CASE REPORT
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The Coexistence of Asthma and Common Variable Immunodeficiency in a Patient with *TNFRSF13B* Gene Mutation

Tayebeh Ranjbarnejad[1], Mansoor Salehi[2], Hassan Abolhassani[3,4], Roya Sherkat[5], and Mohammadreza Sharifi[1]

[1] Department of Genetics and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[2] Cellular, Molecular and Genetics Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[3] Division of Immunology, Department of Medical Biochemistry and Biophysics, Karolinska Institute, Stockholm, Sweden
[4] Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[5] Immunodeficiency Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

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ABSTRACT

Common variable immunodeficiency disorder (CVID) is the most prevalent primary immunodeficiency in adults. Pathogenic mutations of the *TNFRSF13B* gene were identified in CVID patients and associated with autoimmunity and lymphoproliferation. A study on Swedish children unaffected by CVID has shown that rare variants in the *TNFRSF13B* gene increase the risk of asthma. To the best of our knowledge, asthma has not been reported in CVID patients with *TNFRSF13B* gene mutations. We described a patient suffering from asthma and CVID with a heterozygous mutation in the TNFRSF13B gene. According to our findings and previous studies, mutations in the *TNFRSF13B* gene seem to be possibly associated with the occurrence of asthma in CVID patients.

Keywords: Asthma; Common variable immunodeficiency; TACI (*TNFRSF13B*)

INTRODUCTION

Common variable immunodeficiency disorder (CVID) is the most prevalent primary immunodeficiency in adults, which is associated with hypogammaglobulinemia and the inability to produce effective antibody responses upon exposure to vaccines or pathogens.[1]

Most patients with CVID commonly suffer from recurring and severe infections, especially recurrent upper respiratory infections.[2] In addition to recurrent infections, other clinical manifestations, including autoimmune manifestations, lymphoproliferation (splenomegaly), gastrointestinal complications, such as malabsorption, and an increased risk of malignancy, have been described in CVID patients.[3] The genetic diagnosis of CVID can

Corresponding Authors: Roya Sherkat, MD;
Immunodeficiency Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: (+98 913) 327 1126, Fax: (+98 31) 3792 3929, Email: royasherkat@yahoo.com

Mohammadreza Sharifi, PhD;
Department of Genetics and Molecular Biology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: (+98 31) 3792 9037, Fax: (+98 31) 3668 8597, Email: mo_sharifi@med.mui.ac.ir

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have important implications for prognosis and also offers opportunities for therapeutic management by developing new approaches that target the affected protein or pathway.[4] The low proportion of CVID patients has been found to have monogenic defects.[5] Whole exome sequencing (WES) is a powerful method that can be used to identify genetic abnormalities in affected individuals with unknown causes.[6]

TNFRSF13B is a tumor necrosis factor receptor (TNFR) superfamily member, which encodes the TACI (Transmembrane Activator and Calcium modulator ligand Interactor) protein.[7] TACI stimulates B cells to undergo class switch recombination and immunoglobulin (Ig) synthesis. Additionally, it is essential for the development and survival of B cells in peripheral tissues and for generating antibodies against T-independent antigens.[8] The C104R mutation, located in the third exon of the *TNFRSF13B* gene, prevents the binding of ligands to the TACI receptor. TACI receptor's function relies on ligand-induced trimerization or oligomerization to initiate downstream signaling, and disruption of ligand binding leads to defects in Class switch recombination (CSR) and antibody production.[9] Both monoallelic and biallelic mutations in *TNFRSF13B* have been found in CVID patients, and studies have shown that *TNFRSF13B* gene mutations are the most common in CVID patients.[10] CVID patients with *TNFRSF13B* gene mutations exhibited autoimmunity at a slightly elevated rate compared to the overall CVID patient population. Also, lymphoproliferation is one of the common manifestations in patients with this mutation.[11] The coexistence of CVID and asthma in patients with mutations in the *TNFRSF13B* gene has not been reported before. This study describes a heterozygous pathogenic mutation in the *TNFRSF13B* gene in a patient with CVID and asthma phenotype.

CASE PRESENTATION

The case of our study is a 23-year-old male with a medical history of recurrent upper respiratory infections, otitis media, sinusitis, wheezing episodes, coughing, asthma, food allergy, and no history of lymphoproliferative and autoimmune diseases. The symptoms of the disease started at the age of 6, but the diagnosis of CVID was not made until the age of 12. Immunoglobulin replacement therapy (polyclonal immunoglobulin, 400 mg/kg, and every 3 weeks by IV) for the patient started at the age of 13. The patient is the second-born child of consanguineous parents (first cousins) of Iranian descent with no family history of primary immunodeficiency (PID) (Figure 1).

During his evaluation at the asthma clinic, the phenotypic characteristics and spirometry test results aligned with an asthma diagnosis. Spirometry findings indicate significant bronchodilator responsiveness and are consistent with reversible airway obstruction characteristic of asthma (Figure 2).

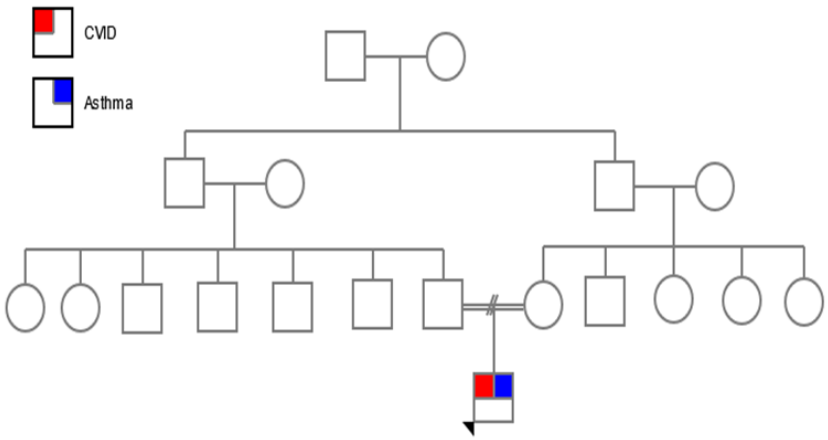

Figure 1. The family pedigree of the patient. The patient in this study is the only case of common variable immunodeficiency (CVID) in the family, and the disease is observed sporadically.

Laboratory findings showed hypogammaglobulinemia (Table 1). The main reason for the slightly low IgE in this patient is the fundamental defect in immunoglobulin production associated with CVID. Therefore, even in the presence of asthma-which typically elevates IgE-serum IgE remains mildly reduced. The diagnosis of CVID was based on the European Society for Immunodeficiencies (ESID) updated clinical diagnostic criteria.

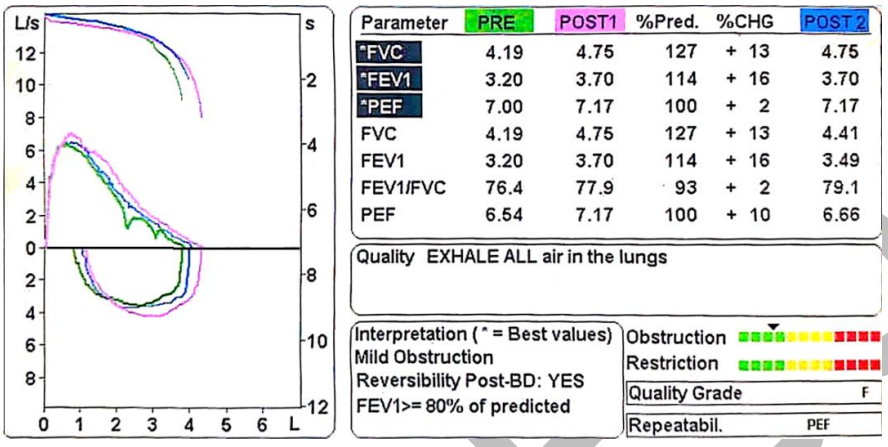

Figure 2. Spirometry results before and after bronchodilator administration. The graph presents key pulmonary function parameters obtained during the patient's evaluation. Post-bronchodilator measurements demonstrated notable improvements: FVC increased from 4.19 L to 4.75 L (a 13.4% increase), FEV_1 from 3.20 L to 3.70 L (a 15.6% increase), and PEF from 7.00 L/s to 7.17 L/s. The FEV_1/FVC ratio rose from 76.4% to 79.1%, findings consistent with a reversible airway obstruction pattern supportive of an asthma diagnosis. FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow; PRE: pre-bronchodilator; POST-BD: post-bronchodilator; POST1/POST2: post-bronchodilator measurement 1/2; Pred: predicted value; CHG: change from baseline.

Table 1. Immunoglobulin and lymphocyte marker levels before intravenous immunoglobulin (IVIG) treatment.

	Value in the patient	Normal range
Immunoglobulin G, g/L	2.58	6–16
Immunoglobulin A, g/L	0.234	0.8–2.8
Immunoglobulin M, g/L	0.40	0.5–1.9
Immunoglobulin E, kU/L	9	10–100
CD8, % of lymphocytes	36	19–48
CD3, % of lymphocytes	72	61–85
CD19, % of lymphocytes	19	7–23
CD20, % of lymphocytes	23	7–23
CD4, % of lymphocytes	38	28–58
$CD16^+CD56^+$, % of lymphocytes	24	2–27

Whole exome sequencing was performed on DNA extracted from the peripheral blood of the patient, and after data analysis, based on the updated guideline of the American College of Medical Genetics and Genomics (ACMG), a heterozygous C104R mutation in the *TNFRSF13B* gene was identified as a pathogenic mutation causative for the development of CVID.

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DISCUSSION

Asthma is a global health problem with a significant worldwide prevalence.[12] Asthma has been reported as one of the comorbidities in CVID disease.[13] The frequency of asthma in patients with CVID differs across studies, with reported rates ranging from 6.5% to 31%.[13,14] In a study on 187 Iranian CVID patients, 22 patients (12%) had asthma and allergy symptoms, which was lower than that found in other studies.[15] The observed variation may be explained by differences in sample size, underlying genetic abnormalities, and ethnic composition among the study populations.[15]

The clinical presentations of asthma and immunodeficiency disorders, such as CVID, can be strikingly similar, often leading to diagnostic challenges.[13] Diagnosing asthma and allergic diseases in patients with CVID is crucial, as it could significantly improve disease management and ultimately enhance the quality of life for these patients.[16] Consequently, clinicians must be informed about these conditions to ensure accurate diagnosis and appropriate treatment.[16]

The etiology of non-infectious problems in CVID patients is still unclear, but dysregulation of the immune system, chronic respiratory infections, specific haplotypes of major histocompatibility complex (MHC), a decreased IgA reaction to luminal allergens, and elevated serum IgE as a compensatory mechanism resulting from hypogammaglobulinemia can contribute to asthma and other atopic diseases in patients with CVID.[15]

The specific mechanisms underlying the probable association between asthma and CVID are not well understood. A 2012 study discovered that Swedish children, unaffected by CVID, with the variations in the *TNFRSF13B* gene had a twofold higher likelihood of experiencing wheezing, as well as a 2.5-fold higher likelihood of developing asthma, regardless of their IgE levels.[17]

TNFRSF13B mutations lead to defective B-cell function, antibody production, and impaired mucosal immunity, causing persistent allergen and pathogen exposure in the airways.[18,19] The TNF superfamily, which includes *TNFRSF13B*, plays a role in activating group 2 innate lymphoid cells (ILC2s). These cells produce type 2 cytokines like IL-5 and IL-13, which are crucial in eosinophil recruitment and activation, contributing to airway tissue damage in asthma.[20] Reduced IgM and disrupted regulation of the complement system, caused by mutations in *TNFRSF13B*, can exacerbate inflammatory reactions, as observed in transplant rejection studies.[21] Chronic inflammation promotes airway remodeling and hyperresponsiveness, which are key pathological features of asthma.[17]

However, the exact impact of variations in the *TNFRSF13B* gene on the development of asthma or atopy is not well understood, and additional research is required to investigate the mechanisms that explain this correlation.

Considering that the subjects in the study on Swedish children were not affected by CVID, and asthma in these patients was associated with the *TNFRSF13B* gene variants, the occurrence of asthma in the patient in our study may also be related to the mutation in the *TNFRSF13B* gene, and we suggest that the asthma phenotype in CVID patients is associated with the *TNFRSF13B* gene mutation. Determining the genotype-phenotype correlations in gene mutations can help predict the complete phenotype and the comorbidities of the disease and determine the prognosis in patients.

It could be recommended that CVID patients with mutations in the *TNFRSF13B* gene be screened for asthma symptoms. We recommend investigating the genotype-phenotype correlations in the *TNFRSF13B* gene in future studies and in a larger number of CVID patients to evaluate the phenotype of asthma and allergic diseases in these patients.

STATEMENT OF ETHICS

This study was conducted following the principles of the ethics committee of the Isfahan University of Medical Sciences (approval number IR.MUI.REC.1401.026). Informed consent was obtained from the patient.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

The FASTQ file is available from the corresponding author (mo_sharifi@med.mui.ac.ir) upon reasonable request.

AI ASSISTANCE DISCLOSURE

The authors declare that no AI-assisted technologies were used in writing or analyzing this manuscript

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