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Pediatrics and Child Health Care

Gaucher Disease in a 15-month-Old Child: A Case Report and Literature Review

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Case Report

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Article Information

Received: 19-07-2022;
Accepted: 06-08-2022;
Published: 22-08-2022.

Abstract

Gaucher Disease (GD) is an autosomal recessive systemic lysosomal storage disorder, characterized by glucocerebroside deposition in cells of macrophage-monocyte system and accumulation of glucosylceramide in different organs as result of deficiency in lysosomal β-glycosidase (glucocerebrosidase). Accumulation of glucosylceramide in tissues leads to multisystem organ involvement including liver, spleen, bone marrow, lungs and central nervous system. GD is a rare genetic disorder. It is the most common among the lysosomal storage disorders. Around 5 cases are identified and diagnosed in UAE in 2013.

Early recognition of GD is crucial as there is effective treatment with enzyme replacement which can decrease morbidity. GD should be considered as differential diagnosis of children with unexplained hepatosplenomegaly. Hereby, we report a case of Gaucher disease in a 15-month-old child, in whom a diagnosis of Gaucher disease was made early based on glucocerebrosidase levels estimation.

Keywords: Gaucher Disease; Hepatosplenomegaly; Diagnosis; Children; Glucocerebrosidase.

Introduction

Gaucher disease is the most diagnosed lysosomal storage disease; it is inherited as an autosomal recessive disease, which is caused by mutations in the GBA1 gene, that make the glucocerebrosidase, which is a key enzyme in the catabolism of the sphingolipid glucosylceramide. The deficiency of this enzyme results in accumulation of glucosylceramide in macrophages. The organs affected by Gaucher disease include spleen, liver, lung, kidney, bone, bone marrow, lymph nodes, tonsils and thymus [1,2,3,4,5].

Incidence of the GD is 1 in 40,000 – 60,000 births in the general population and reach to 1 in 850 in Ashkenazi Jews. Around 5 cases are reported in UAE until 2013 [4,6].

In 1882, GD was first described by Philippe Gaucher, a French dermatologist born in the department of Nièvre; and the storage of glucocerebroside was first recognized by Epstein in 1924. The metabolic defect, which is the deficiency of the lysosomal hydrolase β-glucosidase, or β- glucocerebroside, was identified by Brady et al [7].

Gaucher's MD thesis annotated a new disorder in which he described abnormal cells (histiocytes) in the tissue of a 32-year-old female who passed away from cachexia and massive hepatosplenomegaly. Gaucher concluded that his patient suffered from a neoplasm of the spleen. Interestingly, to this day, malignancy is the first diagnosis considered when a patient presents with the classic clinical signs of Gaucher disease. The Gaucher cells (foamy macrophages) are characteristic of Gaucher disease [19].

Case Report

We are reporting a case of 15 -month- old Syrian toddler boy presented to our hospital with abdominal distension for 1 month and weight loss for 6 months along with night sweats. He was born at term by normal vaginal delivery from first degree relative parents. His development was appropriate to age. The patient's medical history was not significant. His family members, including his parents and two siblings were healthy. However, he has 2 cousins who died at young age with no definitive diagnosis. On examination, the patient was looking pale, his abdomen was distended with firm, non-tender hepato-splenomegaly. No noted icterus or lymphadenopathy. Laboratory investigations were initially showing 2 cell lines defect (thrombocytopenia

Citation: Hamwi S, Mohamed HA, Al Zubaidi AJ, Mehair AS, Shibli AA. Gaucher Disease in a 15-month-Old Child: A Case Report and Literature Review. Medp Pediatr Child Health Care. 2022; 1(2): mppchc-202207001.

and anemia). However, repeated labs after 2 days showed pancytopenia with normal liver function test and elevated inflammatory markers. Electrolytes were acceptable. Blood and urine cultures were negative. See the table (1) below.

Infectious causes were ruled out like cytomegalovirus, Epstein barr virus, brucella and leishmania as they all reported negative.

Table 1: Lab investigations done at presentation.

Lab	Result	Reference Range
Hemoglobin	82g/L	110-140g/L
Platelets	104x10^9/L	140-400 x10^9/L
WBC	4.3x10^9/L	6.0-17.5 x10^9/L
ESR	28mm/hr	0-20 mm/hr
ANA	Negative	-
IgA	1.09g/L	0.20-1.00g/L
IgG	14.4g/L	4.42-8.95g/L
IgM	3.16g/L	0.19-1.46g/L
CMV IgG	Non-reactive	-
CMV IgM	Non-reactive	-
EBV Capsid Antigen IgG	Non-reactive	-
EBV Capsid Antigen IgM	Non-reactive	-
EBV Nuclear Antigen IgG	Non-reactive	-
Anti-Gliadin IgA	<5.2 CU	<=19.9 CU
Anti-Tissue Transglutaminase IgA	<2.8 CU	<=19.9 CU
Leishmania by PCR	Negative	-

Hemoglobin electrophoresis was found to be normal. CT abdomen showed that the spleen is markedly enlarged measuring 14.1 x 7.1 cm. The liver is also enlarged measuring 11.3 cm in span with no frank focal lesion. Fundoscopic examination was normal. Femur x-ray showed evidence of bone broadening of the lower distal femurs, with no evidence of acute fracture.

Bone marrow aspiration was performed to evaluate massive splenomegaly and pancytopenia, which was reported as: cellular marrow with maturing trilineage hematopoiesis and prominent variable sized aggregates of foamy/vacuolated histiocytes morphologically compatible with storage disorder. (Figure 1&2). Confirmation of diagnosis on Gaucher's disease (type 1) was performed by glucocerebrosidase (glucosyl-ceramidase) enzyme activity in leukocytes (Lyso-Gb1) which was 877,0 ng/ml (pathologically increased) (Reference range ≤ 6,8 ng/ml). Our final diagnosis was Gaucher disease.

Discussion

Gaucher's disease is an autosomal recessive disorder, and it is the most common among the lysosomal storage disorders. Gaucher disease manifests with broad phenotypic variation typical of many metabolic disorders, ranging from neonatal lethality to asymptomatic octogenarians. It has long been known that neither the amount of lipid stored, nor the residual enzymatic activity detected, correlates well with symptom severity [8,9].

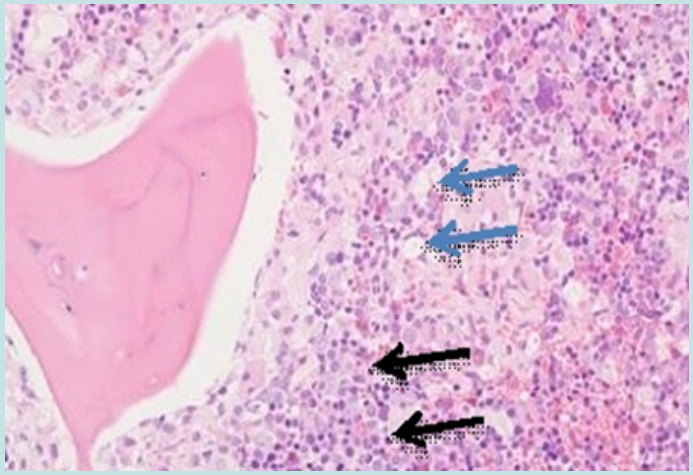


Figure 1: Interstitial small mature lymphocytes (black arrow) are noted in foci associated with aggregates of foamy/vacuolated histiocytes (blue arrow), reticulin stain shows patchy borderline increase in reticulin fibers.

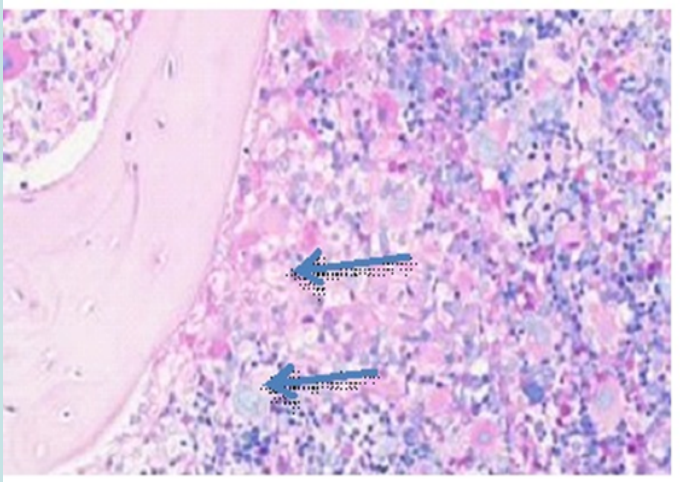


Figure-2: The current core biopsy shows maturing trilineage hematopoiesis and prominent variable sized aggregates of foamy/vacuolated histiocytes (blue arrow) morphologically compatible with storage disorder.

The most common signs and symptoms noted in GD are splenomegaly (95%), hepatomegaly (87%), radiological bone disease (81 %), thrombocytopenia (50%), anemia (40%), growth retardation (34%), bone pain (27%), and bone crisis (9%). A skeletal manifestation is found more often in older children [8,9].

GD has been categorized into three types based on the presence of central nervous involvement [7]:

- Type 1 non-neuropathic form (chronic or adult form): is the commonest variety; it is characterized by hepatosplenomegaly, anemia and thrombocytopenia with bone disease manifested as osteopenia, focal lytic or sclerotic lesions and osteonecrosis; neurological manifestations are absent and have a bimodal presentation, with peaks at 10-15 years and around 25 years, in childhood or early adulthood.

- Type 2 neuropathic form (acute or infantile form): is the severe form, it is characterized with primary neurological disease and onset before 2 years, with limited psychomotor development and rapid progressive course with death between 2 to 4 years.
- Type 3 neuropathic form (subacute or juvenile form): is the milder variety; also has a primary neurological disease with onset before 2 years of age and slow progression with survival into third and fourth decade [10].

Age of onset is variable between 2 months to 80 years of age based on cases reported. Type 1 Gaucher disease may present early in childhood with complications, and others may remain asymptomatic into the eighth decade of life. 66% of patients with type 1 gaucher disease are diagnosed before age of 20 years. It was estimated that the lag time between disease onset and diagnosis ranges from 1 month to 7 years, with average of 2.3 years [11,12].

An Algorithm described for early diagnosis in the pediatric age group proposed by Di Rocco et al, Figure- 4 [13], it started by approaching patient with unexplained splenomegaly, to screen for associated thrombocytopenia and/or anaemia. If the patient has associated thrombocytopenia and/or anemia, then to assess for the presence of any of the following:

- Eye movement disorders (strabismus and/or oculomotor apraxia)
- Growth deceleration or retardation
- Erlenmeyer flask deformity
- Increased level of ferritin
- Increased level of tartrate-resistant acid phosphatase (TRAP).

If one of the above-mentioned features is present, then the glucocerebrosidase enzyme assay must obtained. If splenomegaly and thrombocytopenia, or anemia are present, a bone marrow aspirate should be obtained and evaluated. After excluding signs of blood disorder, malignancy, or infection (e.g., visceral leishmaniasis), metabolic disorders should be considered. If splenomegaly is present without thrombocytopenia or anemia, and no other signs are identified, work up should be pointed for GD. See figure 4 below [14].

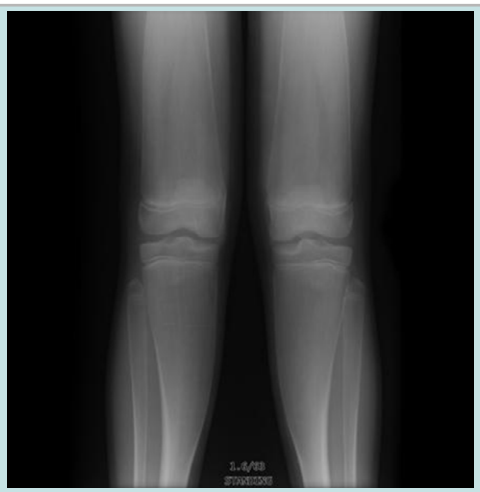


Figure 3: Erlenmeyer flask deformity (EFD), also known as metaphyseal flaring, reduced constriction of the diaphysis and flaring of the metaphysis because of undet tabulation [18].

The diagnosis of Gaucher disease is best established by measuring the acid B-glucosidase activity of peripheral blood leukocytes or in cultured skin fibroblasts from skin biopsy or other nucleated cells or by DNA analysis. Glycosyloslsphingosine (lyso-GL1) is the most reliable and specific biomarker for Gaucher Disease. Normally, lyso-Gb1 is undetectable or found at trace levels in plasma (i.e., <4.9 ng/mL (10.61 nmol/L)) and tissue. In symptomatic patients with type 1 GD, prominent increases in lyso-Gb1 (300-fold) were detected [10,14].

Bone marrow biopsy is useful for distinguishing hematological malignancy from GD but should not be the first choice. Moreover, the presence of Gaucher cells in the bone marrow is not necessarily diagnostic of GD, because 'pseudo' Gaucher cells are often associated with other conditions. Conversely, failure to detect Gaucher cells in a bone marrow aspirate cannot be used to exclude GD [15].

Our patient has presented with the unexplained hepatosplenomegaly with pancytopenia and was showing growth deceleration, x ray of the femur showed Erlenmeyer flask deformity, and according to the above-mentioned algorithm, the next step to proceed for enzyme assay. Glucocerebrosidase enzyme activity in leukocytes was measured in our patient and was at an increased level, confirming the diagnosis of Gaucher disease. The diagnosis was also aided by the findings on the bone marrow aspirate indicating the presence of gaucher cells. Despite the low incidence of Gaucher disease in UAE and the gulf region, Gaucher disease still should be considered as a differential diagnosis, as early diagnosis is fundamental for proper management and best therapeutic response; delayed diagnosis can result in high probability in irreversible complications.

Enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) are the backbone of management. ERT causes a dramatic effect on organomegaly with a 25% of decrease in liver and spleen volume in the first 6 months. Hemoglobin rises by 1.5gm% in the first 4 to 6 months and platelet counts will double in the first year of treatment. However, many patients would still require surgical treatment in the form of splenectomy to correct their pancytopenia [4,7].

Substrate reduction therapy (SRT) is a newer form of therapy that will inhibit the enzyme glucosylceramide synthetase and thus decrease the biosynthesis of glucocerebrosidase. It is considered the second line of treatment when ERT is no longer accepted by the patient or can't be used due to intolerance [4].

Treatment is available in the form of enzyme replacement therapy. For types 1 and 3, substrate inhibition therapy represents a viable alternate approach to enzyme therapy in the treatment of visceral pathology in GD. Bone marrow transplantation may benefit Type 3 individuals. Currently, only supportive therapy is available for Type 2 [13].

Conclusion

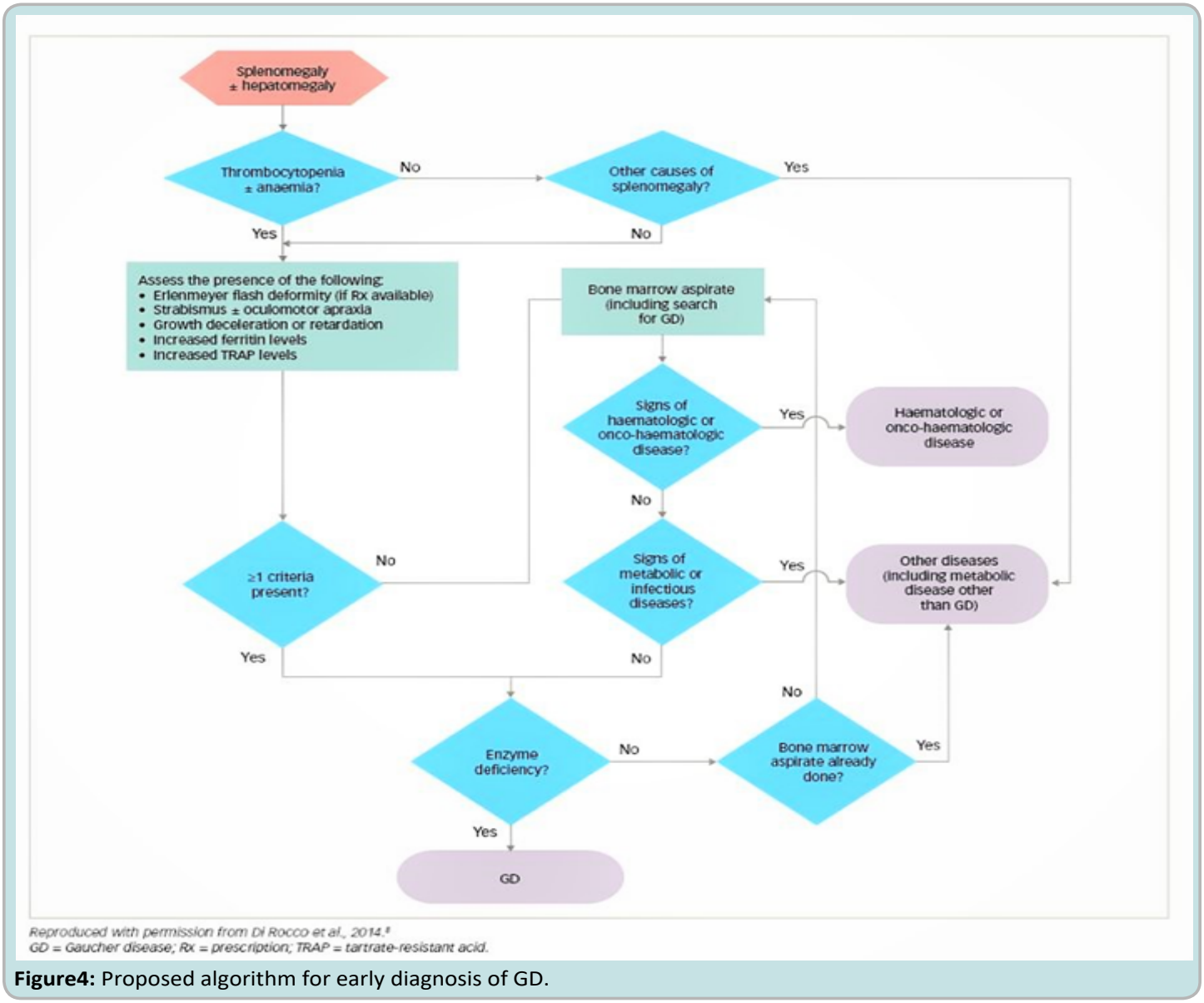
Herein, we described a case of GD that was diagnosed based on clinical and laboratory findings and confirmed by enzyme testing. It is important to keep high index of suspicion as early diagnosis is crucial to establish early treatment and management.

Methodology

This section will discuss the methodology used to conduct. The method of this study is a case report about Gaucher disease. Data was collected from the patient's online portal that is used at Tawam Hospital. Data including patient's demographic information, history, physical examination, laboratory, radiologic and histologic details were obtained and summarized in this

case report. Key words of Gaucher disease, early diagnosis and management have been searched. Case reports have been reviewed as well.

Funding: Nil



Reproduced with permission from Di Rocco et al., 2014.[1]
GD = Gaucher disease; Rx = prescription; TRAP = tartrate-resistant acid.

Figure4: Proposed algorithm for early diagnosis of GD.

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