

Severe Congenital Neutropenia in 2 Siblings of Consanguineous Parents. The Role of *HAX1* Deficiency

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■ Abstract

Severe congenital neutropenia (SCN) is a rare primary immunodeficiency disease that is characterized by persistent severe neutropenia and severe early-onset bacterial infections. We report the case of 2 siblings with SCN who were the children of consanguineous parents. The *HAX1* mutation was identified in both siblings.

Both patients suffered from oral ulcers, candidiasis, respiratory tract infections, and diarrhea. A bone marrow biopsy, performed to determine the cause of their persistent severe neutropenia, revealed myeloid maturation arrest; thus confirming the diagnosis of SCN. Granulocyte colony-stimulating factor and prophylactic antibiotics were started. A molecular study revealed a homozygous W44X mutation of the *HAX1* gene in both cases.

HAX1 deficiency should be considered in any child with severe infections and neutropenia, especially in children of consanguineous parents. Early diagnosis and appropriate treatment could prevent complications in this group of patients.

Key words: Severe congenital neutropenia. *HAX1*. Mutation. Infection.

■ Resumen

La neutropenia congénita grave (NCG) es una rara inmunodeficiencia primaria que se caracteriza por una neutropenia grave persistente e infecciones bacterianas de aparición precoz. Comunicamos el caso de 2 hermanos con NCG que eran hijos de padres consanguíneos. Se identificó la mutación *HAX1* en ambos hermanos.

Los dos pacientes sufrieron de úlceras orales, candidiasis, infecciones del tracto respiratorio y diarrea. Una biopsia de la médula ósea para determinar la causa de su neutropenia grave persistente reveló un arresto de la maduración mieloide, confirmando así el diagnóstico de NCG. Se inició tratamiento con factor estimulador de colonias granulocíticas y antibióticos profilácticos. Un estudio molecular reveló homocigosis de la mutación W44X del gen *HAX1* en ambos casos.

La deficiencia *HAX1* debería considerarse en cualquier niño con infecciones graves y neutropenia, especialmente en niños con padres consanguíneos. Un diagnóstico precoz y un tratamiento apropiado podría prevenir complicaciones en este grupo de pacientes.

Palabras clave: Neutropenia congénita grave. *HAX1*. Mutación. Infección.

Introduction

Severe congenital neutropenia (SCN) is a rare disorder of myelopoiesis, and is characterized by an increased risk of severe bacterial infections in childhood and persistent severe neutropenia due to maturation arrest at the promyelocytic-

myelocytic stage [1-4]. SCN is a rare primary immunodeficiency disease with a frequency of 1-2 cases per million people [1,4,5].

SCN is genetically heterogeneous, and different forms of inheritance, including autosomal dominant, autosomal recessive, X-linked recessive, and sporadic forms have been

reported [1,4]. Heterozygous mutations of the *ELA2* gene cause autosomal dominant and sporadic forms of SCN [6,7], while homozygous mutations of the *HAXI* gene cause the autosomal recessive form [8]. Mutations in other genes, such as growth factor-independent 1 (*GFI1*), Wiskott-Aldrich syndrome gene (*WAS*) and glucose-6-phosphatase catalytic subunit 3 (*G6PC3*), can also cause other forms of SCN [9-11].

Patients with SCN typically experience their first manifestations, such as abscesses, oral ulcers, respiratory tract infections and diarrhea, during the first year of life [1,4]. However, they can also experience other manifestations, which may be associated with different genotypes [12-14].

We describe SCN in 2 siblings from consanguineous parents, and analyze the role of the *HAXI* mutation in their disease.

Case Description

The first patient was a 10-year-old boy, the first child of consanguineous parents (Figure 1), who was referred to our hospital at the age of 6 months with oral candidiasis that had been present since infancy and neutropenia. He was observed to have severe neutropenia when he was admitted for surgery for a left inguinal hernia 1 month before referral. He was admitted again for surgery for a right inguinal hernia 5 months later, when was shown to have severe neutropenia with an absolute neutrophil count of 245/ μL (white blood cells, 4900/ mm^3 ; neutrophils, 5%; lymphocytes, 78%; monocytes, 15%; eosinophils, 6%) (Figure 2). Analysis of bone marrow aspirate revealed myeloid maturation arrest, which confirmed the diagnosis of SCN. Recombinant human granulocyte colony-stimulating factor (G-CSF) was administered. Trimethoprim-sulfamethoxazole was also prescribed as

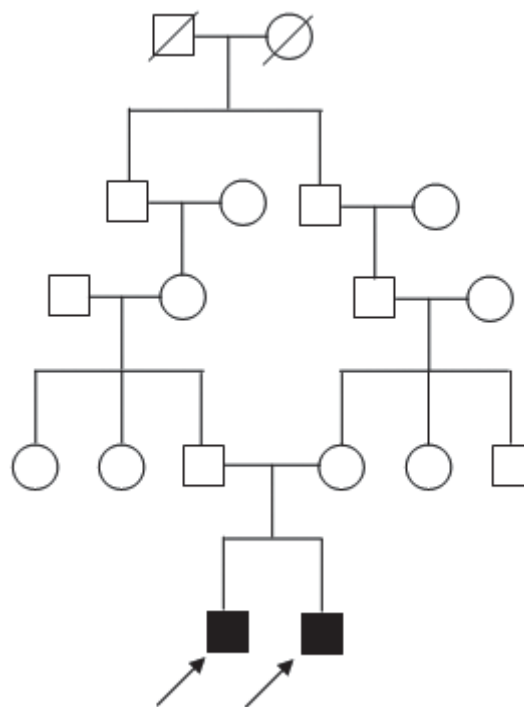


Figure 1. Pedigree showing healthy individuals (open shapes), affected patients (filled shapes), and deceased individuals (shapes with slashes). Boxes indicate males; circles, females.

prophylaxis. Although it was recommended that the patient have regular check-ups, he did not attend our center for follow-up till the age of 6 years, when he experienced pneumonia and

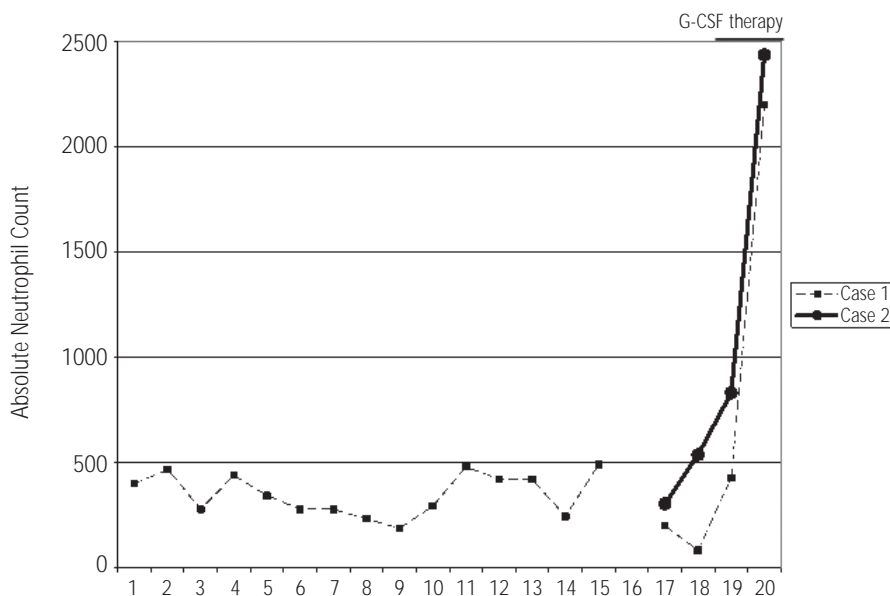


Figure 2. Absolute neutrophil count, cells/ μL .

acute diarrhea. The complete blood count at that time showed severe neutropenia with an absolute neutrophil count of 200/ μL and monocytosis (white blood cells, 4000/ mm^3 ; neutrophils, 5%; lymphocytes, 48%; monocytes, 30%; eosinophils, 16%) (Figure 2). He also had a history of oral ulcers during these years. Hepatomegaly was confirmed by abdominal ultrasonography, although splenomegaly was not detected. Radiography revealed peribronchial thickness and severe chronic sinusitis. Antibiotics and G-CSF were started and the patient was discharged in good health.

The patient's 9-month-old brother was the second child of the family, and had a history of recurrent infections. He experienced mild upper respiratory tract infections at the age of 4 months, and was admitted to hospital 2 months later because of otitis media and pneumonia, which were treated with antibiotics. He experienced another episode of pneumonia and was referred to our center with severe neutropenia (absolute neutrophil count, 305/ μL) (Figure 2), high fever, diarrhea, oral ulcers, and candidiasis. In addition to G-CSF therapy and antibiotics, he underwent surgery for a perianal abscess 1 month later. A bone marrow biopsy revealed myeloid

maturation arrest, and the patient was diagnosed with SCN. He also experienced an episode of febrile seizure with no distinct pattern.

Both patients are receiving G-CSF and prophylaxis with trimethoprim-sulfamethoxazole. They appear well nourished and their weight and height are within the normal range. They have had no serious infectious complications, except oral ulcers and candidiasis.

A recent molecular study sequenced the *ELA2*, *HAX1*, and *CSFR3* genes. A homozygous single-nucleotide insertion (position 130-131insA) leading to a premature stop codon (W44X) in the *HAX1* gene was detected for both patients (Figure 3). There were no somatic mutations in the *ELA2* and *CSFR3* genes.

Discussion

HAX1 deficiency is an autosomal recessive form of SCN that can be observed in children of consanguineous parents. The family history of our patients suggests a genetic pattern of autosomal recessive SCN. More than half of the cases with SCN in our region are from children of consanguineous parents [3] (this rate is much higher than in children from nonconsanguineous parents). Although consanguinity is common in our region, public education programs and facilities for genetic counseling are necessary [15].

Patients with SCN usually experience the first clinical manifestations in early infancy. Recurrent severe infections are the main manifestation, although oral ulcers and neurological manifestations have been observed. The second patient experienced one episode of seizure. Although the R86X mutation of *HAX1* was first described in association with neurodevelopmental delay and epilepsy [13,16], it seems that other mutations in this gene, such as the Q190X mutation, could lead to neurological disorders [17,18]. However, there was no evidence of neurological disease in patients with the W44X mutation [17].

The first patient in this report also had a history of bilateral inguinal hernia, which, although common in the general population, is unusual in this group of patients; however, this does not seem to be related to the mutation detected. *HAX1* deficiency could expose connective tissue, ligaments, and aponeuroses, although this seems unlikely in our case, as no evidence of connective tissue disorder has been shown in patients with *HAX1* mutations. Therefore, this could be considered a new phenotype of SCN or a coincidental finding.

Finally, SCN should be considered in children with severe infections and neutropenia. A delay in diagnosis could lead to chronic infection, irretrievable end-organ damage, and even death.

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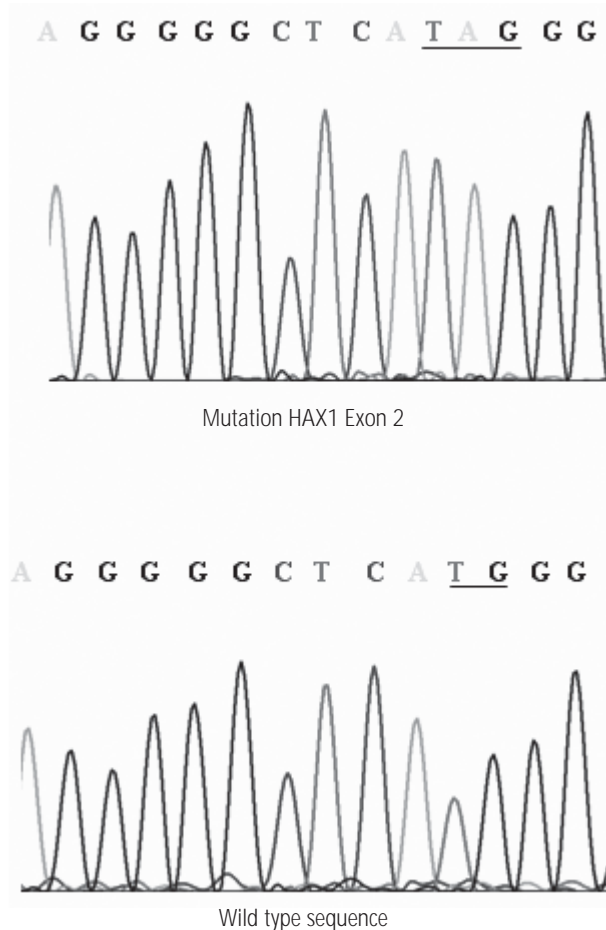


Figure 3. A homozygous single-nucleotide insertion (position 130-131insA) leading to a premature stop codon (W44X) in the *HAX1* gene.

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