality. The evaluation and monitoring of parameters such as FVC, MIP, MEP, blood gases, together with the clinical examination can delineate the profile and the decline in lung function, in order to provide early and effective therapeutic intervention. In patients with restrictive chest wall disease, the indication in VMD should be in the presence of symptoms such as fatigue, dyspnea, morning headaches, disturbed sleep, daytime hypersomnia associ-