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Two Sisters with Gaucher Disease: Focus on the Effectiveness of Imiglucerase Treatment: Case Reports

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MC, SG, SA and AT drafted and wrote the manuscript. Authors AMD, OM, MY and AK reviewed and proofread the manuscript. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Gaucher disease is an autosomal recessive lysosomal storage disease caused by beta glucocerebrosidase enzyme deficiency leading glucosylceramide deposition in reticuloendothelial system (RES) cells. Gaucher cell loaded by glucosylceramide usually infiltrates bone marrow, liver, spleen and lymph nodes, causing multisystemic manifestations. Intravenous replacement of enzymes such as velaglucerase alfa, taliglucerase alfa and imiglucerase, which are recombinant

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DNA-produced analogues of human β-glucocerebrosidase, is the main therapy in Gaucher disease. In this report, we presented two sisters diagnosed with Gaucher disease in our clinic and the effectiveness of 4-year imiglucerase treatment was evaluated.

Keywords: Gaucher disease; imiglucerase; pulmonary hypertension.

1. INTRODUCTION

Gaucher disease is an autosomal recessive lysosomal storage disease caused by beta glucocerebrosidase enzyme deficiency leading glucosylceramide deposition in macrophage-monocyte system [1]. Gaucher cells usually infiltrate spleen, liver, bone marrow and lymph nodes [2]. There are 3 clinical subtypes: Type 1 is chronic non-neuropathic type, Type 2 is acute infantile neuropathic type and Type 3 is juvenile or subacute neuropathic type [3]. Its estimated incidence is 1/100,000. Major manifestations are hematological disorders, hepatosplenomegaly and bone lesions. Definitive diagnosis is determined by measuring glucocerebrosidase enzyme activity in leukocytes, while distinguishing clinical sub-types require taking a good clinical history, physical examination and phenotyping. The main treatment of the disease is enzyme replacement therapy [4]. In this report, we aimed to present clinical, laboratory and radiological characteristics of two siblings born to non-consanguineous Turkish parents, who had type 1 Gaucher disease treated by 4-year imiglucerase replacement therapy.

2. PATIENT AND OBSERVATION

2.1 Case 1

40 year-old female patient was admitted to a hospital with growth retardation, fatigue and abdominal distension 28 years ago. Since hepatomegaly, splenomegaly and thrombocytopenia were detected on examination, she underwent bone marrow biopsy which revealed no pathology. Patient's fatigue increased and thrombocytopenia worsened (<50000) and splenectomy was performed at the age of 18 years. Although fatigue improved after splenectomy, her symptoms worsened at the age of 35 years and she was admitted to our clinic with abdominal distension, fatigue, dizziness and difficulty in daily activities. On physical examination, height was 146 cm and weight was 52 kg. She was pale and liver was palpable on the right midclavicular line 6 cm below costal archus. Table 1 presents laboratory findings of the patient. On abdominal ultrasonography, liver size was 280 mm and spleen was not visible (operated). Since peripheral blood smear revealed predominance of leucoerythroblasts, bone marrow biopsy was performed and Gaucher cells were seen. Gaucher disease was definitely diagnosed according to following enzyme levels: beta glucocerebrosidase: 0.35 nanoU (2.4-3.8), B-galactosidase: 128 nmol/s/mgpr (85-145), chitotriosidase: 2950 nmol/hr/ml (normal: <40). Eye movement examination was performed to rule out type 3 Gaucher disease and it was found to be normal. On upper abdominal MRI, craniocaudal size of liver was 285 mm and liver volume was 5370 cm^3 (ml) (normal: 1500-2500). On bone mineral density examination, L1-L4 total T score was -3.3, Z score was -3.2, which was compatible with osteoporosis. Pelvic MRI of the patient showed subchondral cystic degenerative changes and bilateral focal collapse of femoral head consistent with avascular necrosis. Echocardiographic examination revealed ejection fraction of 67%, (normal: >55%), mild tricuspid and mitral insufficiency and pulmonary pressure of 45 mmHg (normal: 15-25). Imiglucerase treatment at a dose of 40 u/kg was initiated after the diagnosis was established and applied every other week. After 4 years follow up, laboratory parameters (hemoglobin, thrombocyte count, liver enzyme levels) of the patient turned to normal levels (Table 1). For re-evaluation of initial mild pulmonary hypertension, echocardiographic examination was performed after 4 years imiglucerase treatment; pulmonary pressure was found to be increased (65 mmHg),but it was measured as 25 mmHg on right heart catheterization. After 4 years ERT, Zimran score of the patient was calculated as 17 (20 at presentation).

2.2 Case 2

36 year-old female patient presented to a hospital with the symptoms of fatigue and abdominal pain 20 years ago. On physical examination, hepatomegaly, splenomegaly and thrombocytopenia were detected. Bone marrow biopsy was performed and it showed no pathology. Since patient's symptoms (fatigue and abdominal pain) got worse and thrombocyte

counts further decreased, she underwent splenectomy when she was 16 years old. Since her symptoms did not subside after splenectomy, she was admitted to our clinic with same complaints. Physical examination revealed that height was 143 cm and weight was 51,5 kg. She seemed pale and liver was palpated on the right midclavicular line 5 cm below costal archus. Table 1 presents laboratory findings of the patient. Abdominal ultrasonographic examination revealed a liver size of 280 mm and spleen was not visible (operated). On peripheral blood smear, lymphocytes (60%) were predominant and thrombocyte count was 70000. On the examination of bone marrow aspiration, 55% lymphocytes, 35% neutrophils, 5% orthocromatophilic erythroblasts, 5% metamyelocytes and 5% monocytes were detected. Micrograph showed crinkled paper macrophages in the marrow space (Fig. 1). Since her family history revealed Gaucher disease, enzyme levels were measured and they were as follows; beta glucocerebrosidase: 0.38 nanoU (2.4-3.8), B-galactosidase: 188 nmol/s/mgpr (85-145), chitotriosidase: 3580 nmol/hr/ml (<40). She was diagnosed with Gaucher disease according to these results. Eye movement examination was normal. Upper abdominal MRI examination revealed liver with a craniocaudal size of 285 mm and liver volume of 4110 cm^3 (ml) (1500-2500). Bone mineral density examination showed an L1-L4 total T score of -2.7 and a Z score of -2.7, indicating osteoporosis. On echocardiographic examination, ejection fraction of 64%, (normal: >55%), mild tricuspid insufficiency and pulmonary pressure of 40 mmHg (normal: 15-25 mmHg) were detected. Imiglucerase treatment at a dose of 40 u/kg was commenced after the diagnosis was established and applied every other week. Laboratory parameters (hemoglobin, thrombocyte count, liver enzyme levels) of the patient turned to normal levels following 4 years follow up period (Table 1). Since she had a mild pulmonary hypertension at the beginning of the treatment, she was re-evaluated with echocardiography after 4 years imiglucerase treatment; pulmonary pressure was found to be increased (60 mmHg). Right heart catheterization was performed and showed a pulmonary pressure of 27 mmHg. Zimran score of the patient was calculated as 12 (17 at presentation) following 4 years ERT.

Table 1. Evaluation before and after 4 years of enzyme replacement therapy

	Case 1		Case 2	
	Pre-treatment	**Post-treatment**	**Pre-treatment**	**Post-treatment**
Leukocyte (4000-10000 /mm^3)	16400	11480	34300	16390
Hemoglobin (12-18 gr/dl)	7.8 gr/dl	13.3	8.5	12.2
Platelet (150000-400000 u/L)	189000	218000	67000	191000
AST (0-34 U/L)	35	25	56	35
ALT (0-42 U/L)	12	12	20	21
ALP (0-125 U/L)	92	85	92	92
LDH (210-425 U/L)	196	190	208	200
Creatinine (0.57-1.11 mg/dl)	0.35	0.48	0.62	0.6
Liver volume (1500-2500 cm^3)	5370	2250	4110	2750
Splenectomy	+	+	+	+
Bone fracture	-	-	-	-
Aseptic necrosis	+	+	-	-
Pulmonary pressure (0-25 mmHg)	45	65	35	60
Zimran score (mild: 0-10, moderate: 10-25, severe: >25)	20	17	17	12

Table 2. Zimran severity score index (Scores of 0-10: Mild disease; 11-25: Moderate disease; >25: Severe disease) [6]

Feature	Detail	Score
Cytopenia	Non-splenectomized	1
	Splenectomized-leukopenia	1
	Splenectomized-anemia	1
	Splenectomized-thrombocytopenia	1
Splenomegaly	None	0
	Mild	1
	Moderate	2
	Massive	3
Splenectomy		3
Hepatomegaly	None	0
	Mild	1
	Moderate	2
	Massive	3
Liver enzymes	Normal	0
	Some abnormal	1
	All abnormal	2
Signs of clinical liver disease		4
CNS involvement		20
Other organ involvement (kidney, lungs or any other)		4
Bone disease –objective findings	No signs	0
	X-ray or nuclear scan abnormality	1
Bone disease –objective findings	No pain	0
	Mild pain	2
	Chronic pain unrelated with fracture	3
Bone fracture	No fracture	0
	Post-traumatic fracture	1
	Pathologic fracture or aseptic necrosis	5

CNS: Central Nervous System

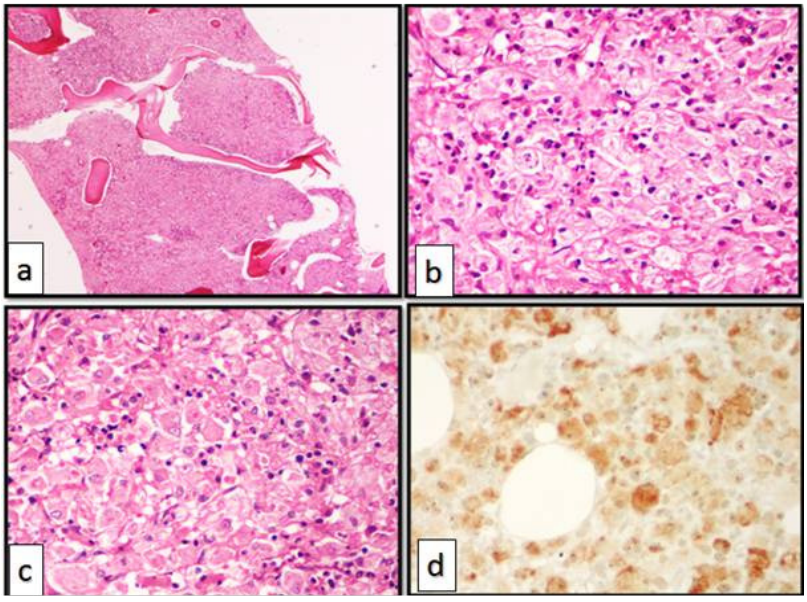

Fig. 1. Infiltrating cells had 'crinkled paper' intracytoplasmic accumulations and histiocytic nature on immunohistochemical examination
(a: H&EX40, b: H&EX200, c: H&EX400, d: CD68X100)

3. DISCUSSION

Ages at the time of presentation (symptoms began at 2nd decade) and clinical manifestations of our two cases were consistent with type 1 chronic non-neuropathic form. During disease process, spleen massively enlarges and sequestrates blood cells; anemia, leukopenia and thrombocytopenia are usually present [2]. Lung involvement may be seen as a result of infiltration of either alveoli, interstitium, bronchi or pulmonary vasculature by the Gaucher's cells [5]. Deficiency of enzyme beta glucocerobrosidase is important for definitive diagnosis. Increased levels of ferritin, serum beta hexosaminidase, plasma angiotensin-converting enzyme, plasma glucocerebroside and decreased levels of plasma cholesterol are other parameters that may help in making the diagnosis [6]. In addition to beta glucocerebrosidase, increased plasma levels of some lysosomal derivated enzymes (beta hexosaminidase, alpha mannosidase, lysozyme, tartarate resistant acid phosphatase) and substances may also be useful to support diagnosis. The most important of them is plasma chitotriosidase activity, which is reported to increase 1000 fold in Gaucher Disease [7]. Enzyme levels of our cases were found to be consistent with the literature. DNA analysis for common mutations of beta glucocerebrosidase gene may be performed for diagnosis and to evaluate other family members. Beta glucocerebrosidase gene may show more than 350 mutations [8]. Genetic *analysis* of our cases demostrated two mutations: c.1226A>G, which is a well-known missense mutation (p.Asn409Ser) and deletion of four nucleotides that leads to a frame–shift and premature stop. Detection of these two mutations confirms Gaucher disease. Zimran disease severity score is used to determine the disease severity, treatment modality and treatment response of patients with Gaucher disease; scores of 0-10 indicate mild disease, scores of 11-25 indicate moderate disease, while the patients with a score of >25 are accepted to have severe disease (Table 2) [6]. Zimran score of our first case was 20 (moderate severity), while it was 17 (moderate severity) for the second case. Enzyme replacement is the main treatment (velaglucerase alfa, taliglucerase alfa, imiglucerase). Initial dose given in enzyme replacement therapy should be individualized according to the age at the time of presentation, the area involved, extent of the disease and the presence or absence of irreversible pathology [1,2]. In recent years, substrate reduction therapy (SRT) has been introduced as an alternative treatment modality. SRT blocks the synthetic pathway of glucosylceramide. Miglustat, the first SRT approved for Gaucher disease, is used in the patients who are not candidates for ERT because of its tolerability profile [9]. Eliglustat tartrate is a new SRT and acts as a specific and potent inhibitor of glucosylceramide synthase [10]. 16 In our cases, 40 u/kg imiglucerase therapy was given every other week. for 4 years. After 4 years follow up, laboratory parameters (hemoglobin, thrombocyte count, liver enzyme levels) of both cases turned to normal levels (Table 1). Mild initial pulmonary hypertension detected echocardiographically in both cases was re-evaluated after 4 years imiglucerase treatment; pulmonary pressures of both cases were found to be increased (65 mmHg for the first case, 60 mmHg for the second case), but the values measured on right heart catheterization were 25 and 27 mmHg, respectively. Pulmonary arterial hypertension may be idiopathic or secondary to other conditions including connective tissue diseases, HIV infection, congenital systemic to pulmonary shunts, portal hypertension and use of some drugs such as appetite suppressants [11]. Pulmonary hypertension is rarely seen in non-neuronopathic type 1 Gaucher disease [12] and may be either primary or secondary. Pulmonary hypertension in Gaucher disease may be related to various mechanisms such as vascular infiltration of Gaucher cells causing obliteration or plugging of capillaries [13]. However, pulmonary hypertension may be more common in patients with severe type 1 Gaucher's disease, which may diminish by a right-to-left shunt in the pulmonary vasculature. Enzyme therapy may close these shunts, which ends up with increased pulmonary arterial pressure [14]. Idiopathic pulmonary arterial hypertension has been found to be more common among splenectomized patients, suggesting a link between splenectomy and this rare vascular condition [13]. Asplenia is strongly associated with severe forms of pulmonary hypertension in GD. Removal of the primary reservoir of storage cells causes excessive accumulation of storage cells in lung tissue [15]. Elstein et al. [16] studied 134 adults with type 1 Gaucher disease (only 73 of the patients were on replacement therapy) with serial echocardiography and detected pulmonary hypertension in 9 of the patients (all were on ERT). Only 6 of these 9 patients were splenectomized. It is unknown whether disease severity or splenectomy is related to the development of pulmonary hypertension

in patients receiving enzyme replacement therapy.

4. CONCLUSION

In our cases, the question of whether pulmonary hypertension was a complication of treatment, asplenia or related to continuing disease process unresponsive to therapy was of practical importance: if it is a treatment complication, treatment should be discontinued, however, if it is due to underlying disease, therapy should be continued and dose increment may be considered. In these situations, the severity of pulmonary hypertension is important. In Gaucher disease, echocardiography should be performed once per year for follow-up of pulmonary hypertension. We also evaluated our patients every year by echocardiography and detected pulmonary hypertension in the 4th year of the treatment, which was considered to be inconsistent with clinical conditions of the patients. We then performed right heart catheterization, a more sensitive method, to make the decision of treatment continuation and detected no severe pulmonary hypertension that warrants treatment discontinuation. As a result, we suggest that right heart catheterization should be considered when echocardiographic findings are indecisive and clinically irrelevant.

CONSENT

All authors declare that written informed consent was obtained from patients for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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