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# Infantile onset Pompe disease presenting with non-immune hydrops fetalis

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Infantile onset Pompe disease (IOPD; MIM# 232300) is an autosomal recessive inborn error of metabolism (IEM), leading to lysosomal accumulation of glycogen due to deficiency of alpha-glucosidase (GAA; EC 3.2.1.20). Clinically, IOPD is characterized by hypertrophic cardiomyopathy, hypotonia, respiratory insufficiency and early death if untreated. Timely and early initiation of enzyme replacement therapy (ERT) leads to significant improvement in outcome, underscoring the importance of early diagnosis [1].

IEMs have been estimated to cause up to 15% of nonimmune hydrops fetalis (NIHF), a life-threatening prenatal condition characterized by fluid accumulation within at least two body cavities [2,3]. Lysosomal storage disorders (LSDs) are the most common class of IEM associated with NIHF [4–7]. IOPD is not among the 14 described LSDs reported to be associated with NIHF (see Table 1). Here we report the first patient with NIHF eventually diagnosed with IOPD. The atypical presentation of NIHF contributed to delayed diagnosis and treatment initiation.

After an unremarkable pregnancy, prenatal ultrasound at 37–5/7 weeks' gestation revealed severe NIHF. After delivery, the patient was diagnosed with bilateral chylothoraces concerning for lymphatic dysgenesis, but subsequent evaluation revealed lymphatic channels and chylous effusion resolution. Echocardiogram revealed pulmonary hypertension with an Ebstein-like tricuspid valve with dilated right atrium and ventricle. Subsequent echocardiograms showed progressive biventricular hypertrophy and depressed systolic function.

Molecular analysis included SNP chromosomal microarray and a Noonan syndrome panel. Metabolic workup included Michigan state newborn screen, plasma amino acids, urine organic acids, acylcarnitine profile, urine mucopolysaccharides, and LSD enzyme panel (did not include GAA). Whole exome sequencing (WES) was obtained after previous workup was non-diagnostic. He was found to be compound heterozygous for two pathogenic variants in *GAA* (c.258dupC,p.Asn87Glnfs*9 in exon 2; and c.1115A > T,p.His372Leu in exon 7). GAA activity was 0.50 pmol/punch/h (normal > 3.88) and urine glucotetrasaccharides (HEX4) was 51.3 mmol/mol/creatinine (normal ≤20). The variant in exon 7 conferred CRIM-positive status. WES was otherwise negative. ERT infusions were initiated and continue at scheduled intervals. The patient is currently 28 months old with significant improvement in cardiac status (normal left ventricular size and systolic function without hypertrophy).

Though LSDs are often in the differential diagnosis of NIHF, this phenotype has not been reported with IOPD. This case demonstrates the importance of considering IOPD as an etiology for infants who present with NIHF, particularly in states that have not included Pompe on the newborn screen. Laboratories offering enzyme or molecular panels for NIHF should include Pompe disease, otherwise delayed diagnosis will continue.

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## Declaration of Competing Interest

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**Table 1**
Lysosomal storage disorders associated with nonimmune hydrops fetalis.

| Lysosomal storage disorder | MIM# |
|---|---|
| Hurler syndrome/Mucopolysaccharidosis, Type I | 607014 |
| Morquio-A/Mucopolysaccharidosis, Type IVA | 253000 |
| Sly syndrome/Mucopolysaccharidosis, Type VII | 253220 |
| Galactosialidosis | 256540 |
| Sialidosis | 256550 |
| Gangliosidosis/GM1 | 230500 |
| Gaucher type 2 | 230900 |
| Niemann-Pick disease types A | 257200 |
| Niemann-Pick disease types C | 257220 |
| Farber granulomatosis | 228000 |
| Wolman disease | 278000 |
| Mucolipidosis II/I-cell disease | 252500 |
| Sialic acid storage disease | 269920 |
| Multiple sulfatase deficiency | 272200 |

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