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A TODDLER WITH TONGUE PROTRUSION AND HYPOTONIA: AN UNMASKING OF INFANTILE POMPE DISEASE

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ABSTRACT

Background:

Pompe disease (glycogen storage disease type II) is a rare autosomal recessive disorder caused by acid alpha-glucosidase (GAA) deficiency, leading to glycogen accumulation in muscle and cardiac tissue. Infantile-onset Pompe disease (IOPD) typically manifests within the first few months of life with hypotonia, macroglossia, cardiomyopathy, and failure to thrive.

Case Summary:

We report a 15-month-old female child born of consanguineous parents who presented with global developmental delay, feeding difficulties, protruded tongue, and axial hypotonia. Examination revealed facial dysmorphism, hypotonia, and areflexia. Investigations showed concentric left ventricular hypertrophy and reduced GAA activity. Genetic testing confirmed a homozygous GAA mutation. A diagnosis of IOPD was established.

Conclusion:

This case emphasizes the importance of early recognition of Pompe disease in hypotonic infants. Prompt diagnosis with enzyme assay and genetic confirmation enables timely referral for enzyme replacement therapy, significantly improving outcomes even in resource-constrained settings.

BACKGROUND

Pompe disease, or glycogen storage disease type II, is a rare autosomal recessive lysosomal storage disorder caused by deficiency of acid alpha-glucosidase (GAA), leading to accumulation of glycogen in multiple tissues, predominantly muscle and cardiac fibers [1,2]. The infantile-onset variant (IOPD) presents within the first few months of life with hypotonia, macroglossia, cardiomyopathy, and feeding difficulties. Without enzyme replacement therapy (ERT), progression is rapid and typically fatal before one year [3,4].

Diagnosis relies on clinical suspicion, biochemical tests showing elevated muscle enzymes, echocardiographic features of concentric left ventricular hypertrophy, reduced GAA activity, and confirmatory genetic testing [5,6]. Advances in molecular diagnostics and newborn screening have enabled early detection, although access to definitive treatment remains limited in many regions [7].

ERT with alfa glucosidase has significantly improved outcomes—particularly when initiated before 6 months of age. Treated children demonstrate longer survival, improved cardiomyopathy, and preserved motor functions [3,8]. However, phenotypic variability exists depending on CRIM status, antibody development, and age at initiation [9].This case highlights a classic presentation of IOPD in a resource-limited setting with delayed diagnosis but a structured approach to management and follow-up.

CASE PRESENTATION

A 15-month-old female child born of third-degree consanguineous parents presented with global developmental delay and inability to sit or stand independently. She had persistent drooling, constipation, regurgitation, and poor motor milestones. There was no history of perinatal asphyxia, seizures, or infections.

Figure 1. Clinical image of child with hypotonia and coarse facies

Examination

On examination, the child was alert, afebrile, and oriented to persons around. She had a shrill cry and was conscious but exhibited global hypotonia. Her anthropometric measurements—weight (7.23 kg), length (70.5 cm), and head circumference (41 cm)—were all below the –2 to –3 standard deviation range for age, indicating failure to thrive and undernutrition. Facial dysmorphism was evident, characterized by a flat nasal bridge, coarse facies, hypertelorism, and a protruded tongue. Notably, persistent drooling of saliva and dry skin were observed. The anterior fontanelle was closed, and there were no neurocutaneous markers or midline spinal abnormalities.

Neurological examination revealed significant axial hypotonia with preserved bulk and no visible wasting. Deep tendon reflexes were absent in both upper and lower limbs. Muscle tone was globally reduced, and power was 4/5 proximally and 3/5–4/5 distally. No scissoring was noted. Vertical suspension demonstrated head lag. Cranial nerve exam was unremarkable, with intact facial movement. Sensory testing showed intact pain, touch, and temperature sensations. Cardiac, respiratory, abdominal, and genital examinations were unremarkable. No organomegaly was found. Ophthalmological exam ruled out cherry-red spots or cataract.

Investigations

In view of persistent hypotonia and global developmental delay, a comprehensive work-up was initiated. Basic labs showed mildly elevated liver enzymes without corresponding hepatomegaly or sonographic liver changes. Thyroid function tests were normal, ruling out congenital hypothyroidism. Metabolic work-up including lactate and ammonia was unremarkable.

MRI brain showed mild diffuse cerebral atrophy without structural malformations, cortical dysplasia, or delayed myelination — findings suggestive of chronic metabolic insult, possibly from intracellular

glycogen accumulation, as seen in lysosomal storage disorders. Spinal imaging was unremarkable.Cardiac evaluation revealed biventricular concentric hypertrophy with preserved ejection fraction and borderline right atrial enlargement, suggestive of metabolic cardiomyopathy. These findings, along with hypotonia, macroglossia, and facial dysmorphism, raised suspicion for infantile Pompe disease.

Targeted enzyme analysis showed significantly reduced acid alpha-glucosidase (GAA) activity. Whole Exome Sequencing (WES) was performed, which revealed compound heterozygous mutations in the GAA gene:**c.1447G>A (p.Gly483Arg)** – a well-documented likely pathogenic missense variant.**c.1560C>A (p.Asn520Lys)** – a novel missense variant with in-silico predictions suggesting pathogenicity, currently classified as a VUS.Together, these are interpreted as likely compound heterozygous mutations, consistent with a diagnosis of **infantile-onset Pompe disease (IOPD)**. No significant CNVs were detected. Parental testing was advised for segregation analysis. Tandem mass spectrometry was sent to rule out metabolic mimics. Karyotyping excluded Turner syndrome. Noonan syndrome was considered but was unlikely due to absence of classic dysmorphic features or cryptorchidism.

DIFFERENTIAL DIAGNOSIS

In evaluating this case of a hypotonic infant presenting with global developmental delay, feeding difficulties, and cardiomyopathy, several differential diagnoses were systematically considered and ruled out. Congenital hypothyroidism was an initial consideration due to the presence of macroglossia, hypotonia, and developmental delay; however, the child's thyroid function tests were completely within normal limits, and there were no accompanying features such as umbilical hernia, bradycardia, or coarse dry skin typically associated with untreated congenital hypothyroidism. Spinal muscular atrophy (SMA) type I (Werdnig-Hoffmann disease) is another classic cause of profound hypotonia and areflexia in infancy. However, SMA is generally characterized by tongue fasciculations, intercostal muscle weakness, paradoxical breathing, and preserved mental status. In this patient, macroglossia was observed without fasciculations, respiratory effort was preserved with a shrill cry, and the presence of hypertrophic cardiomyopathy further differentiated the clinical picture from SMA. Genetic testing for SMN1 deletions was not pursued given the confirmatory findings of GAA deficiency and molecular confirmation of Pompe disease. Congenital muscular dystrophies, particularly alpha-dystroglycanopathies, were also considered, as they may present with hypotonia and motor delay. However, these conditions are typically associated with structural brain abnormalities, ocular findings, and are not usually linked with significant cardiac hypertrophy or macroglossia in infancy. Our patient's brain MRI was normal, and there were no ocular or CNS anomalies. Mitochondrial cytopathies, known for causing multisystem involvement including hypotonia, developmental regression, lactic acidosis, and seizures, were also in the differential. However, there was no evidence of neuroregression, no seizure activity, and metabolic work-up including lactate and tandem mass spectrometry was non-contributory. Ultimately, the clinical triad of macroglossia, hypotonia, and hypertrophic cardiomyopathy was highly suggestive of **infantile-onset Pompe disease (IOPD)**. This suspicion was further strengthened by elevated serum transaminases, reduced acid alpha-glucosidase activity on enzyme assay, and confirmation of a pathogenic homozygous GAA gene mutation on molecular analysis. Other lysosomal storage disorders, such as Gaucher disease or Tay-Sachs disease, were considered but deemed less likely in the absence of hepatosplenomegaly, cherry-red spots, or neurological regression. Thus, a comprehensive clinical evaluation, coupled with targeted investigations, allowed for accurate differentiation from other neuromuscular and metabolic disorders and confirmed the diagnosis of Pompe disease.

DISCUSSION

Pompe disease, or glycogen storage disease type II (GSD II), is a rare autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA), which leads to pathological glycogen accumulation in skeletal, cardiac, and smooth muscle fibers [1,2]. The infantile-onset form (IOPD) is the most severe phenotype, typically presenting in the first year of life with axial hypotonia, macroglossia, hypertrophic cardiomyopathy, and feeding difficulties [3].

Our patient presented with classical features of IOPD—persistent global hypotonia, developmental delay, coarse facies with tongue protrusion, and biventricular hypertrophy on echocardiogram. Enzyme assay revealed markedly reduced GAA activity, prompting genetic evaluation. Whole exome sequencing (WES) identified compound heterozygous mutations in the GAA gene: a known pathogenic

missense variant **c.1447G>A (p.Gly483Arg)**, and a novel variant **c.1560C>A (p.Asn520Lys)**. The former has been previously described in association with IOPD and is listed as likely pathogenic in ClinVar [4], while the latter, though currently a Variant of Uncertain Significance (VUS), had damaging in-silico predictions across multiple tools including PolyPhen-2 and MutationTaster [5].

MRI brain showed mild diffuse cerebral atrophy without structural abnormalities. While not a hallmark feature, similar findings have been reported in advanced IOPD cases, possibly due to glycogen accumulation impairing neuronal function and autophagy [6]. This underscores the need to interpret neuroimaging contextually, especially when clinical signs point towards a systemic metabolic disorder.

Differentials considered included Spinal Muscular Atrophy (SMA), congenital hypothyroidism, Noonan syndrome, and congenital muscular dystrophies. SMA was excluded based on preserved respiratory effort and absence of tongue fasciculations. Hypothyroidism was ruled out by normal thyroid profile. While Noonan syndrome can present with hypotonia and cardiac involvement, the absence of distinctive facies, cryptorchidism, or webbed neck made it unlikely [7]. Karyotyping ruled out Turner syndrome.The genetic diagnosis played a pivotal role not only in confirming Pompe disease but also in family counselling for recurrence risk and long-term care planning. Early initiation of enzyme replacement therapy (ERT) with recombinant GAA (alglucosidase alfa) has been shown to improve survival, reduce cardiomyopathy, and delay ventilator dependence [8,9]. However, therapy outcomes can vary depending on cross-reactive immunologic material (CRIM) status, antibody development, and age at initiation [10].

In conclusion, this case emphasizes the need to consider IOPD in any infant presenting with hypotonia and cardiomyopathy. Timely diagnosis combining clinical suspicion, enzyme assay, and molecular confirmation allows for early intervention. In low-resource settings, increasing awareness among clinicians and improving access to genetic testing can significantly alter disease trajectory.

TREATMENT AND FOLLOW-UP

Supportive care was initiated, including nutritional supplementation, physiotherapy, and cardiac monitoring. The child was referred to a tertiary metabolic center for evaluation and initiation of ERT. Genetic counseling was provided to the family. Follow-up includes serial echocardiography and neurodevelopmental assessments.

PATIENT PERSPECTIVE

The parents were initially shocked by the diagnosis but expressed relief after understanding the nature of the illness. They showed willingness to pursue therapy despite financial concerns. Emotional and logistical support was provided through pediatric social services and counseling.

LEARNING POINTS

- ✓ Pompe disease should be considered in infants with macroglossia, hypotonia, and cardiomyopathy.
- ✓ Enzyme activity testing and genetic confirmation are crucial for diagnosis.
- ✓ ERT improves survival and cardiac/motor function if started early.
- ✓ Multidisciplinary management and family education are essential.
- ✓ Delays in diagnosis can be reduced through better awareness in primary care.

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