CASE REPORT

Late-onset Pompe Disease: A Diagnostic Challenge

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Abstract:

Pompe disease is an autosomal recessive, lysosomal storage disorder wherein affected individuals are deficient in the lysosomal enzyme acid alpha-glucosidase (acid maltase). Here, we describe a case of a 2-year-old male child, who initially presented at the age of 16 months with complaints of difficulty in walking without support associated with frequent falls. On follow-up after 6 months, progressive deterioration in clinical signs was noted. His serum Creatine Phosphokinase (CPK) levels were 2067 U/L. Given the progressive nature of the condition, we ruled out congenital muscular disorder, metabolic and endocrine myopathy. A clinical exome sequence was ordered to check for the myopathy panels. The results revealed a homozygous missense variation in exon 11 of the Acid Alpha Glucosidase (GAA) gene. His alpha-glucosidase levels were 0.8 nmol/hr/mg, which was indicative of the deficient activity of the enzyme in the leukocytes.

Keywords: Pompe disease, Glycogen storage disease II, clinical exome sequence

Introduction:

Pompe disease (glycogen storage disease type II, acid maltase deficiency) is an autosomal recessive, lysosomal storage disorder wherein affected individuals are deficient in the lysosomal enzyme acid a-glucosidase. Abnormal lysosomal glycogen accumulates in various sites, particularly in the myocytes of skeletal, cardiac, and smooth muscle [1]. The classic-infantile form of the disease was first described by Pompe in 1932 [2]. The incidence of Pompe disease is higher in certain populations, such as African–Americans [3]. Classic infantile cases present shortly after birth with generalized, severe muscle weakness, and hypertrophic cardiomyopathy. Patients with non-classic variants of Pompe disease usually have no hypertrophic cardiomyopathy and present with a more slowly progressive limb-girdle muscle weakness, which eventually results in wheelchair dependency, respirator need, and shortened life expectancy [4]. Here we present a case of a non-classic variant of Pompe disease confirmed by clinical exome sequencing.

Case Report:

A 2-year-old male child, an issue of 3rd-degree consanguineous marriage, presented with complaints of difficulty in getting up from the sitting position and climbing stairs. The boy started walking around 16 months of age but subsequently after 2 months (i.e. at 18 months of age), he had difficulty in walking without support associated with frequent falls and slight imbalance while walking. His language and developmental milestones were normal. His birth history was unremarkable. General examination findings were unremarkable. Signs of proximal muscle weakness were noted by positive Gowers signs, lordotic gait, and a pattern of climbing stairs. His lower limb

reflexes were sluggish. Given the predominant proximal muscle weakness in an otherwise normal child, we suspected primary muscle weakness like congenital myopathy as a probable cause.

During his previous consultation with a pediatrician for a routine evaluation at the age of 1 year, his laboratory investigations had revealed persistent high Serum Glutamic Pyruvic Transaminase (SGPT) as 570 U/L and serum Creatine Phosphokinase (CPK) levels as 2067 U/L. However, on palpation, hepatosplenomegaly was not noted. The child was observed for 6 months, but during that time little deterioration was noted.

We sent his blood samples for laboratory investigations looking for CPK, and random Blood Sugar Levels (BSLs), Thyroid Stimulating Hormone (TSH). His serum CPK level was 1724 U/L. His TSH and BSL were reported normal. Besides, a 2D echocardiogram (Echo) test was ordered. The reports were suggestive of early changes of hypertrophic cardiomyopathy, with good biventricular functions. Given the findings, we suspected it to be a case of progressive muscle disease and ruled out congenital muscular dystrophy, metabolic myopathy, and endocrine myopathy. A clinical exome sequence was done to look for the myopathy panel. The genetic report described a homozygous missense variation in exon 11 of the Acid Alpha Glucosidase (GAA) gene (chr17:g.80110945T>C; Depth: 147x) that results in the amino acid substitution of threonine for methionine at codon 519 (p.Met519Thr; ENST00000302262.8) was detected, thus indicating Pompe disease (Glycogen storage disease - II) as the diagnosis.

Since this child had an onset of muscle weakness at the age of 1½ years, with findings inconsistent with classic infantile Pompe, the boy was diagnosed with late-onset Pompe disease. Further, tests were ordered to check the levels of the enzymes alpha and beta-glucosidase. The alpha-glucosidase was 0.8 nmol/hr/mg and the beta-glucosidase was 79.5 nmol/hr/mg. Thus, the deficient activity of alpha-glucosidase was consistent with the diagnosis of Pompe disease (Glycogen Storage Disease type II). The enzyme levels were measured by fluorometry assay with an artificial substrate. The parents were informed about the prognosis and the child was roped into the clinical trial of enzyme replacement therapy (Myozyme). So far, he has been administered with four vials of Myozyme every two weeks of dosage 20mg/kg, for three months. To look for any cardiac changes, an Electrocardiogram (ECG) and, a 2D Echo was repeated. On ECG (Fig. 1), a normal sinus rhythm with HR of 130/min with normal QRS axis with normal PR interval (0.12 sec) with normal QTc interval (0.40 sec) with no ectopic beats was noted. On a 2D Echo, a decrease in the severity of LV wall thickness was seen as compared to the earlier report. It is too early to correlate this finding with the effect of Myozyme administration. Regular visits every 3 months and follow-up 2D Echo after 1 year have been advised.

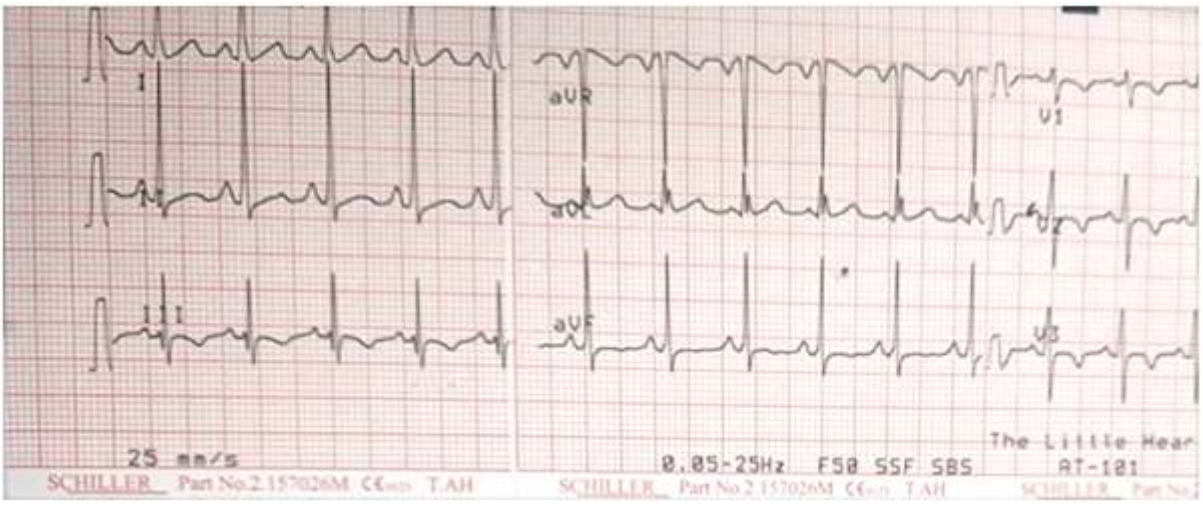

Fig. 1: Electrocardiogram showing Normal Sinus Rhythm

Discussion:

Pompe's disease is a progressive, debilitating neuromuscular disorder resulting from the deficiency of a lysosomal enzyme, GAA. Pompe disease is broadly classified into Infantile Onset Pompe Disease (IOPD) and Late Onset Pompe Disease (LOPD) forms, according to the age of onset [5]. The disease variants are related to the levels of residual GAA activity in muscles; less than 3% of normal enzyme activity is seen in severe infantile cases and residual levels ranging from 3-30% of normal seen in late-onset forms [6]. The infantile-onset Pompe disease form is the most aggressive form of the disease. Almost all the patients with the infantile-onset present with symptoms within the first few months of life and have a rapidly progressive disease course. In comparison, patients with late-onset Pompe disease have a less rapid and variable course, where symptoms may begin from infancy to adulthood. The age of symptom onset, rate of progression, and sequence of muscle involvement vary in each patient [5]. Typical symptoms in children include weakness of the limb-girdle muscles, delayed motor development, and atypical symptoms include disproportionate weakness of the neck flexors, unexplained fatigue, persistent diarrhoea, and an elevation of transaminase levels should be suspected with Pompe disease. In study by Capelle *et al.*, the children underwent measurements of CK, Transaminases (ALT and AST) levels, regardless of symptoms [4]. All the children in their study had elevated CK, ALT, and AST levels. Our patient also has had a persistent elevation in ALT levels for the past year. It is worth noting that, in rare cases, CK, ALT and AST may be normal [4]. Pompe disease should be included in the differential diagnosis in patients presenting with limb-girdle syndrome or symptoms suggestive of respiratory muscle involvement. CK levels are usually elevated (ranging from 1.5 to 15 times the upper limit of normal in adults) in late-onset Pompe disease patients. The determination of partial or complete deficiency of GAA enzyme activity in blood or fibroblasts is the gold standard test for diagnosis in Pompe disease. The currently available GAA enzyme activity assays are both reliable and

sensitive [6]. Elevations of CK, ALT, AST, and LDH levels are sensitive but are non-specific indicators for late-onset Pompe disease as they can be seen in 95% of those affected. Elevation in the transaminases in presymptomatic stages can lead to a mistaken diagnosis of liver disease if CK has not been measured. There are two ways to confirm a diagnosis of late-onset Pompe disease, through a second assay to confirm the reduced activity of the acid α-glucosidase enzyme or through molecular genetic analysis [7]. In our case, we confirmed the diagnosis by clinical exome sequencing and reduced the activity of the acid α-glucosidase enzyme. At present, enzyme replacement therapy with recombinant human acid a-glucosidase, Myozyme is the only option. Regular follow-up visits and routine cardiac function tests are advised for several years to assess the full effect of therapy.

Conclusion:

It is very important to determine the type of Pompe disease since the late-onset has a better prognosis than the classic type. There is little information on presenting signs and symptoms in children who do not fulfil the criteria of classic-infantile Pompe disease, we hope to increase the awareness amongst clinicians about the disease presentation.

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