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Research Article

Pompe Disease: state of art Jorge Sales Marques Center of Diagnosis and Evaluation of Rare Disorders Hospital Cuf Trindade

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Abstract

Pompe disease (PD) is an inherited metabolic disorder caused by a deficiency of acid α-glucosidase (GAA), leading to lysosomal accumulation of glycogen, mainly in skeletal and cardiac muscles as well as the nervous system. Patients with PD develop cellular dysfunction and muscle damage. PD can be classified into two classic forms, namely infantile-onset PD (IOPD) and late-onset PD (LOPD).

Delayed treatment, particularly in IOPD, would result in significant organ damage and early death. Nonetheless, early diagnosis and timely treatment are often hampered by the rarity of PD and its wide variety of, but overlapping, symptoms. This mini review will focus in the common clinical symptoms of PD and outlines the essentials of PD management. The importance of dried blood screening, the implications of newborn screening (NBS), the confirmation of the disease by molecular study and clinical performance of enzyme replacement therapy (ERT) with two different doses are highlighted.

INTRODUCTION

Lysosomal storage diseases (LSD) are a group of 50 metabolic diseases, with the origin changes cause by bad function of the lysosome. The majority of LSD are autosomal recessive disorders. Only 3 are recessive x-linked: Fabry, Hunter and Danon. Ninety percent of LSD are not treated with specific therapy. Pompe disease (PD) is one of the LSD that is inherited as autosomal recessive. It is a metabolic disorder with deficiency in acid α-glucosidase (GAA). The incidence of PD is 1 in 40,000 live births, with prevalence in Austria and Taiwan [1-5]. The deficiency of GAA will lead to lysosomal accumulation of glycogen in three main parts of the body: skeletal, cardiac muscle and nervous system, causing cellular and muscle damage.

Clinical symptoms

The level of the residual GAA activity, is responsible for the severity of PD. There are 2 forms of presentation: infantile (IOPD) and late onset (LOPD).In this last classification, can be divided in childhood, juvenile and adult onset. The first signs may appear in neonatal period with hypotonia. The clinic signs are depending on the type of presentation [Table 1 and 2]. In IOPD, GAA activity is almost completely absent, normally <1%, leading to muscle weakness, hypotonia, macroglossia, hepatomegaly and hypertrophic cardiomyopathy. In LOPD, GAA activity is not abolish completely. The symptoms predominance are respiratory insufficiency and limbs girdle weakness.

Table 1: Infant onset of Pompe Disease

• **Muscle-skeletal**	• **Lungs**	• **Heart**	• **Other symptoms**
• Progressive muscle weakness	• Progressive respiratory insufficiency	• Cardiomegaly	• Difficulty in swalloing, eat and breastfeeding
• Hypotonia	• Frequent respiratory infections	• Left ventricule hypertrophy	• Psycomotor development delay
• Motor delay			• Hepatomegaly
• Macroglossia			
• Absent of reflex			

Patients with residual GAA are classified as cross-reactive immunologic material (CRIM)-positive and those that lack the enzyme completely are CRIM-negative Symptoms of IOPD usually develop with a median age of 2.0 months and diagnosis at 4.7 months. Distal muscle weakness would precede the development of proximal muscle weakness. The age of onset of LOPD can range from less than 1 years old to 50 years of age. Respiratory failure associated with the dysfunction of the diaphragm and accessory muscles of respiration is a major cause of morbidity and mortality in LOPD [1-6].

Diagnosis

Creatine kinase (CK) is a very sensitive marker of Pompe

Table 2: Late onset Pompe Disease

• **Muscle -skeletal**	• **Lungs**	• **Other symptoms**
• Progressive muscle weakness	• Respiratory insufficiency	• Difficulty in swallowing and eat
• Unstable walking – tip of the feet	• Ortopnea	• Hepatomegaly
• Low back pain	• Sleep apnea	• Morning headache
• Reduced reflex	• Effort dyspnea	• Night sonolence
• Difficulties in climbing stairs	• Exercise intolerance	
• Scapula alata	• Respiratory infections	
• Gowers signs (distrophy as result of extreme muscle weakness)		
• Psycomotor development delay		
• Lordosis, scoliosis		

disease. The bigger elevation is in the IOPD (2.000 IU/L), although in the newborn period can be normal. In adults, CK can show normal parameters. The increase of CK (1.5 to 15 times) is observed in the IOPD but not in all cases of LOPD. Pompe dont cause hypoglicemia, like other glicogen disorders. Molecular study is the main test for diagnosis. There are more than 500 mutations identified so far, but only 350 are pathogenic. It is reported that the variant p.Arg854Ter was found in about 50–60% of African Americans with IOPD. Around 50–85% of adults with LOPD have the variant c.336-13T > G [1-6].

Dried Blood Test (DBS)

DBS is recommended is in all patients with suspect of PD. We can divide in two parts, according to the age less or equal do 12 months or more than 12 months. When have two manifestations we do the DBS [Table 2,3].

Newborn screening (NBS)

The first pilot study was done in Taiwan in 2005. This study demonstrated that this practice not only facilitates timely treatment for IOPD but also allows detection of underdiagnosed LOPD and asymptomatic GAA-deficient individuals.

Recently, in 2021, Japan also did a pilot study and the IOPD patient identified was prescribed early ERT before presenting exacerbated manifestations [1, 7-13].

The Importance of CRIM Status

Determination of the patients' CRIM status before initiating treatment is recommended. CRIM-negative individuals may develop resistance against rhGAA during ERT, and modified therapy protocols using immunomodulation may be required. We use methotrexate, rituximab and intravenous immunoglobulin (IVIG) with/without bortezomib before enzyme replace therapy (ERT) [1-7].

Enzyme replace therapy for Pompe disease

A dosage of 20 mg/kg body weight biweekly is used. ERT is crucial for improving survival, reducing the need for ventilation, facilitating earlier independent walking, and enhancing patients quality of life. ERT can reverse the cardiomyopathy and improve the clinical course as well as the expected outcomes of PD patients, but may not completely resolve the symptoms in patients who initiated the treatment after five months of age, or in those with a marked increase in left ventricular mass index (LVMI) [1,3-5].

What about double the dose of ERT?

Chien et al. (2020) treated patients with high-dose ERT (40 mg/kg biweekly). She reported that patients who were late in ERT initiation (p = 0.006) or late in high-dose ERT initiation (p = 0.044) were at a higher risk of motor decline. CK and urinary Glc4 level were correlated with the favorable response to ERT in the patients. These results indicated that prescription of a high-dose ERT immediately upon positive findings at NBS gave the best outcomes, and a dosage increase is needed upon a rise in biomarker levels [14].

Treatment recommendations based on severity of Pompe disease

If the patient is confined to a wheelchair and is using invasive ventilation during the day and at night: ERT is recommended for 1 year, followed by evaluation of the effectiveness of therapy. After one year, ERT is recommended on a case-by-case basis for patients who require continuous invasive ventilation, using the collective information acquired by the multispecialty team. Continue ERT if severe signs and symptoms are stabilized or improved [1, 3-5].

Enzyme replace therapy monitoring

One year followed by reassessment to consider whether to continue the treatment. Patients receiving ERT should be monitored for IgG antibodies every 3 months for 2 years, then annually thereafter [2-4].

Prenatal Diagnosis and Genetic counselling

Pompe disease is a recessive disorder and the risk of inheritance is 25%. We can offer prenatal diagnosis for the couple for the future pregnancy as soon as we confirm the molecular study.

Perspectives in Pompe Disease Management

Early initiation of treatment is the key to optimizing the overall health outcomes in patients with PD, particularly IOPD. Remember that treatment after 5 months may not completely resolve the symptoms in PD. We need do screen more suspect

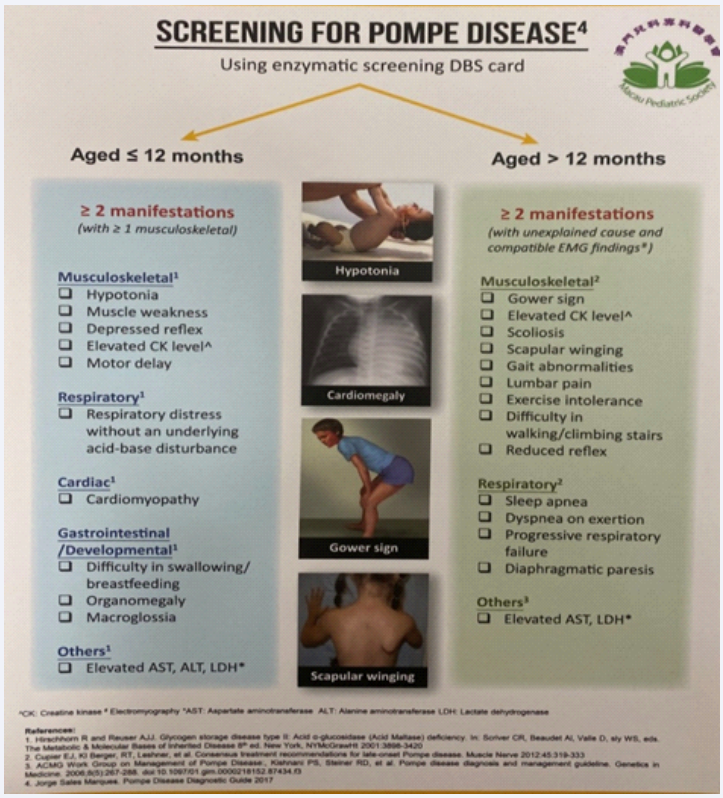

Table 3 Dried blood screening for Pompe disease

cases to avoid late diagnosis. This is the best choice for earlier diagnosis and treatment [1, 3-8,14].

The future

Gene therapy is an alternative treatment in the future and have a huge potential for PD. In a mice model, showed partial biochemical correction of the skeletal muscles and diaphragm, leading to better motor function [1].

CONCLUSION

As soon as we suspect a case of PD, we should do the dried blood screening test and confirm with molecular study. After we need to check the CRIM status before treatment. The ERT dose of 40 mg/kg biweekly of alglucosidase alpha, is the treatment of choice, because with this dose the outcome of the patient is better, mainly in the IOPD.

REFERENCES

1. Jorge Sales Marques. The Clinical Management of Pompe Disease: A Pediatric Perspective .Children (Basel). 2022; 9: 1404
2. Jorge Sales Marques. "Flowchart for Screening of Pompe Disease". EC Paediatrics. 2023; 12: 01-04.
3. Hahn A, Schänzer A. "Long-Term Outcome and Unmet Needs in Infantile-Onset Pompe Disease". The Ann Translational Med. 2019; 7: 283.
4. Martínez M, Romero MG, Guereta LG, Cabrera M, Regojo RM, Albajara L, et al. "Infantile-Onset Pompe Disease with Neonatal Debut: A Case Report and Literature Review". Medicine (Baltimore). 2017; 96: e9186.
5. Dorpel JJAVD, Poelman E, Harlaar L, Kooten HAV, Giessen LJVD, Doorn PAV, et al. "Distal Muscle Weakness Is a Common and Early Feature in Long-Term Enzyme-Treated Classic Infantile Pompe Patients". Orphanet J Rare Dis. 2020; 15: 247.
6. Bay LB, Fainboim A, Denzler I, Durand C, Eiroa H, Frabasil J, et al. "Infantile-Onset Pompe Disease: Diagnosis and Management". Archivos Argentinos de Pediatria. 2019; 117: 271-278.
7. Tchan M, Henderson R, Kornberg A, Kairaitis K, Fuller M, Davis M, et al. "Is It Pompe Disease? Australian Diagnostic Considerations". Neuromuscular Disorders. 2020; 30: 389-399.
8. Sawada T, Kido J, Sugawara K, Momosaki K, Yoshida S, Kojima-Ishii K, et al. "Current Status of Newborn Screening for Pompe Disease in Japan". Orphanet J Rare Dis. 2021; 16: 516.
9. Kronn DF, Day-Salvatore D, Hwu WL, Jones SA, Nakamura K, Okuyama T, et al. Management of Confirmed Newborn-Screened Patients with Pompe Disease Across the Disease Spectrum. Pediatrics. 2017; 140: S24–S45.
10. Saich R, Brown R, Collicoat M, Jenner C, Primmer J, Clancy B, et al. Is Newborn Screening the Ultimate Strategy to Reduce Diagnostic Delays in Pompe Disease? The Parent and Patient Perspective. Int J Neonatal Screen. 2020; 6: 1.
11. Chiang SC, Chen PW, Hwu WL, Lee, AJ, Chen LC, Lee NC, et al. Performance of the Four-Plex Tandem Mass Spectrometry Lysosomal Storage Disease Newborn Screening Test: The Necessity of Adding a 2nd Tier Test for Pompe Disease. Int J Neonatal Screen. 2018; 4: 41.

12. Bodamer OA, Scott CR, Giugliani R, on behalf of the Pompe Disease Newborn Screening Working Group. Newborn Screening for Pompe Disease. Pediatrics. 2017; 140: S4–S13.

13. Sawada T, Kido J, Sugawara K, Momosaki K, Yoshida S, Kojima-Ishii K, et al. Current Status of Newborn Screening for Pompe Disease in Japan. Orphanet J Rare Dis. 2021; 16: 516.

14. Chien YH, Tsai WH, Chang CL, Chiu PC, Chou YY, Tsai FJ, et al. Earlier and Higher Dosing of Alglucosidase Alfa Improve Outcomes in Patients with Infantile-Onset Pompe Disease: Evidence from Real-World Experiences. Mol Genet Metab Rep. 2020; 23: 100591.