CASE REPORT

From the hypertransaminasemia symptoms to the recognition of late-onset Pompe disease in a 12-year-old boy

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ABSTRACT
The paper presents the case of a 12-year-old boy hospitalised due to persistent hypertransaminasemia of unknown origin, in whom rare metabolic disease – Pompe disease, was finally diagnosed. We discuss the possible symptoms and the diagnostic criteria for Pompe disease, as well as modern genetic methods of diagnosing. The importance of including this metabolic disease in differential diagnosis of hypertransaminasemia was underlined. The recombinant human α-glucosidase as the enzyme replacement therapy makes nowadays the early diagnosis of Pompe disease especially important.

KEY WORDS: metabolic disorders, Pompe disease, hypertransaminasemia.

INTRODUCTION
Pompe disease is a rare, autosomal recessive disorder of glycogen storage. The disease affects approximately 1/40,000 in live births, although screening studies demonstrate it may be higher [1-3]. The disease is caused by the mutation of GAA gene, located on 17q25 chromosome, encoding the enzyme α1,4-glucosidase, which intracellularly breaks down glycogen. The first symptoms of the disease appear from infancy to adulthood and depend on the degree of lysosomal α1,4-glucosidase activity deficiency. In the typical infantile-onset form of the disorder, this activity is < 1% and progressive weakness and generalized hypotonia, macroglossia and increasing hypertrophic cardiomyopathy are observed in these patients [1, 2]. In late-onset Pompe disease, the main problem is progressive weakness of skeletal muscles and increasing respiratory disorders [1, 2].

CASE REPORT
The aim of the study is to present the case of a 12-year-old boy hospitalised for due to persistent hypertransaminasemia, in whom Pompe disease was finally diagnosed.

Family, pregnancy and delivery history of the patient was unremarkable. The developmental delay was observed but only in terms of motor development; he walked independently only at 18 months of age. The social activity, speech and intellectual development of the child were normal. At 8 years of age, in routine tests elevated liver enzymes were found, which repeated in follow-up examinations (up to Alat-171 U/l, Ast-136 U/l) and was present for over 6 months. The clinical diagnosis performed at that time excluded α1-antitrypsin deficiency, autoimmune hepatitis, Wilson's disease and the most common infections with hepatotropic viruses. Because of unexplained chronic hypertransaminasemia, liver biopsy was also performed, revealing features of parenchymal lesions with minimal inflammatory activity.

Among many parameters assessed for diagnosis of hypertransaminasemia, the creatine kinase (CK) was also performed at that time, revealing increased activity of CK-1136 U/l. For this reason the child was additionally consulted by the specialist in neurology, but no sings
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of neuromuscular disorder were found. The neurologist recommended periodic assessment of CK and reconsultation. Unfortunately, the scheduled gastrological and neurological control visits were irregular and without CK activity assessment.

On his second admission to the gastroenterology department at the age of 12, elevated values of alanine transaminase, aspartate transaminase, lactate dehydrogenase and creatine kinase were found, with increase both in ALAT, as well as in CK activity (Alat-249 U/l, Ast-213 U/l, LDH-754 U/l, CK-2020 U/l). The abdominal ultrasound, ECG, echocardiography and spirometry examinations showed no deviations. Due to the postural defect, proximal muscle weakness, absent knee and ankle reflexes, and the positive Gowers sign (Figure 1) and Duchenne sign (Figure 2) which were found in the neurological examination, the diagnostic tests were extended to include the determination of alpha-glucosidase activity, showing its decrease in the dried blood spot test, followed by the study of peripheral blood leukocytes. The results of α-glucosidase activity were 0.05 (normal values 0.29-0.49) and respectively 0.07 (normal values 0.31-0.52), suggesting the diagnosis of Pompe disease (the assessment made on request of the hospital in the Laboratory of Psychiatry and Neurology Institute in Warsaw).

Thereafter, the diagnosis of Pompe disease was confirmed by molecular examination of GAA gene, showing the presence of heterozygous c.307T > G and c.32-13T > G mutations. The boy was qualified for enzyme replacement therapy under the drug program.

**DISCUSSION, SYMPTOMS AND POSSIBLE TREATMENT**

In late-onset Pompe disease, the first symptoms may include increased fatigue and muscle pain. Gradually paresis of the pelvic girdle and shoulder girdle increases, causing difficulties in getting up, climbing stairs and raising the arms, among others. An additional indication may be increased values of creatine kinase, often also increased values of alanine transaminase and aspartate transaminase. As the disease progresses, the respiratory muscles, including the diaphragm, are affected, leading to respiratory failure. Patients develop sleep apnea,
headaches may occur secondary to hypoxia. Although
in the late form the dominant symptoms are muscular,
Pompe disease is a multi-system disorder, and the enzyme
defect affects other tissues and organs as well. Patients
may suffer from vascular (including cerebral) disorders,
peripheral and central nervous system disorders, hear-
ing loss, scoliosis, bone mass loss, as well as disorders
of the digestive or urinary system [1, 2, 4]. The absence
of tendon reflexes from the lower limbs in our patient
indicates the coexistence of motor neuropathy with
the symptoms of myopathy [5].

The diagnosis of the disease is based on a documented
deficit in alpha glucosidase activity. It can be determined
by the dried blood spot test, in peripheral blood leuko-
cytes or in skin fibroblasts. For confirmation, molecular
tests are performed [2]. The α-glucosidase gene is locat-
ed on the 17q25.2-q25.3 chromosome. To date, over 500
mutations associated with Pompe disease have been de-
described. The mutation c.307T > G found in the presented
child is a missense mutation, while c.32-13T > G is a mu-
tation leading to impaired exon 2 splicing and reducing
the expression of the alpha glucosidase gene [2, 6, 7]. Un-
like others, the c.32-13T> G mutation is quite common
in patients of Caucasian origin diagnosed with Pompe
disease, and the frequency of this allele in this group is
40% to 70% [7].

Currently, enzyme replacement therapy is available
for the treatment of this disease, and the approved drug
is alglucosidase α (recombinant human α-glucosidase).
It is administered to patients every 2 weeks as an in-
travenous infusion and, according to studies, it slows
disease progression, although in most patients it does
not cause significant disease regression [1, 2, 8]. One
of the reasons for the poorer drug response in skeletal
muscle may be the low abundance of the cation-inde-
pendent mannose-6-phosphate receptor (CI-MPR) that
mediates receptor-mediated uptake of recombinant hu-
mans α-glucosidase. The expression of CI-MPR may be
influenced by adjuvant therapy with β2-agonists [9].
Currently, next-generation enzyme replacement therapies
are in the clinical trial phase, and gene therapy research is
also underway [1, 2, 8].

In the diagnosis of hypertransaminasemia, it is appro-
priate to determine the concentration of creatine kinase.
Moreover, taking into account the natural clinical course
as well as the available therapy, diagnostics for this rare
disease in patients with elevated creatine kinase concen-
tration should be considered. There is to underline,
that in more and more rare diseases we have possibility
to successfully treat the child and stop the development
of the disease. For this reason, early diagnosis of genetic
disorders is very important. There is also to keep in mind
that we have available tools for diagnosing Pompe disease,
starting with simple CK assessment, up to α-glucosidase
activity using the dried blood spot test.

DISCLOSURE

The authors declare no conflict of interest.

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