CASE REPORT

Clinical Manifestation of Hearing Loss in a Boy with Type IIIb Gaucher Disease: A Unique Case Report

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ABSTRACT

Objective • Gaucher disease (GD) is a clinically rare single-gene recessive lysosomal storage disease mainly divided into three subtypes I to III. This report aims to present a case of type IIIb GD in a Chinese child with a focus on the manifestation of hearing loss and the importance of early diagnosis and monitoring.

Methods • The patient underwent a routine physical examination upon admission, followed by CT scans of the chest and abdomen, MRI of the brain, and bone marrow smear examination. The patient's GBA enzyme activity, Lyso-GL-1 levels, and GBA gene expression were analyzed using tandem mass spectrometry (MS/MS) and next-generation sequencing technology. Finally, auditory brainstem response (ABR) testing was conducted.

Results • This report presented a case of a Chinese boy with hematological manifestations as the first symptom, followed by hepatosplenomegaly, and the bilateral femurs showed obvious Erlenmeyer flask-like changes. Combined with GBA enzyme activity, Lyso-GL-1 and GBA genotype analysis results, the boy was initially diagnosed as type I GD. During the follow-up, the boy developed nystagmus, bilateral ABR V wave threshold increased, V/I amplitude ratio <0.5, accompanied by delayed growth and development, and finally diagnosed as type IIIb.

Conclusions • This case suggests the necessity of neuropathy monitoring in patients with type I GD during the early stages of the disease. This includes EEG, neuro-ophthalmological examination, and auditory function assessment, which can help reflect the progression of neuropathy and facilitate the early diagnosis of type III GD. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Gaucher disease (GD) is a rare autosomal recessive lysosomal storage disorder (LSDs) caused by mutations in the GBA gene, which encodes glucocerebrosidase (also known as β-glucosidase). The reduction or deficiency of GBA enzyme activity further leads to the accumulation of the substrate glucocerebroside in macrophage lysosomes, causing multiple organs damage, including liver, spleen, bones, lungs, even brain in a patient.[1,2] Globally, the neonatal standardized incidence rate of GD is (0.39-5.80)/100 000 and the prevalence rate is (0.70-1.75)/100 000.[3] The prevalence among individuals with high-risk Ashkenazi Jewish ancestry is 118/100 000.[4] There are no epidemiological statistics based on large sample data in China so far, while the neonatal screening studies of GD that conducted in East China (Shanghai) and Taiwan showed the incidence is approximately 1 per 80 855 and 1 per 103 134 respectively.[5,6]

GD is mainly recognized as three subtypes based on the degree and progression of patients' neurological damage: non-neuropathic type (type I), acute neuropathic type (type II), and chronic or subacute neuropathic type (type III).[7] Among them, type I is the most common subtype and frequently causes internal organs, blood, and bones involvement, with rare primary nerve system involvement. Type II usually begins between the neonatal period and infancy, mainly manifesting as early-onset and rapidly progressive neurological involvement, and patients typically die before the age of 2 to 4 years. GD Type III is a rare subtype that initially presents similarly to Type I, with symptoms such as hepatosplenomegaly, thrombocytopenia, and anemia. However, it exhibits mild to severe neurological symptoms at the late stage, leading to difficulty in early diagnosis. Due to the similar initial symptoms that type I and III GD have, it is still a great challenge to distinguish them before neurological symptoms appear. According to the difference in clinical manifestations, GD type III can be further divided into three subtypes: GD type IIIa is mainly manifested by rapidly progressive neurological symptoms, including eye movement disorder, spasticity, myoclonus, and

dementia; GD type IIIb has few central nervous system symptoms, but is often accompanied by hepatosplenomegaly and significant bone disease; GD type IIIc, also known as cardiovascular type GD, is mainly characterized by mitral and aortic valve calcification, corneal opacity and horizontal saccade disorder.[8,9]

Apart from routine examinations, GD patients with neuropathy also require neurological examinations, including eye movements, additional neuro-ophthalmological examinations, peripheral hearing, brain imaging, electroencephalography, and neuropsychological testing.[10] Auditory Brainstem Response (ABR) is an important tool for diagnosing hearing impairment. It can reflect the function and status of the cochlea and brainstem-related structures by monitoring nerve potential activities in the auditory conduction pathway. Due to its advantages of simple operation, accuracy, credibility, non-invasive, high specificity and repeatablility, and is not limited by age, state of consciousness or intelligence level, ABR can be better used in diagnosing and following up on hearing loss in children with GD.[11] While hearing loss is a rare neurological manifestation of GD, there have been a few international case reports of it occurring in patients with different types of GD.[12-16] Currently, there are few reports of it in China. In this case, we reported a Chinese child with type IIIb GD who presents with hearing loss, as detailed below.

CASE PRESENTATION

Patient History

The patient was a 11-month-old boy and was admitted to our hospital because of thrombocytopenia for one month and abdominal distension for more than a half month. The child was his mother's first birth and was born by cesarean section at full-term pregnancy, and there was no history of asphyxia rescue after birth.

At the age of 5 months, the complete blood count (CBC) revealed mild anemia and low platelets: hemoglobin (Hb) 105 g/L, platelets (PLT) 99×10^9/L, and neutrophils were 1.46×10^9/L. Subsequently, he was given iron supplements and regular physical check-ups. At the age of 9 months and 2 weeks, the boy caught a cold, and CBC were performed: Hb 85 g/L, PLT 54×10^9/L, and neutrophils were 1.76×10^9/L. Therefore, he was diagnosed with iron deficiency anemia and immune thrombocytopenia, and provided with iron and vitamin C supplements. At 9 months and 3 weeks, his CBC was reviewed: Hb 71 g/L, PLT 50×10^9/L, and neutrophils were 1.89×10^9/L. At the age of 11 months, Hb 99 g/L, PLT 38×10^9/L, and neutrophils 1.40×10^9/L. In addition, the boy's abdomen was distended for more than half a month, and the abdominal ultrasonography showed hepatomegaly, liver palpable 4 cm below costal margin, and splenomegaly (3.4 cm below the umbilicus), so he was hospitalized in the Department of Hematology.

Clinical Examination

The results of physical examination on admission were as follows: normal mind, mentally responsive, normal complexion, flat and soft anterior fontanelle. There were scattered red rash slightly higher than the skin surface on the whole body, especially on the trunk. There were a few pinpoint-sized bleeding points in the abdomen, and swollen lymph nodes of soybean volume were palpable in the neck without tenderness. Soft neck, thick breath sounds in both lungs, no wheezes or moist crackles, a large and firm liver palpable 5 cm below the right costal margin, 4 cm below the xiphoid, and a firm spleen palpable 8 cm below the costal margin.

Figure 1. CT scan of the child's abdomen showing hepatosplenomegaly.

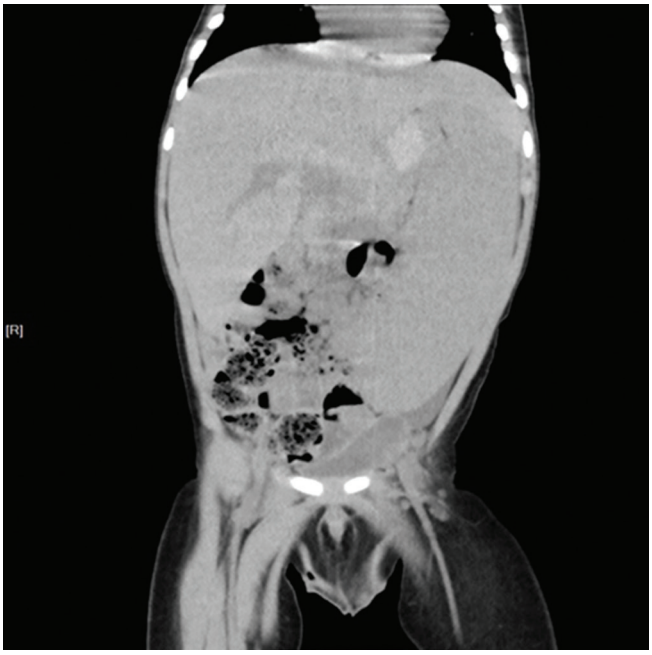


Figure 2. MRI s abnormal signals around the ventricles of the bilateral frontal and parietal lobes. (A-B) The high signal on FLAIR sequence was detected at different positions. (C-D) The patchy high-signal changes on T2WI at different positions correspond to A-B.

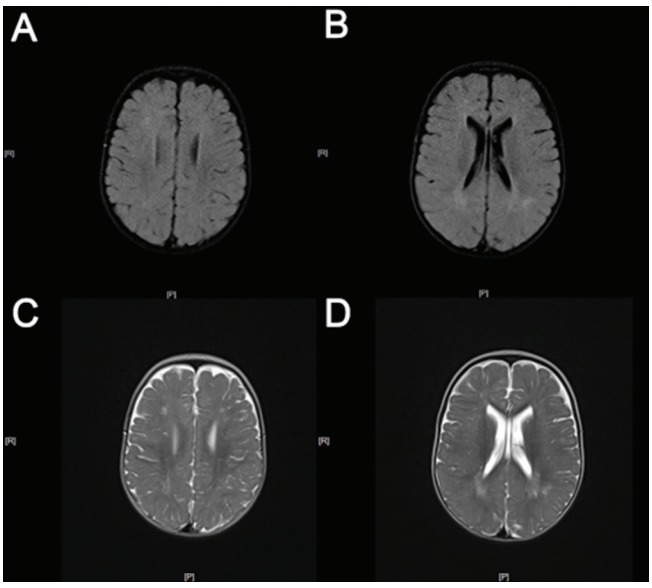


Figure 3. MRI showing the signal of the lumbosacral spine was generally reduced (A: The lumbar MRI on T1WI, B: The lumbar MRI on T2WI), and the bilateral femurs showed obvious Erlenmeyer flask-like changes (C: The femoral MRI on T1WI, D: The femoral MRI on T2WI).

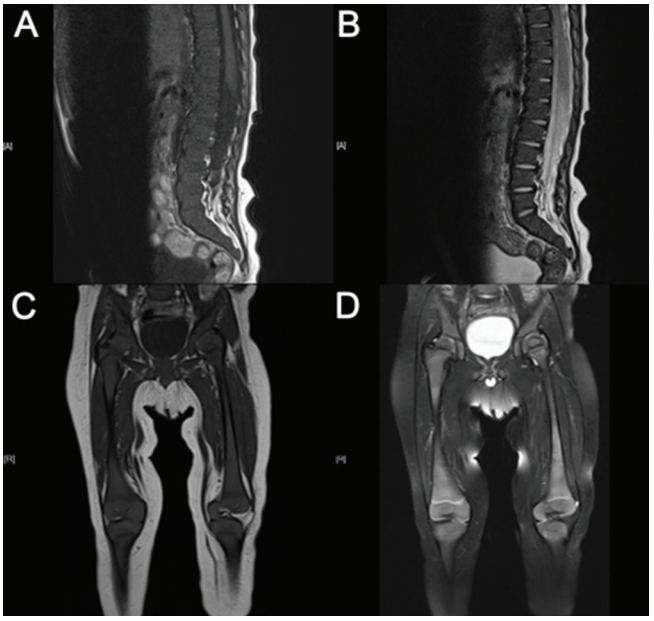


Figure 4. Morphological examination of the bone marrow smear showed Gaucher cells, which were large in size, eccentric in nucleus, condensed chromatin and cytoplasm in an onion skin-like appearance. It mostly clustered at the end of the smear (HE staining, × 400).

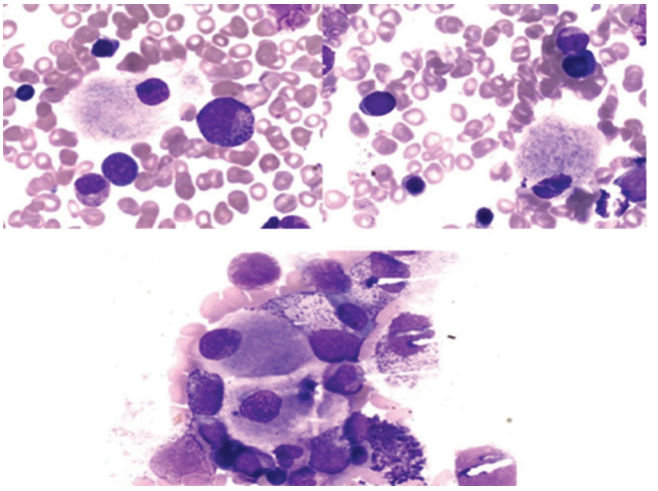


Table 1. GBA and Lyso-GL-1 were tested by MS/MS.

Test Item	Test Result	Reference Interval
GBA (μmol/L/h)	0.57 ↓	1.26-22.23
Lyso-GL-1 (ng/mL)	>400 ↑	<17.41

Table 2. GBA genotype was analyzed by LR-PCR and sequencing technology.

Transcripts and genes	Related diseases and hereditary mode	Chromosomal location	Mutation site	Exon/ Intron	Heterozygosity	GnomAD frequency	Clinical significance
GBA NM_001005741.2	GD (AR)	Chr1: 155205043	c.1448T>C .Leu483Pro	11	heterozygosis	0.0034	pathogenicity
GBA NM_001005741.2	GD (AR)	Chr1: 155204796	c.1601G>A p.Arg534His	12	heterozygosis	0.0000057	Unknown
GBA NM_001005741.2	GD (AR)	Chr1: 155209751	c.233G>A p.Arg78His	4	heterozygosis	0.000087	Unknown

The subsequent laboratory and imaging examination during hospitalization showed no abnormal cells on the rash imprints. Except for hepatosplenomegaly, the head, chest and abdomen CT results showed no obvious abnormality (Figure 1). Brain MRI showed patchy abnormal signals around the ventricles of bilateral frontal and parietal lobes (Figure 2). The signal of the lumbosacral spine was generally reduced (Figure 3A-B), and the bilateral femurs showed severe Erlenmeyer flask deformity. T1 and T2 signals were generally reduced, and the marrow signal was uneven (Figure 3C-D). Bone marrow smear examination showed Gaucher cells, but no malignant proliferative cells were found (Figure 4), so the possibility of leukemia was ruled out. It was essential to emphasize that a bone marrow biopsy is not a necessary requirement for diagnosing GD to avoid any misconceptions or unnecessary invasive procedures.

Diagnostic Evaluation

At this point, we highly suspected that the child had GD. We subsequently sent a dried blood spot (DBS) specimens in order to analyze the GBA enzyme activity, the level of the glucosphingosine (Lyso-GL-1), and the GBA genotype using tandem mass spectrometry (MS/MS) and next-generation sequencing technology, which all analyzed by the PerkinElmer Medical Laboratory (Suzhou, Jiangsu, China). As shown in Table 1, the GBA activity was 0.57 μmol/(L×h) (ref.val. 1.26~22.23), and the level of Lyso-GL-1 was over 400 ng/mL, which was far higher than the reference value of 0~17.41. Moreover, three heterozygous mutations were found in GBA gene. Among them, c.1448T>C (p.L483P) or L444P was pathogenic and inherited from the mother. The clinical significance of the other two missense mutations was unknown, including c.1601G>A (p.Arg534His) or R534H, and c.233G>A (p.Arg78His) or R78H, both were inherited from the father. At the beginning of the disease, the boy performed head MRI. As a result, no neurological clinical manifestation or abnormal electroencephalogram (EEG) was found, so the boy was diagnosed as type I GD. After the first diagnosis, the boy started enzyme replacement therapy (ERT) with imiglucerase (Cerezyme®, 60 U/kg/2 wks).

In view of the early onset, abnormal signals around the ventricles of bilateral frontal and parietal lobes, and the presence of the L444P variant allele, the neurological manifestations of the boy were followed up and monitored during ERT treatment, and the results showed that the EEG remained normal. The boy presented with nystagmus in both eyes at 12 months of age, but the P100 latencies of bilateral monocular flash visual evoked potentials (VEPs) were within

Figure 5. The P100 latencies of bilateral monocular flash visual evoked potentials (VEPs).

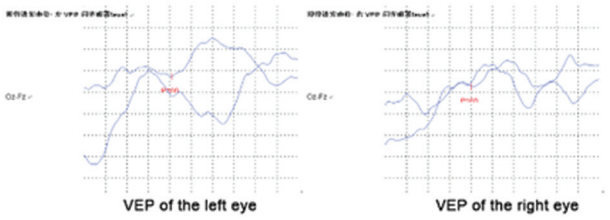
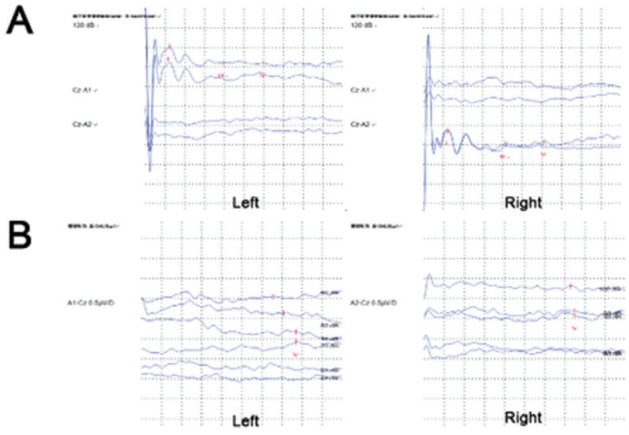


Figure 6. The results of auditory brainstem evoked potential (ABR).



the reference range (Figure 5). The results of auditory brainstem evoked potential (ABR) examination showed: under the stimulation of 120 dBpeSPL sound intensity (equivalent to 85 dBHL), the interval of bilateral waves I~III were slightly prolonged (>1~2 SD), and the interval of each wave were within the range, but the bilateral V/I amplitude ratio was less than 0.5 (Figure 6A). The bilateral ABR V wave threshold (objective hearing threshold) is slightly increased on the left side, which is 70 dBpeSPL (equivalent to 35 dBHL), with a moderate increase on the right side at 90 dBpeSPL (equivalent to 55 dBHL) (Figure 6B). In addition, the boy had slight growth retardation compared with children of the same age. Combining the neurological symptoms observed above and other clinical manifestations including significant hepatosplenomegaly and bone disease, the child was eventually diagnosed with type IIIb GD and started on oral ambroxol.

Follow-up

In the 16-month follow-up of the boy (February 21, 2022), the latest CBC showed an Hb level of 123 g/L, and the platelet count was 78 × 10^9/L; both values were significantly higher than the previous ones. There was no further development of hepatosplenomegaly, and the frequency of nystagmus remained similar.

DISCUSSION

The phenotypes of Type III GD are highly heterogeneous, especially concerning neurological involvement. The neurological symptoms in young children with GD are often overlooked, making it challenging to distinguish between types I and III until overt neurological symptoms are observed. Some children initially diagnosed with type I GD gradually developed more pronounced neurological symptoms as they aged and the disease progressed. They were subsequently re-diagnosed as type III GD.[12,13] Therefore, patients who present early and have a suspected genotype should receive a general diagnosis rather than a specific type of diagnosis. This approach helps prevent the oversight of symptoms and ensures appropriate treatment. The boy in this case was initially diagnosed with type I GD based on enzyme activity, Lyso-GL-1, and GBA genotype analysis. However, in the subsequent follow-up, the boy successively developed nystagmus, bilateral ABR V wave threshold (objective threshold) increased, accompanied by delayed growth and development, combined with neurological symptoms, and other clinical symptoms such as normal EEG, hepatosplenomegaly and significant bone disease, and was finally diagnosed as type IIIb GD at the age of 12 months.

Although hearing loss is a rare clinical manifestation of GD, it can reflect the progress of neuropathy to a certain extent, which is helpful for early diagnosis and disease evaluation. There are few reports on hearing loss in GD, but there are case reports of deafness or abnormal ABR detection in all GD subtypes. In a study of 99 GD patients, 30 (32.6%) with type I GD exhibited neurological symptoms, including 8 (8.7%) with deafness.[14] Another 5-year-old boy with type I GD who had middle-ear involvement was reported to present with symptoms of bilateral hearing loss and conductive hearing loss on pure-tone audiometry with flat tympanic audiometry traces.[15] Other studies also reported that children with type III GD have abnormal acoustic reflexes, medial olivine cochlear system function, and ABR test results, indicating that the auditory conduction pathway is impaired.[16] The above cases all suggest that sensorineural hearing loss is a sequela of GD. Another study conducted the ABR test on a 5-month-old infant, and found that the III wave was poor and the IV and V waves were absent. After 2 months, other neurological symptoms such as opisthotonus occurred rapidly, and the infant was finally diagnosed as type II GD.[17] In this case, under the stimulation of 120 dBpeSPL (equivalent to 85 dBHL), the ABR of the child with type IIIb showed a slight prolongation of the bilateral I-III wave interval (>1-2 SD), and the bilateral V/I amplitude ratio was less than 0.5; bilateral ABR V wave threshold (objective hearing threshold) were increased. This suggests that ABR abnormalities can be detected before the central nervous system symptoms appear. When performing ABR tests on infants and young children, we should be alert to the possibility of type III GD once abnormal waveforms are found. Therefore, ABR testing, being a crucial tool for diagnosing hearing impairments, can accurately assess the hearing condition of GD patients, contributing to the early classification of GD.

ERT is the standard treatment for Gaucher disease, but it does not cross the blood-brain barrier, and thus does not

treat the neurological symptoms in nGD. Imiglucerase for injection (Cerezyme®) is currently the only ERT-specific drug approved in China for long-term use in both type I and type III GD. After the diagnosis of type I GD, the patient in this case was started with imiglucerase (Cerezyme®) ERT for injection, 60 U/kg every 2 weeks. However, this treatment has limited improvement in neurological symptoms due to the blood-brain barrier. A study examining the ABR of 8 children with type III GD who received high-dose (120 U/kg every 2 weeks) ERT for 1 to 3 years found that ABR monitoring results continued to deteriorate, suggesting ERT is ineffective in preventing brainstem lesions progress.[18] Therefore, the treatment of neurological symptoms in GD requires additional options, including molecular chaperone therapy. This patient started oral ambroxol after being diagnosed with type IIIb GD at the age of 12 months. The patient is alive and on treatment, pending ongoing evaluation and clinical monitoring of treatment effects and neuropathy.

CONCLUSION

This boy is a reported case of type IIIb GD with hearing loss in China. This case suggests that type IIIb GD is difficult to distinguish from type I before neurological symptoms appear. For infants with hearing loss indicated by ABR test, the possibility of a diagnosis of type III GD should be considered as well. Comprehensive examinations, including EEG, audiological examination, and neuro-ophthalmological examination, can provide information about the severity of the patient's nervous system involvement and disease progression. Therefore, incorporating the comprehensive examination mentioned above as a routine test for diagnosing GD and monitoring patients in the long term is beneficial for early diagnosis, treatment, and disease assessment of GD. This study also had limitations, such as a small sample size, making it challenging to draw definitive conclusions. Future research could consider expanding the sample size to conduct a more in-depth investigation.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

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AUTHOR CONTRIBUTIONS

Xiaoyan Sun, Peng Wu and Yao Xue contributed equally to this work. XS, PW, YX and YF designed the study and performed the experiments, JH and RL collected the data, XS, PW and YX analyzed the data, XS, PW, YX and YF prepared the manuscript. All authors read and approved the final manuscript.

ETHICAL COMPLIANCE

This study was approved by the ethics committee of the Children's Hospital of Nanjing Medical University.

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