Case Series

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Patients with Gaucher Disease Type 1 and Their Outcome: A Case Series

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Received: 12 August 2023 **Revised:** 17 October 2023 **Accepted:** 30 October 2023

ARTICLE INFO

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Keywords:
Gaucher Disease;
Manifestations;
Enzyme Replacement Therapy;
Storage Disease

ABSTRACT

Background: Gaucher disease is the most common lysosomal storage disease. Defective activity of the acid β-glucosidose which is encoded by the *GBA*1 gene, leads to the accumulation of excess amounts of the glucosyl ceramide lipid. Gaucher disease is clinically classified into three variants based on the relative degree and progression of neurological involvement. Gaucher disease type 1 manifests markedly variable phenotypes ranging from asymptomatic individuals to children who have massive hepatosplenomegaly, pancytopenia, and severe skeletal abnormalities.

Case Report: We report a case series of four patients with Gaucher disease type 1 with variable clinical manifestations treated with enzyme replacement therapy (ERT). In follow-up, three patients showed visceral and hematological improvements, while one case did not respond to ERT and died due to liver failure.

Conclusion: Gaucher disease should be considered with differential diagnosis of patients with unexplained organomegaly, who bruise easily and have bone pain which can be treated with ERT.

Introduction

Gaucher disease (GD) is an autosomal recessive disorder that results from pathogenic mutations of the *GBA* gene encoding the enzyme glucocerebrosidase (acid β-glucosidase), which is located on chromosome 1q21.31.[1] Deficient activity of this lysosomal enzyme leads to the accumulation of undegraded glycolipid substrates, particularly glucosylceramide, in

cells of the reticuloendothelial system.[2] GD is the most common lysosomal disorder and a multisystemic lipidosis characterized by hematologic abnormalities, organomegaly, and skeletal involvement.[3] The latter is usually manifesting as bone pain and pathologic fractures.[3] Although massive hepatomegaly occurs, hepatic failure or cirrhosis is uncommon and usually associated with intercurrent hepatitis, particularly hepatitis C.

Three clinical subtypes of GD, are characterized by the absence or presence and progression of neurologic manifestations: type 1 or the adult, non-neuropathic form, type 2 the infantile or acute neuropathic form and type 3 the juvenile or sub-acute neuropathic form. Type 1, which accounts for 99% of cases, occurs with high frequency in the Ashkenazi Jewish population (1:1000).[2,4]

Gaucher type 1 presents with markedly variable phenotypes, ranging from asymptomatic individuals in their 8th to 10th decades to children with massive hepatosplenomegaly, pancytopenia, and severe skeletal abnormalities. Asymptomatic splenomegaly with or without cytopenia is the most common presentation. Associated hypersplenism, epistasis, easy bruising, and hepatomegaly are common. Pancytopenia develops due to hypersplenism and infiltration of the bone marrow.[5] Bone marrow examination usually demonstrates the presence of Gaucher cells. Determination of the acid β-glucosidase activity in isolated leukocytes or cultured fibroblasts as well as identification of their specific acid β-glucosidase gene mutations is needed to confirm all suspected diagnoses.[2]

Enzyme replacement therapy (ERT) is safe and effective in the treatment of type 1 GD.[6,7] ERT (60 Iu/kg) administered by IV infusion every other week can reverse most symptoms (organomegaly, hematologic indices, bone pain) and the bone involvement can also be stabilized or improved.[8]

Case report

Case 1: An 18-month-old girl with huge hepatosplenomegaly since 11 months, growth failure, and a history of left hand fracture in the previous year was referred to our center. Her development was normal. She was not born to consanguineous parents. The results of her laboratory tests are presented in Table 1.

Table 1. Laboratory Findings of Case 1 before Enzyme Treatment Therapy

Parameter	Value before ERT
WBC/mm^3	3600 (PMN=30%)
Hb (g/dL)	10.2
PLT/mm^3	46000
SGOT (U/L)	93
SGPT (U/L)	13
Alkp (U/L)	315

The patient was suspected of having storage disease, so she was subjected to an enzyme examination, which revealed a decrease in β-Glucosidase enzyme activity [108.53 pmol/spot 20h (Reference range: 200-2000)]. The patient underwent enzyme therapy (first with Cerezyme and then with Abcertin) at 60 Iu/kg every two weeks. In the patient's 5-year follow-up, the patient was well, and the size of the liver and spleen decreased, the results of her laboratory tests were as follows: WBC = 4900 (PMN = 30%), Hb = 11.5 and PLT = 121000 in the tests.

Case 2: A 2- year- 9- month- old boy referred to our center due to abdominal distension from 4 months ago, and growth failure. He had a normal development. The parents of the patient were consanguineous. Abdominal examination showed hepatosplenomegaly. The span of the liver was 11 cm, and the edge of the spleen was palpable 3 cm below the edge of the rib. Tables 2 and 3 show his growth indices and laboratory data.

Table 2. Growth Indices of Case 2

Weight	11 kg (<5%)
Height	85 cm (<5%)
SDS	-3
Head circumference	48.5 cm (25-50%)

Table 3. Laboratory Findings of Case 2 prior to Enzyme Treatment Therapy

Parameter	Value
WBC/mm^3	11300 (PMN=26%)
Hb (g/dL)	8.8
PLT/mm^3	235000
SGOT (U/L)	42
SGPT(U/L)	16
Alkp (U/L)	697

The patient was suspected to have storage disease, so he was subjected to an enzyme examination, which showed β-Glucosidase = 0.5 µmol/lit (NL > 1.5), suggesting the diagnosis of Gaucher disease, which was confirmed by genetic testing. The patient underwent enzyme therapy (Abcertin 60 Iu/kg every two weeks). In the patient's 3-year follow-up, the patient was well, and the size of the liver and spleen had decreased.

Case 3: A 13- year- 3- month- old girl was admitted to our center due to abdominal distension and petechiae, growth failure, and delayed puberty. She had a normal development. Table 4 shows her growth indices. She was born out of a consanguineous marriage. She had a huge hepatosplenomegaly in the abdominal examination.

Table 4. Growth Indices of Case 3

Weight	26.5 kg (<5%)
Height	133 cm (<5%)
SDS	-4.5

The edge of the liver and spleen could be felt up to the pelvis. In the genital examination, she had BIPISMR. Her laboratory findings are presented in Table 5.

Table 5. Laboratory Findings of Case 3 prior to Enzyme Treatment Therapy

Parameter	Value
WBC/mm^3	2600 (PMN=50%)
Hb (g/dL)	8.1
PLT/mm^3	125000
SGOT(U/L)	33
SGPT(U/L)	18
Alkp (U/L)	383

Due to the suspicion of storage disease, she was subjected to an enzyme analysis, which revealed a decrease in β-Glucosidase enzyme activity. Gaucher disease diagnosis was confirmed by genetic analysis. The patient underwent enzyme therapy (Abcertin 60 IU/kg every 2 weeks). In the patient's 5-year follow-up, the size of the liver and spleen had decreased, and secondary sexual characteristics had also developed. Her laboratory data after enzyme treatment therapy were as follows: WBC = 4100 (PMN = 50%), Hb = 11.2, and PLT = 41000.

Case 4: A 20-month-old boy with huge hepatosplenomegaly, skin ecchymosis for 10 months, and growth failure was referred to our center for further treatment. Parents were consanguineous. The results of his laboratory tests are presented in Table 6. Foam cells were reported in the bone marrow aspiration. In the enzyme examination, the activity of the β-Glucosidase enzyme was decreased. The patient was diagnosed with Gaucher disease and had undergone enzyme therapy.

Table 6. Laboratory Findings of Case 4 Before Enzyme Treatment Therapy

Parameter	Value
WBC/mm^3	5800 (PMN=50%)
Hb (g/dL)	6
PLT/mm^3	125000
SGOT (U/L)	130
SGPT (U/L)	11
Alkph (U/L)	235
PT	18.5
PTT	41
INR	2
Albumin (mg/dL)	2.7

The patient was treated with packed cells, platelets, albumin, and vitamin K. In endoscopy, severe hypertensive gastropathy and esophageal varices grade I were reported. Therefore, the patient was treated with Inderal (10 mg/daily) and Cerezyme at a dose of 60 Iu/kg every 2 weeks, but he did not have a good response. The patient died 4 months later with severe ascites, extremities edema, and liver cirrhosis.

Discussion

Gaucher disease is the most common lysosomal storage disease.[9] Historically, three clinical phenotypes are recognized. Type 1 is defined by the lack of neurological symptoms. There is wide variability in the pattern and severity of the symptoms, from extremely handicapping to asymptomatic forms, with most symptomatic patients having visceral, hematological, and (more frequently in adults) skeletal disease. Children often show severe splenomegaly, generally associated with hepatomegaly, but the degree of visceromegaly is highly variable. This may lead to anemia, thrombocytopenia, and thus a bleeding tendency. Children may show delayed growth and puberty. We reported four patients with Gaucher disease Type 1 with variable clinical manifestations including hepatosplenomegaly, pancytopenia, growth failure, and liver failure. Hepatomegaly is usually not associated with liver disease, but there may be elevated transaminases, cirrhosis, esophageal varices, or hepatic failure. They were diagnosed with enzyme assay and genetic study. Patients treated with ERT and in follow-up clinical response have been evident in visceral (hepatosplenomegaly) and hematological (anemia and thrombocytopenia) in three patients (cases 1 to 3). Case 4 did not respond to ERT and died due to liver failure.

Conclusion

Gaucher disease type 1 should be considered with differential diagnosis of patients with unexplained organomegaly, who bruise easily and have bone pain which can be treated with ERT.

Conflict of Interest

The authors declare no competing interest.

Acknowledgments

The authors would like to thank the patients' families for their cooperation in this study.

Funding

No funding.

Ethical Considerations

The present study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.REC.1402.056).

Author's Contribution

N.A.M. performed the examination of the patients, and was a major contributor in writing the manuscript. S.M. wrote the first draft of the manuscript. M.S.A. wrote and edited the manuscript. All authors read and approved the final manuscript.

How to Cite: Mirhosseini NA, Saeida-Ardekani M, Mirhosseini S. Patients with Gaucher Disease Type 1 and Their Outcome: A Case Series. World J Peri & Neonatol 2023; 6(1): 56-60.
DOI: 10.18502/wjpn.v6i1.14253

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