

# Atrophic Thymus in the First Case of the Interleukin 10 Receptor Beta Deficiency due to the Homozygous Large Deletion

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## Abstract

Interleukin 10 (IL-10) and IL-10 receptor (IL-10R) deficiencies are among the primary immunodeficiency disorders (PIDs) caused by the loss-of-function mutations in the IL-10 or IL-10R encoding genes. IL-10 and IL-10R deficiencies are not prevalent and only a few cases have been reported in this regard so far. Among the patients, very early onset of the inflammatory bowel disease (VEO-IBD), usually during the infancy is the most common clinical manifestation of the disease. Almost all the patients come from the consanguineous families and present a similarly severe state of the disease. Therefore, in this study, the case of a 7-month-old girl, admitted with severe dehydration due to the watery diarrhea, fever, and repeated hospitalization with atrophic thymus was reported. According to the patient's past medical history, she came from a family with consanguineous marriage, and her sister also had died from the chronic diarrhea. She was nominated for the genetic examination to identify the underlying causes of her disease because of the normal laboratory analysis and standard immunological workup. Genetic evaluation by the whole exome sequencing revealed a homozygous mutation in the gene encoding the IL-10RB with a large deletion in the exons 3-7. Unfortunately, she deceased at the age of one before the hematopoietic stem cell transplantation.

**Keywords:** IL-10R deficiency, VEO-IBD, Pediatrics, Chronic Diarrhea

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## Introduction

Interleukin-10 (IL-10) is an anti-inflammatory cytokine with an inhibitory role in the production of pro-inflammatory cytokines, such as interferon-gamma (IFN- $\gamma$ ), interleukin 1beta (IL-1 $\beta$ ), and interleukin 6(IL-6), and expression of interleukin 12(IL-12). Moreover, IL-10 inhibits the release of tumor necrosis factor (TNF) and is critical for maintenance of the immune homeostasis in the gastrointestinal tract. Its receptor (IL-10R) is composed of two different subunits of  $\alpha$  and  $\beta$ . The alpha subunit is expressed on the hematopoietic cells (such as T, B, NK, mast, and dendritic cells), while the beta subunit is ubiquitously expressed (1-5). As a result of loss-of-function mutations in the genes encoding the IL-10 or IL-10R, lipopolysaccharides (LPS)-mediated TNF release leads to presentation of the severe immune dysregulation (1, 6, 7).

Since, IL-10 and IL-10R deficiencies are classified as the primary immunodeficiency disorders (PIDs); recurrent respiratory and skin infections, such as chronic folliculitis, multiple abscesses due to the epithelial barrier defects as well as arthritis are commonly manifested in a severe state of the disease in almost all the patients (8-11). However, the inflammatory bowel disease (IBD) is the most common clinical manifestation of the mutant IL-10R usually occurring accompanied with the refractory colitis, recurrent bloody diarrhea, anal fissures and fistulae, significant weight loss, and failure to thrive (FTT) during the infancy (5, 6, 12-14).

Therefore, here, a case is presented with a homozygous deletion in exons 3-7 of IL-10RB gene and very early-onset gastroenteritis symptoms, such as diarrhea, abdominal pain and dehydration as well as urinary tract infection due to the *Escherichia coli* and atrophic thymus. The patient is the fifth patient identified in the Iranian primary immunodeficiency registry (IPIIDR) with this genetic defect.

## Case Presentation

The patient was a 7-month-old- girl born through

the vaginal delivery from the consanguineous parents who was referred to the Tabriz Children Hospital (Tabriz, East Azerbaijan province, Iran) due to the recurrent gastroenteritis, severe dehydration, watery stool, and fever. According to the patient's past medical history, she was suffering from the phlegmatic watery diarrhea from 4 months prior to her admission with severe dehydration, which resulted in hospitalization for more than 4 times. She had a normal birth weight (3.450 kg), but she was diagnosed with the FTT at the time of admission. In the fifth round of hospitalization, urine culture was positive for the *Escherichia coli* (E.coli), while the stool exam and culture for microbes and Eltor were negative. In the family history, her elder sister had died at 11 months of age due to the recurrent gastroenteritis without any specific etiology. In the physical examination, she was pallor and had the sugar baby's face. No organomegaly was found in the patient. Chest X-ray showed the atrophic thymus with reticular opacities in central lobes of the lung.

**Table 1** shows the data of the laboratory and immunological tests for the patient. The case showed the anemia and thrombocytosis. Anisocytosis and poikilocytosis with hypochromia in the peripheral blood smear, and megakaryocytes increased with the normal array of erythroid and myeloid cells in bone marrow aspiration were observed. Absolute counts of the neutrophils and lymphocytes, immunoglobulin levels, and lymphocyte subsets were normal, ruling out the possibility of severe congenital neutropenia and classic severe combined immunodeficiencies (SCIDs). Quantitative determination of the oxidative burst was normal, which excluded the possibility of the chronic granulomatous disease. Colonoscopy revealed the diffused ulceration and pseudo polyps, in favor of the chronic inflammatory colitis. History of the dead sister in her family, the consanguinity of the parents, and manifestation of the very early-onset colitis suggested the possibility of the inherited deficiencies.

**Table 1.** Laboratory and immunologic data of the patient

Laboratory test	Patient	Reference Intervals
WBC ( $10^3/\mu\text{l}$ )	17.7	6-17.5
Lym (%)	39.8%	47-77
PMN (%)	49	15-45
Hb (gr/dl)	8.3	11.3-14.1
Hematocrit (%)	30.6	31-41
PLT ( $10^3/\mu\text{l}$ )	1	250-450
IgM (mg/dl)	87	24.2-162
IgG (mg/dl)	1115	242-977
IgA (mg/dl)	126	6.68-114
IgE (IU/ml)	16	Up to 15
CD3 (%)	46	43-77
CD4 (%)	23	21-53
CD16 (%)	11	4-41
CD56 (%)	8	2-25
CD19 (%)	38	11-41
CD20 (%)	36	3-15
HIV Ab	neg	
Anti HBS (IU/L)	200	$\geq 100$
LDH (U/L)	484	160-490
Reticulocytes (%)	2	1-2
Fe (g/dl)	7	<11
TIBC ( $\mu\text{g/dl}$ )	183	100-400

WBC, white blood cell; Lymph, lymphocytes; PMN, Polymorphonuclear leukocyte; capacity; PLT, platelet; Hb, hemoglobin, Ig, immunoglobulin; CD, cluster of differentiation; HIV, The human immunodeficiency viruses; LDH, lactate dehydrogenase; TIBC, Total iron-binding

Genetic evaluation was performed using the whole-exome sequencing (WES) to investigate the underlying genetic defect, and homozygous large deletion removing exons 3-7 of IL-10RB encoding gene in the cytogenetic location 21q22.11 was identified with an autosomal recessive inheritance, which was compatible with the clinical and immunological phenotype of the mentioned proband. The patient was a candidate for the hematopoietic stem cell transplantation, but her parents refused to follow up until she died at 12 months of age due to the recurrent diarrhea and severe gastroenteritis.

## Discussion

IL-10, as an important anti-inflammatory cytokine is secreted by a variety of cells and has a

major role in inhibition of the pro-inflammatory cytokines, such as TNF, as well as providing the stability of the gut's immune homeostasis (15). On the other hand, in the absence of IL-10, activation of the inflammatory reactions due to the cytokine release can cause extensive damage to the several tissues including gut tissue.

IBD is manifested by the abdominal pain, watery or bloody stool, and weight loss. Very early -onset IBD (VEO-IBD) is the gut inflammation presenting similar to the IBD and is manifested in the children before six years of age (6, 7). The effects of the prolonged inflammation on the growth and global development in children are more obvious due to the chronic nature of the disease(4). IBD classification has recently been modified to cover the younger age group, but this may not be compatible with the heterogeneous VEO-IBD phenotype (12). IL-10 or IL-10R deficiencies have been shown to be responsible for the VEO-IBD resulting in an alteration in the intestinal immune homeostasis (4, 16).

Herein, a patient with severe, early-onset IBD, refractory watery diarrhea, abdominal pain, and atrophic thymus was presented. Similar to majority of the previously reported patients, the gastrointestinal disease and colitis was also the main presentation in our patient. Our patient was 7 months old at the time of diagnosis, which is consistent with the average age for clinical diagnosis of the VEO-IBD. Overall, she was diagnosed with the VEO-IBD due to her chronic recurrent watery, phlegmatic, and sometimes bloody diarrhea from the early ages, the history of dead sister in her family with the same clinical manifestation and gut inflammation disease, as well as her consanguineous parents. WES was performed on the patient's genome, and a large deletion mutation was detected in the IL-10RB encoding gene. Although, the mutation identified in our study is not novel, a large deletion mutation in the IL-10RB encoding gene has not yet been reported in this disease (17).

There are two types of IL-10R deficiency: IL-10RA and IL-10RB. According to the several studies,

IL-10RA deficiency is more common in the Asian populations while in the European countries, the number of both IL10RA and IL10RB mutations is equal but the clinical phenotype is more severe and begins early in the cases with mutated IL10RB and it seems to be the main type in the Iranian reports of the primary immunodeficiency disorders with 5 cases (16, 17). Although, some studies have suggested that the arthritis and skin presentations could be seen in the patients with IL-10RB deficiency (15, 17), our patient did not show any of these manifestations, which could be due to her short life span.

The immunological workup of the patients with IL-10 and IL-10R deficiencies has shown the non-specific abnormalities, without any genotype-phenotype correlation. Also, variations in the number of T-cell, B-cell, NK cell, and serum immunoglobulin levels may occur in the different phenotypes of the disease except for anemia, which could be a result of her chronic malnutrition (14). Her peripheral blood smear (PBS) and bone marrow aspiration (BMA) examination showed an increased number of the platelets and megakaryocytes, which has not been reported in the previous studies and could be due to the chronic inflammation in her gastrointestinal tract.

Similar to our patient, in a survey for differential diagnosis of the PIDs that could be accompanied with the gastrointestinal involvement, laboratory analysis showed the microcytic and hypochromic anemia partly reflecting the presence of micronutrient deficiencies (12, 18-20). Second-line investigations, such as genetic diagnostics are an important tool for diagnosis of the patients with VEO-IBD. Genetic evaluation in our patient confirmed the diagnosis of the IL-10RB deficiency (17).

## Conclusion

Overall, given that, many monogenic diseases can present with an IBD-like phenotype the recurrent diarrhea, FTT, intermittent fever, immunological workup, and genetic diagnostics constitute the important stratification tools for diagnosis of the pa-

tients with VEO-IBD. Since, the PIDs can present similarly to the IBD, basic immune components and functions need to be investigated (9, 21).

## Conflict of Interest

The authors declare that they have no conflicts of interest.

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