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Case Report

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Clinical and Genetic Characterization of Late-Onset Pompe Disease in an Adolescent Carrying a Rare GAA Coding Mutation

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ABSTRACT

Background: Pompe disease (Glycogen Storage Disease Type II) is a rare autosomal recessive neuromuscular disorder caused by acid α-glucosidase (GAA) deficiency. Late-onset Pompe disease (LOPD) exhibits variable clinical presentations, often delaying diagnosis.

Case Report: We describe a 12-year-old male presenting with progressive proximal lower limb weakness, exercise intolerance, and persistent hyperCKemia. Neurological examination revealed macroglossia and mild proximal hypotrophy. EMG showed a myopathic pattern. Biochemical testing revealed markedly reduced GAA activity, and genetic analysis confirmed compound heterozygosity for c.2480_2426del (rare frameshift) and c.-32-13T>G (common LOPD splicing mutation). Pulmonary assessment indicated diaphragmatic weakness. The patient was initiated on enzyme replacement therapy with avalglucosidase alfa, resulting in modest functional improvement.

Conclusion: This case highlights the importance of early recognition, enzymatic testing, and genetic confirmation in pediatric LOPD, particularly in patients harboring rare or underreported mutations.

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Introduction

Pompe disease, also referred to as glycogen storage disease type 2 (GSD2) or acid maltase deficiency, is a rare, progressive, and heterogeneous neuromuscular disorder. It results from deficiency of the lysosomal enzyme acid α-glucosidase (GAA), caused by pathogenic variants in the GAA gene located on chromosome 17q25.2–q25.3. Over 560 mutations have been described to date, encompassing missense, nonsense, splicing, and frameshift variants, reflecting a broad genetic heterogeneity. The disease follows an autosomal recessive inheritance pattern [1-5].

Epidemiologically, the prevalence of Pompe disease varies by population, estimated at 1:50,000 in China and 1:40,000 in Caucasian populations. Newborn screening (NBS) programs have revealed a higher incidence than previously recognized, approximately 1 in 18,700 live births globally, although significant regional variation exists. The wide phenotypic spectrum and nonspecific early clinical manifestations often lead to delays in diagnosis, particularly in late-onset forms [3, 6-8].

Case Presentation

Our patient is a 12-year-old male, from Chihuahua, Mexico, with no relevant family history. He was referred in March 2025 to the Neuromuscular Outpatient Clinic due to progressive muscle weakness and pain.

His past medical history was unremarkable except for an Epstein-Barr virus infection 3 months before consultation. Developmental milestones were appropriate for age. The patient reported onset of exercise intolerance 3 years prior, characterized by early fatigue compared to peers. Two years later, he developed difficulty climbing stairs, requiring pauses every 5–6 steps. One year prior to consultation, he began experiencing proximal lower limb weakness and myalgias, progressive and continuous, exacerbated by physical activity. No dysphagia, dysarthria, visual disturbances, cardiopulmonary symptoms, or sensory complaints were reported.

Neurological Examination Cranial nerves were intact except for macroglossia noted on inspection. Motor examination revealed proximal weakness in lower limbs (iliopsoas 4+/5, quadriceps 4+/5, hamstrings and hip abductors 4-/5 bilaterally), with preserved distal strength and normal tone. Mild proximal hypotrophy was observed. Upper limb strength was preserved (5/5). Deep tendon reflexes were normal. Gait was slightly myopathic but

not markedly compensatory.

General Examination

Cardiovascular and Pulmonary Evaluations were within Normal Limits. Abdomen Globose without Organomegaly.

Diagnostic Work-up and Reasoning

The initial suspicion of a neuromuscular disorder was raised by the combination of progressive proximal lower limb weakness, exercise intolerance, and persistently elevated CK levels (2239 U/L) (Table 1). Differential diagnoses considered included inflammatory myopathies (dermatomyositis, polymyositis), limb-girdle muscular dystrophies, and metabolic myopathies.

Table 1: Laboratory Test

Liver Function Tests		Reference
Total protein	7.41	6.0 – 8.3 g/dL
Albumin	3.63	3.5 – 5.0 g/dL
Total bilirubin	0.36	0.3 – 1.2 mg/dL
Direct bilirubin	0.08	0.1 – 0.3 mg/dL
Indirect bilirubin	0.28	0.2 – 0.9 mg/dL
Aspartate aminotransferase	401	10 – 40 U/L
Alanine aminotransferase	326	7 – 56 U/L
Lactate dehydrogenase	630	140 – 280 U/L
Alkaline phosphatase	477	44 – 147 U/L
Gamma-glutamyl transferase	15	9 – 48 U/L
Creatine kinase	2239	55 – 170 U/L

Inflammatory myopathies were initially considered given the presentation with progressive proximal muscle weakness and elevated serum CK. However, this possibility was deemed unlikely in view of the negative extended autoimmune panel-including anti-Mi-2, anti-SAE1, anti-Jo-1, anti-MDA5, and other myositis-specific antibodies-as well as the complete absence of systemic inflammatory features such as fever, rash, or arthralgias.

Limb-girdle muscular dystrophies (LGMDs) also represent an important diagnostic consideration, as they frequently present with proximal limb weakness and chronic hyperCKemia. Nevertheless, the absence of a positive family history, the presence of macroglossia, and the relatively rapid progression of symptoms argued against a dystrophic process and instead favored a metabolic etiology.

Ultimately, the marked reduction of acid α-glucosidase activity (0.21 nmol/ml/hr; reference 1.29–25.7) provided strong biochemical evidence in favor of Pompe disease. This enzymatic deficiency is highly specific and, when correlated with the patient's phenotype, represents a diagnostic hallmark distinguishing glycogen storage disease type II from other hereditary myopathies.

Genetic Testing Confirmed Compound Heterozygosity for two Pathogenic GAA Variants (Table 2):

Table 2: Sequence Variants Gene GAA

Variant Coordinates	Amino Acid Change	Zygosity /SNP Identifier	In Silico Parameters *	Allele Frequencies **	Type and Classification ***
NM_000152.3:c.2480_2426del	p.(Gln803Profs*39)	Heterozygous / rs763048948	PolyPhen:N/A SIFT: N/A Mutation taster: N/A Conservation_nt	gnomAD:0.000012 ESP:- 1000 G:-	Frameshift, pathogenic
NM_000152.3:c-32-13T>G	p.(?)	Heterozygous / rs386834236	PolyPhen:N/A SIFT: N/A Mutation taster: N/A Conservation_nt	gnomAD:0.0034 ESP:- 1000 G:-	Splicing, pathogenic

ESP = Exome Sequencing Project, 1000G = 1000 Genomes Project, nt Conservation = Nucleotide conservation.
* In silico parameters include PolyPhen, SIFT, MutationTaster, nucleotide conservation, and splicing predictors (Ada and RF scores).
** Allele frequencies based on the Genome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), and 1000 Genomes Project (1000G).
*** Classification according to ACMG (American College of Medical Genetics and Genomics) recommendations.

Declarations Disclosures

Maria Elena Meza Cano, MD: Reports No disclosures. Verónica Ivonne López Diaz, MD: Reports No disclosures. Ana Carolina Aguilar Venegas, MD: Reports No disclosures.

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Ethics Approval

Not Required. The Case Report did not Meet Criteria for Research Involving Human Subjects per Institutional Guidelines.

Consent to Participate

Written informed consent to participate in this case report was obtained from the patient's legal guardians. Supplementary 1.

Written Consent for Publication

Written informed consent for publication of this case, including clinical information and relevant diagnostic findings, was obtained from the patient's legal guardians. All potentially identifying details have been removed to ensure patient confidentiality.

Availability of Data and Material

All data supporting the findings of this case report are included within the article. Additional de- identified information is available from the corresponding author upon reasonable request.

Code Availability

No custom code or specialized software was used in the preparation of this case report.

Authors' Contributions

M.E.M.-C. contributed to the study design, performed the clinical evaluation, supervised the study, and reviewed and approved the final version of the manuscript.

V.I.L.-D. contributed to the study design, drafted the manuscript, and prepared the figures and tables.

A.C.A.-V. performed the clinical evaluation and collected the study data. All authors reviewed the manuscript.

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