CASE REPORT
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Single Mutation Different Clinical Findings: IGLL1 Defect

Sezin Naiboğlu[1], Alper Gezdirici[2], Selami Ulaş[1], Işılay Turan[1], Mehmet Halil Çeliksoy[1], and Çiğdem Aydoğmuş[1]

[1] Pediatric Allergy and Immunology Clinic, University of Health Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey
[2] Department of Medical Genetic, University of Health Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey

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ABSTRACT

Agammaglobulinemia is a rare inherited immunodeficiency disorder characterized by low or absent B cells with absent immunoglobulins. While X-linked agammaglobulinemia (XLA) is the most common type other genetic forms of agammaglobulinemia have been identified. During early childhood, passively transferred maternal Immunoglobulin G protects against various infections. The depletion of these antibodies begins between 6 and 12 months of age, resulting in recurrent sinusitis, bronchitis, and pneumonia in children with X-linked agammaglobulinemia. However, less common autosomal recessive forms of agammaglobulinemia present with more severe clinical features, leading to earlier diagnosis. Herein we present the case of a two-month-old male with IGLL1 gene defect and different clinical findings of family members with the same mutation.

Keywords: Agammaglobulinemia; Autosomal recessive; Children; Non-bruton type

INTRODUCTION

B cells are generated from hematopoietic stem cells in the bone marrow. Various signals originating from the bone marrow, the microenvironment, and interaction with antigen and T cells play an important role in B cells generation. Interruptions and/or changes to the steps involved in B cells generation may halt immunoglobulins production, resulting in immune deficiency.[1-5]

Agammaglobulinemia develops due to a mutation in the Bruton Tyrosine Kinase (BTK) gene, which has X-linked inheritance, in 85% of the cases, and a defect in the autosomal recessive IGHM, CD79A, CD79B, IGLL1, BLNK, LRRC8A and PIK3R1 genes in 15% of the cases.[1-5]

Corresponding Author: Sezin Naiboğlu, MD
Pediatric Allergy and Immunology Clinic, University of Health Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey. Tel: (+90 506)9613736, Email: sezin_ctnol@hotmail.com

Common findings in both X-linked agammaglobulinemia (XLA) and autosomal recessive agammaglobulinemia (ARA) are absence of B cells in peripheral blood and recurrent bacterial infections. In XLA, clinical manifestations appear within the first 5 years of life, whereas in ARA, they appear in early infancy and progress more rapidly. Therefore, genetic analysis is important in diagnosis.[1-3]

The present study aims to describe the case of a Turkish patient with IGLL1 gene deficiency and his family based on the literature available at the time.

CASE REPORT

A two-month-old male case presented herein was born weighing 2250 g at the 36th gestational week as one of the twins of a consanguineous marriage. He was treated for congenital pneumonia and meconium plug syndrome in the neonatal period. He was admitted to the hospital when he was two months old due to

symptoms of lower respiratory tract infection (LRTI). In physical examination, his body temperature was measured at 38°C, he was tachypneic, and crepitant rales were detected in both lungs. He was hospitalized and started antibiotic therapy. Laboratory tests indicated his normal complete blood count and high acute phase indicators. Pneumonic infiltration was detected in the lower zone of the right lung on the chest X-ray. The sweat test was normal. Serum immunoglobulin levels were measured due to the patient's second lower respiratory tract infection. The results showed agammaglobulinemia, so he was tested further. Considering that CD19 and CD20 were<1% in lymphocyte subgroup analysis, a preliminary XLA diagnosis of was made. Accordingly, he was started on intravenous immunoglobulin replacement therapy at a dose of 0.4-0.6 g/kg every 3-4 weeks, and further genetic analyses were performed. Other male members of the family were invited to the hospital for examination and screening tests. The results of the complete blood count, immunoglobulins blood test and lymphocyte subgroup analyses of both brothers were found to be within the normal range as per their age. Upon the detection of homozygous IGLL1 defect (c.258delG) in the genetic analysis of the patient, genetic analysis was requested from all family members. Consequentially, it was determined that the father and both brothers had heterozygous defect in IGLL1 gene, whereas the mother and 9-year-old sister had homozygous IGLL1 defect (Figure 1).

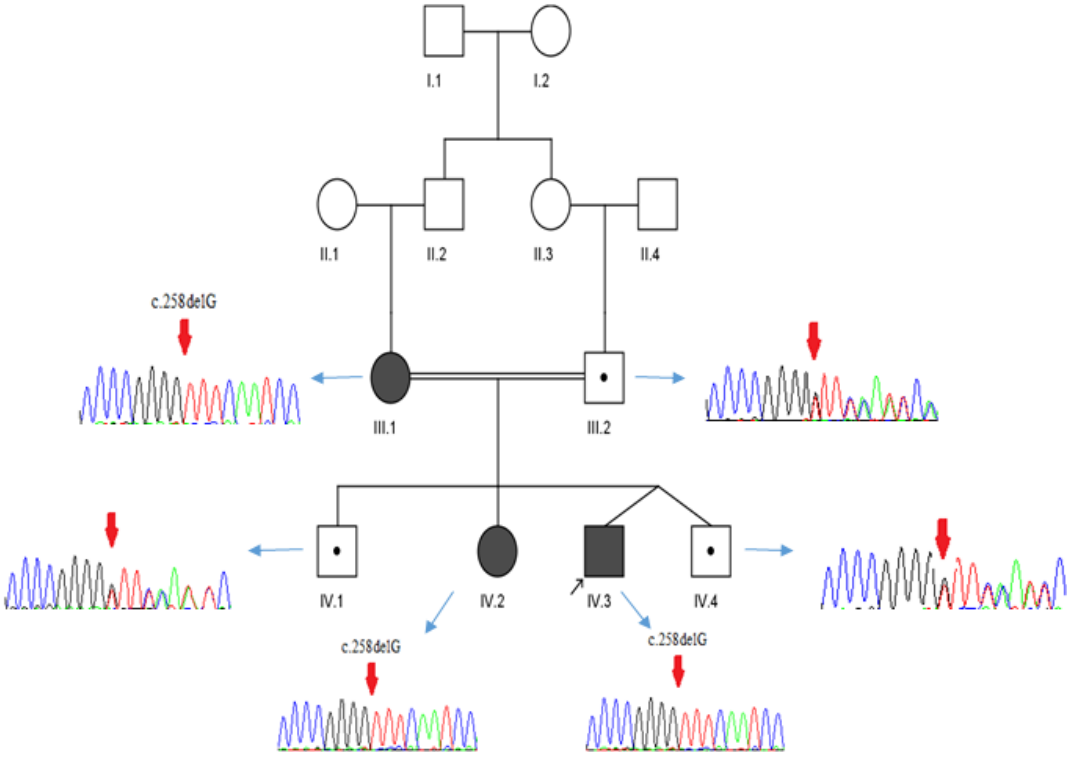

Figure 1. Pedigree of the Family. IV-3 is proband. III-1 and III-2 are the parents. Sanger sequencing of the family showed the c.258delG on the IGLL1 gene in a homozygous state in the proband (IV-3), elder sister (IV-2) and mother (III-1). Father (III-2) and other siblings (IV-1, IV-4) has heterozygous state.

Therefore, the complete blood count, immunoglobulins and lymphocyte subgroup analyses of the mother and sister were requested. The physical examination of the 9-year-old sister revealed that she had no history of hospitalization or serious infection, though she had the homozygous mutation. The 34-year-old mother indicated that both had palpable lymph nodes and normal tonsils. Additionally,

laboratory tests revealed that the sister's immunoglobulin values were completely normal with a slight decrease in CD19+B cells, whereas that the mother had hypogammaglobulinemia and very low CD19+B cells. The demographic characteristics and laboratory test results of the patient and other family members are given in Table 1.

The patient, who is currently 2 years old, has been treated with Immunoglobulin (Ig) replacement therapy and followed up without infection or hospitalization to this day. In parallel, the mother and sister, who are asymptomatic, have also been followed up clinically without treatment.

Table 1. Clinical and demographic characteristics and laboratory findings of the patient and his family

Name	Index patient	Mother	Father	Sister	Twin brother	Brother
Age,year	2	34	42	9	2	11
Complaint	symptomatic	asymptomatic	asymptomatic	asymptomatic	asymptomatic	asymptomatic
WBC count, 10^9/L(5.98-13.5)	7.78	7.92	6.78	6.54	9.78	6.37
Hgb,g/dL (10.1-12.5)	11.4	11.3	14.2	12.8	12	12.8
Lymphocyte count 10^9/L(1.52-8.09)	4.1	1.73	3.44	2.58	4.55	3.2
Neutrophil count 10^9/L(1.19-7.21)	2.4	5.57	1.44	3.5	4.44	2.79
Ig G g/L	0.7(0.29-11.6)	8.91(0.91-18.8)	10,4(0.91-18.8)	11.1(8.4-19.4)	7.18(6-19,4)	10,8(8.4-20.9)
Ig A g/L	0.1(0.13-0.72)	1.73(1.3-3.7)	1.52(1.3-3.7)	1.32(0.6-3.9)	0.29(0.2-2.9)	1.36(0.6-4.3)
Ig M g/L	0.1(0.3-1.5)	0.98(0.8-3.2)	0.57(0.8-3.2)	1.01(0.5-3.9)	0.88(0.6-2.2)	0.79(0.4-4.8)
CD19 (%)	**2.3(14-44)**	**1.07(10-30)**	13(10-30)	**6.5(10-27)**	38(11-31)	15.7(10-30)
CD20 (%)	**2.4(14-44)**	**1.1(10-30)**	13(10-30)	**6.5(10-27)**	38(11-31)	14.9(10-30)
Molecular analysis	**IGLL1 Homozygous**	**IGLL1 Homozygous**	IGLL1 Heterozygous	**IGLL1 Homozygous**	IGLL1 Heterozygous	IGLL1 Heterozygous

WBC: White Blood Cell Count, Hgb: Hemoglobin, Ig: Immunoglobulin CD: Cluster of Differentiation

DISCUSSION

In the early stages of B cell development, the formation of the pre-B cell receptor complex is extremely important. This complex plays a critical role in intracellular signal transduction, immunoglobulin rearrangement, and cell survival. ʎ5 and VpreB Ig found in the structure of the receptor complex of light chains and encoded by the IGLL1 gene. Ig μ has a vital role in the transport and expression of the heavy chain to the pre-B cell surface.[2-3]

Although autosomal recessive agammaglobulinemia (ARA) is observed in 15% of all agammaglobulinemia cases, the incidence of IGLL1 defect is <5%. Currently, very few cases reported in the literature. Clinical findings of ARA appear in early

infancy and are more pronounced than XLA. The clinical findings of the case presented in this study appeared within the first 2 months and he was diagnosed at the age of 3 months.[1-4]

The first ARA patient reported in 1998 and other cases reported in the later periods were mostly in the form of recurrent sinopulmonary infections. The laboratory findings of these patients indicated agamma/hypogammaglobulinemia and absence of B cells. Similarly, the case presented herein also had recurrent lower respiratory tract infections, hypogammaglobulinemia and no B cells in the peripheral blood (<1%).[1-5] Similar to X-linked agammaglobulinemia, other agammaglobulinemia mutations often have sinopulmonary and gastrointestinal infections. Conditions such as neutropenia, arthritis and malignancy are less common. According to an independent study with XLA, mild mutations in the BTK gene (defined as amino acid substitutions or splice defects in conserved, non-invariant, or consensus sequences) were associated with later ages and a higher number of peripheral B cells. A higher serum IgM level was associated with mild mutations. Our patient's mother was asymptomatic and had a mild phenotype. It is suggested that epigenetic factors may have affected the phenotype.[8] In addition, asymptomatic adult-onset cases have been reported in X-linked agammaglobulinaemias.[6]

The variant detected in the IGLL1 gene has previously been described in the literature. An article in the literature reported that two patients with the same variant as our patients had 6% and <1% B lymphocytes in the peripheral blood, respectively. They also had increased susceptibility to bacterial infections.[9] In the case report published by Gemayel et al., it was reported that other family members did not have any complaints, had normal immunological test results, and that the genetic analysis revealed a heterozygous mutation in the mother.[2] In comparison, the analysis of the family of the patient presented herein indicated that the father and two brothers were asymptomatic, had normal immunological test results, were heterozygous for the mutation, that the mother was asymptomatic, had very low Ig levels and B cell counts in the peripheral blood, and homozygous for the mutation, and that the 9-year-old sister was asymptomatic, homozygous for mutation as is the case in patient, had Ig levels consistent with her age and slightly low peripheral B cell count. Accordingly, the characteristics of the patient's mother and sister differed from the family characteristics of ARA patients reported in the literature.

In addition, hypogammaglobulinemia is defined as serum immunoglobulin levels below 2 standard deviations for age. In contrast, agammaglobulinemia is characterized by serum IgG level below 500 mg/dL in children older than 12 months. The reason why our patient's mother was asymptomatic may be that her serum immunoglobulin level was at the level of hypogammaglobulinemia rather than agammaglobulinemia. Several studies have shown that serum immunoglobulin levels above 500 mg/dL protect against recurrent infections. The treatment of patients with agammaglobulinemia, both X-linked and autosomal recessive, includes primarily infection control and Ig replacement.[1-5] The patient of this study was also on Ig replacement when he was 3 months old. Since receiving Ig replacement, he has not been hospitalized for a serious infection. In conclusion, this study demonstrates the necessity of genetic analysis in patients with agammaglobulinemia. Based on the results of the genetic analysis, a final diagnosis can be made and agammaglobulinemia patients and genetic counseling is recommended for their families.

STATEMENT OF ETHICS

The study protocol was approved by the local ethics committee of Basaksehir Cam and Sakura City Hospital (approval number: KAEK/11.10.2023.490). Written informed consent was obtained from the patient.

FUNDING

Not applicable

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable

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