Familial Pompe Disease

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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, hypotonia, 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, hepatosplenomegaly 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 value was 296 U/L (29-168U/L). EMG results were consistent with myopathy. The vital capacity was low on respiratory function tests. 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.

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, pCO2 of 62.6 mmHg and pO2 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

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accumulation of the lysosomal glycogen that cannot be
alcohol maltase amount. The disorder develops with the
acid alpha glycosidase) enzyme. The severity of the clin-
der type-II) is a deficiency of the acid maltase (lysosomal
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3. DISCUSSION
was a marked increase of the exercise capacity.
recovery in the difficulty breathing and weakness. There
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 hypotonic in all
extremities. The family history revealed that a sibling
had similar problems. Blood tests showed high CK levels
(normal range >3.3 µmol/l/h). Genetic analysis revealed
the two mutations of c.32-13T>G and c.896T>C. A diag-
nosis of Pompe disease was made and enzyme replace-
ment 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 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 fa-
tigue 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 screen-
ing revealed an alpha glycosidase enzyme level of 0.3
µmol/l/h. No treatment was started as the clinical find-
ings were not significant.
3. DISCUSSION
The cause of Pompe disease (Glycogen storage disor-
der type-II) is a deficiency of the acid maltase (lysosomal
acid alpha glycosidase) enzyme. The severity of the clin-
ic picture depends on the age of onset and the residu-
al 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 pa-
tient but severe hypotony, muscle weakness, cardiomy-
opathy 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 mus-
cle weakness in proximal muscles, respiratory problems,
fatigue, ptosis, scoliosis, contractures, macroGLOSSIA, dif-
ficulty chewing, muscle cramps, diarrhea and left ven-
tricle hypertrophy (9-10). Both our patients had muscle
weakness. The respiratory problem was the most signifi-
cant symptoms of the male patient and he had been elec-
tively intubated for this reason once.
The differential diagnosis of Pompe disease in-
cudes polymyositis, Limb-girdle muscular dystrophy,
Duchenne-Becker muscular dystrophy, McArdle dis-
ease and facioscapulohumeral muscular dystrophy in
adult onset cases (8). Two of our patients had been fol-
lowed-up with a diagnosis of muscular dystrophy and
received symptomatic treatment especially for their res-
piratory problems.
The treatment of Pompe disease can be evaluated un-
der two main headers as specific treatment and support-
ive treatment. Pompe patients show a wide range of clin-
ic 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 treat-
ment approach should include supportive treatment for
shortness of breath and cardiomyopathy in addition to
the enzyme treatment. Most patients suffer from short-
ness of breath, and respiratory failure is the main cause
of death in both children and adults (13). The general ap-
proach 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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