

Pompe disease, a late-onset – misleading form of diagnosis in a patient with persistent hepatic cytolysis syndrome

Smaranda Diaconescu^{1,2}, Cristina Rusu^{1,2,3}, Laura Bozomitu^{1,2}, Alina Costina Luca^{2,4}, Ecaterina Vlad⁵, Oana-Larisa Ciobanu-Matei⁵, Ramona Babici⁵, Silvia Strat⁵, Lorenza Donea⁵

¹Paediatric Gastroenterology, "Sf. Maria" Emergency Clinical Hospital for Children, Iasi, Romania

²"Gr.T. Popa" University of Medicine and Pharmacy, Iasi, Romania

³Regional Centre for Medical Genetics, Iasi, Romania

⁴Paediatric Cardiology, "Sf. Maria" Emergency Clinical Hospital for Children, Iasi, Romania

⁵"Sf. Maria" Emergency Clinical Hospital for Children, Iasi, Romania

ABSTRACT

The article discusses a clinical case of late-onset Pompe disease in a 15-year and 6-month-old adolescent hospitalised in a Paediatric Gastroenterology department to investigate persistent liver cytolysis, without response to hepato-protective therapy. After excluding viral, autoimmune, metabolic and toxic drug aetiologies, a storage disease was suspected and imposed biochemical and genetic tests which confirmed a type II glycogenosis (Pompe disease), both by α -glucosidase (GAA) deficiency, as well as by the identification of two gene mutations on 17q25.2-q25.3 chromosome.

Keywords: Pompe disease, brothers, hepatocytolysis

INTRODUCTION

The alpha-glucosidase deficiency (Pompe disease) is a disease with autosomal recessive transmission, affecting the metabolism of glycogen that causes its accumulation in tissues. The complete alpha-glucosidase deficiency causes a progressive lethal cardiac muscle and skeletal disorder known as the Pompe disease. The most severe is the classic (infantile) form, with early onset at infant age, characterized by: cardiomegaly, hepatomegaly, hypotonia, with unfortunate evolution before the age of 2 years due to cardio-respiratory failure. Partial deficiency produces mild phenotypic manifestations and late onset. The late form can be named, according to the age of onset, as: non-classical infantile, infantile, juvenile and adult form Pompe disease (1).

CASE PRESENTATION

Patient aged 15 years and 6 months, normally developed in terms of body posture and weight (weight = 61 kg, height = 170 cm, BMI = 21.1 kg/m², percentiles 48), born prematurely at 26 weeks, known with minimal cardiac impairment from the age of 4 months (grade I-II mitral reflux, grade I-II tricuspid reflux, minimal aortic reflux), for which he is supervised every six months in the Paediatric Cardiology Department, presents for the investigation of a syndrome of hepatocytolysis that persists despite treatment with hepatoprotective agents.

The patient is the fourth child of an apparently healthy couple (mother 30 and father 32 years old at the time of conception). The couple also has a seemingly healthy girl and boy and a child deceased at 3

Corresponding author:
Oana-Larisa Ciobanu-Matei
E-mail: oana.cmatei@yahoo.com

Article History:
Received: 28 May 2020
Accepted: 16 June 2020

days of age, without being able to specify in official documents the cause of death. No other cases of congenital anomalies, genetic diseases, intellectual disability or reproductive disorders are reported in the family anamnesis.

Postnatal psychomotor development was apparently normal: he held his head at 1-2 months, sat without support at 6 months, walked at the age of 1 year.

Clinical examination shows microcephaly (PC = -3 SD), low tolerance to physical exertion, by installing fatigue when climbing stairs up to the 3rd floor; the child was not exempted from physical education and sports classes. The objective neurological examination was normal, with no signs of central deficit or intracranial hypertension.

Abdominal ultrasound does not show any pathological changes.

Electrocardiography examination reveals sinus bradycardia with electrocardiographic signs of left ventricular hypertrophy and echocardiography examination identifies mitral valve prolapse, with grade I-II mitral regurgitation (figures 1A, 1B).

Respiratory function tests: FVC = 3.36 l, PEF = 358 (l/min), FEF25-75 = 4.69 l/s, FEF50 = 4.81 l/s. Restrictive respiratory dysfunction is not present.

Biological investigations: CBC (complete blood count), blood coagulation tests, bilirubin, urinary copper, ceruloplasmin were within normal limits, hyperammonemia (63.73 ng/dl, NV = 11-51 μ mol/l), hepatic cytolysis (AST = 227 U/l, ALT = 148 U/l,

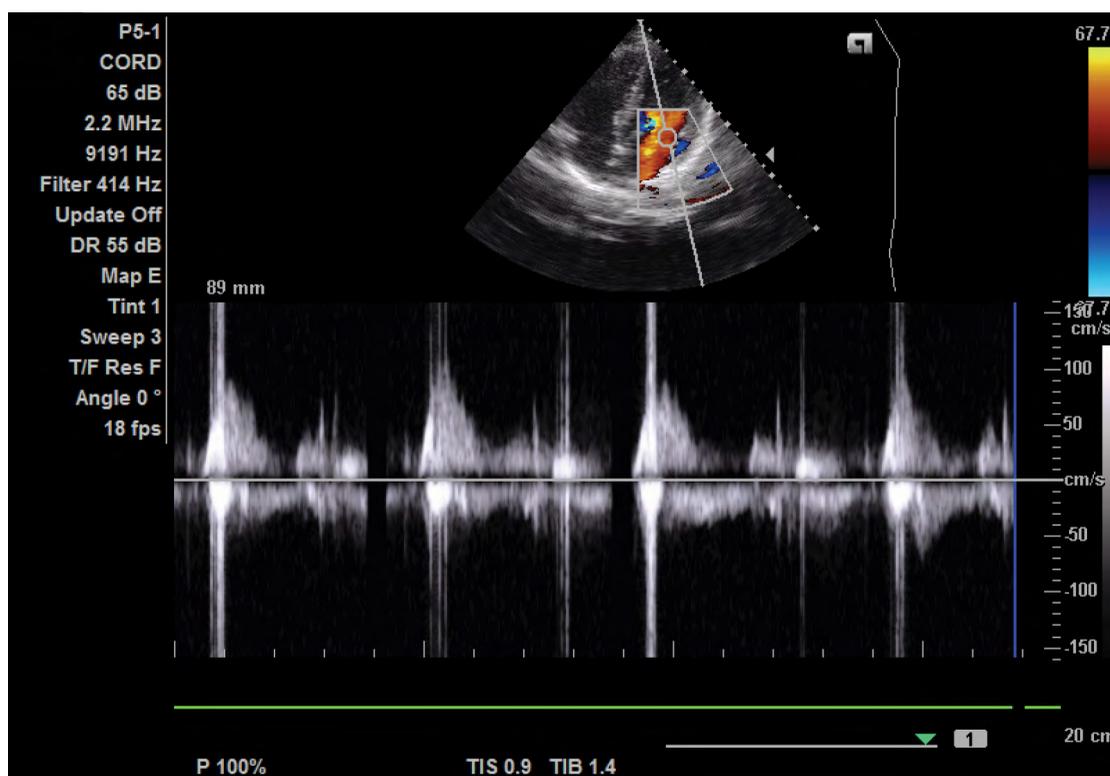


FIGURE 1A. EKG

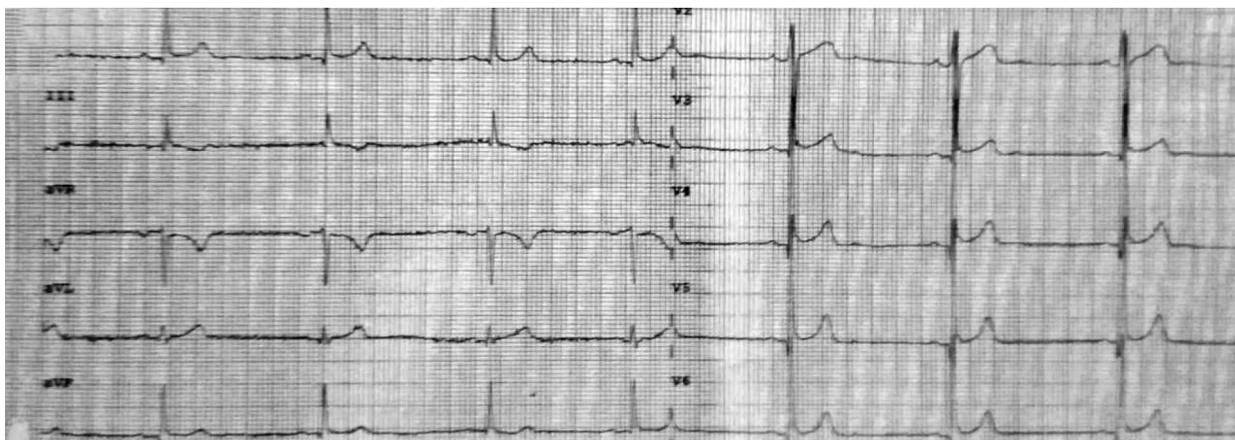


FIGURE 1B. Echocardiography

3xNV), rhabdomyolysis (CPK = 659 U/l, NV = < 308 U/l, LDH = 659 U/l, NV = 300-600 U/l), negative viral serology for hepatitis B and C, negative lupus cells. Anti-LKM antibodies, ANA-9 profile does not support an autoimmune disease. The investigations for the Pompe disease were positive: enzymatic test (No. 192007415-EMPO) - alpha 1.4 glucosidase activity): 0.5 $\mu\text{mol/l/h}$ (reference value > 2), molecular test - DNA extraction, PCR amplification, sequencing (No. 192012026 EMPG/11.09.2019): 2 pathogenic variants in the GAA gene (compound heterozygous status) c.[-32-13T>G]; and [406T>A].

The genetic consultation recommends the assessment of asymptomatic relatives for the diagnosis of affected persons and the early initiation of the therapy, prenatal tests for high-risk pregnancies and adequate management of the entire family.

Following the investigation, the parents were identified as healthy carriers (heterozygous), and an apparently healthy brother was confirmed with the diagnosis of Pompe disease.

Clinically, the brother showed no signs of impaired muscle strength, but palpation of the calf muscles reveals the “orange pulp”-like feeling (possible glycogen stores). The exercise stress test was negative.

Laboratory data revealed a minor hepatocytolysis syndrome (2 x NV), discrete hyperbilirubinemia based on the direct fraction; rhabdomyolysis (CPK 5 x NV).

Cardiological examination revealed anterior mitral valve prolapse, minimal mitral reflux, grade II-III tricuspid reflux, small atrial septal defect (ASD) type ostium secundum without pulmonary arterial hypertension (PAH), sinus bradycardia, FC = 43 b/min.

Respiratory function tests did not show restrictive changes at the time of examination. Thorax X-ray examination revealed accentuated perihilar and bilateral hilio-basal lung pattern, and normal appearance as for the rest.

Abdominal ultrasound showed liver with homogeneous echo-structure, moderate hepatomegaly.

The enzymatic and molecular test for the Pompe disease revealed the reduced activity of alpha 1,4 glucosidase and the presence of the same c.[- 32-13T>G] and [406T>A] mutations.

At present, both patients diagnosed in our department have been included in the National Rare Diseases Programme; the enzymatic substitution treatment was initiated with Myozime® in the recommended dose of 20 mg/kg/dose, with a favourable evolution to date.

DISCUSSIONS

The clinical aspects of the Pompe disease vary with age of onset and correlate with the degree of

GAA enzymatic activity. Classical forms of early-onset disease are caused by the complete absence of the GAA function, while partial enzyme deficiency may be associated with the onset of symptoms during childhood, which are generally limited to skeletal muscle. The term of classical form is used for children who die in the first year of life; in the case of the presented patient, there could be a possible correlation between the death of the brother in the postnatal period and the familial aggregation of the Pompe disease (2).

The Pompe disease with late onset can occur at any age after infancy and is generally difficult to diagnose. Some studies show that in about 1/3 of cases the diagnosis is delayed by 5-30 years (3).

The clinical picture may include changes in the spectrum of a progressive myopathy. The signs of onset are fatigue, muscle aches and cramps, and mobility disorders with difficulty in walking, some of which also being reported in our patient.

The incidence of cardiac manifestations is not well documented in older children and adults with Pompe disease. The cardiomyopathy diagnosed in all cases of early infantile onset is not present in patients with late onset, probably due to residual enzymatic activity. Some authors have found in patients with the Pompe disease the presence of the Wolff-Parkinson-White syndrome and other abnormalities, assuming that they are caused by the selective accumulation of glycogen in the cardiac conduction system. Interference with conductive cardiac tissue causes a shortening of the atrium-ventricular interval (PR) on the EKG, observed in the presented case and which is clinically manifested by sinus bradycardia (4).

The accumulation of glycogen in the cardiac conducting tissue classifies patients in the group at high risk of sudden death, especially under stress, in an infectious context or during anaesthesia, which is why these patients are approached in a multidisciplinary team.

Depending on the degree of enzymatic activity, the heart impairment evolves to moderate hypertrophy or even heart failure. In our patient, an incipient left cardiac hypertrophy was detected on the EKG pathway, without echocardiographic confirmation (5).

The high levels of CPK, LDH and transaminases are sensitive but non-specific indicators of Pompe disease, with elevated levels occurring in 95% of confirmed disease cases. The identification of a minor hepatocytolysis syndrome in an asymptomatic patient may be a diagnostic challenge, especially in cases where creatine-phosphokinase has not been dosed. In evolution, it seems that the GOT value tends to remain high while the other hepatic enzymes can nor-

malize, which, in correlation with the increased value of the CPK, leads to rhabdomyolysis to the detriment of hepatocytolysis (6).

The treatment of the Pompe disease is represented by enzyme replacement therapy with alpha-glucosidase or GAA (Myozyme™ / Lumizyme™), which has been approved since 2006, and aims to ameliorate symptoms by improving motor function and respiratory function, maintaining or increasing the patient's independence and the quality of life in general. Many authors consider that the enzymatic treatment is effective for reducing the accumulation of glycogen in tissues, intervening in the pathophysiological mechanisms with the improvement of clinical symptoms in both early and late onset forms (6).

Treatment with alglucosidase alpha is generally well tolerated, the most common side effects being skin rash, hyperhidrosis, chest discomfort, cough, vomiting, high blood pressure. All of these side effects are generally minimal or moderate and respond favourably to symptomatic treatment. The most severe side effects reported in patients receiving enzyme treatment are allergic reactions, including anaphylactic shock (7).

There are studies that discuss the effectiveness of enzyme therapy; although it appears that a percentage of patients experienced a clinical decline after 3-5 years of enzyme replacement therapy, after 10 years of treatment more than half of the patients had the

same walking abilities and lung function parameters as at the time of inclusion in the protocol (8).

Data from the literature suggest that long-term enzyme replacement therapy is well tolerated, slows the progression of the disease but does not completely stop it (9).

Advances in molecular medicine are not long in coming; thus, we can say with conviction that, currently, patients can benefit from more effective therapeutic strategies, based on the specific therapy that acts on the pathological mechanism (10).

CONCLUSIONS

Similar to other severe neuromuscular diseases, Pompe disease progresses to an advanced disability status and to chronic respiratory failure, a situation in which existing treatments are ineffective.

Early diagnosis of this disease and early inclusion in enzyme replacement therapy programmes ensures survival and preservation of the quality of life by maintaining mobility, preserving muscle strength and preventing complications.

The investigation of a persistent minor hepatocytolysis syndrome must also take into account the rare, underdiagnosed storage diseases, as well as the family aggregations of these pathological entities.

Technological advances and molecular therapies represent a tangible future for these patients.

REFERENCES

1. Çim A, Coşkun S, Yılmaz A, Onay H. Pompe disease: A case report. *Dicle Tıp Dergisi*. 2016;42(4):518-521.
2. Lorenzoni PJ, Kay CSK, Higashi NS, D'Almeida V, Werneck LC, Scola RH. Late-onset Pompe disease: what is the prevalence of limb-girdle muscular weakness presentation? *Arq Neuropsiquiatr*. 2018; 76(4):247-251.
3. Menzella F, Codeluppi L, Lusuardi M, Galeone C, Valzania F, Facciolongo N. Acute respiratory failure as presentation of late-onset Pompe disease complicating the diagnostic process as a labyrinth: A case report. *Multidiscip Respir Med*. 2018;13:32.
4. Chana J, Desaia AK et al. The Emerging Phenotype of Late-Onset Pompe Disease: A Systematic Literature Review. *Molecular Genetics and Metabolism*. 2017;120(3):163-172.
5. Hundtberger T, Schoser B, Leupold D, Rösler KM, Putora PM. Comparison of recent pivotal recommendations for the diagnosis and treatment of late-onset Pompe disease using diagnostic nodes-the Pompe disease burden scale. *J Neurol*. 2019;266(8):2010-2017.
6. Spada M, Porta F, Vercelli L et al. Screening for Later-Onset Pompe's Disease in Patients with Paucisymptomatic Hyperckemia. *Mol Genet Metab*. 2013;109(2):171-3.
7. Echaniz-Laguna A, Carlier RY, Laloui K et al. Should Patients with Asymptomatic Pompe Disease Be Treated? A Nationwide Study in France. *Muscle Nerve*. 2015;51(6):884-9.
8. Laurike Harlaar et al. Large Variation in Effects During 10 Years of Enzyme Therapy in Adults With Pompe Disease. *Neurology*. 2019; 93(19):e1756-e1767.
9. Hitoshi Nagura, Jiro Hokugo, Kazuo Ueda. Long-Term Observation of the Safety and Effectiveness of Enzyme Replacement Therapy in Japanese Patients With Pompe Disease: Results From the Post-marketing Surveillance. *Neurol Ther*. 2019;8(2):397-409.
10. Bellotti AS, Andreoli L, Ronchi D et al. Molecular Approaches for the Treatment of Pompe Disease. *Mol Neurobiol*. 2020;57(2):1259-1280.

Conflict of interest: none declared

Financial support: none declared