From liver enzymes to lysosomes: A serendipitous diagnosis of late-onset Pompe disease

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ABSTRACT

Late-onset Pompe disease (LOPD) is a glycogen storage disease caused by biallelic mutations in the GAA gene. When untreated, LOPD causes progressive myopathy with respiratory failure. A 30-year-old Chinese female was incidentally found to have elevated transaminases, prompting a liver biopsy showing marked lipid accumulation, concerning for lysosomal storage disease. She had mild hip flexor weakness. She had two pathologic mutations in the GAA gene (c.1935C>A, p.Asp645Glu and c.569G>A, p.Arg190His). She started enzyme replacement therapy. While on treatment, she became pregnant and delivered a healthy baby. The c.1935C>A, p.Asp645Glu variant accounts for 40-80% of infantile-onset Pompe disease in Asian populations, and the c.569G>A, p.Arg190His has been reported in three teenage patients. This combination of variants has previously been reported in a patient with onset at age 10. Surprisingly, our patient had minimal symptoms. Literature suggests that early treatment initiation can improve morbidity and mortality and is safe in pregnancy.

Background

Late-Onset Pompe Disease (LOPD) is an autosomal recessive glycogen storage disease, also known as acid maltase deficiency, caused by biallelic pathogenic variants in the GAA gene located on chromosome 17q25. Mutations in the GAA gene cause reduced or absent acid alpha-glucosidase enzyme activity, preventing the hydrolysis of glycogen to glucose in the lysosome.[1] This leads to glycogen accumulation in lysosomes in skeletal and cardiac muscle. Infantile-onset Pompe Disease (IOPD) is differentiated from LOPD based on age of onset being less than 12 months. LOPD can be further categorized into childhood-, juvenile-, and adult-onset disease. In general, the earlier the onset, the more rapid the rate of progression and the higher the severity of disease.[2]

LOPD causes a progressive myopathy involving limb-girdle and paraspinal muscles, with early respiratory involvement. Lower limb predominance with early adductor magnus and semimembranosus involvement is common. Muscle pain and exercise intolerance may be the initial manifestations.[3] Left untreated, LOPD progresses to wheelchair dependence and respiratory failure. Pompe disease is diagnosed by a deficiency of acid alpha-glucosidase enzyme activity, which is assessed using dried blood spots or blood-based assays. Confirmatory molecular genetic testing typically follows an abnormal result. Pompe disease is now included on newborn screening in 29 states in the United States and eight countries around the world. Newborn screening identifies patients with mutations in the GAA gene known to cause both IOPD and LOPD. Enzyme replacement therapy with alglucosidase alfa has been FDA-approved for IOPD as well as LOPD since 2006. It is dosed every two weeks through intravenous infusion.

Case Report

A 30-year-old healthy Chinese female presented to the emergency department for vomiting and diarrhea. During the initial workup, she was incidentally found to have elevated transaminases. She was diagnosed with viral gastroenteritis and recovered without intervention. At follow-up with her primary care physician, repeat transaminases remained elevated, which was then noticed to be a historical trend since 2017, with aspartate aminotransferase ranging from 35 to 74 international units per liter (IU/L) and alanine aminotransferase ranging from 40 to 65 IU/L. Her hepatic function panel, including bilirubin, alkaline phosphatase, and gamma-glutamyl transferase, was normal. She was referred to gastroenterology, where she underwent a liver biopsy. Liver biopsy showed marked lipid accumulation, raising concerns for lysosomal storage disease, which prompted genetic testing. The lysosomal storage disease gene panel through Mayo Clinic revealed two pathogenic mutations in the GAA gene (c.1935C>A, p.Asp645Glu and c.569G>A, p.Arg190His). She was then referred to neurology. At her initial visit to our neuromuscular clinic, she denied any neurologic symptoms other than occasional dysphagia. She specifically denied weakness or shortness of breath. She did not have any family history of neurologic disease. Her neurologic examination was notable for mild weakness of her hip flexors with a Medical Research Council scale grade of 4/5. The remainder of her examination was normal. Nerve conduction studies were normal (Figure 1). Electromyogram showed myopathic motor units with rapid recruitment and myotonic discharges in proximal muscles and lumbar paraspinal muscles (Figure 2). MRI of her

NCS+
Motor Nerve Results

Site	Latency (ms)	Norm	Amplitude (mV)	Norm	F-Lat (ms)	Segment	Distance (cm)	CV (m/s)	Norm	Comment
Right Fibular (EDB) Motor										
Ankle	4.4	< 6.5	3.5	> 2.6						
Bel Fib Head	10.0	-	3.1	-		Bel Fib Head-Ankle	29	52	-	
Pop Fossa	11.3	-	3.3	-		Pop Fossa-Bel Fib Head	9	69	> 42	
Right Tibial (AHB) Motor										
Ankle	4.8	< 6.1	8.3	> 5.3	44.6					

Sensory Nerve Results

Site	Latency (Peak) (ms)	Norm	Amplitude (P-P) (µV)	Norm	Segment	Distance (cm)	CV (m/s)	Norm	Comment
Right Sural Sensory									
Calf-Lat Mall	3.5	< 4.5	22	> 4	Calf-Lat Mall	-	-	> 35	

Figure 1: Nerve conduction studies (NCS) showing normal right fibular and tibial motor responses and normal right sural sensory response.

EMG+

Side	Muscle	Nerve	Root	Ins Act	Fibs	Fasc	Psw	Amp	Dur	Poly	Recrt	Int Pat	Comment
Right	Vastus Lat	Femoral	L2-L4	Nml	Nml	Nml	Nml	Nml	Nml	0	Nml	Nml	
Right	Add Magnus	Obturator, Posterior...	L2-L4	Nml	2+	2+	2+	Decr	Nml	0	Rapid	Nml	myotonic discharges
Right	Iliopsoas	Femoral	L2-L3	Nml	2+	2+	2+	Decr	Nml	0	Rapid	Nml	myotonic discharges
Right	Gluteus Med	Sup Gluteal	L5-S1	Nml	1+	1+	1+	Decr	Nml	0	Rapid	Nml	myotonic discharges
Right	Gluteus Max	Inf Gluteal	L5-S2	Nml	Nml	Nml	Nml	Decr	Nml	0	Nml	Nml	
Right	Lumbo Parasp (Mid)	Rami	L3-L4	Nml	Nml	Nml	Nml						myotonic discharges
Right	Biceps	Musculocut	C5-C6	Nml	Nml	Nml	Nml	Nml	Nml	0	Nml	Nml	

Figure 2: Electromyograph demonstrating abnormal spontaneous activity indicating muscle membrane irritability as well as rapid recruitment of myopathic motor units in proximal muscles. Key: EMG (electromyography), Ins Act (insertional activity), Fibs (fibrillations), Fasc (fasciculations), PSW (positive sharp waves), Amp (amplitude), Dur (duration), Poly (polyphasia), Recrt (recruitment) Int Pat (interference pattern).

thigh and pelvis demonstrated abnormal T2 hyperintensity and enhancement involving multiple proximal thigh and hip girdle muscles (Figure 3). Laboratory testing revealed elevated urine glucotetrasaccharides (17.7 millimoles/mole creatinine), low acid alpha-glucosidase (0.55 nanomoles/hour/milligram of protein), and a normal creatine kinase (185 units/liter). On pulmonary function testing, her sitting forced vital capacity (FVC) was 92% of predicted FVC for age. She underwent a muscle biopsy of the right rectus femoris, which showed mild myopathic features with glycogen deposits (Figure 4). Targeted variant testing was obtained for her parents, which confirmed that the pathogenic variants in the GAA gene were in trans. The patient was diagnosed with LOPD, and she was started on enzyme replacement therapy (ERT) with recombinant human acid alpha-glucosidase. While on ERT, she became pregnant and continued ERT throughout her pregnancy. She delivered a full-term, healthy infant via uncomplicated, spontaneous vaginal delivery. She has not had any progression in her disease since treatment initiation, and she plans on breastfeeding.

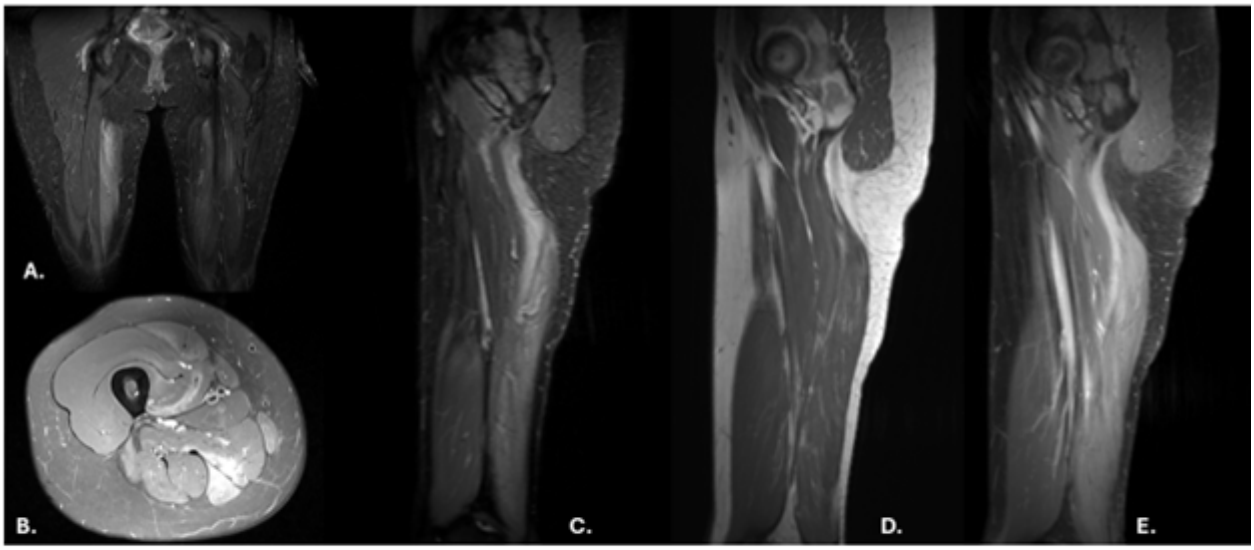

Figure 3: MRI thigh showing increased signal intensity and contrast enhancement most prominent in the adductor magnus and adductor longus. A. Coronal short tau inversion recovery (STIR). B. Axial intermediated-weighted fat-suppressed turbo spin echo (TSE). C. Sagittal STIR TSE. D. Sagittal T1-weighted Pre-contrast. E. Sagittal T1-weighted Post-contrast.

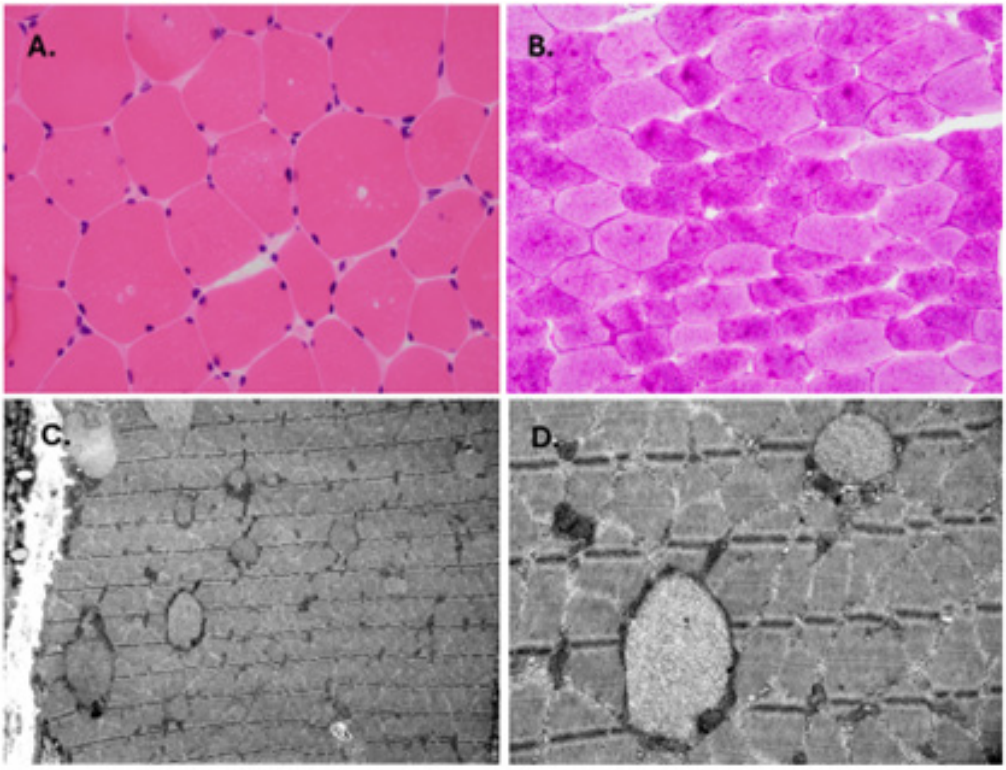

Figure 4: A. Snap-frozen, H&E-stained sections (400X) demonstrated occasional myofibers with vacuoles of various sizes. B. PAS stain (200X) demonstrated myofibers with increased glycogen content. C&D. Electron microscopy showed membrane-bound accumulations of glycogen granules (5000X and 15000X).

Discussion

The GAA gene is located on chromosome 17q25 and is the only gene associated with Pompe disease. Some mutations cause a complete absence of GAA enzyme activity, while others allow for low levels of the normal enzyme. This results in the phenotypic variability seen in Pompe disease.[4] The known mutations associated with Pompe Disease are reported in the Pompe Disease GAA variant database, which allows for a growing understanding of the genotype-phenotype relationships, helping to predict clinical onset and severity.[5] Mutations known to cause an absence of protein expression, such as c.2560C>T, p.(Arg854*) and c.525del, p.(Glu176Argfs*45), result in IOPD. There is greater phenotypic variability seen in mutations that allow for some level of functional protein expression. One of the variants seen in our patient, the c.1935C>A, p.Asp645Glu variant, accounts for 40-80% of infantile-onset Pompe disease in Chinese individuals.[6] The other variant, c.569G>A, p.Arg190His, has been reported in three patients with symptom onset in their teenage years.[7] This combination of variants has previously been reported in a patient with onset at age 10.[8] Surprisingly, our patient had minimal symptoms in her 30s despite these two mutations. Variants in modifier genes are proposed to be responsible for the phenotypic variability and inability of genetics alone to predict the clinical course, though more research is needed to fully understand this phenomenon.[4,9]

Elevated AST and ALT in isolation are seen most often in hepatocellular disease but when serum CK and LDH levels are also elevated, suspicion for primary muscle pathology should be higher.[10,11] Various isozymes are contained within skeletal muscle and are therefore released into the blood with muscle breakdown. These isozymes include AST, ALT, lactate dehydrogenase (LDH), and CK. In this case, the elevated transaminases may have been from hepatocellular injury due to lipid accumulation in the liver as seen on biopsy. This is supported by the fact that her CK was normal, which has been reported to rise in tandem with AST and ALT in muscle pathology.[12] Isolated elevations in transaminases may be an early, even pre-symptomatic sign of Pompe disease. Incidentally identified elevations in AST and ALT have been reported to be the first sign of various muscle diseases, including muscular dystrophies, inflammatory myopathies, and Pompe disease.[10,12,13]

Newborn screening is now identifying a growing number of infants who harbor mutations associated with LOPD, though we cannot predict when clinical symptoms will manifest. This may cause unnecessary emotional stress for these families of infants who may not develop symptoms until adulthood. This also raises the question of when to start treatment in those who are known to have these mutations. The timing of treatment may influence the response to therapy. We have also learned from IOPD that while ERT can reverse and stabilize the hypertrophic cardiomyopathy seen in IOPD, there is a waning effect with regard to muscle strength in long-term survivors.[14] Most patients with IOPD treated with ERT go on to develop muscle weakness, progressive scoliosis, and even neurocognitive deficits attributed to glycogen accumulation in the brain.[14] Response to ERT in LOPD varies widely, ranging from long-term response, initial response followed by a progressive decline, and no response at all.[14,15] The reasons behind this variability are not fully understood. The European Consensus states that presymptomatic patients with subtle objective signs should begin treatment with ERT immediately, while patients without signs or symptoms should be monitored clinically without treatment.[16] There is some literature suggesting improved outcomes with early initiation of ERT in this pre-symptomatic phase with subtle objective findings.[17] Though our patient had minimal manifestations at the time of diagnosis, she did have subtle exam findings as well as abnormalities on EMG and muscle biopsy, justifying treatment initiation. This will likely become a more common situation as we follow pre-symptomatic patients identified on newborn screening, allowing for early recognition of subtle objective findings before functional limitations develop. The treatment of Pompe Disease will likely continue to evolve with a growing number of clinical trials investigating more effective ERT and gene therapy.[18-20] There are also numerous studies investigating possible biomarkers to help guide when to initiate treatment and monitor response.[14, 21] Ongoing tracking of those patients treated with ERT with only subtle findings will better inform recommendations for future management.

While sparse, the literature suggests that ERT is safe during pregnancy. One study that retrospectively analyzed pregnancy outcomes in Pompe disease found a higher incidence of stillbirths and anesthesia complications. Other outcome measures, such as mode of delivery and pre-term labor, were similar to national databases. Some patients reported worsening symptoms during pregnancy. Four patients in the study were treated with ERT during pregnancy, with no incidences of congenital birth defects or adverse events in those babies.[22] There is little published on lactation while on ERT, but one case report describes successful delivery and lactation. In this report, the enzyme activity in the breast milk peaked at 2.5 hours and returned to pre-infusion levels at 24 hours post-infusion[23].

Conclusion

This case underscores the importance of timely diagnosis and treatment initiation in Late-Onset Pompe Disease (LOPD). The patient's diagnosis was facilitated by the uncommon presenting feature of elevated transaminases, identified incidentally during routine follow up for viral gastroenteritis. Despite the presence of two pathogenic mutations in the GAA gene, the patient

exhibited minimal symptoms, emphasizing the phenotypic variability of Pompe disease and the potential influence of modifier genes.

The decision to initiate enzyme replacement therapy (ERT) was based on subtle clinical findings, including mild weakness and abnormalities on electromyography and muscle biopsy. This approach aligns with the European Consensus, which recommends starting ERT in presymptomatic patients with objective signs to prevent disease progression. This case also illustrates the safety and efficacy of ERT during pregnancy, providing reassurance for similar future cases.

References

Labella B, Piccinelli SC, Risi B, Filomena C, Damioli S, Bertella E, et al. A Comprehensive Update on Late-Onset Pompe Disease. Biomocules. Aug 2023;13(9):1279. doi: 10.3390/biom13091279

Leslie N, Bailey L. Pompe Disease. GeneReviews. 2023.

Meena NK, Raben N. Pompe Disease: New Developments in an Old Lysosomal Storage Disorder. Biomolecules. 2020;10(9):1339. doi: 10.3390/biom10091339

Kishnani, PS, Steiner RD, Bali D, Berger K, Byrne B, Case L, et al. Pompe disease diagnosis and management guideline. Genetics in Medicine. 2006; 8(5)267-288. doi: 10.1097/01.gim.0000218152.87434.f3

Pompe Disease GAA Variant Database. (n.d.). List of Pompe mutations. Retrieve April 18,2025, from https://www.pompevariantdatabase.clmz.nl/pompe_mutations_list.php?orderby=aMut_ID1 se

Fukuhara Y, Fuki N, Yamazaki N, Hirakiyama A, Kamioka T, Seo JH, et al. A molecular analysis of the GAA gene and clinical spectrum in 38 patients with Pompe disease in Japan. Mol Genet Metab Rep. 2017 doi: 10.1016/j.ymgmr.2017.10.009

Wens S, Kroos MA, de Vries JM, Hoogeveen-Westerveld M, Wijgerde MGJM, van Doorn PA, et al. Remarkably low fibroblast GAA activity in three adults with Pompe disease. Mol Genet Metab. 2012 doi: 10.1016/j.ymgme.2012.09.003

Leslie N and Bailey L. Pompe Disease. GeneReviews 2007

Kuperus E, Van der Meijden JC, In 't Groen SLM, Kroos MA, Hoogeveen-Westerveld M, Rizopoulos D, et al. The ACE I/D polymorphism dose not explain heterogeneity of natural course and response to enzyme replacement therapy in Pompe Disease. PLoS ONE. 2018; 13, e0208854. doi: 10.1371/journal.pone.0208854.

Morse RP, Posman NP. Diagnosis of occult muscular dystrophy: Importance of the "chance" finding of elevated serum aminotransferase activities. *Journal of Pediatrics*. Feb 1993. 122(2)254-256. DOI: 10.1016/S0022-3476(06)80126-5

Ghobrial C, Abdelhamid N, El-Karaksy H. Incidental hypertransaminasemia in children: Potential delay in diagnosis of muscle disease. *Egyptian Pediatric Association Gazette*. Dec 2018. 66(4)112-114. DOI: https://doi.org/10.1016/j.epag.2018.09.002

Hoeksma M, Boon M, Niezen-Koning KE, van Overbeek-van Gils L, van Spronsen FJ. Isolated elevated serum transaminases leading to the diagnosis of asymptomatic Pompe disease. *Eur J Pediatr*. Aug 2007;166(8):871-4. DOI: 10.1007/s00431-006-0315-9

Sanders KJC, Hermans MCE, Koek GH. Persistently elevated hepatic transaminases: a patient with late-onset Pompe disease. *Ned Tijdschr Geneeskd*. 2016:160:A9904. PMID 27229694

Meena NK, Raben N. Pompe Disease: New Developments in an Old Lysosomal Storage Disorder. Biomolecules. 2020 Sep;10(9):1339. doi 10.3390/biom10091339

Harlaar L, Hogrel JY, Perniconi B, Kruijshaar ME, Rizopoulos D, Taouagh N, et al. Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease. Neurology. 2019 Nov;93(19) e1756-e1767 doi: 10.1212/WNL.0000000000008441

Cupler EJ, Berger KI, Leshner RT, Wolfe GI, Han JJ, Barohn RJ, et al. Consensus treatment recommendations for late-onset Pompe disease. Muscle Nerve. 2012;45(3):319-33. doi: 10.1002/mus.22329

Porcino M, Musumeci O, Usbergo C, Pugliese A, Arena IG, Rodolico C, et al. Management of Presymptomatic juvenile patients with late-onset Pompe disease (LOPD). Neuromuscular Disorders. 2025Feb;47, 105277 doi: 10.1016/j.nmd.2025.105277

Byrne P.I., Collins S., Mah C.C., Smith B., Conlon T., Martin S.D. Phase I/II trial of diaphragm delivery of recombinant adeno-associated virus acid alpha-glucosidase (rAAaV1-CMV-GAA) gene vector in patients with Pompe disease. Hum. Gene Ther. Clin. Dev. 2014;25:134–163. doi: 10.1089/humc.2014.2514.

Corti M., Liberati C., Smith B.K., Lawson L.A., Tuna I.S., Conlon T.J., et al. Safety of Intradiaphragmatic Delivery of Adeno-Associated Virus-Mediated Alpha-Glucosidase (rAAV1-CMV-hGAA) Gene Therapy in Children Affected by Pompe Disease. Hum. Gene Ther. Clin. Dev. 2017;28:208–218. doi: 10.1089/humc.2017.146.

Unnisa Z, Yoon JK, Schindler JW, Mason C, van Til NP. Gene Therapy Developments for Pompe Disease. Biomedicines. 2022 Jan;10(2):302 doi: 10.3390/biomedicines10020302

Molares-Vila A, Corbalan-Rivas A, Carnero-Gregorio M, Gonzalez-Cespon JL, Rodriguez-Cerdeira C. Biomarkers in Glycogen Storage Diseases: An Update. Int J Mol Sci. 2021 Apr;22(9):4381. Doi: 10.3390/ijms22094381

Goker-Alpan O, Kasturi VG, Sohi MK, Limgala RP, Austin Sl, Jennelle T, et al. Pregnancy Outcomes in Late Onset Pompe Disease. Life (Basel). 2020;10(9):194 doi: 10.3390/life10090194

de Vries JM, Brugma JD, Ozkan L, Steegers EA, Reuser AJ, Van Doorn PA, van der Ploeg AT. First experience with enzyme replacement therapy during pregnancy and lactation in Pompe disease. Mol Genet Metab. 2011;104: 552-5 doi: 10.1016/j.ymgme.2011.09.012