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CASE REPORT

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Hyper IgM Syndrome with a Novel Mutation in the *AICDA* Gene: Easy to Diagnose

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ABSTRACT

Hyper IgM syndrome (HIGM) is a rare primary immunodeficiency (PID) characterized by low IgG and IgA and normal or high IgM levels. The *AICDA* gene mutations lead to HIGM, the most prevalent autosomal recessive HIGM with intrinsic B cell defects. We present a patient with recurrent otitis media complicated by tympanic membrane perforation who was diagnosed with HIGM syndrome due to a novel mutation in the *AICDA* gene. Despite the fact that the symptoms began in early childhood, the patient was diagnosed seven years later, when complications developed. First-line immunological examination using serum immunoglobulin levels and antibody responses can rapidly detect antibody deficiencies. Keeping primary antibody deficiencies in mind in patients with recurrent sinopulmonary infections may contribute to an early diagnosis and prevention of complications. Being aware is the most important step in detecting PIDs.

Keywords: Hyper IgM Syndrome, recurrent otitis media, primary immunodeficiency, *AICDA* gene

INTRODUCTION

Hyper IgM syndrome (HIGM) is a rare primary immunodeficiency (PID) that is categorized as a primary antibody deficiency with low blood IgG and IgA levels and normal or high IgM levels (1). HIGM constitutes 0.3-2.9% of all patients with PIDs (2).

Since the discovery of mutations in the genes encoding the CD40 ligand (CD40L) was identified in patients with HIGM in 1993 (3), more than 200 gene abnormalities including CD40L, CD40, UNG and activation-induced cytidine deaminase (*AICDA*) have been discovered to have a role in the pathogenesis (4,5) The *AICDA* gene encodes the protein activation-induced cytidine deaminase (AID), a DNA editing enzyme expressed by B cells that deaminates cytosine into an uracil residue from exposed single-strands of DNA which are the essential triggering region for both class switch recombination (CSR) and somatic hypermutation (SHM). The mutations in the *AICDA* gene causes HIGM that presents the most frequent autosomal recessive HIGM, resulting in intrinsic B cell defects (6,7).

The majority of patients with HIGM syndrome have a variety of clinical symptoms, including susceptibility to recurrent bacterial and opportunistic infections frequently appearing in infancy, pulmonary complications, gastrointestinal manifestations, autoimmune diseases, hematologic abnormalities, lymphoproliferation, and cancers (8).

Herein, we report a patient with recurrent otitis media complicated with perforation in the tympanic membrane, diagnosed as Hyper IgM syndrome with a novel mutation in the *AICDA* gene. Informed consent was obtained from the patient's parents.

CASE REPORT

A 12-year-old male patient presented to the hospital with the complaint of recurrent infections since 5 years of age. When he was 3 days old, he was hospitalized in the neonatal intensive care unit for a week with the diagnosis of neonatal sepsis. After discharge, the patient had no serious infections and was not hospitalized again until he was five years old. The patient was vaccinated in accord-

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ance with Turkey's vaccine schedule without any complications. At 6 years of age, he suffered from recurrent otitis media and sinusitis and was treated with oral antibiotics several times. His physical examination revealed tonsillar hypertrophy and he underwent adenotonsillectomy. Recurrent otitis media continued after adenotonsillectomy. During his follow-up, he experienced protracted diarrhea several times and he was hospitalized for septic arthritis in his knee and was given broad spectrum antibiotics. His family history revealed consanguinity between his parents (second-degree cousin marriage) and a similar history in his younger brother. His physical examination showed growth retardation (weight: 31 kg (3-10 P), height: 140 cm (3-10 P)), bilateral tympanic membrane perforation and 1.5 x1 cm tender and soft lymphadenopathy in the right cervical region. The immunological evaluation shown in Table I revealed leukocytosis, neutrophilia, low IgA and IgG and high IgM levels, reversed CD4/CD8 ratio in lymphocyte subgroups. The patient was evaluated for respiratory complications and tuberculosis. PPD was negative. Chest computed tomography revealed bronchiectasis and lung function tests with spirometry was normal. Immunoglobulin replacement therapy and antimicrobial prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) were initiated with the diagnosis of Hyper IgM syndrome. Whole-genome sequencing (WES) which we

Table I: Immunological evaluation of the patient on admission and follow-up

	On admission (12 years of age)	Follow-up (12.5 years of age)	Reference range
Complete Blood Count			
Hb (g/dL)	12.7	12.4	11.1-14.1
WBC (/mm^3)	**11.700**	**9200**	4400-8100
ANC (/mm^3)	**6500**	4400	1700-5700
ALC(/mm^3)	3200	**3600**	1400-3300
AEC (/mm^3)	400	400	< 500
Platelet (/mm^3)	311.000	272.000	150-400.000
ESR(mm/h)	31	20	0-20
CRP(mg/dL)	**2.57**	0.49	0-0.8
Immunoglobulins (mg/dL)			
IgA	**<6.67**	**<6.67**	67-433
IgG	**<10.0**	**702**	835-2094
IgM	**1380**	**679**	47-484
Total IgE (kU/L)	**<1.00**	**<1.00**	
Anti Hbs (mIU/mL)	263.28	-	
Isohemagglutinin titers	Anti B 1/256	-	
Lymphocyte subgroups (% and absolute numbers)			
CD3	80% **2560**	83% **2988**	56-84% 100-2200
CD4	**25%** 800	**27%** 972	31-52% 530-1300
CD8	**43%** **1376**	**46%** **1656**	18-35% 330-920
CD16+56	4% 128	4% 144	3-22% 70-480
CD19	14% 448	10% 360	06-23% 110-570

AEC: Absolute eosinophil count, **ALC:** Absolute lymphocyte count, **ANC:** Absolute neutrophil count, **CRP:** C- reactive protein, **ESR:** Erythrocyte sedimentation rate, **Hb:** Hemoglobin **WBC:** White blood cell. Abnormal values are shown in bold.

performed for the genetic diagnosis revealed a novel missense homozygous variant in the exon 3 of *AICDA* gene (c.332C>T/p. A111V), which was confirmed with Sanger sequencing, as shown in Figure 1. The mutation affects the APOBEC-like domain of the gene. He continues to be followed up with the department of gastroenterology for the treatment of malnutrition and growth retardation; the department of Ear-Nose-Throat owing to the perforation in the tympanic membrane; and the department of pulmonology for the bronchiectasis and pulmonary complications that may develop in follow-up.

DISCUSSION

In this study, we presented a boy who developed recurrent otitis media at an early age and was diagnosed with Hyper IgM syndrome with a novel mutation in the *AICDA* gene. Although the symptoms began in early childhood, the patient was diagnosed 7 years later, when complications developed. In patients with PIDs, a delayed diagnosis leads to a more complex course and early mortality.

Immunodeficiencies that cause primary antibody deficiency (PAD) include common variable immunodeficiency, agammaglobulinemia, and HIGM syndrome. PADs have a similar clinical presentation, usually beginning in infancy and early childhood and characterized by recurrent sinopulmonary infections such as otitis media, sinusitis, and pneumonia, affecting 90% of the patients. Other types of infections that are prevalent include gastrointestinal, meningeal, joint, bone, and skin infections (9,10). Previous research found a delay of 2.9 to 4.5 years in the diagnosis in cases of HIGM (11,12). In our patient, the diagnostic delay was longer.

Several individuals with *AICDA* mutations have been reported to have comparable sinopulmonary bacterial infections, including pneumonia, persistent otitis media, and tonsillar hyperplasia. Our patient also suffered septic arthritis and diarrhea. Meningitis and urinary tract infections have been reported in patients with the *AICDA* mutation by Caratao et al and Fazel et al., respectively (13,14)

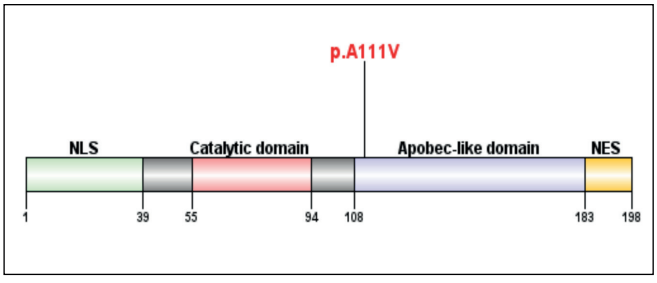

Figure 1. Demonstration of the patient's *AICDA* gene mutation.

Recurrent otitis media is one of the ten warning signs for primary immunodeficiencies listed by the Jeffrey Modell Foundation. In comparison to the healthy group without PID, patients with PID were shown to have significantly higher rates of ≥4 episodes of otitis media in a year, ≥2 episodes of sinusitis in a year, and a family history of PID (15).

It is easy to diagnose antibody deficiencies in patients using first-line immunological tests such as serum immunoglobulin levels and antibody responses. Antibody deficits should be evaluated in patients with multiple organ infections, particularly respiratory and gastrointestinal infections. Immunoglobulin replacement therapy (IgRT) and antibiotic prophylaxis may prevent patients from recurring infections and complications (16,17). Due to delayed diagnosis and treatment, our patient developed complications such as tympanic membrane perforation, malnutrition, growth retardation, and bronchiectasis. We initiated prophylaxis with trimethoprim-sulphametaxozole (TMP-SMX) and IgRT (400 mg/kg/month) regularly. The patient did not have an infection recurrence during the first 6-month follow-up following therapy. In addition to recurrent infections, patients may develop autoimmune diseases as well as benign and malignant lymphoproliferation as a result of immune dysregulation, In this regard, the patient will be monitored at routine outpatient clinic visits.

In conclusion, we reported a patient with a novel mutation in the *AICDA* gene. Antibody deficiencies may be easily detected by first-line immunological evaluation with serum immunoglobulin levels and antibody responses. Keeping primary antibody deficiencies in mind in patients with recurrent sinopulmonary infections may help to make an early diagnosis and prevent complications. The most critical step in identifying PIDs is raising awareness.

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Conflict of Interest

The authors declare no conflict of interest.

Authorship Contributions

Concept: **Saliha Esenboga, Ilhan Tezcan,** Design: **Deniz Cagdas, Ilhan Tezcan,** Data collection or processing: **Cansu Ozdemiral,** Analysis or Interpretation: **Cansu Ozdemiral, Hacer Neslihan Bildik,** Literature search: **Cansu Ozdemiral,** Writing: **Cansu Ozdemiral, Saliha Esenboga,** Approval: **Cansu Ozdemiral, Saliha Esenboga, Hacer Neslihan Bildik, Deniz Cagdas, Ilhan Tezcan.**

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