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This is a pre print version of the following article:

Original

Nystagmus in Infantile Pompe Disease: a new feature? / Emanuela Claudia Turco, ; Carlotta, Facini; Benedetta, Piccolo; Pisani, Francesco. - In: ACTA BIOMEDICA. - ISSN 2531-6745. - 91:3(2020). [10.23750/abm.v91i3.8366]

Availability:

This version is available at: 11381/2877239 since: 2020-09-20T11:11:02Z

Publisher:

Mattioli 1885

Published

DOI:10.23750/abm.v91i3.8366

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Nystagmus in infantile Pompe disease: a new feature?

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Summary. We describe a 3 month-old female floppy infant with hypertrophic cardiomyopathy, serum enzyme levels, which were characterized by an aspartate aminotransferase level of 144 U/l, alanine transaminase 240 U/L and creatine kinase level of 543 U/l. On the basis of the clinical signs and laboratory results, acid α -glucosidase activity was determined from dried blood spots resulting lower than the normal range (0.2 mmol/L/h: normal reference range: 1,86-21,9 mmol/L/h) and leading to a diagnosis of infantile Pompe disease. She also showed multi-directional nystagmus. Refractive errors, ptosis and strabismus are described in infantile Pompe Disease, while nystagmus is rarely reported before. Therefore with this paper we highlight an atypical ocular symptom, whose uncertain pathogenesis, to be taken into consideration, because by now, with increasing survival with ERT, new phenotypes of Pompe disease are taking shape. (www.actabiomedica.it)

Key words: eye movements, Pompe disease

Introduction

Pompe disease (Glycogen storage disease type II, acid maltase deficiency) is a rare, progressive metabolic autosomal recessive neuromuscular disorder caused by a deficiency of acid α -glucosidase (GAA), a lysosomal enzyme which breaks down glycogen, resulting in glycogen accumulation primarily in skeletal, cardiac, and smooth muscle (1). The clinical spectrum of Pompe disease varies broadly, with significant differences existing in age of onset, rate of disease progression, and overall clinical phenotype (2). We still know about it because, although it is typical to think Pompe disease as a muscle disease, glycogen is known to be present also in several other tissues like smooth muscle, brain, eye, liver and other organs (3). In fact there are some reports about ptosis, strabismus and refractive errors in infantile Pompe Disease, while nystagmus rarely was described.

Case report

A 3 month-old female infant was transferred from another hospital with hypertrophic cardiomyo-

pathy; her clinical findings were respiratory distress, muscle weakness, perioral cyanosis with feeding difficulties and failure to thrive.

The baby was the first born by spontaneous full term delivery to consanguineous parents, after an uncomplicated antenatal course. Apgar score at 1st and 5th were normal.

Mother didn't report any infections during pregnancy and there was no exposure to drugs, alcohol or tobacco during pregnancy. She described normal fetal movements during pregnancy.

At neurological examination the baby was awake, alert and looking around. Pupils were both round and reactive to light. There was inconstant visual tracking, no ptosis, while involuntary, rhythmic, multi-directional oscillation of the eyes were noted. Fundus oculi were normal. Furthermore she showed open drooping tent-shaped mouth; her palate was intact and tongue was midline without any fasciculations. Her crying and cough were weak. There was mild atrophy of muscles. The tone was significantly decreased in the 4 extremities: she demonstrated characteristic posture of full abduction and external rotation of the legs as well

as a flaccid extension of the arms. When traction is delivered as also shoulder and ventral suspension, there is a prominent head lag. She had weak but symmetric movements of the 4 extremities with subsequently delay in achievement of motor milestones. Deep tendon reflexes were present in the 4 extremities. The scarf sign was positive.

Chest examination revealed no significant heart murmur but he had coarse breathing sounds, and his precordial maximal impulse was shifted to left. There was marked hepatomegaly but no splenomegaly. Brachial and femoral pulses were normal. Neither nail bed cyanosis nor clubbing fingers were noted. Blood tests were normal except for creatine phosphokinase (CPK) 543U/L, alanine transaminase (ALT) 240 U/L, aspartate amino transferase (AST) 144 U/L. Cerebral ultrasound and EEG were normal.

ECG revealed a short PR interval, high QRS voltage, ST-T changes and prominent Q wave in the left precordial leads. The echocardiogram demonstrated bi-ventricular and inter-ventricular hypertrophy but no left ventricular outflow tract obstruction.

For the presence of cardiomyopathy, general weakness and hyperckemia with hypertransaminasemia, infantile Pompe disease was suspected and confirmed by diagnostic from Dried Blood Spot that revealed alpha-glucosidase levels of 0,2 (normal values 1,86-21,9 mmol/L/h) at pH 3.8 and subsequently by genetic test.

Discussion

Pompe disease is a rare autosomal recessive, inherited disorder of glycogen metabolism with an overall disease frequency of 1 in 40000 and an incidence of 1 in 138000 for classic infantile disease.

It is described as a disorder of lysosomes, glycogen and muscles; however glycogen backlog, due to mutation in the gene responsible for production of lysosomal alpha-1, 4-glucosidase, responsible for glycogen breakdown, was not observed only in the cardiac and skeletal muscles but also in several other tissues like smooth muscle, brain and other organs (4).

There are some reports about ptosis and strabismus in infantile Pompe Disease (5), presumably relat-

ed to muscle weakness. Also refractive errors like myopia and astigmatism are reported (6). The explanation for these clinical signs lies in the histological findings about vacuolar myopathy and glycogen accumulation in every ocular tissue according to the previous reports.

Instead nystagmus is rarely reported (3) and there are no reported electrophysiological studies on children. The features of this clinical sign like jerky variant and multidirectional oscillation, suggest a brainstem origin: therefore it might be a malfunctioning of pons generators that, together with all the nuclei of oculomotor nerves tied to one another through the medial longitudinal fasciculus, which allows the complete integration necessary for the correct execution of the conjugated movements. The involvement of cerebellum cannot also be excluded.

Brain involvement in infantile onset of Pompe disease is not yet clear probably because most patients died before brain illness could be investigated. However in some neuroimaging studies conducted on patients with infantile Pompe disease a delay in myelination has been observed, in particular concerning periventricular white matter and corpus callosum, white matter tract changes in capsula interna, cerebral peduncles and mesencephalon/pons area (7).

From the histopathologic point of view, the extensive glycogen accumulation was observed in central and peripheral nervous system including neurons and glial cells of the white matter with regard to cortex, midbrain, pons, medulla, cerebellum and spinal cord (7). Otherwise, nystagmus would be secondary to a very high refractive error, for example, myopia as reported by Baruteau et al (3) where an increase in axial length or changes in the refractive power of the cornea or lens, alter central vision from the very first phases of life, manifesting the above-mentioned symptom.

Congenital or vestibular nystagmus cannot be excluded, even though it is unlikely.

It was not possible to carry out a more in-depth examination of the child (neuroimaging and quantitative eye movement recordings) as she was transferred to a tertiary center to start enzymatic replacement therapy (ERT), where sadly, she died shortly after, following cardiovascular complications. Furthermore, the information we received is that an autopsy was not performed.

Conclusion

In literature various manifestations of ocular involvement due to glycogen accumulation are described and nystagmus may be an additional one. A limitation is that we did not perform further neuroradiological investigation and that histological findings of autopsy and information about the outcome after enzyme replacement therapy are not available.

In this paper we highlight an ocular sign, whose uncertain pathogenesis, rarely described before, must be taken into consideration, because by now, with increasing survival with ERT, a new phenotype of Pompe disease is taking shape.

Conflict of interest: None to declare

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Received: ??????

Accepted: ??????

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