

# Gaucher's Disease in a 2 Years Old Child: A Case Report

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**Abstract:** Gaucher's Disease (GD) is an autosomal recessive systemic lysosomal storage disorder, characterized by glucocerebroside deposition in cells of macrophage-monocyte system as result of deficiency in lysosomal  $\beta$ -glycosidase (glucocerebroside). GD is a rare genetic disorder. It is the most common among the lysosomal storage disorders. Hereby we report a 2-year-old male presented with weakness, pallor and gradually enlarge belly. In the beginning the diagnosis was suspected acute leukemia, an abnormality in hematooncology due to bisitopenia and organomegaly. Therefore patient was gone through Bone Marrow Aspiration (BMA) to confirm the diagnosis, however the results of 3 times BMA were not align with acute leukemia. Moreover the history and clinical examination pointed to be a lipid storage disease. Finally patient was diagnosed as GD after the smear of BMA showed foam cell. In addition the confirmation of Gaucher's disease was performed by measurement of glucocerebroside level, which resulted low in  $\beta$ -Glukosidase 0.97 uM/hr (normal level > 1.8 uM/hr). Therefore we emphasize the importance of early recognition by clinical manifestation and histological findings. GD should be considered as differential diagnosis of children with unexplained hepatosplenomegaly. Patients suspected with acute leukemia should be examined for possibility of GD from bone marrow smear. Furthermore, early recognition of GD would lead to safe and effective treatment with enzyme replacement which can decrease morbidity.

**Keywords:** Gaucher's Disease, Hepatosplenomegaly, Children

## 1. Introduction

Gaucher's disease (GD), a lysosomal storage disorder is caused by defect in the housekeeping gene lysosomal glucocerebroside which present on the first chromosome (1q 22). It was first described by a French physician, Philippe Charles Ernest Gaucher in a 32-year-old woman whose liver and spleen enlarged [1, 2]. The incidence of GD in worldwide is approximately 1/57,000 to 1/75,000 births. In Ashkenazi Jews, the incidence is 1/800 births [3]. In India, GD is believed to be extremely rare and has been reported only in a few case reports [1].

Out of the three types of GD, type 1 is the most common type, which represents 95% of all cases. It is generally characterised by hepatosplenomegaly, bone and lung disease, hematologic abnormalities such as anemia, thrombocytopenia and coagulation abnormalities. It occurs commonly among Ashkenazi Jews. Type 2 has severe progression with onset prior to 2 years, accompanied by neurologic disease,

hepatosplenomegaly and lung disease. Death usually occurs between 2 and 4 years of age due to lung failure. Patient with type 3 may have onset prior to 2 years of age, but the progression is not severe. Thus patient may survive into the third and fourth decade. Apart from this, a perinatal lethal and cardiovascular form of GD also exist. The main cause of cytopenia, splenomegaly, hepatomegaly and bone lesions associated with the disease is considered to be the infiltration of Gaucher cells in bone marrow, spleen and liver [1].

Glucocerebroside accumulation contributes to fatigue, bleeding and easy bruising (due to pancytopenia from bone marrow and splenic sequestration), distended abdomen (due to hepatosplenomegaly), diffuse infiltrative pulmonary disease, severe bone pain and pathologic fractures (due to bone marrow infiltration and macrophage produces cytokines). Bone marrow aspiration is not mandatory to confirm a diagnosis of GD, but it may be performed in patients without a diagnosis accompanied with isolated thrombocytopenia and/or hepatosplenomegaly moreover it

can help when Gaucher cells are found [4].

Macrophage directed Enzyme replacement therapy (ERT) has been the most accepted form of treatment for GD. Therapeutic goals for patients with GD on ERT have been well established which involve changes in liver and spleen size, improvement in hematological parameters, bone pain and bone crises. However, less than 50% of patients with GD on therapy are expected to meet all these therapeutic goals [4]. However, ERT is time-consuming and expensive since the modified enzyme must be administered intravenously approximately every 2 weeks [5].

There is a need for healthcare professionals working with GD patients to assess concurrently immediate stressors, physical health concerns, quality of life issues and psychological well-being. An increased knowledge about the emotional health of these patients and the psychosocial effects of living and coping with GD would aid treatment beneficially [6].

## 2. Case Report

A two year old male child, Hindu religion, born from non-consanguineous marriage was admitted to a tertiary care hospital with chief complain enlarged belly since 4 months ago (figure 1). His belly was said enlarging without pain. The parents also complained reddish spots all over his body which was noticed since October 2017. Patients also had respiratory problems such as persistent stridor and laryngitis and had to use tracheostomy tube. Meanwhile clinical examination showed hepatosplenomegaly and bicytopenia.

In the beginning the diagnosis was suspected as acute leukemia malignancy (ALL and AML). Bone Marrow Aspiration examination was carried out 3 times to ensure the diagnosis. However from the those three BMA, all showed normal result and neither of it lead to malignancy.

The patient was the second child of 2 siblings. The patient's sister was said suffered leukemia and died at the age of 4 years old. There was no family history of the same complaints; difficulty in urination; palpitation; corticosteroid or chemotherapy. Patient was born by sectio caesarean at 38 weeks of gestational age. There was no history of any hormonal or genetic disease or mental retardation in the patient's family. The patient's developmental history was said normal.



**Figure 1.** Male, 2 years old with hepatosplenomegaly.

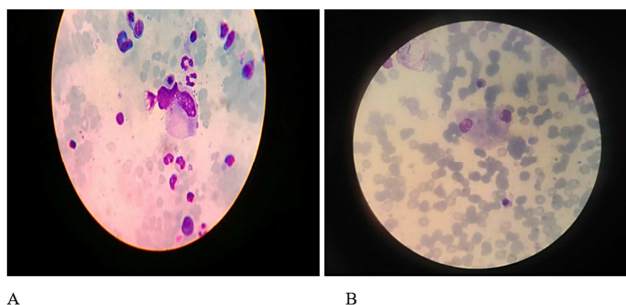
The child showed normal milestones and good nutritional state. On physical examination, he looked pale, with petechiae on his limb and trunk. Liver was palpable 5 cm below the right costochondral margin, his spleen was palpable (schuffner 7) and supported by ultrasonography result that showed the presence of hepatosplenomegaly. Peripheral blood smear revealed bicytopenia. Haemoglobin was 8.8 g/dl and platelet count was  $47,86 \times 10^3/\mu\text{L}$ . Bone marrow biopsy was performed and it showed sheets of Gaucher cells (Figures 1 & 2) seen as histiocytes with abundant granular and fibrillar cytoplasm. These cells had small eccentrically placed nuclei. The gaucher cells showed crumpled tissue paper appearance. Final diagnosis of GD was reported after performing bone marrow smear and found gaucher cell/foam cell. The diagnosis of Gaucher's disease was confirmed by measurement of glucocerebrosidase level, which was low in  $\beta$ -Glucosidase 0.97 uM/hr (normal level  $> 1.8 \text{ uM/hr}$ ) (table 1).

**Table 1.** Enzyme activity result, which is low in  $\beta$ -Glucosidase 0.97 uM/hr.

| Clinical diagnosis:                                      |        |                                 |
|--|--------|---------------------------------|
| Assay: Enzyme activity (MS/MS or 4MU-Fluorometric assay) |        |                                 |
| Enzym  | Result | Reference range unit            |
| $\beta$ -Glucosidase:                                    | 0.97   | $> 1.8 \text{ uM/hr}$           |
| Shpomyelinase:   | 7.93   | $> 0.5 \text{ uM/hr}$           |
| Chitotriosidase:   | 5.00   | $< 109.9 \text{ nmol/ml WB/hr}$ |

Result: Low  $\beta$ -Glucosidase activity, and suggest confirmation with molecular test

Low Chitotriosidase activity, may be with Chit gene exon 10 24-bp duplication



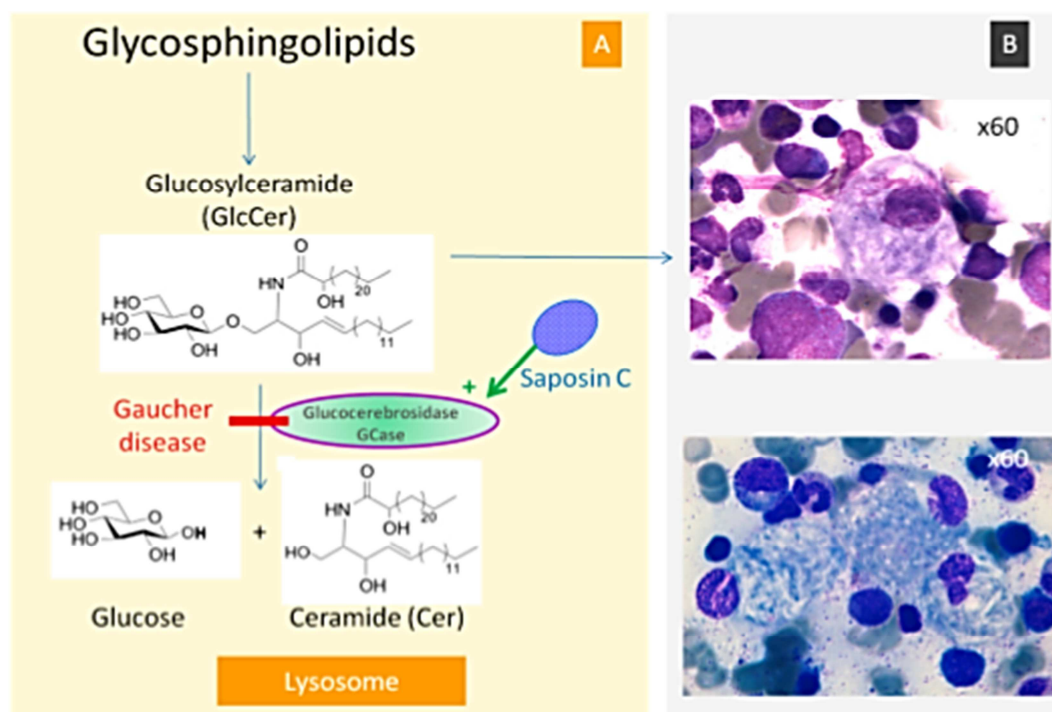
**Figure 2.** Bone marrow biopsy, high power view: sheets of histiocytes, with the abundant, granular and fibrillar cytoplasm resembling crumpled tissue paper. Most of them had single nucleus with eccentrically placed nuclei-consistent with "Gaucher cells" (H&E smear).

## 3. Discussion

Gaucher disease (GD) is the most common sphingolipidosis. GD is a rare, autosomal, recessive genetic disease caused by mutations in the GBA1 gene, located on chromosome 1 (1q 21). This leads to a markedly decreased activity of lysosomal enzyme, glucocerebrosidase (GCase, also called glucosylceramidase or acid  $\beta$ -glucosidase, which hydrolyzes glucosylceramide (GlcCer) into ceramide and glucose (Figure 3) [2]. The incidence of GD worldwide is approximately 1/57,000 to 1/75,000 births. In Ashkenazi Jews, the incidence is 1/800 births. Glucocerebrosidase accumulation contributes to fatigue, bleeding and easy bruising (due to pancytopenia from bone marrow and splenic

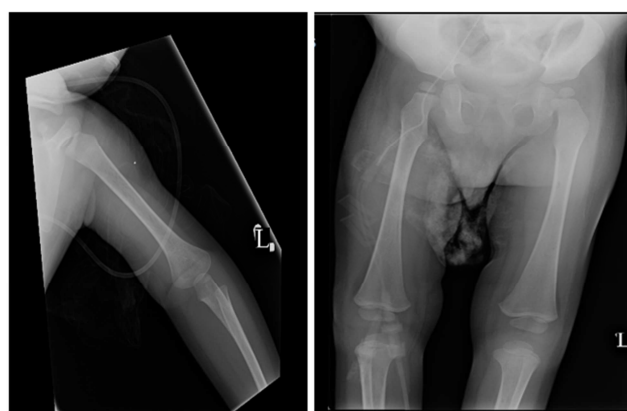
sequestration), distended abdomen (due to hepatosplenomegaly), diffuse infiltrative pulmonary disease, and severe bone pain and pathologic fractures (due to bone marrow infiltration and cytokines from macrophage). Bone marrow aspiration is not mandatory to confirm a diagnosis of GD, but it may be performed on patients without a diagnosis

when isolated thrombocytopenia and/or hepatosplenomegaly are found and it can help when Gaucher cells are found [4]. In our case, 2 years old patient with anemia, thrombocytopenia, hepatosplenomegaly, gaucher cell/foam cell, with low in  $\beta$ -Glucosidase (0.97 uM/hr).



**Figure 3.** Hydrolysis of glucosylceramide (GlcCer) by glucocerebrosidase (GCase) in the lysosome (A). GCase is activated by saposin C. In lysosomal storage diseases, an enzyme deficiency is responsible for the accumulation of its substrate in the cell lysosome (overload disease). Gaucher disease is caused by a deficiency in glucocerebrosidase (GCase) (or  $\beta$ -glucosidase), which leads to an accumulation of GlcCer. GlcCer forms fibrillar aggregates that accumulate in macrophages and result in the cell cytoplasm presenting a characteristic “crumpled tissue paper” appearance (B), personal pictures, with the courtesy of Fabrice Camou and Rachid Seddik). These cells, known as Gaucher cells, infiltrate various organs (e.g., bone marrow, spleen, and liver) and are responsible for the major

Skeletal disease affects more than 80% of GD type 1 patients. It is the most debilitating aspect of GD and has greater impact on quality of life than haematological or visceral manifestations. The main skeletal manifestations are substandard growth in childhood and adolescence, bone deformity, osteopenia, bone crisis, osteonecrosis, osteosclerosis, chronic bone pain, pathological fracture and vertebral collapse. The vertebrae, femora, humeri and tibiae are the most common affected. The basis of bone disease is infiltration of glucocerebroside engorged cells, termed Gaucher cells, into bone marrow. However, the underlying mechanism is still unknown, several processes are thought contribute to the pathophysiology including altered bone formation (remodelling defects), altered bone resorption (osteolysis, osteopenia and osteoporosis) and focal lesions (osteonecrosis, osteosclerosis and fractures). It has been hypothesised that marrow expansion resulted from Gaucher cell infiltration lead to raised intraosseous pressure and consequent vascular occlusion, but no direct data exist to support this theory [7, 8]. In our case, the bone survey showed mild osteopenia in humerus and femur, without fracture, dislocation or lytic lesion.



**Figure 4.** Mild osteopenia of humerus and femur.

Patients with GD were reported had (a) emotional distress (e.g., feelings of isolation and ignorance about the disease); (b) uncertainty (e.g., symptoms may vary in severity and chronology); and (c) complicated decision-making (e.g., around marriage and having children) [9]. The clinical manifestations of GD can be extensive, painful and even life



threatening for affected individuals. GD has unique features as chronic illness, it often presents with mild symptoms and is frequently diagnosed in older child or in adulthood. The treatment, enzyme replacement therapy (ERT), is efficacious. However, that treatment is intrusive, expensive and requires patient to restructure their work and personal schedules. Since the age of presentation can be anytime between infancy and the eighth decade, the diagnostic process can be prolonged and stressful. A study reported several reactions noted while establishing diagnosis of GD, including concern (68%), shock (39%), relief (39%), disappointment (36%), sadness (32%) and fear (29%). Twenty-five percent participants reported sadness and depression and 35% reported anxiety, worry or increased stress about: the possibility of physically hurting themselves; their futures; losing or changing jobs and associated insurance coverage; and fearfulness about missing infusions [6]. In our case, patient is a child, whom often plays alone and sad since only had few friends whom want to interact with him. His parents also worried about the effect of the disease on their child's future and also regarding ERT therapy plans that require long-term monitoring and the expenses.

Gaucher disease (GD) is an autosomal-recessive lysosomal storage disease caused by deficiency of enzyme glucocerebrosidase, resulting in accumulation of lipid-laden storage cells in multiple organs such as bone marrow, liver, spleen, and lungs [10]. The Gaucher disease severity scoring system (GD-DS3) is typically used to assess disease severity accounting for skeletal, hematologic and visceral disease [11]. In addition to being time consuming for the clinician to calculate the scores, some of the assessments are subjective

and may falsely increase or decrease disease severity. Recently the development of DS3 scoring system helps provider to correlate laboratory values and qualitative measurement with a standardized severity score, allowing them to monitor patient's progression over time. A study reported significant positive correlation between increasing liver stiffness and increasing composite GD-DS3 scores. Since liver stiffness appears to be correlated with severe GD, it is possible that including it in the DS3 may yield more accurate measurement of disease severity. It is also possible that liver stiffness could be used independently as quantitative method for monitoring disease severity and progression since it has been shown to be a reliable and reproducible imaging biomarker [12].

Currently, there is limitation in understanding the underlying mechanism of hepatic fibrosis in Gaucher disease. This is largely due to the poorly understood link between Gaucher cells and the onset of hepatic fibrosis. The primary reason for organomegaly in GD is thought to be the increased expression and release of inflammatory mediators by Gaucher cells. This chronic inflammatory state in addition to splenectomy and iron overload may be the reason why Gaucher disease is associated with the long-term liver-related complication of fibrosis and eventually cirrhosis in some individuals [13]. In our case, patient had enlarged liver which can lead to liver fibrosis. DS3 score of this patient was 8 (splenomegaly, hepatomegaly, anemia, and thrombocytopenia) and categorized into "marked disease". Thus the severity of the disease and hepatomegaly necessitate us to perform elastography. In our center, MRE is not yet available, but there has been Ultrasound (US) elastography which can also be used to monitor the degree of liver fibrosis [13].

| GAUCHER DISEASE SEVERITY SCORING SYSTEM (GD-DS3) |  |  |   |   |   |   |   |   |   |                              |                         |                  |
|--|--|--|---|---|---|---|---|---|---|------------------------------|-------------------------|------------------|
| DOMAINS  | ASSESSMENTS                                | DISEASE SEVERITY SCORE                   |   |   |   |   |   |   |   |                              |                         | ASSESSMENT SCORE |
|  |  | 0  | 1 | 2   | 3 | 4 | 5                                       | 6 | 7 | 8                            | 9                       | 10               |
| VISCERAL   | SPLENOMEGALY (Volume as MN)                | ≤ 5                                      |   | > 5, ≤ 15                                 |   |   | > 15, SPLENECTOMIZED                    |   |   |                              |                         |                  |
|  | HEPATOMEGALY (Volume as MN)                | ≤ 2.5                                    |   | ≥ 2.5                                     |   |   |   |   |   |                              |                         |                  |
|  | GAUCHER-RELATED PULMONARY DISEASE          | ABSENT                                   |   |   |   |   |   |   |   | PRESENT                      |                         |                  |
| HEMATOLOGIC                                      | ANEMIA                                     | > 12 g/dL (male)<br>> 11 g/dL (female)   |   | > 12 g/dL (male)<br>> 11 g/dL (female)    |   |   | < 8 g/dL                                |   |   |                              |                         |                  |
|  | BLEEDING                                   | NONE TO MILD TENDENCY; BRUISING          |   | MODERATE; NO TRANSFUSION                  |   |   |   |   |   | SEVERE; TRANSFUSION REQUIRED |                         |                  |
|  | THROMBOCYTOPENIA                           | ≥ 120 × 10 <sup>3</sup> /mm <sup>3</sup> |   | 21-119 × 10 <sup>3</sup> /mm <sup>3</sup> |   |   | < 20 × 10 <sup>3</sup> /mm <sup>3</sup> |   |   |                              |                         |                  |
| BONE   | BONE MARROW INFILTRATION                   | 0-4 (MILD)                               |   |   |   |   |   |   |   | 5-8 (MODERATE)               | 9-16 (MARKED TO SEVERE) |                  |
|  | BONE MINERAL DENSITY Z-SCORE               | > -1                                     |   | > -2, ≤ -1                                |   |   |   |   |   |                              | ≤ -2                    |                  |
|  | LYTIC LESIONS, AVN, PATHOLOGICAL FRACTURES | ABSENT                                   |   |   |   |   |   |   |   | PRESENT                      |                         |                  |
|  | BONE/JOINT PAIN (PAST 30 DAYS)             | NONE TO VERY MILD                        |   | MILD                                      |   |   | MODERATE                                |   |   | SEVERE                       | EXTREME                 |                  |
|  | NO. BONE CRISIS IN PAST 12 MONTHS          | 0-1                                      |   | ≥ 2                                       |   |   |   |   |   |                              |                         |                  |
|  |  |  |   |   |   |   |   |   |   |                              | TOTAL GD-DS3 SCORE      | XX               |

**Figure 5.** GD-DS3 scoring criteria adapted from Weinreb et al., 2010. The individual assessment scores are added for each disease domain (bone, hematological, and visceral) and divided by the number of assessment scores completed to obtain the average domain score. The sum of the three domain scores is the total GD-DS3 score (0–3=borderline to mild disease; 3–6=moderate disease; 6–9=marked disease; ≥9=severe disease).

Macrophage directed Enzyme replacement therapy (ERT) has been the most accepted form of treatment for GD. Therapeutic goals for patients with GD on ERT have been well established, involving changes in size of liver and spleen, improvement in hematological parameters, bone pain and bone crises. However, less than 50% of thus treated patients are expected to meet all these therapeutic goals [5]. It is recommended to start early treatment in symptomatic children with GD to avoid irreversible bony and visceral damage as well as other long-term growth and development issues. Short stature or growth retardation are frequent problems in patients with both GD. Prior to development of ERT, patients with severe phenotypes of GD often experienced puberty delay. When treated, these children had normalized onset of puberty and corrected growth curve, both in stature and lean body mass. However, treated patients may not fully reach expected height [14, 15]. A research study the role of delay in initiation therapy of GD patients, which correlate with symptoms like avascular necrosis and other complications versus immune alterations. It showed positive correlation between those two values, with  $r = 0.55$  ( $P=0.0018$ ) indicating that longer delay in starting therapy, the more severe the symptoms [16]. In our case, patient had not started ERT therapy. Parents are still constrained in financing his therapy, since ERT can only be performed in Jakarta. At present, the patient's condition is stable, but the delay in starting therapy can aggravate the disease.

## 4. Conclusion

Gaucher disease is a genetic disorder that affects different organs and tissues of the body. It is characterized by a spectrum of phenotypes that can present with varying degrees of severity. The presentation depends on the type of the disease. That is importance of early recognition by clinical manifestation and histological findings. GD should be considered in the differential diagnosis of children with unexplained hepatosplenomegaly. Patient with acute leukemia suspicion, parallel is examined for possible GD from bone marrow smears. Moreover, the early recognition of GD would lead to safe and effective treatment with enzyme replacement which can decrease morbidity.

## Funding

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