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Fatigue in Gaucher Disease, a Key Quality-of-Life Concern: A Case Series

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Abstract

Background: Gaucher disease is an autosomal recessive lysosomal storage disease characterized by glucosylceramide accumulation in the lysosomes of macrophages. Common clinical features of Gaucher disease include hepatosplenomegaly, pancytopenia, and bone manifestations. Treatment may involve enzyme replacement therapy, substrate reduction therapy, and supportive care. Patients with Gaucher disease often present with chronic, debilitating fatigue and consider absence of fatigue to be one of the most important management goals.

Methods: In an effort to demonstrate the importance of fatigue in Gaucher disease, we describe the presentation, treatment, and outcome of five patients with Gaucher disease who presented with fatigue.

Results: The patients ranged in age from 17 to 66 years, and each experienced improvement in fatigue after initiating enzyme replacement therapy.

Conclusion: Although the regulatory criteria for the use of enzyme replacement therapy and substrate reduction therapy in patients with Gaucher disease in Israel do not include fatigue, these case examples suggest that fatigue should be regarded as a criterion to initiate treatment and improve quality of life in patients with Gaucher disease. Inflammation and autoimmunity may play a role in the etiology of fatigue in patients with Gaucher disease.

Keywords: Gaucher disease; Lysosomal storage diseases; Glucosylceramide; Enzyme replacement therapy; Fatigue; Quality of life

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Background

Gaucher Disease (GD), a lysosomal storage disorder caused by autosomal recessive mutations in the β-Glucocerebrosidase (GBA) gene leading to deficiency in the activity of glucocerebrosidase, the enzyme responsible for lysosomal glucosylceramide degradation [1]. Glucosylceramide accumulates in lysosomes of macrophages resulting in Gaucher cells formation, leading to Hepatosplenomegaly (HSM), pancytopenia, and bone manifestations [1-4]. GD is a pan-ethnic disorder, classified into three clinical subtypes. Type 1 (GD1), the most common, a non-neuronopathic form, especially common among Ashkenazi Jews, in which the N370S mutation predominates [1]. Type 2, the most severe form, associated with acute neurologic symptoms in infancy and generally fatal by 2 years of age [1,2,4,5]. Type 3, subacute neuronopathic form, chronic, with milder neurologic symptoms that become apparent in children, adolescents, and adults [1,2,4].

Fatigue is one of the most common complaints of GD patients, results in functional disability and impaired quality of life, as it interferes with school, work, leisure activities, and social life [6-15]. Although fatigue does not always correlate with visceral, hematologic, and skeletal manifestations of GD, it is often the presenting symptom. Fatigue in GD is multifactorial, resulting from numerous causes, in addition to anemia, such as muscle-tendon weakness [13], although many causes have not yet been clearly identified [6-8,15]. A recent publication showed that GD macrophages induce production of inflammatory cytokines [16]; this observation, together with that of GD storage induction resulting in complement-activating autoantibodies [17], may explain the fatigue experienced by patients with GD.

Management options for GD include Enzyme Replacement Therapy (ERT), Substrate Reduction

Therapy (SRT), and supportive care [4,6,14,18], the effects of which are routinely evaluated by monitoring signs, symptoms, biomarkers, and organ imaging. Although commonly used expert consensus guidelines, assess treatment effect, including reduction in fatigue, as a therapeutic goal for anemia, they do not include measurement of fatigue [19]. In contrast, new management goals put forth in 2018 by the European Working Group on Gaucher Disease were developed with patient input and include improvement in patient-reported outcome measures, such as fatigue as a general well-being goal (not anemia related), as patients identified absence of fatigue as one of the most important management goals. According to these recommendations, fatigue should be measured by a validated scoring system. Several validated tools are available to measure fatigue, but none is specific for GD [15].

Methods

Ethical considerations

This study was approved by the ethics committee at Clalit Medical Services, Israel (218-17). Patient consent was not applicable as the cases were evaluated in Israel where consent was not required.

Objectives and study design

Demonstrate the importance of fatigue in GD through case examples, discuss the etiology of fatigue as it relates to these case examples of GD, and provide an overview of the regulatory process of approval of patients for ERT in Israel.

Case Series

Case examples of five GD1 patients (two females, three males), age range 17 to 66 years, presenting with a main complaint of fatigue, are discussed below.

Case 1

A 24-year-old female diagnosed with GD1 at 16 years of age, homozygous for N370S mutation. Her main complaint at admission to the GD clinic was fatigue that made her unable to work and greatly limited her social activity. She also experienced periodic bone pain. Physical examination revealed mild splenomegaly without hepatomegaly; unremarkable neurologic examination. Normal echocardiography, without evidence of pulmonary hypertension. Bone Mineral Density (BMD) test was normal; however, BM infiltration by Gaucher cells was evident on Magnetic Resonance Imaging (MRI) of her femurs, based on a "salt and pepper" appearance (Figure 1).

Laboratory analyses revealed normal Hemoglobin (Hb) level of 14.2 g/dL, normal White Blood Cell (WBC) count of 7300/mL with normal differential, normal platelet level of 205,000/mL. Her High-Density Lipoprotein (HDL) cholesterol was normal (53.7 mg/dL). Liver Function Tests (LFTs), Prothrombin Time (PT), and Partial Thromboplastin Time (PTT) were within normal ranges, as were C-Reactive Protein (CRP), Thyroid-Stimulating Hormone (TSH), vitamin B12, and folate. Ferritin and chitotriosidase levels were high (441 ng/mL and 42,000 nm/mL/h, respectively).

ERT was recommended because of fatigue and was approved due to impaired quality of life, Gaucher cell BM infiltration, and high chitotriosidase level. The patient received ERT with low-dose taliglucerase alfa 30 U/kg monthly (Elelyso®; Pfizer Inc., New York, NY). After 10 weeks of treatment with taliglucerase alfa, she noticed a significant amelioration of fatigue and, after 16 weeks of treatment, she was able to perform normal daily activities.

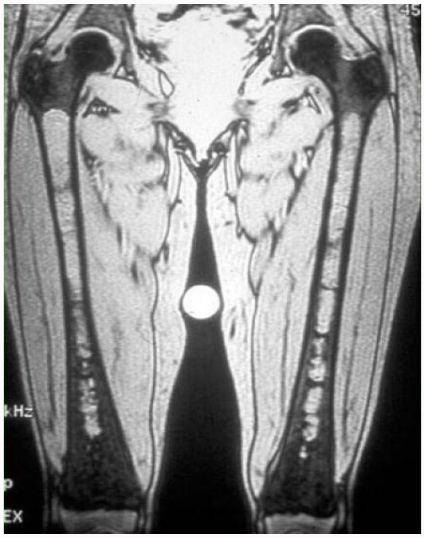

Figure 1: Case 1: Femurs MRI demonstrating bone marrow infiltration with a "Salt and Pepper" appearance.

Case 2

A 66-year-old male of Ashkenazi Jewish origin had experienced chronic fatigue requiring bed rest during the day, which ultimately led to his retirement at 56 years of age. He was referred to the GD clinic after reporting fatigue to a hematologist at another clinic. He had a history of hip replacement (left hip at 44 years of age; right hip at 48 years of age) owing to Avascular Necrosis (AVN), and a history of aseptic osteomyelitis in the left femur in childhood. He also had a known history of HSM and pancytopenia; laboratory analyses confirmed a low Hb level (12.5-13.0 g/dL), leukopenia (3000/mL), and thrombocytopenia (55,000-60,000/mL).

Physical examination revealed cachexia, splenomegaly (palpable 18 cm below the costal margin, multiple splenic nodules on ultrasound (Figure 2)), and hepatomegaly (palpable 16 cm below the costal margin). BM aspiration and biopsy for suspected hematologic malignancy revealed massive infiltration by aggregates of Gaucher cells (Figure 3A) and mild fibrosis (Figure 3B); no clonal B cells were detected in the BM aspirate by flow cytometry.

The patient presented to the GD clinic at 67 years of age with complaints of fatigue and early satiety. He was homozygous for the N370S mutation, with glucocerebrosidase activity <1.0 µmol/L/h, enabling the diagnosis of GD1. Laboratory analyses revealed anemia (Hb 12.5 g/dL), leukopenia (WBC 3400/mL), and thrombocytopenia

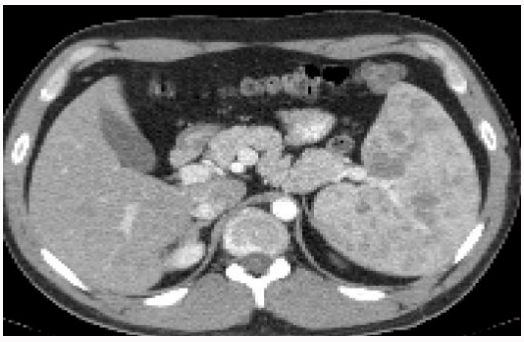

Figure 2: Case 2: Abdominal computed tomography shows hepatosplenomegaly with splenic nodules.

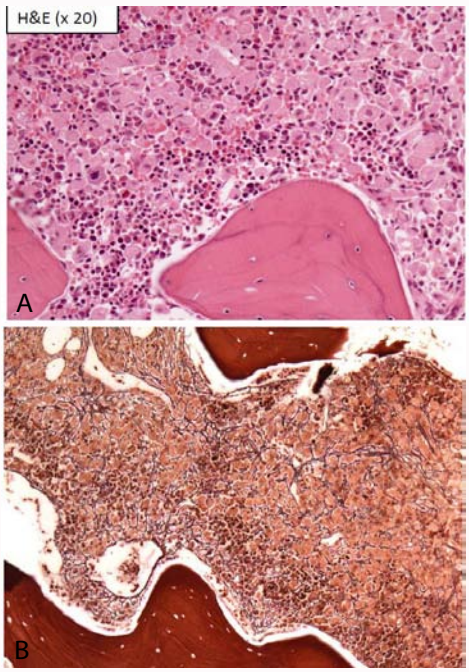

Figure 3: Case 2: Findings from bone marrow biopsy: (A) infiltration by Gaucher cells and (B) reticulin stain showing bone marrow fibrosis.

(platelets 68,000/mL). LFTs were within normal limits. Biomarkers for symptomatic GD were typically abnormal, hyperferritinemia (1882 ng/mL), high glucosylsphingosine (300 ng/mL), high angiotensin-converting enzyme (ACE, 105 U/L), and low HDL cholesterol (26 mg/dL) levels. The patient had a biclonal gammopathy, with an IgGk level of 0.2 g/dL, IgA level <0.12 g/dL, normal levels of polyclonal immunoglobulins.

BMD test revealed osteoporosis, with spine T-score of –3.0. Transthoracic echocardiography demonstrated normal pulmonary artery pressure. Liver elastography conducted using FibroScan revealed increased fibrosis.

ERT with imiglucerase (Cerezyme®; Genzyme Corporation, Cambridge, MA) was initiated promptly after GD diagnosis and establishment of the disease parameters and biomarker profile. After 8 weeks of ERT, the patient's fatigue disappeared, enabling to resume normal daily activities. After 2 years of ERT, the patient is doing well, but visceromegaly and thrombocytopenia (approximately 90,000/μL) persist. His glucosylsphingosine and HDL cholesterol levels have not changed significantly; however, his anemia improved, ferritin level decreased by 15%, and ACE level has decreased by 45%. The dose of ERT was doubled due to persistent organomegaly and thrombocytopenia.

Case 3

A 17-year-old female diagnosed with GD1 at 11 years of age, homozygous for N370S mutation. Fatigue made it difficult for her to perform normal daily activities and required her to sleep for several hours during the day. Physical examination during treatment for a viral upper respiratory tract infection revealed mildly enlarged spleen palpable 3 cm below the costal margin. She had normal WBC and platelet counts (4800/mL and 170,000/mL, respectively), Hb level 11.7 g/dL, mild splenomegaly, and no bone manifestations.

ERT (regimen unknown) was recommended due to fatigue, and the patient was treated in another Gaucher clinic. She reported that ERT resulted in improvement of her quality of life. The patient reported substantial improvement and did not require additional hours of sleep during the day.

Case 4

A 39-year-old male of Ashkenazi Jewish origin referred to the hematology unit due to purpura and thrombocytopenia. A short course of steroids prescribed for suspected immune thrombocytopenia cleared the purpura, but thrombocytopenia remained. The patient had a history of recurrent episodes of fatigue and knee pain. Physical examination revealed marked splenomegaly (palpable 13 cm below the costal margin) and hepatomegaly (palpable 6 cm below the costal margin), no purpura or petechiae were noted. Abdominal ultrasound confirmed splenomegaly (span of 20 cm) with two hypoechogenic nodules and hepatomegaly (span of 18 cm).

Laboratory analyses showed a normal Hb level (13.9 g/dL) and WBC count (4900/mL), a normal PT and PTT, low platelet count (32,000/mL), and mildly elevated LFTs (alanine aminotransferase, 63 U/L; aspartate aminotransferase, 46 U/L). Hepatitis B and C serology was negative. GD was suspected; thus, GD genotype and glucocerebrosidase activity were evaluated. Compound heterozygosity for 84GG and R495H mutations and low glucocerebrosidase activity of 2.4 nmol/hour/mg were found, enabling GD1 diagnosis. Bone marrow aspiration and biopsy were performed to rule out concomitant hematological malignancy. Typical Gaucher cell infiltration and numerous atypical forms of megakaryocytes were noted (Figure 4), with mildly compromised erythropoiesis and myelopoiesis. These findings, together with the detection of anti-platelet antibodies, enabled confirmation of the diagnosis of GD with concomitant immune thrombocytopenia. Analysis of GD biomarkers found high ACE levels (173 U/L) and hyperferritinemia (523 ng/mL), low HDL (23 mg/dL) and C4 levels, and normal immunoglobulin, anti-nuclear factor, anti-dsDNA, and C3 levels.

ERT Taliglucerase alfa, 60 U/kg /month was administered. High-dose gammaglobulin (Gammaplex® 0.4 g/kg/day; Bio Products Laboratory Ltd., Elstree, UK) was given for 4 days for retinal bleeding, recurrence of purpura, and decrease in platelet count to 20,000/μL. This resulted in disappearance of the bleeding but no change in the platelet count. Prednisolone was tapered after 6 weeks when no bleeding phenomena detected, platelet count had Stabilized ERT (taliglucerase alfa, 60 U/kg administered every other week) 60 U/ month was administered High-dose gammaglobulin (Gammaplex® 0.4 g/kg/day; Bio Products Laboratory Ltd., Elstree, UK) was given

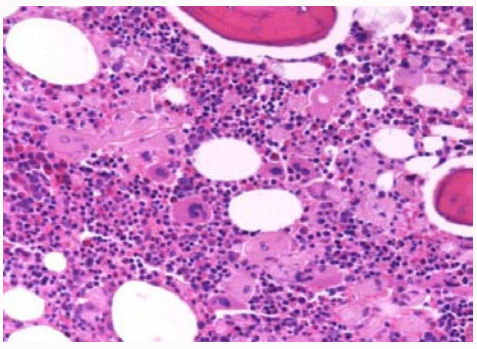

Figure 4: Case 4: Bone marrow biopsy showing infiltration by Gaucher cells and numerous atypical megakaryocytes.

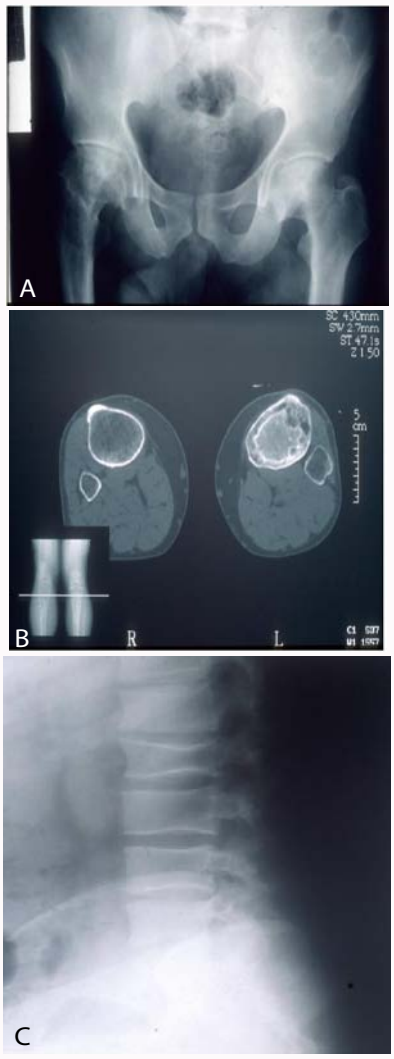

Figure 5: Case 5: (A) Frontal pelvic radiograph showing bilateral AVN of hip joints, (B) Computed tomography image showing bone infarcts in the left tibia, (C) collapsed L2 vertebra shown in lateral cervical spine radiograph.

for 4 days for retinal bleeding, recurrence of purpura, and decrease in platelet count to 20,000/μL. This resulted in disappearance of the bleeding but no change in the platelet count. Prednisolone was tapered after 6 weeks when no bleeding phenomena detected, platelet count had stabilized at approximately 30,000/mL. Fatigue disappeared after the first 6 weeks of ERT. The patient's spleen and liver volumes decreased to approximately 80% of the initial volume after 6 months of ERT, but thrombocytopenia persisted. Splenectomy was not considered because of the known postoperative bone complications in GD patients. Rituximab was given to prevent the recurrence of wet purpura, with only a short effect on the platelet count.

The dose of ERT was doubled to 120 U/kg/month, and romiplostim, a thrombopoietin receptor agonist, was given with a satisfactory response after 3 weeks of therapy. Platelet count increased up to a range of 60,000 to 90,000/μL, with no bleeding phenomena or side effects; after 18 months of romiplostim therapy, normal platelet levels were reached, enabling cessation of treatment. After 10 years of follow-up with ERT, the dose was tapered to 45 U/kg/month. The patient is stable and feeling well, with no fatigue or bleeding phenomena.

Case 5

A 41-year-old male was diagnosed with GD at 17 years of age, homozygous for N370S mutation. He had a history of hip joint pain at 6 years of age suspected to be osteomyelitis or Paget's disease, left tibia pain diagnosed as aseptic osteomyelitis and knee effusion at 16 years of age.

At admission at 41 years of age, he presented with fatigue, easy bruising, lower back and bilateral hip pain, and psoriasis, which enabled him to work. Physical examination revealed splenomegaly (palpable 6 cm below the costal margin). Bone imaging showed bilateral hip joint AVN and a collapsed L2 vertebra (Figure 5A-5C). His Hb level (13.9 g/dL) and WBC count (6500/mL) were normal, but his platelet count was low (70,000/mL).

ERT was prescribed due to bone complications, splenomegaly, and thrombocytopenia. After 2 years of ERT, the patient underwent a total right hip joint replacement due to pain and a collapsed femoral head. The patient decided to stop ERT 2 years after surgery. Over the next 3 years, he presented with fatigue, weight loss, early satiety, axillary lymphadenopathy, splenomegaly, and gallstones. Positron Emission Tomography (PET) and Computed Tomography (CT) scans revealed axillary lymphadenopathy and a large mesenteric mass with prominent pathologic uptake in these regions (Figure 6A). Needle biopsies from the axillary lymph node and abdominal mass showed massive infiltration of Gaucher cells with no evidence of a lymphoproliferative disorder (Figure 6B). The patient was diagnosed with a mesenteric Gaucheroma.

ERT was resumed, after which the patient's fatigue disappeared, and his splenic volume was reduced. Axillary lymph nodes size decreased, but the size of the mesenteric mass was unchanged. Over 16 years of ERT, the patient had no fatigue, mild splenomegaly, improvement in bone pain, and a mild decrease in the size of the abdominal Gaucheroma. His liver was enlarged, and his liver enzymes were mildly elevated. Liver elastography with a FibroScan

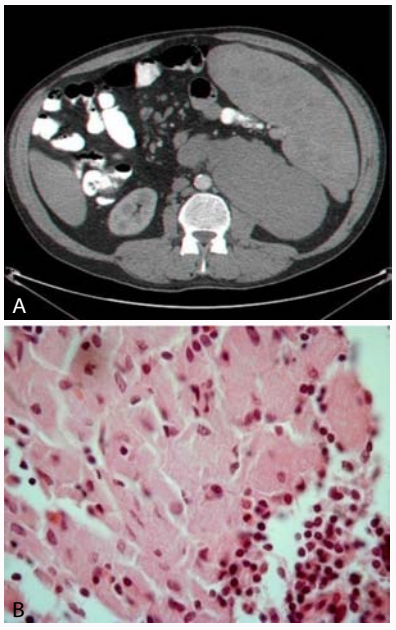

Figure 6: Case 5: Mesenteric "Gaucheroma": (A) Abdominal mass demonstrated on CT scan (B) biopsy of abdominal mass shows massive infiltration by Gaucher cells.

revealed increased fibrosis. Liver biopsy findings were compatible with cirrhosis, with no signs or symptoms of portal hypertension. The patient died of metastatic lung cancer at 61 years of age.

Discussion

Novel, validated approaches to measure fatigue in patients with GD are needed to monitor patients and to encourage healthcare authorities and treating physicians not to ignore or minimize the role of fatigue in GD [6,7]. It is very important to monitor quality of life in patients with chronic disorders; patients with GD in particular consider quality of life and fatigue factors of great importance for improvement [6]. In a survey of GD1 patients diagnosed for a median of 15.5 years, fatigue was ranked highest in importance, over bone pain, liver/spleen volume, bone density, biomarkers, and complete blood count [7].

The results of this case series suggest that fatigue may be regarded as a criterion to initiate treatment in patients with GD. Currently in Israel, fatigue is not included in the criteria for the use of ERT or SRT in GD. Adult GD1 patients are approved to receive either ERT or SRT if they present with symptomatic disease (splenomegaly, anemia, thrombocytopenia, or bony complications) [20,21], or if they have a genotype associated with severe disease (*e.g.*, compound heterozygous) [21]. Four patients met the criteria for initiation with ERT or SRT. One patient presented with fatigue only, with no significant organomegaly, bone manifestations or cytopenia. ERT in this patient as in the others resulted in improvement of quality of life. The findings from these case studies suggest that fatigue should be considered as a criterion to initiate treatment in GD, as fatigue may be the presenting and only symptom of GD. A validated instrument to assess fatigue in GD is needed in order to support fatigue alone as a criterion for initiating treatment.

Information on the etiology of fatigue in GD is limited; however, possibilities include elevated levels of cytokines and ferritin associated with inflammation [22-25], hypercatabolism associated with organomegaly [26], and musculoskeletal complications [13]. Among the current cases, Cases 2 and 5 were in a hypercatabolic state, with marked hepatosplenomegaly, liver fibrosis, weight loss, and cachexia. Case 4 presented with autoimmunity, immune thrombocytopenia, and low C4 levels. Glucosylceramide accumulation in GD induces immune dysregulation [27] and complement-activating IgG autoantibodies [17,28]. Both inflammation and autoimmunity may contribute to the fatigue typically observed in patients with GD. Delays in diagnosis and treatment administration may enable the progression of bone complications and impair quality of life [22,29], as demonstrated in Cases 2 and 5. In case 1, the fatigue may have been related to the high burden of Gaucher cells, as reflected by the elevation of biomarkers (ferritin and chitotriosidase). The etiology of the fatigue in case 3 is unclear.

Conclusion

These five cases illustrate that fatigue may be the main complaint or presenting symptom of patients with GD. A validated tool to assess fatigue in GD should be developed. Providing treatment to patients complaining of fatigue results in multiple benefits, including both patient quality-of-life and clinical benefits.

Funding

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