Case report

http://wjpn.ssu.ac.ir

A Case Report on the Outcome of Infantile Pompe Disease

Naser Ali Mirhosseini[1,2,3], Mostafa Behjati-Ardakani[4], Parisa Sadat Fakhimpour[5*]

[1] Children Growth Disorder Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2] Department of Pediatrics, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3] Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[4] Cardiovascular Research Center, Non-communicable Diseases Research Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[5] Department of Pediatrics, Naein Heshmatie Hospital, Naein, Iran

Received: 03 August 2024 **Revised:** 23 November 2024 **Accepted:** 02 December 2024

ARTICLE INFO

Corresponding author:
Parisa Sadat Fakhimpour

Email:
psf1369@gmail.com

Keywords:
Infantile Pompe disease,
Hypertrophic cardiomyopathy,
Enzyme replacement therapy

ABSTRACT

Background: Pompe disease, or glycogen storage disease Type II, is an autosomal recessive disorder caused by a deficiency of acid α-1,4-glucosidase, leading to lysosomal glycogen accumulation in muscle tissues. Infantile Pompe disease (IPD) typically presents within the first weeks of life and is often fatal without enzyme replacement therapy (ERT). This report details the clinical course and outcome of a seven-month-old male diagnosed with IPD.

Case Presentation: A seven-month-old male infant, born full-term to consanguineous parents, was admitted due to a severe respiratory infection. Clinical features included hypotonia, swallowing difficulties, and failure to thrive (weight: 6 kg, <5th percentile). Laboratory tests showed elevated SGOT (95), SGPT (235), and CPK (700). An ECG revealed a short PR interval and prolonged QRS duration. Echocardiography indicated severe hypertrophic cardiomyopathy with systolic dysfunction. Enzyme assays confirmed critically low α-1,4-glucosidase levels (0.1 μmol/L/h), and genetic testing identified a homozygous mutation (c.1942 G > C), confirming Pompe disease. The infant passed away before ERT could be initiated.

Conclusion: This case highlights the challenges in diagnosing and managing Pompe disease in infants. The child's symptoms and lab results indicated a metabolic disorder, underscoring the multisystem impact of IPD. Rapid disease progression and consanguinity were significant factors. The delayed diagnosis led to a tragic outcome, emphasizing the need for early recognition and intervention. Timely ERT is crucial, as IPD can be fatal without it. This case underscores the importance of increased awareness and improved diagnostic protocols, particularly in consanguineous families and atypical presentations. Early diagnosis and intervention are essential for better outcomes.

Introduction

Pompe disease, or glycogen storage type II, is an autosomal recessive disorder caused by a deficiency of the enzyme acid α-1,4-glucosidase, which is crucial for glycogen breakdown into glucose in lysosomes. Its incidence is about 1 in 40,000 among Caucasians and 1 in 18,000 in Han Chinese, though screenings suggest the prevalence may be significantly higher (between 1 in 9,132 and 1 in 24,188). The disease accumulates glycogen in various tissues, particularly affecting muscle and nerve cells. The clinical presentation varies with age; infantile-onset Pompe disease usually appears within the first few months of life with severe symptoms such as cardiomyopathy, hypotonia, hepatomegaly, and feeding difficulties, often leading to fatality within the first year if untreated. In contrast, late-onset Pompe disease arises from childhood to adulthood an is characterized by progressive weakness primarily in proximal muscles, with less cardiac involvement. The condition stems from mutations in the GAA gene, which impair glycogen degradation and cause cellular damage.[1,2]

Diagnosis involves biochemical tests assessing acid α-glucosidase activity, imaging to evaluate structural changes, and genetic testing for GAA mutations located on chromosome 17q25.2. Infantile Pompe disease (IPD), often fatal without enzyme replacement therapy (ERT) using alglucosidase alfa, presents in the early weeks of life with hypotonia and organomegaly, leading to cardiorespiratory failure. ERT has significantly improved treatment outcomes by providing patients with a functional enzyme to reduce glycogen accumulation and alleviate symptoms, specifically when initiated early in infantile cases to promote better motor development. Diagnostic tests typically reveal elevated creatine kinase, SGOT, SGPT, and LDH levels. Imaging for IPD commonly includes chest X-rays, which show significant cardiomegaly, and echocardiography to detect ventricular thickening. Diagnosis is confirmed via enzyme assays in dried blood spots or muscle tissue and gene sequencing of the GAA gene. ERT with alglucosidase alfa can prevent or reverse declines in muscle function.[3]

Case Presentation

A seven-month-old male infant, born full-term via normal vaginal delivery to consanguineous parents, was admitted due to a severe respiratory infection. The infant had a history of hypotonia and swallowing issues since birth, as well as significant failure to thrive, evident by a weight of only 6 kg (less than the 5th percentile). His growth metrics included a length of 70 cm (90th percentile) and a head circumference of 38 cm (less than the 5th percentile), with a head circumference of 34 cm at birth. Upon examination in the hospital, the following laboratory results were obtained: SGOT was 95, SGPT was 235, and CPK was 700. An ECG revealed a short PR interval and a prolonged QRS duration. Echocardiography demonstrated severe hypertrophic non-obstructive cardiomyopathy with evident systolic dysfunction. Given the clinical findings and suspicion of a metabolic disorder, the infant was evaluated for Pompe disease. The analysis showed dangerously low levels of α-1,4-glucosidase at 0.1 μmol per liter per hour (normal range > 2). Despite aggressive treatment for heart failure and management of the respiratory infection, the infant unfortunately passed away before the initiation of enzyme replacement therapy.

Genetic testing has confirmed a diagnosis of Pompe disease through the identification of a homozygous mutation: c.1942 G > C (p.(Gly648Arg)). This variation noted as NM_000152.5(GAA):c.1942G>A(p.Gly648Ser), is a single nucleotide variant involving a solitary base pair change. It is located at cytogenetic position 17q25.3, with genomic coordinates of 17:80112929 in the GRCh38 assembly and 17:78086728 in the GRCh37 assembly. Assigned Variation ID: 188902 carries an accession number of

VCV000188902.42. This alteration leads to the substitution of glycine for serine at the 648th amino acid position in the protein, potentially affecting its functionality and relation to associated phenotypes.

Discussion

Classic infantile Pompe disease is a rapidly progressive cardiomyopathy that often leads to death within the first year. Identifying the enzyme defect has revealed a spectrum of variants. Symptoms of the infantile form typically appear within weeks or months of birth, with some infants showing signs at birth. Early symptoms may include poor feeding and failure to thrive, followed by cyanosis and dyspnea, culminating in rapid cardiac failure. Death usually results from congestive heart failure, sometimes complicated by terminal pneumonia.[4]

The presented case highlights the challenges in diagnosing and managing Pompe disease, a lysosomal storage disorder caused by α-1,4-glucosidase deficiency. The infant exhibited symptoms such as hypotonia, swallowing difficulties, and failure to thrive, along with elevated liver enzymes and creatine phosphokinase (CPK), suggesting a metabolic disorder. Severe hypertrophic cardiomyopathy and abnormal ECG findings underscored the disease's multisystem impact, particularly in early-onset cases. Genetic testing confirmed a homozygous mutation in the GAA gene (c.1942 G > C, p.Gly648Arg), reflecting the autosomal recessive inheritance pattern common in consanguineous families. The infant's severe symptoms, including hypotonia, failure to thrive, respiratory infections, and heart failure, exemplified the profound effects of GAA deficiency, while elevated serum transaminases and CPK indicated multisystem involvement. Although enzyme replacement therapy (ERT) offers a treatment option, the delayed diagnosis and rapid disease progression led to a tragic outcome, emphasizing the need for early recognition and intervention in metabolic disorders. Genetic counseling is crucial for affected families to understand the risks and implications of the disorder. Ongoing research into the mechanisms of the identified mutation and advancements in treatment strategies hold promise for improving outcomes in individuals with Pompe disease.

Research shows that Pompe disease exhibits diverse phenotypes influenced by specific GAA gene mutations. Studies have examined the incidence, clinical characteristics, genetic mutations, and treatment responses, particularly ERT.[5,6] For example, Elenga et al. (2018) highlighted the varying incidence of infantile Pompe disease across populations, shaped by mutational profiles, including novel variants like p.Gly648Arg.[7] Broomfield et al. (2016) emphasized that the efficacy of ERT in UK patients with infantile-onset Pompe disease depends on the genetic alterations present.[8] Furthermore, studies by Pittis (2008) and Kroos (2012) stressed the importance of functionally characterizing mutations to understand their effects on enzymatic activity, noting that variants like p.Gly648Arg might influence enzyme stability and lysosomal trafficking, impacting clinical outcomes.[9,10] The clinical spectrum of Pompe disease, as described by Müller-Felber et al. (2007) and Schoser et al. (2007), reveals distinct symptoms between infantile and late-onset cases, with the p.Gly648Arg variant potentially leading to a more severe infantile presentation.[11] Long-term studies are needed to determine the correlation between this mutation and disease progression, as well as treatment responses. Additionally, Flanagan (2009) proposed that pharmacological chaperones could enhance the stability and activity of misfolded enzymes, potentially improving outcomes for patients with mutations like p.Gly648Arg.[12] Thus, while the 1942 G > C (p.Gly648Arg) variant is documented, further investigation is required to clarify its role in disease pathogenesis, phenotype expression, and therapeutic responses, alongside prioritizing genetic counseling and comprehensive evaluations for

affected patients to guide appropriate management strategies.

Conclusion

Infantile Pompe disease is fatal without enzyme replacement therapy using alglucosidase alfa, making early treatment crucial, especially for infants, due to the disease's rapid progression. This case underscores the need for greater awareness and improved diagnostic protocols for Pompe disease and other inherited metabolic disorders, particularly in populations with higher consanguinity rates. Timely symptom identification and genetic testing are essential for effective management. The progression of Pompe disease emphasizes the importance of healthcare providers recognizing signs of metabolic disorders in infants. Ongoing education and training for clinicians on these rare diseases can lead to quicker interventions, reducing the risk of severe complications and enhancing the quality of life for those affected.

Conflict of Interest

The authors declare that there is no conflict of interest.

Acknowledgments

The authors express their gratitude to the patient's family for their cooperation during this study.

Funding

The authors declare that no funding was received for this research.

Ethical Considerations

This study received approval from the Ethics Committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.REC.1403.120).

Author's Contribution

Conducting patient examinations, N.M. and M.B.-A.; writing and editing the manuscript, P.F. All authors have reviewed and approved the final version of the manuscript.

How to Cite: Mirhosseini NA, Behjati-Ardakani M, Fakhimpour PS. A Case Report on the Outcome of Infantile Pompe Disease. World J Peri & Neonatol 2024; 7(1): 51-55.
DOI: 10.18502/wjpn.v7i1.17328

References

1. Dos Santos OCC, Schultz R. The infantile-onset form of Pompe disease: an autopsy diagnosis. Autops Case Reports 2015; 5(4): 45-51.
2. Morales A, Poling MI, Páez MT, Cabrera J, McCormick RJ. c.1437G>A intron 9 substitution on acid α-glucosidase gene associated with classic infantile-onset Pompe disease phenotype. BMJ Case Rep 2015; 2015: bcr2015210688.
3. Kliegman R, St. Geme JW. Nelson textbook of pediatrics. Amsterdam, Netherlands: Elsevier; 2024; 1. p. 8–22.
4. Nyhan WL, Hoffmann GF. Atlas of Inherited Metabolic Diseases. 4th ed. Boca Raton, Fl: CRC Press; 2020.
5. Moschetti M, Lo Curto A, Giacomarra M, Francofonte D, Zizzo C, Messina E, et al. Mutation Spectrum of GAA Gene in Pompe Disease: Current Knowledge and Results of an Italian Study. Int J Mol Sci 2024; 25(17): 9139.
6. Taverna S, Cammarata G, Colomba P, Sciarrino S, Zizzo C, Francofonte D, et al. Pompe disease: pathogenesis, molecular genetics and diagnosis. Aging (Albany NY) 2020; 12(15): 15856–74.
7. Elenga N, Verloes A, Mrsic Y, Basurko C, Schaub R, Cuadro-Alvarez E, et al. Incidence of infantile Pompe disease in the Maroon population of French Guiana. BMJ Paediatr Open 2018; 2(1): e000182.
8. Broomfield A, Fletcher J, Davison J, Finnegan N, Fenton M, Chikermane A, et al. Response of 33 UK patients with infantile-onset Pompe disease to enzyme replacement therapy. J Inherit Metab Dis 2016; 39(2): 261–71.
9. Kroos M, Hoogeveen-Westerveld M, van der Ploeg A RA. The genotype-phenotype correlation in Pompe disease. Am J Med Genet C Semin Med Genet 2012; 160C(1): 59–68.
10. Pittis MG, Donnarumma M, Montalvo AL, Dominissini S, Kroos M, Rosano C, et al. Molecular and functional characterization of eight novel GAA mutations in Italian infants with Pompe disease. Hum Mutat 2008; 29(6): E27-36.

11. Müller-Felber W, Horvath R, Gempel K, Podskarbi T, Shin Y, Pongratz D, et al. Late onset Pompe disease: clinical and neurophysiological spectrum of 38 patients including long-term follow-up in 18 patients. Neuromuscul Disord 2007; 17(9–10): 698–706.

12. Flanagan JJ, Rossi B, Tang K, Wu X, Mascioli K, Donaudy F, et al. The pharmacological chaperone 1-deoxynojirimycin increases the activity and lysosomal trafficking of multiple mutant forms of acid alpha-glucosidase. Hum Mutat 2009; 30(12): 1683–92.