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CASE REPORT

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Familial Pompe Disease

Mehmet Tecellioglu, Ozden Kamisli

Neurology department, Faculty of medicine, Inonu University, Malatya, Turkey

Corresponding author: Mehmet Tecellioglu, MD. **E-mail:** mehmettecelli@hotmail.com

ABSTRACT

Introduction: Pompe disorder is a rare glycogen storage disorder that is due to a deficiency of the lysosomal alpha glycosidase enzyme. The heart, skeletal muscle, liver and nervous system can be affected from the lysosomal glycogen accumulation. Symptoms such as muscle weakness, hypotony, myopathy and respiratory failure develop. The onset may be at the infantile, adolescent or adult period depending on the enzyme level. The CK level is high in almost all patients. The diagnosis is made with enzyme level measurement and genetic analysis. **Case report:** We present a family with Pompe disease consisting of the asymptomatic mother and two siblings who presented with muscle weakness and respiratory failure and who had been followed-up with a diagnosis of muscular dystrophy for a long time.

Key words: Pompe disease, acid maltase deficiency, myopathy.

1. INTRODUCTION

Pompe disease is an autosomal recessive glycogen storage disorder due to a deficiency of the acid maltase (lysosomal alpha 1,4 glycosidase-GAA) enzyme (1). There is glycogen accumulation in the lysosomes, especially in the skeletal muscles and the heart. The clinical picture can include muscle weakness, hypotonia, myopathy, respiratory failure, hepato-splenomegaly and difficult feeding (2-3). The incidence is approximately 1/40000 but could be higher when the misdiagnosed or undiagnosed patients are considered. The clinical signs depend on the level of enzyme deficiency. There are infantile, juvenile and adult onset subtypes. The enzyme level is under 1% of normal in the infantile type and the clinical picture is more severe. The enzyme activity is 1-40% of normal in the adult types and symptoms may include muscle weakness, early fatigue, difficulty in performing usual physical activities, morning and night headaches, nausea and difficulty sleeping (4-5). The serum CK level may be very high as in dystrophies. Electromyography (EMG) may show fibrillation, positive spikes and occasional myotonic discharges. The clinical findings can be very variable. We present the clinical differentiation and features of a family consisting of 2 siblings and their mother who were not diagnosed for Pompe disease for a long time in this study.

2. CASE REPORTS

Case 1

A 35-year-old male presented with difficulty going up stairs, falling and shortness of breath. Neurological evaluation revealed proximal 4/5 and distal +4/5 muscle power in bilateral upper extremities and proximal 3/5 and distal 4/5 muscle power in bilateral lower extremities. Deep tendon reflexes were hypoactive in all extremities. There were seven siblings but only the older sister had similar complaints and the others were healthy. Full blood count, biochemical tests, sedimentation, CRP, thyroid function tests, Vitamin B12 and Vitamin D results were normal. The CK value was 296 U/L (29-168U/L). EMG results were consistent with myopathy. The vital capacity was low on respiratory function tests. Blood gas evaluation revealed a pH of 7.29, pCO_2 of 62.6 mmHg and pO_2 of 36.4 mmHg. ECG and echocardiography findings were normal. The history revealed that he had been evaluated at an external center 14 years ago because of weakness in all extremities. Respiratory problems had been added to the weakness 2 years later and a diagnosis of muscular dystrophy had been made. He had been admitted to hospital by the chest diseases department several times in this period and had also been electively

intubated once for respiratory acidosis. The respiratory problems had recently increased. Alpha glycosidase enzyme measurement and genetic analysis were ordered. The alpha glycosidase enzyme level was 0.2 μmol/l/h (normal range >3.3 μmol/l/h). Genetic analysis revealed the two mutations of c.32-13T>G and c.896T >C. A diagnosis of Pompe disease was made and enzyme replacement therapy (Alpha glycosidase enzyme [Myozyme®] 20 mg/kg once every two weeks) was started. The patient was also recommended a diet rich in protein and poor in carbohydrates together with exercise. There was partial recovery in the difficulty breathing and weakness. There was a marked increase of the exercise capacity.

Case 2

A 37-year-old female presented with difficulty going up stairs, difficulty sitting and standing down, and falling. Neurological examination revealed proximal and distal 4/5 muscle strength in bilateral upper and lower extremities. Deep tendon reflexes were hypoactive in all extremities. The family history revealed that a sibling had similar problems. Blood tests showed high CK levels (534 U/L) while other results were normal. EMG results were consistent with myopathy. Respiratory function test and blood gas evaluation results were normal. The ECG and echocardiography results were normal on cardiology evaluation. The personal history included appendectomy and inguinal hernia surgery. She had presented to the hospital at the same period as her male younger brother. Muscle biopsy had been performed for myopathy and she had similarly been diagnosed with muscular dystrophy. Both siblings had presented to our hospital when the symptoms progressed. A preliminary diagnosis of Pompe disease was made as the younger brother had similar but more severe symptoms and alpha glycosidase enzyme measurement and gene analysis were ordered. The alpha glycosidase enzyme level was 0.2 μmol/l/h (normal range >3.3 μmol/l/h). Genetic analysis revealed the 2 mutations of c.32-13T>G and c.896T >C. A diagnosis of Pompe disease was made and enzyme replacement therapy started with alpha glycosidase enzyme (Myozyme) 20 mg/kg once every two weeks.

Case 3

This subject was the mother of the two patients above. There was no marked symptom but when queried she mentioned symptoms she had ignored such as easy fatigue and occasional weakness of the legs. She had never seen a physician for these problems. The blood tests were within normal limits. The blood sent for family screening revealed an alpha glycosidase enzyme level of 0.3 μmol/l/h. No treatment was started as the clinical findings were not significant.

3. DISCUSSION

The cause of Pompe disease (Glycogen storage disorder type-II) is a deficiency of the acid maltase (lysosomal acid alpha glycosidase) enzyme. The severity of the clinical picture depends on the age of onset and the residual acid maltase amount. The disorder develops with the accumulation of the lysosomal glycogen that cannot be broken down in the lysosome and cytoplasm, resulting in muscle fiber destruction. The heart, skeletal muscle, diaphragm and liver can be involved (1). The diagnosis is made with the clinical findings, acid alpha glycosidase enzyme measurement and genetic analysis (6-7).

The CK level may be very high in Pompe disease. AST,ALT and LDH are higher than normal in most cases. Only the CK levels were high in our patients.

The clinical findings vary greatly from patient to patient but severe hypotony, muscle weakness, cardiomyopathy and hepatomegaly are seen in the infantile period and are progressive. The patient usually dies around 1.5 years of age. Adult onset forms may cause marked muscle weakness in proximal muscles, respiratory problems, fatigue, ptosis, scoliosis, contractures, macroglossia, difficulty chewing, muscle cramps, diarrhea and left ventricle hypertrophy (9-10). Both our patients had muscle weakness. The respiratory problem was the most significant symptoms of the male patient and he had been electively intubated for this reason once.

The differential diagnosis of Pompe disease includes polymyositis, Limb-girdle muscular dystrophy, Duchenne-Becker muscular dystrophy, McArdle disease and facioscapulohumeral muscular dystrophy in adult onset cases (8). Two of our patients had been followed-up with a diagnosis of muscular dystrophy and received symptomatic treatment especially for their respiratory problems.

The treatment of Pompe disease can be evaluated under two main headers as specific treatment and supportive treatment. Pompe patients show a wide range of clinical pictures and functional disturbances and therefore require a multidisciplinary approach. Specific treatment is with the lifelong use of recombinant alpha glycosidase enzyme. This treatment has been reported to increase survival in the infantile onset type and provide recovery in some adult onset patients (11-12). Early diagnosis is very important as starting treatment early is the best way to ensure treatment response. The diagnosis of both our cases was delayed for about 15 years and the disorder had shown marked progression during this period. The treatment approach should include supportive treatment for shortness of breath and cardiomyopathy in addition to the enzyme treatment. Most patients suffer from shortness of breath, and respiratory failure is the main cause of death in both children and adults (13). The general approach includes exercises to strengthen the respiratory muscles, close monitoring for respiratory infections and providing mechanical respiratory support if needed. The patient's cardiac health should be monitored closely with periodic cardiac evaluation. Physical therapy exercises should be offered and the patient mobilized as long-term immobilization will increase muscle breakdown. Feeding support is always needed due to the weakened chewing muscles. Our patients were started recombinant alpha glycosidase enzyme treatment once the diagnosis was definite. They were also evaluated for respiratory and cardiac functions by the chest diseases and cardiology departments. Physical therapy exercises were started.

The clinical picture of Pompe disease corresponds to the GAA gene mutation. All the defined mutations and

polymorphisms are in the GAA gene on chromosome 17 q25. More than 300 variants have been defined and most have been in a small population or family. Most patients are heterozygous. The most common mutation is c.32-13T>G in the white race (14). We found the two mutations of c.32-13T>G and c.896T>C in our patients. Genetic counseling should be available for all families and should include providing information on inheritance and the risks of other family members. The carrier test for Pompe disease requires DNA analysis as the acid alpha glycosidase enzyme activity is not markedly different between carriers and healthy subjects (8). Our family consisted of 7 siblings but only our 2 patients had relevant clinical signs. The other siblings were provided genetic information and follow-up scheduled.

4. CONCLUSION

In conclusion, patients presenting with muscle weakness, shortness of breath and elevated CK should prompt the inclusion of adult onset Pompe disease in the differential diagnosis. Good results are obtained with alpha glycosidase enzyme replacement therapy that has been in use since 2006 and early diagnosis plays an important role in successful treatment.

CONFLICT OF INTEREST: NONE DECLARED.

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