Infantile-Onset Pompe Disease

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Introduction and history: The glycogen storage disorders may show two different presentations. One group present with permanent and progressive weakness (such as GSD II, GSD III and GSD IV).Another group have intermittent episodes of weakness, muscle pain and/or myoglobinuria(such as Mc Ardle disease). Glycogen storage disease type 2 is caused by acid maltase deficiency. GSD II is an autosomal recessive disorder that was first described by Dutch pathologist Joannes C. Pompe in 1932. And can be categorized into two types, based on the age of onset of disease and degree of organ involvement: infantile (**the most severe presentation**),and late type (childhood and adult). Pompe disease is caused by deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA) or acid maltase. and is the only members of glycogen storage diseases that is classified also as a lysosomal storage disorder.

- **genetic and Pathology:** The incidence of pompe disease has been estimated to be 1 in 40,000 live births and its prevalence about 1 in 146000. The defective gene is located on chromosome 17q25.2-25.3.The main pathologic feature of pompe disease is a vacuolar myopathy and intralysosomal accumulation of glycogen in cardiac, skeletal and smooth muscle fibers, but there is also aggregation of large amounts of PAS positive materials in another sites (liver, renal tubules, anterior horn cells of spinal cord and brain stem nuclei).

Clinical features: Acid maltase has no function in maintaining blood glucose; therefore hypoglycemia is not a feature of this disease. Because hypotonia and muscle weakness are part of manifestations of this disease, it has also been classified as a neuromuscular disease or a metabolic myopathy. Symptoms of infantile pompe disease may begin from neonatal period, but usually appear at a mean age of 1-2 months. Initial symptoms are profound hypotonia without atrophy, feeding difficulties, weakness and respiratory impairment. These patients have little spontaneous movements and weak cry. Gradually cardiomegaly and respiratory insufficiency
develops and serial echocardiography shows progressive left ventricular enlargement. Macroglossia and Hepatosplenomegaly are also present. Deep. tendon reflexes are progressively lost due to anterior horn cell involvement. Without enzyme replacement therapy (ERT), pompe disease ultimate's in profound generalized weakness and hypertrophic cardiomyopathy with rapid progression to death occurring before 2 years of age. Late- onset forms of pompe disease including childhood, juvenile and adult type usually show progressive proximal muscle weakness and typically not including severe

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cardiomyopathy(or absence of cardiomyopathy).

Laboratory tests: EKG in these patients reveals abnormalities, including short PR intervals, depressed ST segment, inverted T wave and high QRS complexes. The CXR shows massive cardiomegaly and EMG illustrates myopathic changes. Other useful diagnostic tests are echocardiography and pulmonary function test that can demonstrate hypertrophic cardiomyopathy and respiratory compromise, respectively .Elevated creatine kinase(CK) levels is seen(as high as 2000 UI/L). Evaluation of muscle and liver biopsy by light and electron microscopy demonstrates large amounts of glycogen with normal structure, although abscence of glycogen in muscle biopsy is not against the diagnosis of pompe disease. Measurement of acid alpha glucosidase activity by using skin biopsy and culture of fibroblasts or purified lymphocytes from peripheral blood smear is diagnostic. Molecular genetic testing, mutation analysis and prenatal diagnosis are available. There is increasing evidence of the value of a specific **glucose tetrasaccaride (GLc4)** in urine which has near to 100% sensitivity in detecting patients with infantile pompe disease. Nowadays, **Dried Blood Spot test (DBS)** in which blood sample obtained by heel prick, finger stick, or blood draw has prepared rapid detection of pompe disease. This test is also suitable for newborn screening test but it should be mentioned that positive result of this test in not enough for definite diagnosis and a second confirmatory test such as fibroblast enzyme study or genetic mutation analysis, is needed.

Differential Diagnosis: Since pompe disease is a rare condition and on the other hand its symptoms are nonspecific, the diagnosis of this disorder poses a diagnostic dilemma. The most important differential diagnosis of infantile pompe disease have been shown in table 1.

Management: Pompe disease needs to a multidisciplinary team to handle its multisystem disturbances. Before the last few years there was no practical treatment for pompe disease. Enzyme replacement therapy (ERT) became available in the late 1990s and Myozyme received FDA approval for acid maltase deficiency in 2006. Children with infantile Pompe disease are now surviving beyond infancy with some gaining independent walking and level of daily activity never before possible.

Keywords: Pompe disease, Infantile pompe disease, Cardiomyopathy, Dried Blood Spot test

Tab.1: Differential diagnosis of infantile pompe disease

Differential Diagnoses	Shared Signs & Symptoms
1-Spinal muscular atrophy I(SMA I)	Hypotonia, Progressive proximal muscle weakness, Absent reflexes, Feeding difficulties, Elevated creatine kinase (CK)
2-Hypothyroidism	Hypotonia, Macroglossia
3-Congenital muscular dystrophy	Hypotonia (severe),Muscle weakness
4-Danon disease	Hypertrophic cardiomyopathy, Skeletal muscle myopathy, Vacuolar glycogen storage, Elevated CK
5-Carnitine deficiency	Cardiomyopathy, Muscle weakness
6-Glycogen storage diseases (GSD) III & IV	Hepatomegaly, Hypotonia, Cardiomegaly, Muscle weakness, Elevated CK
7-Myocarditis, Idiopathic hypertrophic cardiomyopathy	Biventricular hypertrophy, Cardiomegaly
8-Peroxisomal disorders	Hypotonia, Hepatomegaly
9-Mitochondrial/respiratory chain disorders	Hepatomegaly, Cardiomyopathy, Myopathy, Elevated CK

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