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Short Communication

Coexistence of Gaucher Disease and severe congenital neutropenia

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ABSTRACT

Gaucher Disease (GD) is the most common lysosomal storage disorder has traditionally been classified into three clinical phenotypes. Type 3 GD is characterized by neurological involvement but neurological symptoms generally appear later in life than in type 2 disease. Neutropenia is much rarer than other hematological manifestations in GD and has not been scrutinized adequately. Severe congenital neutropenia (SCN) is a rare disease entity which is characterized by a paucity of peripherally circulating neutrophils with arrest of neutrophil maturation at the promyelocyte stage and consequent increased susceptibility to severe and recurrent infections. We report a patient who presented in the first year of life with visceral involvement and severe neutropenia in whom the propositus had a unique coexistence of Gaucher Disease and severe congenital neutropenia associated with a mutation in HAX1. In contrast to his expired siblings he had experienced no severe infections. These clinical observations suggest that enzyme replacement therapy may display a modulating factor with respect to the clinical course of SCN.

Synopsis: Our patient is the only report of the combination of Gaucher Disease and Kostmann Syndrome in the literature. The clinical course of our patient is not severe when comparing with exitus siblings and other Kostmann Syndrome patients. But when considering the patient's only clinical difference is ERT, this case is very important to emphasise the role of enzyme replacement therapy in bone marrow.

1. Introduction

Gaucher Disease (GD) is an autosomal recessive lysosomal storage disorder, in which a deficiency of the enzyme glucocerebrosidase leads to the accumulation of glucocerebroside in the lysosomes of monocytes and macrophages. The disease has traditionally been classified into three clinical phenotypes: type 1 – adult, non-neuronopathic; type 2 – an infantile or acute neuronopathic form (rapidly progressive neurovisceral storage disease, with death during infancy); and type 3 – a juvenile or chronic neuronopathic form (less rapidly progressive neurovisceral storage disease). Hepatosplenomegaly and pancytopenia are typical for all types [1].

Genotype-phenotype correlations in GD are poor, although various mutations are known to predispose to certain disease type [2]. The presence of the N370S mutation on one or both alleles is thus associated with type 1 disease. The presence of the L444P/L444P or D409H/D409H (c.1342 G > C) mutation is associated with the development of neurological manifestations at some time during the subject's life. Mean age at diagnosis in patients who are homozygous for the L444P mutation is 2.3 years, and type 3 is dominant (75% of cases) [3,4].

Severe congenital neutropenia (SCN) is a heterogeneous group of diseases progressing with arrest of maturation in bone marrow. It is characterized by recurring skin, lung, and deep tissue infections from the first months of life [5]. Clinically, SCN is characterized by a paucity of peripherally circulating neutrophils with arrest of neutrophil maturation at the promyelocyte stage and consequent increased susceptibility to severe and recurrent infections. SCN also exhibits genetic heterogeneity. Inheritance may be autosomal dominant, autosomal recessive, X-linked or sporadic [6]. Historically, ELANE is the gene responsible for the first identified SCN. However, ELANE gene defect was not determined in the Kostmann family in which the disease was identified, and the HAX1 gene has been found in studies of Swedish and Turkish patients [7]. ELANE defect is inherited in an autosomal dominant manner, and the autosomal dominant form is more common

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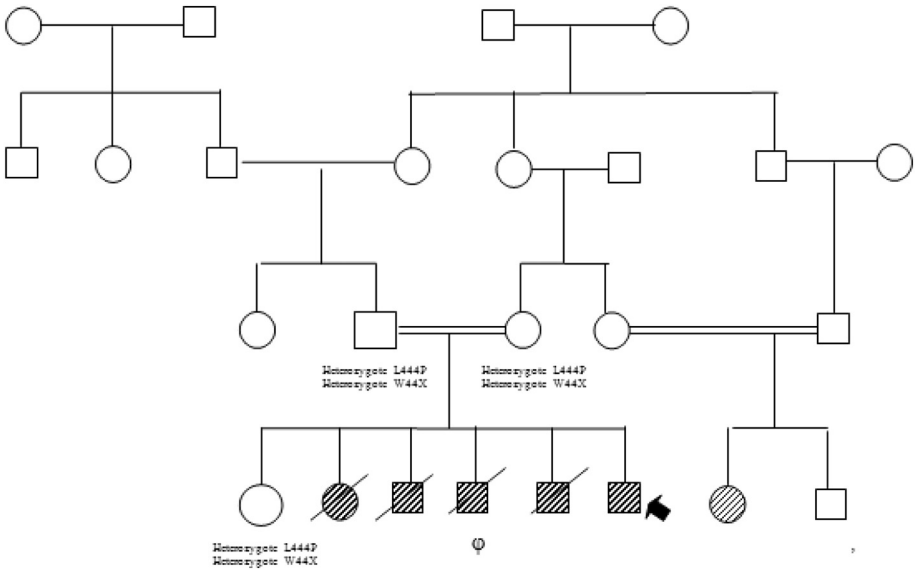

Fig. 1. Family pedigree; φ: the sibling who was diagnosed as Gaucher Disease and died in 39 months of old.

Table 1
Family history.

	Proband	Sibling 1	Sibling 2	Sibling 3	Sibling 4
Gender	Male	Male	Male	Male	Female
Age of manifestation	Neonatal period	Neonatal period	2 months	4 months	Neonatal period
Hepatosplenomegaly	+	+	+	+	+
Nervous system involvement	−	+ Intractable convulsions	−	+ Intractable convulsions	+ Intractable convulsions
Infections	Recurrent bacterial pneumonia and anal abscess	Recurrent pneumonia	Recurrent pneumonia Anal abscess	Early neonatal sepsis	Pneumonia Anal abscess
Neutrophil count	100–300 (before c-GSF)	< 100	100–500	Unknown	100–500

worldwide However, SCN associated with autosomal recessively inherited HAX1 gene defect is more frequent in Europe, probably due to the presence of migrants of Turkish and Arab origin [5]. The HAX-1 gene encodes HCLS1-associated protein X-1. HCLS1-associated protein X-1 is principally present in the mitochondrial membrane, and also in the nuclear membrane and endoplasmic reticulum. It controls the integrity of mitochondrial membrane protein and protects myeloid cells against apoptosis [8].

GH and SCN are rare diseases that both affect hematopoietic cells. To the best of our knowledge, no case of comorbid GD and SCN has to date been described in the literature. We report a case of Gaucher Type III disease and SCN associated with a mutation in the HAX1 gene.

2. Case report

The patient was referred to us at 4 months of age because of anemia and neutropenia. He was born prematurely in the 32nd gestational week with a birth weight of 1660 g. His complex previous history was remarkable for admission to the neonatal intensive care unit at another hospital due to premature delivery and recurrent severe infections during hospitalization. The family history revealed that he was born from a first-degree consanguineous marriage between healthy parents, with four siblings with a history of mortality (family pedigree shown in Fig. 1 and sibling history is detailed in Table 1).

At physical examination the patient weighed 5400 g (3–10th percentile), height was 56 cm (3–10th percentile) and his head circumference was 41 cm (25th percentile). His neurodevelopmental milestones were head control in the 1st month. In the follow-up period he was able sit unsupported at 5 months and to speak single words at 12 months. His liver was palpable 2 cm from the costal margin, and no splenomegaly was present. Apart from these findings, his physical examination was normal.

His initial laboratory tests revealed severe neutropenia [absolute neutrophil count (ABC) 230/μL] and anemia (Hb: 5.8 g/dL). No thrombocytopenia was present. Acute phase reactants were within normal limits. Serological investigations for infectious diseases were also normal. GD was suspected on the basis of the previous family history. His beta glycosidase enzyme level was very low for his age (0.13 nmol/mL/h). Molecular screening of the GBA gene revealed L444P homozygote substitution, and Gaucher Type III was diagnosed. Parents of the proband were found as heterozygous carriers for L444P variant. Enzyme replacement therapy (imiglucerase - 120 IU/kg/dose) was initiated. During 6-month follow-up with ERT, the anemia improved, but persistent severe neutropenia without evidence of oscillation with a maximum ANC of 0.3×10^9/L was observed.

Bone marrow findings showed early-stage maturation arrest of myelopoiesis (cellularity 80%–100%, myeloblasts 3.0%, promyelocytes 0.7%, myelocytes 2.2%, metamyelocytes 0.5%, band neutrophils 0.2%, and segmented neutrophils 0.0%), with an M:E ratio of 0.43:1. Cytogenetic results from the bone marrow were normal. Congenital neutropenia was suspected in the light of the patient's and siblings' medical histories and bone marrow findings. Molecular study revealed a homozygous single-nucleotide insertion (position 130-131insA) leading to a premature stop codon (W44X) in the HAX1 gene. Molecular investigation of the proband's parents confirmed carrier status for the mutation W44X. Electropherograms of the patient's and parents' Sanger sequencing pattern for HAX1 and GBA variants are shown in Fig. 2.

Our patient was given G-CSF therapy at 5 μg/kg/dose, three times a week. ANC count was initially monitored weekly, and then monthly, and was kept above 1000×10^9/L (Fig. 3).

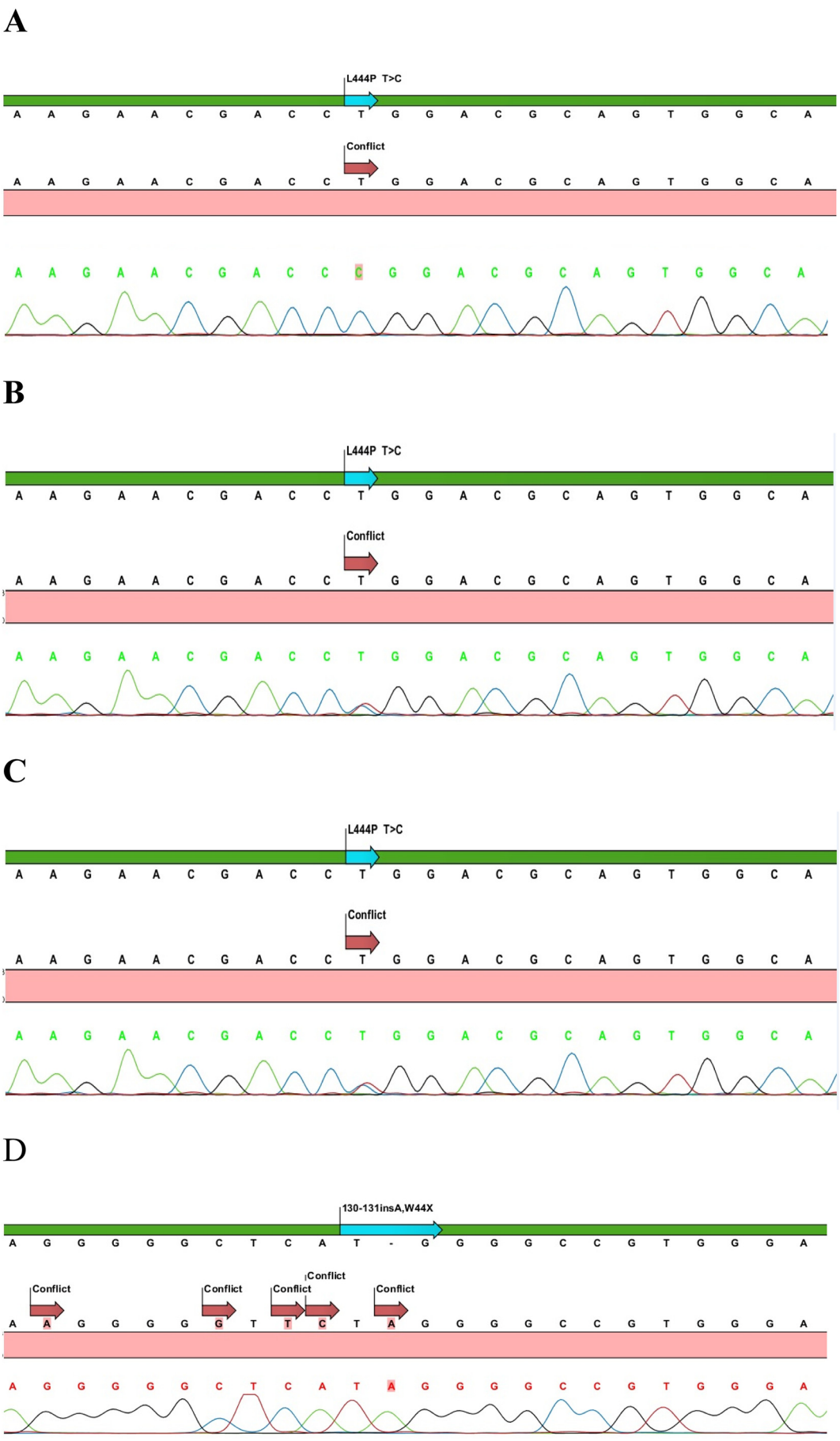

Fig. 2. Electropherogram images of GBA variants of proband (A), father (B), mother (C) and HAX1 variants of proband (D), father (E), mother (F).

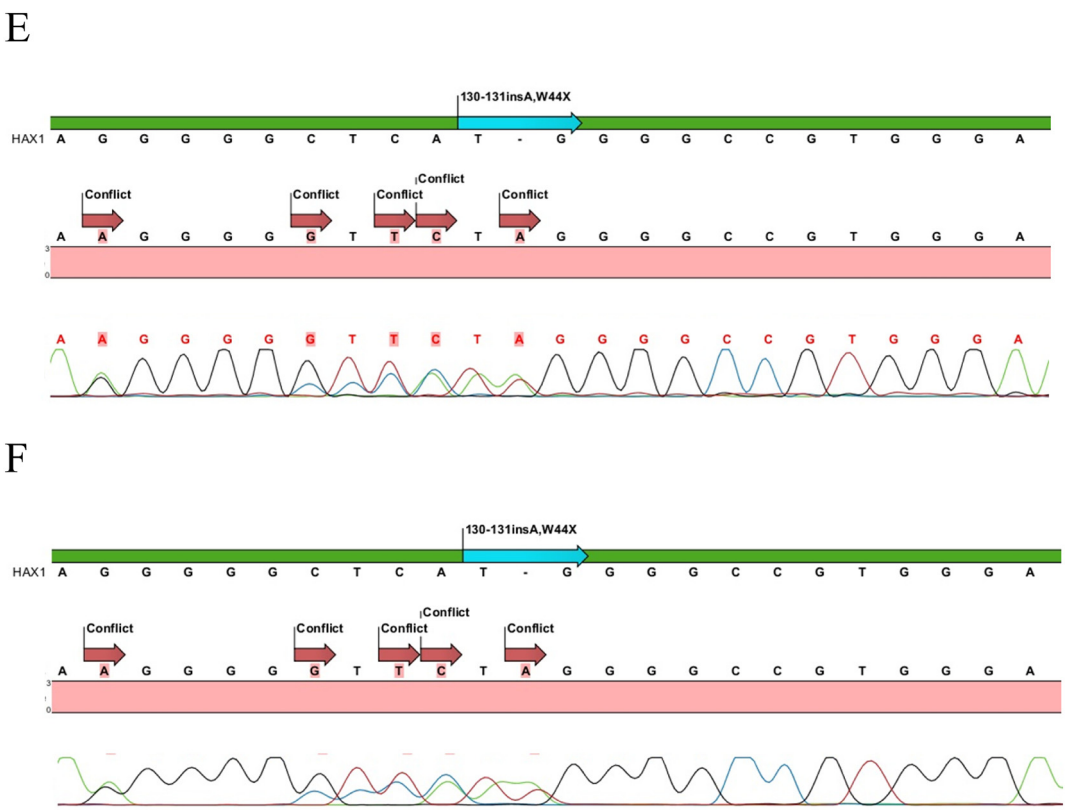

Fig. 2. (*continued*)

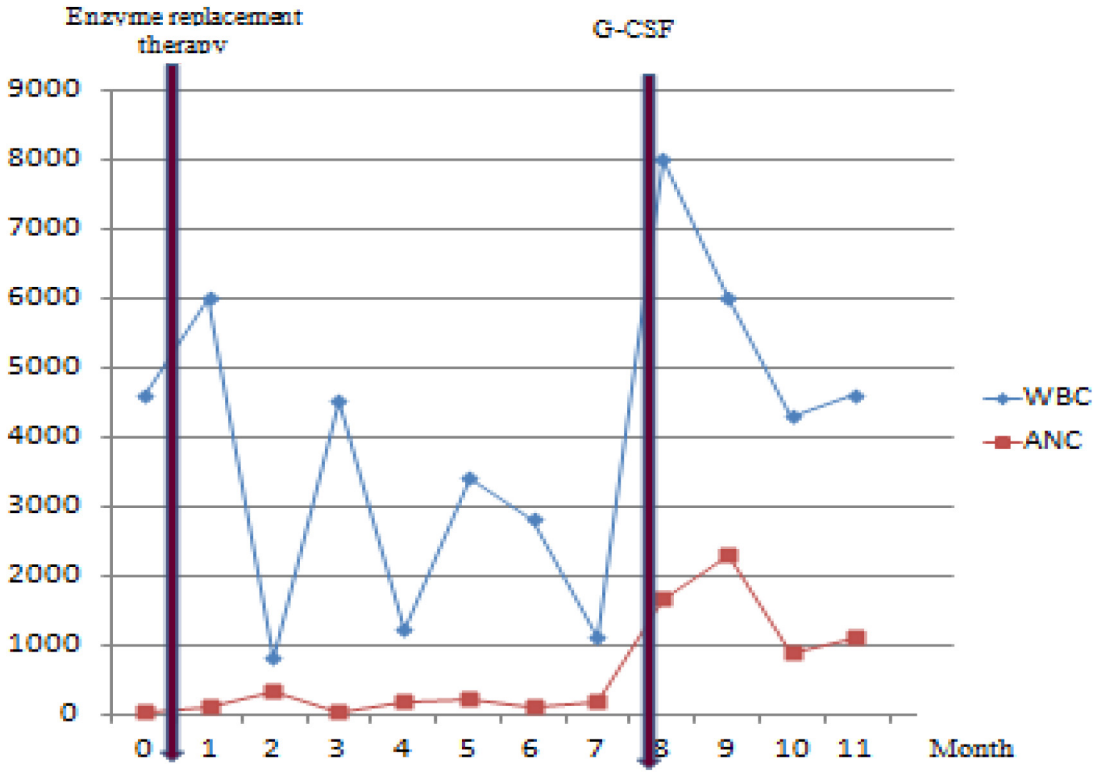

Fig. 3. Change in the peripheral blood count after enzyme replacement therapy and then after subcutaneous injections of 15 μg/kg of G-CSF (arrows). ANC, absolute neutrophil count; WBC, white blood cells.

Neurologic examination revealed no regression during the course of follow-up. MRI of the brain and magnetic resonance spectroscopy were normal. Electroencephalography revealed no abnormalities.

3. Discussion

SCN has recently been recognized as a genetically heterogeneous disorder with multiple modes of inheritance, including autosomal recessive, autosomal dominant, X-linked and sporadic transmission [9]. Mutations associated with SCN have been identified in HAX1, ELA 2, GFI1, WAS, CSF3R and G6PC3 [10]. While the majority of patients with autosomal dominant or sporadic SCN bear heterozygous mutations in the neutrophil elastase (ELA-2/ELANE) gene [11], biallelic mutations in the gene encoding the antiapoptotic protein HS1-associating protein X-1 (HAX-1) can cause autosomal recessive SCN in approximately 15% of SCN patients [7,8]. HAX-1 is a ubiquitously expressed predominantly mitochondrial protein involved in signal transduction and organization of the cytoskeleton [12]. Most HAX1-deficient patients identified to date have exhibited the p.Trp44X mutation, and their phenotype appears to be limited to neutropenia. However, HAX1 deficiency may also cause a phenotype in the nervous system, ranging from mild cognitive defects to severe developmental delay and/or epilepsy in addition to congenital neutropenia [13]. Recent studies have revealed the existence of several transcript variants of HAX1. Genotype–phenotype studies have shown that HAX1 mutations affecting both isoforms A and B are associated with neurological involvement, whereas mutations affecting only isoform A cause SCN without neurological abnormalities [14,15].

Our patient's HAX1 mutation (W44X) is known to affect only isoform A, and neurological abnormalities will not therefore be expected [14,15]. However his form of GD (type III) also requires neurological monitoring. Neurological examination, eye movement examination, neurophthalmological examination, brain imaging by MRI, electroencephalography and neuropsychometric tests were normal and supported our thesis.

The absence during diagnosis of hepatosplenomegaly and thrombocytopenia may be regarded as an important phenomenon in terms of our patient's clinical manifestation. Hepatosplenomegaly is seen in 90% of GD patients at time of diagnosis [16]. Hepatosplenomegaly is inevitable in the homozygous L444P mutation phenotype determined in our patient's GBA1 gene analysis. Considering the presence of clinical variations among patients with congenital neutropenia associated with HAX1 defect in our patient and the non-surviving siblings, and even in the previous literature, we think that our patient's findings are a modifying factor. Therefore, although we found no scientific evidence of a relation between both genes and protein, we think that homozygous HAX1 mutation modifies the GD phenotype, and that the pathogenic L444P variant in the GBA1 gene modifies the clinical manifestation of congenital neutropenia in association with the HAX1 gene defect.

Neutropenia in GD has not been the subject of sufficient research to permit diagnosis. However, our patient's most prominent laboratory parameter was neutropenia. There is some information in the literature about severe neutropenia in GD, but this is not as detailed as in the case of anemia or thrombocytopenia. Leukopenia in GD may occur secondary to infiltration of bone marrow Gaucher cells and/or hypersplenism. There is an apparent increased tendency toward infections in patients with GD, but this is primarily because of defective neutrophil function in many of these patients, rather than of decreased absolute neutrophil numbers. This defect will self-correct together a decrease in the tendency to infections with the advent of enzyme therapy [17,18], possibly due to correction of abnormalities in neutrophil chemotaxis [19]. Our patient was started on ERT (Imiglucerase) in the 5th month of life. ERT has been administered to GD patients for several years. The Gaucher Registry summarized the effects of 2–5 years of treatment on specific manifestations of type 1 GD. Anemic patients exhibit an increase in hemoglobin concentrations to normal or near-normal levels within 6–12 months, with a sustained response over 5 years. Thrombocytopenia in patients with intact spleens responds most significantly during the first 2 years, with slower improvement thereafter. Limited data are available concerning the effects of ERT on leucopenia and neutropenia. Nonetheless, evidence exists that that WBC counts increase during ERT [20]. Our patient's anemia improved very rapidly after commencement of ERT. In contrast, and as described earlier, neutropenia did not respond. We attribute this lack of response to the neutropenia being caused not by GD, but rather by SCN. Therefore, when persistent neutropenia is seen in GD patients, and neutropenia fails to respond to ERT, congenital neutropenias should be considered, no matter how rare these may be. Until recently, it was thought that the effects of macrophages were responsible for the entire pathophysiology of GD. Recently, however, it has been realized that the effects of several immune cell types and even immune functions are also involved.

Although studies have investigated the effect of the immune system in GD, there has been insufficient research into the underlying molecular basis [21]. However, immune cells exhibit organ-specific dysfunction. In addition, impairment in T-cell maturation, abnormal B-cell augmentation, and increased antigen presentation are also seen. Hannun et al. attributed this to the antiproliferative effects of abnormal sphingoid accumulation [22]. From that perspective, we still do not know whether the effects of accumulating sphingolipids on the immune system also caused a change in the SCN manifestation in our patient. The male Gaucher patient described in this report exhibited no typical clinical manifestations of SCN. The only alarming finding was severe neutropenia that could not be raised above 300/μl, but which may also be considered a finding of the hematological spectrum of GD. It is important to reconsider SCN in case of recurrent bacterial infections and neutropenia.

Following diagnosis and initiation of ERT for Gaucher Type III, our patient experienced only one febrile episode during follow-up, and no increase in acute phase reactants was observed. Our patient's clinical course was much less severe, particularly in terms of recurrent infections, in comparison with the non-surviving siblings with GD and probably SCN. This suggested that ERT exerted a modifying effect. The mechanism involved in this modifying effect of ERT is very difficult to explain. However, the effect of ERT may be exerted not on the neutrophil directly, but rather on either a chemokine or even on monocytes/macrophages whose function may be impacted by GD [23] especially during the months prior to starting G-CSF when ANC continued to be dangerously low despite ERT.

While the idea that ERT has a modifying role on SCN clinical findings may appear unexpected, since ERT represents the only clinical difference between our patient and the non-surviving siblings with probable SCN + GD, it is very difficult to explain the clinical results of the patient's upturn for SCN in the light of the current literature.

Our patient is now 3 years old, and we have been monitoring him for 32 months; he has no neurological symptoms and has experienced only one febrile attack, which was not associated with increased acute phase reactants.

This report describes and discusses a patient with GD Type III and SCN by evaluating his clinical characteristics in the light of the current literature. To the best of our knowledge, this is the only report to date of comorbid GD and Kostmann syndrome.

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