

Gaucher's Disease: A Case Report

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Abstract

Gaucher's disease (GD) is an uncommon genetic disorder with an autosomal recessive inheritance pattern. It is known as the most common lysosomal storage disorders (LSDs) worldwide and occurs due to a deficit of the enzyme glucocerebrosidase owing to a mutation in the acid- β -glucosidase (GBA1) gene. This characterization of this metabolic defect is abnormal accumulation of glucocerebrosides in the lysosomes of cells. It is exhibited with wide range of phenotypic variations; abdominal swelling, hepatosplenomegaly, anemia, thrombocytopenia, and bone diseases. Diagnosis is confirmed on the basis of identification of deficiency of glucocerebrosidase activity. Enzyme replacement is the mainstay of treatment although oral administration of inhibitors of glucosylceramide biosynthesis is also used. In this study, a case of GD in a 5-year-old boy with massive splenomegaly and lymphadenopathy is reported. This case report is an effort to emphasize the significance of early diagnosis of this disorder to ensure its proper prognosis and treatment at an early stage.

Key Words: Gaucher's disease; Genetic Disorder; Glucocerebrosidase Activity

Introduction

Lysosomal storage disorders (LSDs) are a collection of several genetic disorders occurred due to the mutation in genes that encode for enzymes involved in the degradation of complex macromolecules [1]. Deficiency of these enzymes results in cellular dysfunction and various

clinical manifestations. Of the several known LSDs, Gaucher's disease (GD) is the one of the most commonly known worldwide. It is an autosomal recessive disorder that occurs due to a mutation in the gene acid- β -glucosidase (GBA1) located on chromosome 1. The gene encodes for the enzyme glucocerebrosidase that converts glucosylceramide (GlcCer) into ceramide and glucose [2]. Decreased activity of glucocerebrosidase affects in accumulation of undegraded glucocerebrosides in the lysosomes of macrophages in the liver, spleen, and bone marrow, thereby transforming these macrophages to Gaucher's cells. The associated systemic indicators include anemia, thrombocytopenia, hepatosplenomegaly, and skeletal complications [3,4]. The accumulation of lipid aggregates inside the Gaucher's cells make them appear as highly enlarged cells with eccentric nuclei and condensed chromatin [5].

The disease was first defined in 1882 by Philippe Gaucher in a leukemia patient with splenomegaly [2]. The storage of glucocerebrosides in the lysosomes was discovered by Epstein in 1924, whereas the metabolic defect leading to GD, that is, deficiency of glucocerebrosidase was reported by Brady et al. [6].

The GD is characterized by a wide spectrum of clinical presentations and in certain forms can also cause neurological impairment. Moreover, based on the severity of neurological manifestations, it can be categorized into three types. Type 1 is the most common and not associated with any neurological damage. Type 2 and type 3 are more severe with acute neuropathic and subacute neuropathic symptoms, respectively. Both these types involve an early involvement of the central nervous system [7]. However, the distinction between the three types is not absolute as evident from the reports of peripheral neuropathy and parkinsonism in patients with type 1 GD [8,9]. Type 1 GD has a prevalence of 90 to 95%, with an invariable clinical presentation that ranges from being asymptomatic throughout the life to early-onset of symptoms in the childhood. Although type 1 GD is not life threatening, it decreases the quality of life and increases the morbidity. Fatigue is very common in

children; other symptoms include retarded growth, delayed puberty, splenomegaly, hepatomegaly, and mucocutaneous bleeding [10-13]. Type 3 GD occurs in 5% of cases, with heterogenous phenotypes, ranging from moderate systemic involvement to more severe neurological symptoms such as progressive myoclonus epilepsy, cerebellar ataxia or spasticity, and dementia [14-16]. This type has been reported to be more common in young children, with behavioral changes and death reported in few patients [15,17]. Type 2 GD occurs in less than 2% of case. The disease manifests itself at a very early stage in the infancy and is associated with severe neurological impairment [14]. Splenomegaly has always been reported along with thrombocytopenia, growth retardation, lung lesions, and pulmonary infiltration by Gaucher cells. Death is usually reported before the third year of life [18,19].

A typical challenge associated with rare diseases, including GD, is the delay in diagnosis. This is attributed to the fact that it often takes several years before first clinical signs are observed [20]. The diagnosis of GD is established by clinically establishing the deficiency of glucocerebrosidase in the leukocytes or cultured fibroblasts. Another diagnostic method is flow cytometry analysis of blood monocytes [21,22]. In addition, several clinical abnormalities such as thrombocytopenia, hemostatis abnormalities such as prolonged prothrombin time (PT) and activated partial thromboplastin time (APPT), and several disease biomarkers such as hitotriosidase, CCL18, glucosylsphingosine, and ferritin are being employed to test the presence of GD [23-25]. Other biological tests involve liver function tests (free and conjugated bilirubin, transaminases, alkaline phosphatase, gamma GT), serum calcium for bone infarction, and lipid profile [26,27]. To add to this, radiological interventions including magnetic resonance imaging (MRI) and computed tomography (CT) are employed for assessing the liver and spleen dimensions [28].

The prevalence of GD is approximately 1/40,000 to 1/60,000 births; however, a comparatively higher prevalence of 1/800 has been reported in Ashkenazi Jews [29]. In this

study, a case of GD in a 5-year-old boy who presented with massive splenomegaly and lymphadenopathy is reported.

Case Report

A 5-year-old boy presented to the clinic with ecchymosis and bloody urine, abdominal distention, fever, loss of appetite, and extreme weight loss. His past 6-month history revealed that he easily got fatigued. He had also been suffering from recurrent epistaxis since past 1 year.

The child was born to parents with second-degree of consanguinity. The patient's father had spinocerebellar ataxia (SCA). His family members, including his younger sister, were normal and did not report any similar condition. Upon admission, the patient looked pale and had fever. On physical examination, bilateral palpable cervical lymphadenopathy was reported.

He had firm, non-tender massive splenomegaly and a non-tender, mild hepatomegaly. There were zero signs of ocular motor problems or other neurological irregularities. Rest of the systemic examination was basically normal. He had firm, non-tender massive splenomegaly, approximately 14 cm BCM (Below costal Margin). However, there was no hepatomegaly. Laboratory investigation revealed cytopenia in two cell lines ((hemoglobin = 7.9 g/dL, white blood cells = $3.2 \times 10^9/L$, and platelets = $89 \times 10^9/L$). A slight increase in the levels of liver enzymes (aspartate aminotransferase = 40.8 IU/mL and alanine aminotransferase = 9.9 IU/mL) was observed. However, serum proteins and albumin levels, kidney function test, and urine analysis were unremarkable. PT was 14.7 s [international normalized ratio [INR] = 1.2] and PTT was 36 s. Peripheral blood film analysis revealed microcytic hypochromic anemia. Bone marrow aspiration revealed normal erythropoiesis and Gaucher's cells in a background of normal erythroid, myeloid, and megakaryocytic lineage cells. Gaucher's cells were large with a thin outer border, one or two eccentric nuclei with few cytoplasmic content. These

cells contained hyperplastic macrophages and had a crumbled tissue paper-like appearance and were seen performing erythrophagocytosis (Figure 1).

A few megakaryocytes were observed with occasional presence of megakaryoblasts. No parasite was observed and fundoscopy was normal. GD was confirmed by assessing the levels of β -glucosidase, which was below the reference range ($8.02 \text{ pmol/spot} \times 20 \text{ h}$) (Figure 2). Genetic analysis detected 2 mutations (c.[1448T>C];[1448T>C] and (p.[Leu483Pro];[Leu8482Pro]), which confirmed the diagnosis to be GD.

Discussion

The GD is genetic disorder that is inherited in an autosomal recessive pattern. It has been reported to affect all races and ethnic groups with an occurrence of approximately 1:40,000 individuals [30]. However, the prevalence is higher among Ashkenazi Jews. Among the several LSDs known, GD is the most common [2]. The disorder is characterized by diverse clinical and physical manifestations including splenomegaly (95%), hepatomegaly (87%), radiological bone disease (81%), thrombocytopenia (50%), anemia (40%), growth retardation (34%), bone pain (27%), and bone crisis (9%) [31]. One of the challenges that clinicians face is to differentially diagnose the disease at an early stage. This is due to the fact that although GD is common in adults, 66.7% of patients present symptoms not before the age of 20 years. Differential diagnosis involves consideration of broad range of diseases that have similar presentations as that of GD, for instance, hepatosplenomegaly, anatomical abnormalities, congestion, infection, and hematologic disorders. Despite the fact that hematologic disorders could explain organomegaly, several haematological manifestations including chronic hemolytic anemia, myeloproliferative disorders, and sickle-cell disease were ruled out in this case. This decision was based on the absence of additional symptoms like jaundice, abnormal hemoglobin electrophoresis, painful crisis, and leukocytosis. With regard to infiltrative processes, malignant neoplasms and histiocytic disorders are considered. Numerous pediatric

cancers, such as leukemia, lymphoma, and primary splenic tumors, could explain hepatosplenomegaly. However, symptoms associated with majority of these cancers are acute and rapidly developing as compared to the slow progressing course in this case. In addition, the patient did not present other characteristic symptoms of such cancers. Considering the patient's age, other cancer types were not studied. Histiocytic disorders were also ruled out owing to his age as well as lack of presentation of related symptoms, such as rapid clinical deterioration, fever, wasting, skin rash, and irritability. Thus, based on the clinical presentations of the patient, the disorder is diagnosed to be GD, as confirmed by bone marrow examination and demonstration of deficiency of acid β -glucosidase activity in isolated leukocytes. The deficiency was further confirmed by the genetic analysis that revealed two mutations in this gene.

Conclusion

Diagnosis of GD should be based on differential diagnosis in case of patients presenting with unexplained splenomegaly, particularly if symptoms last for extended time duration. The present case sheds light on the significance of clinical examination and bone marrow finding in the diagnosis of GD. Since the disease is rare, the possibility that the diagnosis is delayed is high. Therefore, an early diagnosis is essential for effective treatment. An early detection together with treatment using enzyme replacement can considerably reduce the morbidity.

Funding: None

Acknowledgement: None

Conflict of Interest: None

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Figure Legends:

Figure 1. Representative images of hyperplastic macrophages. Gaucher's cells are seen as large cells with a thin outer border, one or two eccentric nuclei with few cytoplasmic content (arrows).

Figure 2. Activity of beta-glucosidase is below the reference range, indicating Gaucher's disease.

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