American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2024; 25: e943398
DOI: 10.12659/AJCR.943398

Received: 2023.12.06
Accepted: 2024.01.26
Available online: 2024.01.31
Published: 2024.03.21

Gaucher Disease Coexisting with Cytomegalovirus Infection: A Rare Presentation in an Infant

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ADE Zhaoxia Zhang
ABCDEF Dong Liu
DF Zhangbin Yu
A Zhihui Xiao
EF Keying Zhou
AD Bo Li

Department of Pediatrics, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affiliated Hospital, Southern University of Science and Technology), Shenzhen, Guangdong, PR China

Corresponding Author: Dong Liu, e-mail: liudong86755@hotmail.com
Financial support: This work was supported by the Foundation of Shenzhen Science and Technology Innovation Commission (grant No. JCYJ20210324114207020) and the Cultivation Project of Shenzhen People's Hospital (grant No. SYJCYJ202007)
Conflict of interest: None declared

Patient: Female, 4-month-old
Final Diagnosis: Gaucher disease
Symptoms: Progressive hepatosplenomegaly since birth • sensory neurological hearing loss
Clinical Procedure: —
Specialty: Genetics • Infectious Diseases • Metabolic Disorders and Diabetics • Pediatrics and Neonatology

Objective: Rare disease

Background: Gaucher disease is a rare autosomal recessive disorder characterized by mutations in the glucocerebrosidase gene, resulting in deficient enzyme activity and accumulation of glucocerebroside in macrophages, which leads to pathological changes in affected organs. The atypical clinical manifestations of Gaucher disease often contribute to delays in diagnosis and treatment.

Case Report: We present the case of a 4-month-old female infant admitted to the Department of Pediatrics with progressive hepatosplenomegaly since birth. Concurrently, she had cytomegalovirus infection and sensory neurological hearing loss. Gaucher disease diagnosis was confirmed through whole-exome sequencing and validated by a glucocerebrosidase activity test, revealing the mutation site as c.1448T>C. This report outlines the differential diagnosis process for Gaucher disease in this infant before confirmation, contributing valuable insights for early diagnosis.

Conclusions: Our case underscores the challenge of diagnosing Gaucher disease due to its atypical presentation. The coexistence of cytomegalovirus infection complicates the clinical picture, emphasizing the need for careful differential diagnosis. Unfortunately, delayed diagnosis is all too common in rare diseases like Gaucher disease, even when the clinical presentation is seemingly typical. This highlights the need for increased awareness and education within the medical community to facilitate early recognition, which is essential for prompt intervention and improved outcomes. This report contributes valuable clinical and genetic information, aiming to enhance awareness and deepen the understanding of Gaucher disease in infants, particularly those with concurrent infections.

Keywords: Cytomegalovirus Infections • Gaucher Disease • Hearing Loss, Sensorineural • Whole Exome Sequencing

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/943398

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Introduction

Gaucher disease (GD) is an uncommon genetic disorder inherited in an autosomal recessive manner. It is characterized by mutations in the glucocerebrosidase gene (GBA1), leading to deficiency of this enzyme's activity. Consequently, there is an accumulation of glucocerebroside in macrophages within human organs, ultimately resulting in pathological changes within the affected organs [1].

GD is a rare condition with non-specific manifestations that are found in many other disorders, often causing delays in both diagnosis and treatment. This report aims to provide a concise summary of the clinical characteristics and gene sequencing findings pertaining to an infant diagnosed with GD concurrently experiencing cytomegalovirus (CMV) infection.

Case Report

A 4-month-old female was referred to the pediatric department due to liver and spleen enlargement persisting for 4 months. Born at 40 weeks of gestational age with no prenatal or perinatal risk factors, the infant received treatment 18 hours after birth for "jaundice accompanied by fever for 3 hours." Hepatosplenomegaly was observed during hospitalization, with both liver and spleen positioned 3 cm below the ribs. A color ultrasound revealed a spleen size of 6.5×3.0 cm, positioned 2.8 cm below the ribs, displaying a regular shape and uniform internal echo. The liver parenchyma exhibited uniform echo, with clear intrahepatic bile ducts and blood vessels. Complete blood count analysis revealed white blood cell count 18.76×10^9/L, red blood cell count 4.89×10^{12}/L, hemoglobin 174 g/L, platelet count 69×10^9/L, neutrophil percentage 58.6%, lymphocyte percentage 30.8%, monocyte percentage 7.6%, high-sensitivity C-reactive protein 6.52 mg/L, and procalcitonin 3.36 ng/ml. Platelet count returned to normal on the 11th day of anti-infection treatment. Platelet autoantibody testing revealed no abnormalities. The mother had no history of immune thrombocytopenia. Comprehensive testing for hepatitis B and C viruses showed no abnormalities. No abnormalities were detected in liver function or TORCH tests. After a 2-week course of anti-infection treatment, the infant was discharged with a diagnosis of "neonatal sepsis, neonatal hyperbilirubinemia, thrombocytopenia, and neonatal intracranial hemorrhage (restricted to the germinal matrix of the brain)."

Subsequent periodic ultrasound reviews indicated progressive aggravation of hepatosplenomegaly. Family history of genetic or infectious diseases and hepatosplenomegaly was denied by the parents. Physical examinations after admission revealed hepatosplenomegaly, with both the liver and spleen positioned 4 cm below the ribs, exhibiting good texture. Laboratory test results, including complete blood count, liver function, ceruloplasmin, blood lactic acid, or glycogen staining, were normal before admission. Coagulation function, blood ammonia, blood lactic acid, electrolytes, liver and kidney function, myocardial enzymes, C-reactive protein, and immunoglobulin, and complement levels were normal after admission. Additional tests, such as thalassemia gene, hepatitis A, B, E, Epstein-Barr (EB) virus, and respiratory tract viruses, yielded normal results. Lipid profile tests showed elevated triglyceride levels (4.44 mmol/L, normal range: 0.4-2.3 mmol/L), maintained between 3.44 mmol/L and 3.75 mmol/L during hospitalization. It is important to note that at the time of CMV infection diagnosis and the subsequent diagnosis of Gaucher disease at the age of 4 months, repeated complete blood count examinations consistently showed no recurrence of thrombocytopenia.

CMV testing indicated elevated IgM antibody levels (9.86 S/CO, normal <1S/CO) and IgG antibody levels (219.1 AU/mL, normal <6 AU/mL). CMV nucleic acid levels in urine were 2.78 E3 copies/ml (normal value <1 E3 copies/ml). CMV antibody affinity tests revealed low-affinity antibodies. Auditory brainstem response (ABR) tests indicated short ABR response values of 80 dBnHL for the left ear and 70 dBnHL for the right ear. Fundus screening demonstrated fully developed retinal blood vessels. Blood and urine screening for metabolic diseases, including amino acid, acylcarnitine, and organic acid levels, yielded normal results. Abdominal color ultrasound revealed specific details of liver and spleen dimensions. Color echocardiography displayed no abnormalities in cardiac morphology and function, and brain magnetic resonance imaging showed no anomalies. Following clinical observations not entirely aligning with the expected disease course, whole-exome sequencing was conducted on the blood samples from the infant and her parents. The sequencing results revealed a significant variation in GBA1 that correlated with the clinical presentation of the infant. Analysis of the GBA1 revealed a homozygous variation in the infant, specifically NM_001005741.2: c.1448T>C (p.Leu483Pro) (**Figure 1**). This mutation, occurring at the 1448th base in the coding region, resulted in the substitution of leucine with proline at the 483th amino acid position in the coding protein. The whole-exome sequencing of her parents confirmed a heterozygous variation at this locus, as illustrated in **Figures 2 and 3**. The patient was discharged without further examinations or treatments per parental request.

The glucocerebrosidase activity detected in outpatient follow-up, measuring 0.32 μmol/L/h (reference value: 1.26-22.23 μmol/L/h), was conducted at a children's hospital, as our institution did not offer this specific testing. Knee joint X-rays and electroencephalograms showed no abnormalities. During outpatient follow-up, the patient displayed neurological abnormalities, with poor movement and focusing function of the eyes. These manifestations, including oculomotor dysfunction, align with

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

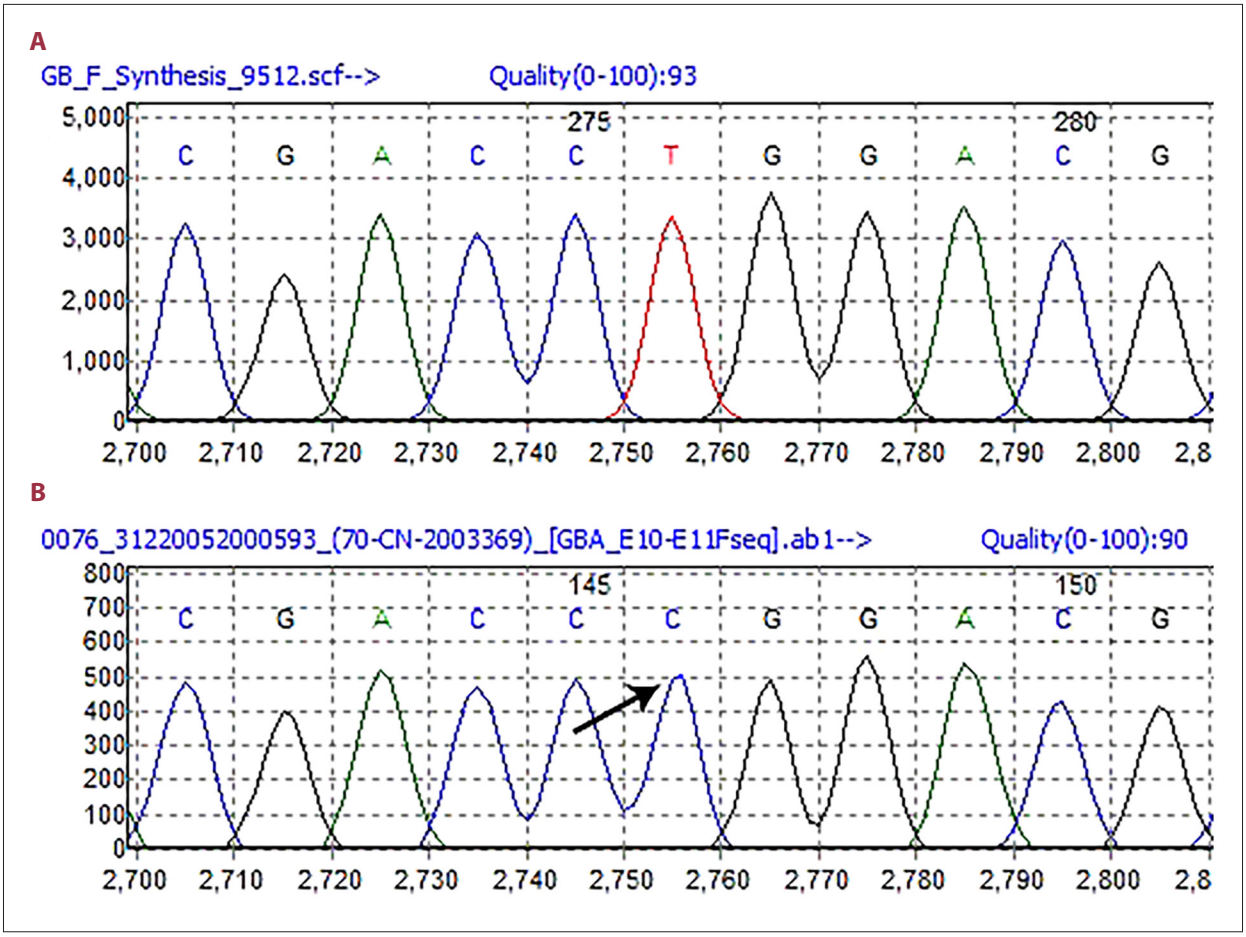

Figure 1. Whole-exome sequencing analysis of the infant. (**A**) Reference sequence: This segment illustrates the reference sequence representing the normal genomic configuration. (**B**) Sequencing results: Results of the sequencing analysis. The identified homozygous variation, NM_001005741.2: c.1448T>C (p.Leu483Pro), is emphasized, indicating the substitution of the 1448th base in the coding region (marked by the arrow). This alteration leads to the change from T to C, consequently modifying the 483th amino acid from leucine to proline.

recognized early findings in neuronopathic GD. Notably, the assessment did not reveal other neurological abnormalities such as convulsions or myoclonus. Regrettably, due to outpatient follow-up at a children's hospital, imaging data was unavailable, and post-discharge follow-up from our hospital was conducted via telephone. The patient had been receiving imiglucerase treatment beginning 4 months after the diagnosis.

Discussion

The clinical manifestations of GD are often atypical, posing challenges to accurate clinical diagnosis. In this case, the patient presented with hepatosplenomegaly immediately after birth, with an unknown etiology. Liver and spleen enlargement progressively worsened, accompanied by abnormal triglyceride levels. The confirmation of GD diagnosis was achieved through whole-exome sequencing and glucocerebrosidase activity test.

In discussing GD, it is essential to recognize its 3 main types based on clinical features, age of onset, and organ involvement. Type 1 GD (GD1), or non-neuronopathic, manifests with hepatosplenomegaly, cytopenia, and bone abnormalities. On the other hand, type 2 (GD2) and type 3 (GD3), referred to as neuronopathic, present acute and chronic forms, respectively. This classification is pivotal for understanding the diverse clinical spectrum and guiding appropriate management [2].

GD is mainly caused by pathogenic mutations in the GBA1. The GBA1, located on chromosome 1Q21, has over 300 mutations, with their prevalence varying across different races [3]. Significantly, the c.1226A>G (N409S) mutation is prevalent among individuals in Europe and is also identified as one of the common mutations in North Africa, the Middle East, India, and China [4]. Conversely, the c.1448T>C (L483P) and c.754T>A (F252I) mutations are more prevalent in Asians [5]. Different types of GD are associated with distinct gene mutations, with

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

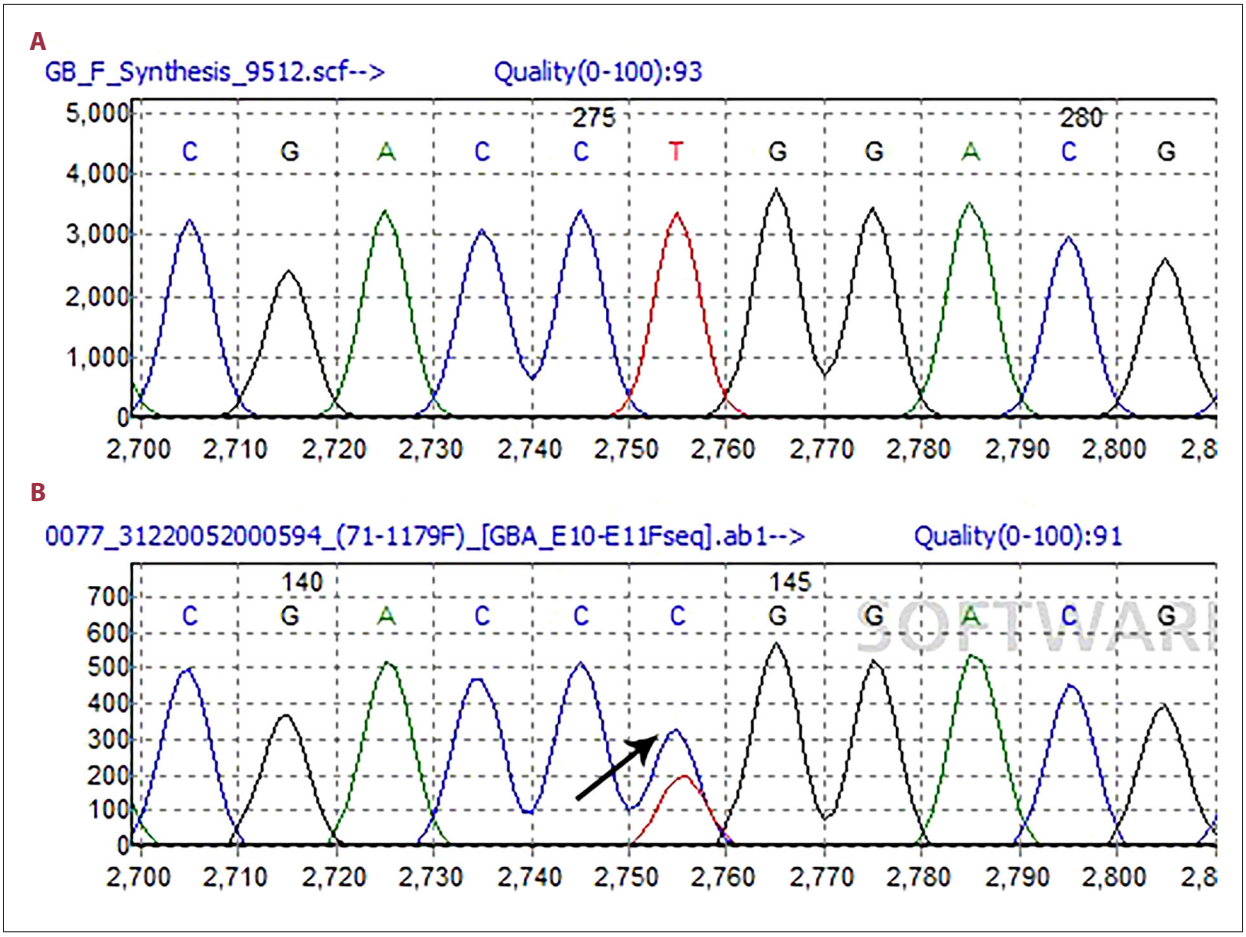

Figure 2. Whole-exome sequencing of the infant's father. (**A**) Reference sequence: This segment illustrates the reference sequence representing the normal genomic configuration. (**B**) Sequencing results: Results of the sequencing analysis. The figure depicts a heterozygous variation on the GBA1 (marked by the arrow), observed at the same locus as indicated in Figure 1.

c.115+1G>A (IVS2+1), c.1504C>T (R463C), and c.1604G>A (R496H) being more common [6]. Mutations in c.1448T>C (L483P) and c.754T>A (F252I) are linked to GD2 and GD3 in Asians [5]. Notably, the L483P variants, whether in homozygous or compound heterozygous states, lead to the development of GD2 or GD3 not only in East Asia but also in countries such as Sweden, Poland, Turkey, and Egypt [7,8]. The L483P allele is intricate, exhibiting variations ranging from simple point mutations to complex recombinations with the glucosylceramidase beta pseudogene, often resulting in more severe outcomes. The identified homozygous pathogenic mutant gene in this infant aligned with the common c.1448T>C (L483P) mutation in Asian populations. The patient was considered to have GD3, diagnosed based on subacute neuropathic variation, as evidenced by previous reports, along with distinctive eye findings, hearing loss, and the identified genotype.

Neurological manifestations of GD encompass a range of symptoms, including bulbar palsy, ocular motor disorders, epileptic seizures, opisthotonus, cognitive impairment, cerebellar ataxia, and myoclonus [1]. However, in this case, no such symptoms were observed, except for sensorineural hearing loss reported after admission. Sensorineural hearing loss is a rare feature in GD, but it has been documented in cases of GD3, where children exhibited abnormal acoustic reflection, medial olivary cochlear system function, and altered auditory brainstem response after audiological tests [9]. Another reported case involved a 5-year-old patient with GD2 who showed abnormal changes in auditory brainstem response 2 months before the onset of opisthotonus and strabismus [10].

After admission, CMV infection was confirmed in this case. While CMV infection was not the primary cause of hepatosplenomegaly after birth, it may have contributed to its aggravation. Some researchers propose that CMV infection can trigger the clinical manifestations of GD. However, a study involving 99 cases of GD1 combined with EB virus and/or CMV virus revealed no direct correlation between the severity of GD1 and viral infection [11]. Nevertheless, CMV infection can interfere with recognition of GD symptoms. GD2 and GD3

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

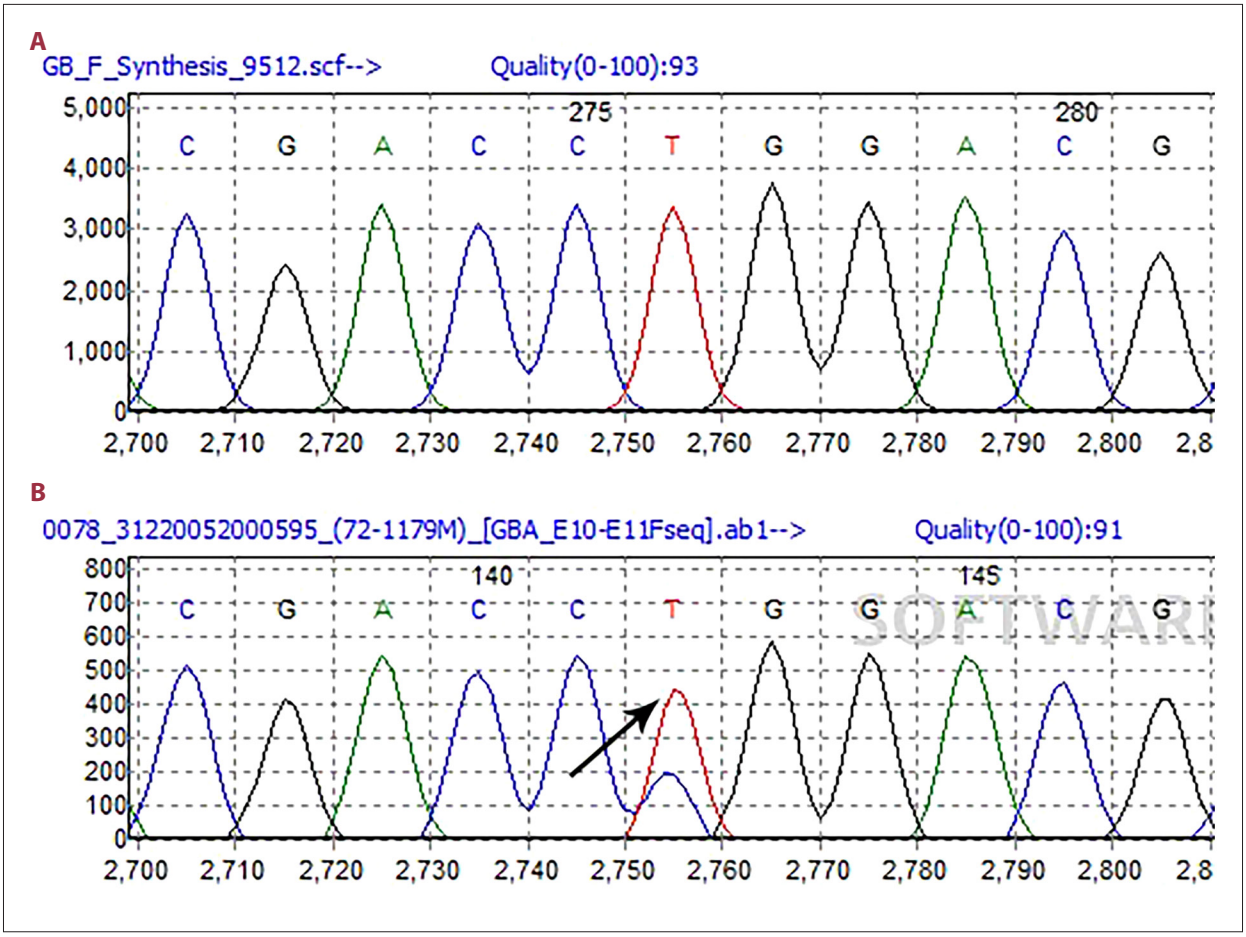

Figure 3. Whole-exome sequencing of the infant's mother. (**A**) Reference sequence: This segment illustrates the reference sequence representing the normal genomic configuration. (**B**) Sequencing results: Results of the sequencing analysis. The figure illustrates a heterozygous variation on the GBA1 (marked by the arrow), detected at the same locus as presented in Figure 1.

present with various neurological symptoms, including hearing loss, while CMV infection itself can cause sensorineural hearing loss. Before the GD diagnosis, the patient underwent evaluation and received antiviral therapy with ganciclovir based on evidence of CMV infection and sensory nerve hearing loss. Although many researchers believe that CMV infection with hearing loss alone necessitates antiviral treatment, there is no consensus on this recommendation [12]. In this case, CMV infection and GD coexisted, and the exact cause of sensorineural hearing loss remains uncertain. Hearing impairment may manifest in the early stages of GD. Therefore, it is essential to differentiate children with hepatosplenomegaly and hearing impairment from those with the neuropathic variant GD.

The treatment landscape for GD predominantly revolves around regular intravenous enzyme replacement therapy (ERT), recognized as the primary approved intervention for symptomatic pediatric cases [1]. The emphasis on prompt ERT initiation for pediatric GD patients aligns with literature advocating its efficacy in mitigating hepatosplenomegaly, improving blood parameters, and enhancing overall quality of life. Notably, ongoing research into experimental approaches, such as gene therapy and pharmacological chaperones [13,14], contributes to the broader understanding of GD treatment strategies, emphasizing the importance of early intervention and the exploration of novel therapies for comprehensive patient care.

However, it is crucial to acknowledge the limitations of this study, notably the lack of imaging data due to outpatient follow-up at a different hospital, which may have affected full assessment of neurological abnormalities. Additionally, reliance on telephone follow-up introduces a potential constraint on data completeness. Despite these limitations, this study sheds light on the diagnostic challenges associated with coexisting GD and cytomegalovirus infection in infants.

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Conclusions

Our case underscores the challenge of diagnosing GD due to its atypical presentation. The coexistence of CMV infection complicates the clinical picture, emphasizing the need for careful differential diagnosis. It is important to consider that infants presenting with progressive hepatomegaly and splenomegaly may raise suspicion of a genetic liver disease. However, it is essential to emphasize that thorough laboratory investigations are imperative to exclude the possibility of a concurrent infection affecting these 2 organs. Unfortunately, delayed diagnosis is all too common in rare diseases like GD, even when the clinical presentation is seemingly typical. This highlights the urgency for increased awareness and education within the medical community to facilitate early recognition. Early diagnosis is paramount for prompt intervention and improved outcomes. This report contributes valuable clinical and genetic information, aiming to enhance awareness and deepen the understanding of GD in infants, particularly those with concurrent infections.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Weinreb NJ, Goker-Alpan O, Kishnani PS, et al. The diagnosis and management of Gaucher disease in pediatric patients: Where do we go from here? Mol Genet Metab. 2022;136(1):4-21
2. Kong W, Lu C, Ding Y, Meng Y. Update of treatment for Gaucher disease. Eur J Pharmacol. 2022;926:175023
3. Riboldi GM, Di Fonzo AB. GBA, Gaucher disease, and Parkinson's disease: From genetic to clinic to new therapeutic approaches. Cells. 2019;8(4):364
4. Grabowski GA, Antommaria AHM, Kolodny EH, Mistry PK. Gaucher disease: Basic and translational science needs for more complete therapy and management. Mol Genet Metab. 2021;132(2):59-75
5. Hughes DA, Pastores GM. Gaucher disease. 2000 Jul 27 [Updated 2023 Dec 7]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1269/
6. Hruska KS, LaMarca ME, Scott CR, Sidransky E. Gaucher disease: Mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA). Hum Mutat. 2008;29(5):567-83
7. Emre S, Gürakan F, Yüce A, et al. Molecular analysis of Turkish Gaucher disease patients: Identification of novel mutations in glucocerebrosidase (GBA) gene. Eur J Med Genet. 2008;51(4):315-21
8. Tylki-Szymańska A, Keddache M, Grabowski GA. Characterization of neuronopathic Gaucher disease among ethnic Poles. Genet Med. 2006;8(1):8-15
9. Tullo MG, Cerulli Irelli E, Caramia F, et al. The spectrum of neurological and sensory abnormalities in Gaucher disease patients: A multidisciplinary study (SENOPRO). Int J Mol Sci. 2023;24(10):8844
10. Okubo Y, Goto M, Sakakibara H, et al. The absence of later wave components in auditory brainstem responses as an initial manifestation of type 2 Gaucher disease. Pediatr Neurol. 2014;51(6):837-39
11. Pines G, Morag A, Elstein D, et al. Viral infections and phenotypic heterogeneity in Gaucher disease. Blood Cells Mol Dis. 2001;27(2):358-61
12. Luck SE, Wieringa JW, Blázquez-Gamero D, et al. Congenital cytomegalovirus: A European Expert Consensus Statement on Diagnosis and Management. Pediatr Infect Dis J. 2017;36(12):1205-13
13. Sam R, Ryan E, Daykin E, Sidransky E. Current and emerging pharmacotherapy for Gaucher disease in pediatric populations. Expert Opin Pharmacother. 2021; 22(11):1489-503
14. Tran ML, Génisson Y, Ballereau S, Dehoux C. Second-generation pharmacological chaperones: Beyond inhibitors. Molecules. 2020;25(14):3145

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]