S1.3 Adult-onset Pompe disease

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Introduction

Clinical diversity is a common phenomenon in lysosomal storage diseases and has led to the introduction of clinical subtypes. The natural course of Pompe disease is primarily dictated by the type of mutations in the acid alpha-glucosidase gene (GAA) or rather by the residual enzyme activity of acid alpha-glucosidase resulting from the combination of the mutated allelic products. Thirty per cent of normal acid-alpha-glucosidase activity in skeletal muscle is the critical threshold below which lysosomal glycogen storage starts and disease symptoms manifest. Patients with late onset Pompe disease generally have more acid-alpha-glucosidase activity in muscle cells and/or fibroblasts than severely affected infants with classic infantile Pompe disease. These latter never have more than 2% of normal acid-alpha-glucosidase activity. The so-called adult form of Pompe disease is not an autonomous entity with respect to the classic and juvenile ones, but differs from them mainly for the lower speed of accumulation of glycogen within the lysosomes which explains the late onset of skeletal muscle tissue changes and clinical manifestations.

Epidemiology and first diagnosis

The adult form of Pompe disease has an incidence of one on 57.000 newborn per year. It manifests by convention after eighteen years of age. Actually if we consider data from the literature and our own it emerges that the first diagnosis is usually made within the third or the fourth decades of life (the mean age of the patients at the diagnosis ranges 27-41.4 years, in the series of van der Beek (1) and Müller-Felber (2), respectively). By careful history collection, however, it is almost always possible to date many years back the early disease manifestations (3 to 10 years on average). This relatively long and variable time interval between first symptoms and correct diagnosis is mainly related to the slow progression of symptoms which are relatively unspecific at least in the first phases of the disease. This frequently leads both the patient and his doctor to underestimate the importance of the early symptoms and an incorrect diagnosis at this phase of the disease is usually the rule. A further element of confusion for many practitioners is that Pompe disease is better known as an infantile disease and is ignored, as a rule, in conditions which involves adults.

It is interesting, that in his series of patients with adult-onset Pompe disease Müller-Felber (2) calculated that it passes 7 years on average between the first medical consultation for symptoms related to the disease and the correct diagnosis. This time interval decreases to 3 years, on average, in the series of Dutch patients of van der Beek (1). This better performance is likely due to the widespread awareness of the disease among the physicians of the same country of doctor Pompe. These data demonstrate how important is to organize educational events to improve the knowledge of Pompe disease among medical professionals.

Symptoms at onset

The symptoms more frequently complained by patients are reported in Table 1. These are represented by slowly progressing reduction of muscle strength, which mainly involves lower limbs. This causes difficulties with running and walking, climbing up and down stairs, getting up easily from chairs, and rising up from a lying position. Almost all the patients retrospectively remember difficulties during physical education or athletic games during their childhood. These symptoms are associated with, or often preceded by, diffuse muscle pain, lumbar pain and muscle cramps at the lower limbs. Profound tiredness even after moderate exercise as well as frequent downfall are reported. In about 13% of the patients the very first symptoms are represented by respiratory difficulties, with recurrent pulmonary infections, dyspnea even after moderate exercise, as well as snoring, headache at awakening and daytime sleepiness due to sleep-disordered breathing and nightly hypoventilation. Gradual body weight loss, due to lack of appetite and difficult swallowing, cardiac arrhythmias, hearing loss and moderately increased Creatine Kinase (it is often an incidental finding) are less frequently reported symptoms which should lead back to the disease.

As mentioned above onset symptoms are nonspecific and are not likely to suggest Pompe disease, unless the diagnosis has already been made in some relatives. In the later case, even the most trivial of these symptoms becomes a wake-up call to the patient and the physician. Otherwise it is only the progressive deterioration of motor performance and/or respiratory conditions to lead the patient to a specialist of neuromuscular diseases.

Clinical features

The clinical picture in these patients is that of a proximal myopathy (Table 2), the severity of which varies from patient to patient being mainly related to the duration of the disease at the time of the observation. Pelvic girdle muscles and proximal muscles of lower limbs are almost always earlier and more severely affected than those of the shoulder girdle and upper limbs. In particular, in this disorder there is a preferential involvement of glutei, adductors of the thigh, and paraspinal muscles. This

Table 1. Symptoms at onset.

Progressive limitation in walking
Diffuse myalgias, muscle cramps
Intolerance to exercise
Frequent falls
Recurrent pulmonary infections
Dyspnea on exertion
Morning headaches
Daytime sleepiness
Weight loss
Difficulty in swallowing
Heart rhythm disturbances
Hearing loss
Elevated CK

explains the waddling gait, the lumbar hyperlordosis sometimes accompanied with scoliosis, and the Gower's maneuver, which usually occur in these patients. Subsequently, the weakening manifests, even if to a lesser extent, at the shoulder girdle muscles. Particularly involved are the fixators of the scapula (lower trapezius, rhomboid, and subscapularis), and the neck flexors (sternocleidomastoid) and this explains features such as winging scapula and difficulty of the patient in lifting his head while lying in the supine position. The weakness of segmental and axial muscles is associated with a more or less early weakness of the respiratory muscles (diaphragm and intercostals muscles). For this reason, it is always advisable in the clinical evaluation of these patients to inquire if they complain of related disorders such as orthopnea, exertional dyspnea, ineffective coughing, which are initial signs of respiratory failure. For this purpose, it is useful to invite the patient to count out loud during the expiratory phase, first supine and then sitting. A lower count in the supine position is indicative of a reduced vital capacity. The finding of a reduced vital capacity is important from the point of view of the diagnostic process, and should prompt physicians to refer the patient to the pulmonologist for a more thorough clinical and instrumental evaluation.

The phenotypic spectrum of late-onset forms has, however, enriched with other features (3), although rare (Table 3). Apart from the involvement of the muscles of mastication and swallowing, cases have been reported with ptosis and a distribution of muscle weakness with a scapulo-peroneal pattern. Rhythm disturbances such as Wolf-Parkinson-White syndrome have been reported, as well as aneurysms of the basilar artery, the carotid arteries, and the thoracic aorta. The frequent detection of such abnormalities should prompt a search for their presence in all patients with Pompe disease. The muscle weakness is always associated with a gradual muscle wasting and reduced reflexes. Cognitive, sensory and cerebellar disorders as well as a cardiomyopathy have never been observed.

Differential diagnosis

The clinical presentation of Pompe disease in the adult, which is almost always that of a predominantly proximal myopathy with prevailing expression at level of the pelvic girdle, is nonspecific, and such to induce to make an alternative diagnosis, in the first instance. Some of these alternative diagnosis are shown in Table 4. Many of these conditions are easily refuted by applying the usual diagnostic protocol for neuromuscular diseases. A differential diagnosis may be challenging with some forms of autosomal recessive limb-girdle dystrophies, especially the 2A or calpainopathy and the 2I, as well as with the Danon disease, a vacuolar myopathy in which, however, there is always a cardiomyopathy. Several diagnostic algorithms have been proposed for the diagnosis of Pompe disease in the adult (4). All are modeled in their general lines and in the early stages on the protocol that is implemented for each neuromuscular disorder: clinical evaluation, measurement of muscle enzymes in serum (this must be done in all patients with respiratory disorders not related to lung and/or cardiac diseases and in all patients with an involvement of the diaphragm!), and EMG/ENG evaluation. The detection of suggestive features of Pompe's disease or of a nonspecific myopathy places the indication to a muscle biopsy. This last showing a vacuolar myopathy with accumulation of glycogen suggests Pompe disease and leads to perform the assay acid alpha-glucosidase activity in various tissues (this can be done on skeletal muscle, fibroblasts, or blood). Values of enzyme activity equal to or less than 30% of normal indicate by themselves the diagnosis of Pompe disease, which must be finally confirmed by bio-molecular analysis of GAA gene.

Conclusions

An early diagnosis offers the patient the opportunity to start a therapy that, today, appears able to positively modify the natural course of the disease, and address the family to genetic counseling. It should not be forgotten that the natural course of the disease, although mild and slow, has led invariably to muscle impairment of variable degree, prior the enzyme replacement therapy was available. Muscle impairment significantly impacts on the quality of life of these patients, causing reduction of physical performances, worsening of general health, resizing of family and social roles related to physical efficiency, and social withdrawal. In fact, the progression of the disease leads

Table 2. Main clinical features.

Skeletal muscles
Weakness of the pelvic girdle muscles (glutei), proximal lower extremities (thigh adductors) and paraspinal muscles
• Waddling gait
• Gowers' maneuver
• Lumbar hyperlordosis with scoliosis
Weakness of the shoulder girdle muscles
• Winging scapula
Respiratory muscles
Weakness of diaphragm and accessory muscles
• Orthopnea
• Exertional dyspnea
• Invalid cough

Table 3. Less frequent clinical features.

Weakness of the muscles of mastication and swallowing
Ptosis
Muscle weakness with scapulo-peroneal pattern of distribution
Rhythm disturbances such as Wolff-Parkinson-White
Basilar and carotid arteries aneurysms, thoracic aorta aneurisms

Table 4. Differential diagnosis.

Becker muscular dystrophy
Limb-girdle muscular dystrophies (2A and 2I)
Dystrophy of Emery-Dreifuss
Spinal Muscular Atrophy type III
Danon disease
Myofibrillar myopathies
Nemaline Myopathy adult form
Metabolic myopathies
Muscle glycogen storage disease (type V, VII)
Polymyositis

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.

References

1. Van der Beek NA, Hagemans ML, van der Ploeg AT, et al. Pompe disease (glycogen storage disease type II): clinical features and enzyme replacement therapy. Acta Neurol Belg 2006;106:82-6.
2. Müller-Felber W, Horvath R, Gempel K, et al. Late onset Pompe disease: clinical and neurophysiological spectrum of 38 patients including long-term follow-up in 18 patients. Neuromuscul Disord 2007;17:698-706.
3. Van der Ploeg AT, Reuser AJJ. Lysosomal storage disease 2. Pompe disease. Lancet 2008;372:1342-53.
4. American Association of Neuromuscular & Electrodiagnostic Medicine Diagnostic criteria for late-onset (childhood and adult) Pompe disease. Muscle Nerve 2009;40:149-60.

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-