

Gaucher's disease in a 4-year-old child at Sanglah General Hospital, Bali, Indonesia



Ekarini Katharina Yunarti Nabu^{1*}, Ni Nyoman Mahartini², Ida Ayu Putri Wirawati², Sianny Herawati², Betti Bettavia Hartama Pardosi¹, Ni Komang Krisnawati¹, Anak Agung Ayu Lydia Prawita¹, I Putu Yuda Prabawa¹

ABSTRACT

Background: Gaucher's disease is a rare Lysosomal Storage Disorder (LSD) caused by the accumulation of glucosylceramide/glucocerebroside. There are several types of Gaucher, such as non-neuronopathic, infantile-onset neuronopathic and juvenile-onset neuronopathic. This case study aims to evaluate Gaucher's disease in a 4-year-old child at Sanglah General Hospital, Bali, Indonesia.

Case Presentation: A 4-years-old child is admitted to the hospital with a chief complaint of enlargement in the stomach. There is no pain in the bone as well as no sign of bleeding. The patient's parents are blood relatives. On physical examination, hepatosplenomegaly was found, a decreased level of hemoglobin and thrombocytes was also found in the hematology examination. There was an increase of level ferritin, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), globulin, and triglycerides from chemistry evaluation, also decreasing level total cholesterol. From bone marrow aspiration was found an increase of activity of the megakaryocyte and Gaucher's cell. The result from enzyme examination found a decrease of activity enzyme β -glucosidase. Suggestion to this patient is Enzyme Replacement Therapy (ERT).

Conclusion: Gaucher's disease is a rare case and difficult to diagnose. A biochemistry examination using the enzyme β -glucosidase is necessarily needed as well as a suggestion of ERT.

Keywords: Gaucher's disease, Gaucher Cell, Lysosomal Storage Disorder, β -glucosidase.

Cite This Article: Nabu, E.K.Y., Mahartini, N.N., Wirawati, I.A.P., Herawati, S., Pardosi, B.B.H., Krisnawati, N.K., Prawita, A.A.A.L., Prabawa, I.P.Y. 2021. Gaucher's disease in a 4-year-old child at Sanglah General Hospital, Bali, Indonesia. *Bali Medical Journal* 10(2): 724-727. DOI: 10.15562/bmj.v10i2.2479

¹Clinical Pathology Specialist Program, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia;

²Department of Clinical Pathology, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia;

*Corresponding author:

Ekarini Katharina Yunarti Nabu; Clinical Pathology Specialist Program, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Bali, Indonesia; katharinanewar15@gmail.com

Received: 2021-05-23

Accepted: 2021-07-26

Published: 2021-08-10

INTRODUCTION

Lysosomal Storage Disorders (LSD) are a group of diseases that occur due to the accumulation of glucosylceramide/glucocerebroside and several related compounds in the lysosome.¹ Gaucher's disease is the most common of the various disorders included in LSD.²

Gaucher disease consists of three types: type 1 called neuronopathic Gaucher disease, type 2 called infantile onset acute neuronopathic Gaucher disease, and type 3, commonly called juvenile-onset neuronopathic Gaucher disease. Gaucher disease is estimated to occur 1 in 57,000 to 75,000 people in the general population.³ Type 1 is the form most often encountered. This disorder usually occurs in Ashkenazi Jews (Eastern and Central Europe), with a prevalence of 1 in 800 births. The National

Gaucher Foundation (United States) states that the incidence of Gaucher disease is about 1 (one) in 20,000 live births. About 100 people in the general population in America are Gaucher type I carriers.^{1,2,4,5}

Although Gaucher cases are very rare, at the Sanglah Central General Hospital in Denpasar since January 2018, there have been 2 reported incidents of Gaucher. Based on those mentioned above, this case report aims to evaluate Gaucher's disease in a 4-year-old child at Sanglah General Hospital, Denpasar.

CASE DESCRIPTION

A male-4-years-old with complaints of enlarged stomach since the age of 9 months. The stomach feels bigger and bigger. There were no signs of bleeding and shortness of breath. The patient also

denies nausea and vomiting. Eat and drink well-no history of bruising, no complaints of bleeding. The patient also did not complain of bone pain or fractures. The patient's medical history had been treated at Sanglah Hospital Denpasar in October 2018. A Computerized Tomography (CT-Scan) examination of the abdomen was carried out, and it was said that the patient had blood cell disorders. The patient's birth weight was 2900 grams, and complete history of basic immunization. The patient is the fourth child of four children. The second child is said to have died at the age of two with suspicion of blood cell malignancy. Both of the patient's parents are related by blood.

From the physical examination, it was found that awareness of *compos mentis*, pulse 102 beats/minute, respiration 18

times/minute with a temperature of 36.5°C, height 90 cm, and body weight 16.1 kg. An examination of the head and neck revealed anemic conjunctiva and sclera jaundice. Examination of generalist status found abnormalities in the abdomen where the liver was palpable 7 cm below the rib arch, 3 cm below the xiphoid process, and the splenic felt Schuffner VIII.

Complete Blood Count (CBC) using Cell-Dyn Ruby showed anemia (Hb 7.22 g/dL) and thrombocytopenia ($28.87 \times 10^3/\mu\text{L}$) (Table 1). Examination of bone marrow images showed slightly decreased megakaryocyte activity and found cells with small, eccentric round nuclei, cytoplasm-like tangled tissue resembling Gaucher cells, suspecting a metabolic disorder (Figure 1). On clinical chemistry examination using Cobas E-501, there was an increase in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST), an increase in ferritin levels, an increase in globulin, a decrease in total cholesterol levels and an increase in triglycerides (Table 2). On immunoserology examination using Cobas E-601, normal levels of Thyroid-Stimulating Hormone (TSH) and free T4 (FT4) were found, as shown in Table 2. In the results of enzyme examination, a decrease in β -glucosidase enzyme activity was demonstrated in Table 2.

Based on the history, physical and supporting examination, the patient was diagnosed with Gaucher disease with marasmus type malnutrition in the stabilization phase. The therapy was a 150 ml Packed Red Cells (PRC) transfusion with intravenous premedication of 9 mg furosemide, 65 mg paracetamol every 4 hours if the axilla temperature was ≥ 38 °C, administration of F100 12 x 100 ml, and 1 tablet of vitamin B complex every 24 hours. Patients are advised to undergo enzyme replacement therapy in Jakarta.

DISCUSSION

Gaucher is a genetic disease in which the fat substance (glucocerebroside) accumulates in specific cells or organs.⁶ This disease is part of the Lysosomal Storage Disease (LSD) group of diseases. In Gaucher's disease, the blueprint for producing the enzyme glucocerebroside is impaired, resulting in a deficiency

Table 1. Complete Blood Count Examination.

| Parameter | 21/01/2019 | Reference | Interpretation |
|----------------------------|------------|-------------|----------------|
| WBC ($10^3/\mu\text{L}$) | 4.06* | 6.0-14.0 | Low |
| %Neu | 51.19* | 18.30-47.10 | High |
| %Lym | 41.21 | 30.00-64.00 | Normal |
| %Mono | 3.72 | 2.0-11.0 | Normal |
| %Eos | 3.24 | 0.0-5.0 | Normal |
| %Baso | 0.64 | 0.0-0.70 | Normal |
| RBC ($10^6/\mu\text{L}$) | 2.82* | 4.0-5.2 | Low |
| HGB (g/dL) | 7.22* | 12.0-16.0 | Low |
| HCT (%) | 21.44* | 36.0-49.0 | Low |
| MCV (fl) | 75.92* | 78.0-102.0 | Low |
| MCH (pg) | 25.58 | 25.0-35.0 | Normal |
| MCHC (g/dl) | 33.69 | 31-36 | Normal |
| RDW (%) | 19.81* | 11.6-18.7 | High |
| PLT ($10^3/\mu\text{L}$) | 28.87* | 140-440 | Low |
| MPV (fl) | 10.36* | 6.80-10.0 | High |

WBC: White Blood Cells; Neu: Neutrophil; Lym: Lymphocytes; Mono: Monocytes; Eos: Eosinophils; Baso: Basophils; RBC: Red Blood Cells; HGB: Hemoglobin; HCT: Hematocrit; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; RDW: Red Cells Distribution Width; PLT: Platelet/Thrombocytes; MPV: Mean Platelet Volume; *Not in a normal reference range.

Table 2. Clinical chemistry, immunoserology, and enzyme activity (MS/MS or 4 MU-fluorometric assays) evaluation.

| Parameter | 21/01/2019 | Reference | Interpretation |
|--------------------------------------|------------|---------------|----------------|
| Serum Iron (SI) ($\mu\text{g/dl}$) | 54.17 | 40-100 | Normal |
| TIBC ($\mu\text{g/dl}$) | 344.0 | 100.00-400.00 | Normal |
| Ferritin (ng/ml) | 540* | 30-400 | High |
| Total Bilirubin (mg/dl) | 0.95 | 0.00-1.00 | Normal |
| Direct Bilirubin (mg/dl) | 0.39 | 0.00-0.30 | Normal |
| Creatinin (mg/dl) | 0.75 | 0.70-1.20 | Normal |
| BUN (mg/dl) | 9.00 | 8.00-23.00 | Normal |
| AST (U/L) | 63.8* | 11.00-30.00 | High |
| ALT (U/L) | 78.5* | 11.00-50.00 | High |
| Total Protein (g/dl) | 7.8 | 6.00-8.00 | Normal |
| Albumin (g/dl) | 3.70 | 3.50-5.20 | Normal |
| Globulin (g/dl) | 4.10* | 3.2-3.7 | High |
| Calcium (mg/dl) | 8.6* | 9.20-11.00 | Low |
| Natrium-serum (mmol/L) | 137 | 136-145 | Normal |
| Potassium-serum (mmol/L) | 4.11 | 3.50-5.10 | Normal |
| Total Kolesterol (mg/dl) | 69* | 140-199 | Low |
| Triglycerides (mg/dl) | 186* | < 150 | High |
| HDL (mg/dl) | 42 | 40-65 | Normal |
| LDL (mg/dl) | 30 | <130 | Normal |
| Random Blood Glucose (mg/dl) | 98 | 60-100 | Normal |
| Free T4 (ng/dl) | 1.03 | 0.93 - 1.70 | Normal |
| TSHs ($\mu\text{IU/mL}$) | 3.18 | 0.27 - 4.20 | Normal |
| β -glucosidase (uM/hr) | 0.97* | >1.8 | Low |
| Sphingomyelinase (uM/hr) | 7.93 | > 0.5 | Normal |
| Chitotriosidase (nmol/mlWB/hr) | 5.00 | < 109.9 | Normal |

TIBC: Transferrin Iron Binding Capacity; BUN: Blood Urea Nitrogen; AST: Aspartate Transaminase; ALT: Alanine Transaminase; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; TSHs: Thyroid-Stimulating Hormone; *Not in a normal reference range.

of the enzyme.⁷ The gene that codes for the enzyme glucocerebroside is one of the pairs on the autosomal chromosome. Gaucher disease is classified

as an autosomal recessive disorder, which means that a person must inherit two copies of the affected gene, each from both parents.⁷⁻¹⁰ The gene that causes Gaucher

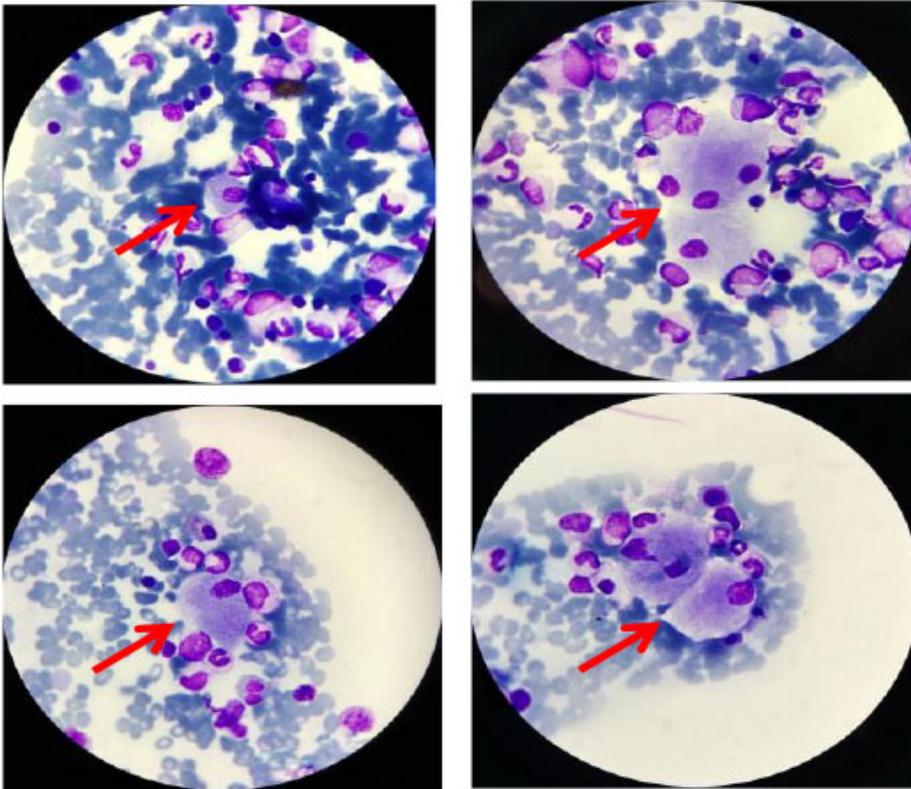


Figure 1. Bone marrow with a slightly decreased megakaryocyte activity, and positive-Gaucher cells, suspects a metabolic disorder.

fourth child of four children with both parents who are still related by blood. The patient's older brother (2nd child) has died with suspicion of blood cell malignancy. From several studies, it is said that 50% of their genes will be passed on to each child for parents who have a Gaucher carrier.^{11,12} A child will develop Gaucher's disease only if the child inherits the two defective genes from both parents.³

On physical examination, signs of anemic and jaundice, hepatomegaly and splenomegaly can be found. Symptoms of the skeletal system can occur at any time as well as hepatosplenomegaly.^{4,10} In Gaucher disease, a person may experience a 5 to 80-fold increase in spleen size (mean spleen weight 0.2% body weight). Enlargement of the spleen tends to be rapid in children with Gaucher's disease.¹³ The nodules on the surface of the spleen indicate areas of extramedullary hematopoiesis and accumulation of Gaucher cells. Hepatomegaly occurs in Gaucher type 1 patients.¹³ Increased levels of liver function are also common. This condition indicates impaired hepatocellular synthetic function. The existence of hyperbilirubinemia is thought to be a result of the hemolysis process. Increased serum ferritin levels are often found in Gaucher's disease.^{14,15} In these patients, there was an increase in AST and ALT levels, as well as an increase in ferritin levels.

The manifestations of the skeletal system of Gaucher disease type 1 vary from the absence of symptoms to symptoms of deformity to pathological fractures, usually of the femur, vertebral collapse.¹³ Bone pain is the result of bone infarction. This patient had no symptoms of the skeletal system. Hematologic manifestations of Gaucher disease include cytopenia and coagulopathies.^{10,13} Cytopenia suffered by the patient is the result of the infiltration of Gaucher cells into the bone marrow. Various immunological disorders can also be found in individuals with Gaucher disease, including hypergammaglobulinemia, T-lymphocyte deficiency in the spleen and chemotaxis disorders of neutrophils.¹⁴ In this patient, there was a decrease in Hb levels, increased neutrophils, and thrombocytopenia.

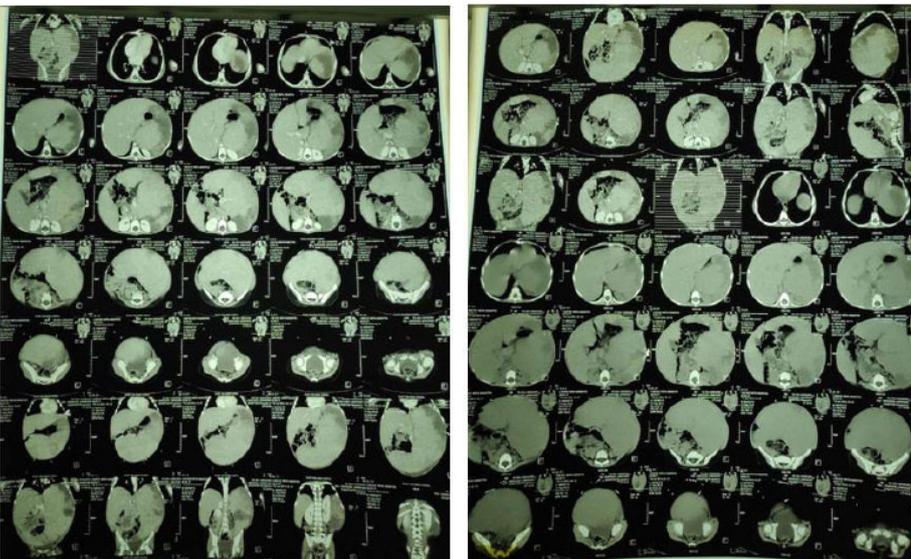


Figure 2. CT- Scan Abdomen suggests hepatomegaly and splenomegaly with multiple hypodense lesions on the upper and lower spleen poles.

disease is a mutation in the glucosidase beta acid (GBA) gene, a gene located on the first chromosome, which regulates the instructions for making the enzyme beta-glucocerebrosidase.^{1,3,7,8}

Efforts to establish a diagnosis need to

be carried out by detailed history taking, careful physical examination and assisted by the necessary supporting examinations. From the history, this patient had complaints of an enlarged stomach from the age of 9 months. The patient is the

Glucocerebrosidase (GBA) gene mutations will significantly reduce the activity of the enzyme beta-glucocerebrosidase.¹⁶ Without adequate amounts of this enzyme, glucocerebrosidase can become toxic in the affected tissue cells and organs through abnormal accumulation and storage giving clinical symptoms to the Gaucher patient. The accumulation of glycolipids can cause the appearance of Gaucher cells, which are lipid-containing macrophages with the appearance of untidy tissue paper and the cell nucleus being shifted towards the edges.¹⁷ Lysosomes, which are responsible for digesting leukocytes and erythrocytes, are unable to break down glucocerebroside. As a result, glucocerebroside accumulates in macrophage cells, and the cell nucleus moves to the edge and the shape of the cell changes like untidy tissue paper.¹⁷ These damaged macrophages are called Gaucher cells.^{10,18} In this patient, there was a decrease in the levels of β -glucosidase and chitotriosidase.

Gaucher type 1 disease management is based on two main approaches in specific therapy, namely enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). In these patients, ERT therapy is recommended. ERT works by adding or replacing enzymes needed in Gaucher disease. ERT cannot be applied to patients with symptoms that already affect the central nervous system.^{4,18} However, the authors could not assess the prognosis of the patient by ERT therapy due to the unavailability of medications at Sanglah General Hospital, Bali, Indonesia. So, the patient is advised to undergo enzyme replacement therapy in Jakarta.

CONCLUSION

Gaucher is a rare disease. The incidence of type 1 Gaucher disease is most common. The patient is a child from the marriage of two blood-related parents. The typical clinical symptom of a patient is hepatosplenomegaly. The patient was diagnosed with Gaucher disease by looking

at the results of bone marrow images showing the presence of Gaucher cells and supported by the results of enzyme tests that showed decreased β -glucosidase levels. The patient is advised to undergo enzyme replacement therapy in Jakarta.

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

ETHICS CONSIDERATION

This case study has followed the COPE and ICMJE guidelines based on the publication ethics and informed consent obtained from the patient.

FUNDING

None.

AUTHOR CONTRIBUTIONS

All authors equally contribute to the study from the conceptual framework, data analysis, data gathering until reporting and interpreting the case study results through publication.

REFERENCES

1. Marques ARA, Saftig P. Lysosomal storage disorders - challenges, concepts and avenues for therapy: beyond rare diseases. *J Cell Sci.* 2019;132(2):jcs221739.
2. Essabar L, Meskini T, Lamalmi N, Ettair S, Erreimi N, Mouane N. Gaucher's disease: report of 11 cases with review of literature. *Pan Afr Med J.* 2015;20:18.
3. Nalysnyk L, Rotella P, Simeone JC, Hamed A, Weinreb N. Gaucher disease epidemiology and natural history: a comprehensive review of the literature. *Hematology.* 2017;22(2):65-73.
4. Grabowski GA. Gaucher disease and other storage disorders. *Hematology Am Soc Hematol Educ Program.* 2012;2012:13-18.
5. Shemesh E, Deroma L, Bembi B, Deegan P, Hollak C, Weinreb NJ, et al. Enzyme replacement and substrate reduction therapy for Gaucher disease. *Cochrane Database Syst Rev.* 2015;(3):CD010324.

6. Ilan Y, Elstein D, Zimran A. Glucocerebroside: an evolutionary advantage for patients with Gaucher disease and a new immunomodulatory agent. *Immunol Cell Biol.* 2009;87(7):514-524.
7. Beutler E, Demina A, Gelbart T. Glucocerebrosidase mutations in Gaucher disease. *Mol Med.* 1994;1(1):82-92.
8. Mazzulli JR, Xu YH, Sun Y, Knight AL, McLean PJ, Caldwell GA, et al. Gaucher disease glucocerebrosidase and α -synuclein form a bidirectional pathogenic loop in synucleinopathies. *Cell.* 2011;146(1):37-52.
9. Alaei MR, Tabrizi A, Jafari N, Mozafari H. Gaucher Disease: New Expanded Classification Emphasizing Neurological Features. *Iran J Child Neurol.* 2019;13(1):7-24.
10. Thomas AS, Mehta A, Hughes DA. Gaucher disease: haematological presentations and complications. *Br J Haematol.* 2014;165(4):427-440.
11. Fasouliotis SJ, Ezra Y, Schenker JG. Gaucher's disease and pregnancy. *Am J Perinatol.* 1998;15(5):311-318.
12. Guggenbuhl P, Grosbois B, Chalès G. Gaucher disease. *Joint Bone Spine.* 2008;75(2):116-124.
13. Linari S, Castaman G. Clinical manifestations and management of Gaucher disease. *Clin Cases Miner Bone Metab.* 2015;12(2):157-164.
14. Bohra V, Nair V. Gaucher's disease. *Indian J Endocrinol Metab.* 2011;15(3):182-186.
15. Nagral A. Gaucher disease. *J Clin Exp Hepatol.* 2014;4(1):37-50.
16. Mata IF, Samii A, Schner SH, Roberts JW, Griffith A, Leis BC, et al. Glucocerebrosidase gene mutations: a risk factor for Lewy body disorders. *Arch Neurol.* 2008;65(3):379-82.
17. Cox TM. Gaucher disease: understanding the molecular pathogenesis of sphingolipidoses. *J Inherit Metab Dis.* 2001;24 Suppl 2:106-88.
18. Rosenbloom BE, Weinreb NJ. Gaucher disease: a comprehensive review. *Crit Rev Oncog.* 2013;18(3):163-175.



This work is licensed under a Creative Commons Attribution