# Autoimmunity and Inborn Errors of Immunity: Two Faces of the Same Coin!

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## Abstract

Autoimmune disorders are a heterogeneous group of disorders characterized by immune dysregulation and are associated with a loss of tolerance to self-antigens. Autoimmunity in patients with inborn errors of immunity (IEI) has always been a puzzling phenomenon! Autoimmunity may be the first clinical presentation or sequel in patients with IEI. In this paper, we discuss the mechanisms of autoimmunity in IEI and present a few clinical cases highlighting the need to consider an IEI in patients presenting with autoimmunity and infections, polyautoimmunity, and polyendocrinopathy.

**Keywords:** Autoimmunity, Immune deficiency, Immune dysregulation.

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## Introduction

Autoimmune disorders are a heterogeneous group of disorders characterized by immune dysregulation and are associated with a loss of tolerance to self-antigens. Autoimmunity in patients with IEI has always been a puzzling phenomenon! However, with a better understanding of the immune development pathways, it is observed that IEIs and autoimmunity are interlinked by common mechanisms.[1]

Autoimmunity may be the first clinical presentation or sequel in patients with IEI. The expanding spectrum of IEIs now includes diseases with autoimmunity, which have been classified as "syndromes with autoimmunity" by the International Union of Immunological Societies Expert Committee on IEI in 2019.[2]

**When should one suspect an IEI in a patient with autoimmunity?**

- Onset of autoimmunity at a young age.
- Presence of polyautoimmunity.
- Autoimmunity with infections.
- Family history of autoimmunity.

### Pathogenesis of Autoimmunity in IEI

The pathophysiology of different autoimmune manifestations in IEIs is complex and has been associated with decreased central and peripheral tolerance, with the presence of autoreactive T and B cells. Some of the proposed mechanisms are:

- Defective clearance of autoreactive T cells.

*AIRE* gene mutations are associated with impaired clearance of autoreactive T cells in the thymus, as well as affecting the development of T regulatory (Treg) cells. The associated conditions are autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) and Omenn syndrome. *RAG 1/RAG 2* genes are crucial for the rearrangement of T and B cell receptors by facilitating variable (V) diversity (D) joining (J) recombination. The mutations in these genes hinder the negative selection of autoreactive T cells in the thymus. The leakage of autoreactive T cells may provide the link between infections and autoimmunity in patients with RAG defects.

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- Infection and autoimmunity.

Patients with IEI are unable to clear infections effectively. The molecular mimicry of the pathogen with human tissues leads to autoreactivity, and the cellular debris which is presented to autoreactive T cells triggers the autoimmune cascade, known as "bystander activation." Also, infections with organisms like *Staphylococcus* and *Mycoplasma* produce superantigens which result in nonspecific polyclonal activation of T cells and cytokine production.

- Defects in Treg development.

T regulatory cells are a subset of T cells that play an important role in tolerance and prevent autoimmunity. The defects in the development of Treg cells are associated with loss of inflammatory control and result in autoimmunity. This has been reported in patients with APECED who have low forkhead box protein P3 (FOXP3), which is important for Treg cell activation and development. Other IEIs associated with autoimmunity and low Treg cells are immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), CD25 deficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome, CTLA4 deficiency, LRBA deficiency, STAT3 GOF mutations, BACH2 deficiency, CD122 deficiency, DEF6 deficiency, and FERMT1 deficiency (Table 1).

Let us discuss a few cases.

## Case 1

A 6-year-old boy born to a non-consanguineously married Indian couple presented with chronic diarrhea for over a year. He had lost 4 kg weight over 1 year.

**Past history:** He was noted to have blood in stools at 4 years of age and had a history of recurrent episodes of wheeze-associated lower respiratory tract infections as a young boy.

**Family history:** He had a significant family history. His father, a 35-year-old gentleman, had a history of autoimmune hemolytic anemia (AIHA) since the age of 15 years. He was suffering from chronic diarrhea, which was responsive to steroids. His paternal grandmother, a 55-year-old lady, had three relapses of AIHA. Interestingly, she too was suffering from chronic diarrhea, which was found to be responsive to steroids (autoimmune enteropathy) (Fig. 1).

**On evaluation:**

CBC—hemoglobin (Hb): 9 gm/dL, total count (TC): 10200/mm$^3$, and platelet count (PC): 340000/mm$^3$.

Coombs test: Negative.

Immunoglobulin (Ig) levels, lymphocyte subset analysis: Normal.

Nitroblue tetrazolium and dihydrorhodamine assay: Normal.

Fecal calprotectin levels: 1220 µg/gm (high).

Colon biopsy: Features suggestive of inflammatory bowel disease (IBD).

**Genetic test:** Pathogenic heterozygous mutation in *CTLA4* gene in the child, father, and paternal grandmother.

**Diagnosis:** CTLA-4 haploinsufficiency with autoimmune infiltration (CHAI).

**Table 1:** Errors of immunity which present with autoimmunity as a key feature

| *Inborn IEI* | *Associated gene* |
|---|---|
| CTLA-4 haploinsufficiency | CTLA-4 |
| LRBA deficiency | LRBA |
| Autoimmune lymphoproliferative syndrome | TNFRSF6 |
| APECED | AIRE |
| IPEX | FOXP3 |
| STAT3 GOF mutation | STAT3 |
| Very-early onset IBD | IL-10, IL-10R |

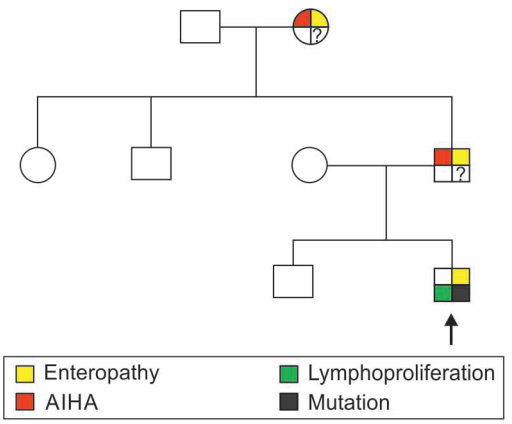


**Fig. 1:** Pedigree

**CTLA-4 haploinsufficiency with autoimmune infiltration (CHAI)**

- Cytotoxic T lymphocyte antigen-4 is a critical and potent inhibitor of T cell proliferation—"checkpoint" of immune responses.
- Polyautoimmunity is the key manifestation of CHAI.
- Caused by mutation in *CTLA-4* gene.
- Autosomal dominant in inheritance.
- Abatacept and sirolimus are useful in controlling immune dysregulation.
- Hematopoietic stem cell transplant is the treatment of choice in patients with severe disease manifestations/partial response to therapy.

Message: Autoimmunity in multiple family members—one must evaluate for IEI.

## Case 2

A 4-year-old girl presented with a history of malar rash, oral ulcers, and alopecia for 1 year. She also had a history of recurrent otitis media from a young age and one episode of meningitis at 3 years of age.

**On examination:** She had ulcers over the hard palate and erythematous malar rash (butterfly rash).

**On evaluation:**

ANA by IF: 3 +.

C3 and C4: Normal.

CH50: <10 units/mL (30–60).

ANA profile: dsDNA negative and anti-Smith antibody +.

**Genetic test:** Pathogenic homozygous mutation in the *C1QA* gene.

**Diagnosis:** Monogenic lupus—C1q deficiency.

**C1q deficiency**

- Rare genetic disorder.
- Strong association with systemic lupus erythematosus.
- Present with oral ulcers, cutaneous, and renal involvement.
- Caused by mutation in any one of the three *C1Q* genes.
- Inherited as an autosomal recessive disease.
- Associated with infections caused by encapsulated bacteria.

Message: Early onset lupus (<5 years) with recurrent infections—one must think of IEI.

## Case 3

A 40-year-old lady with a history of recurrent pneumonia from a young age now presented with polyarthritis for 1 year.

**On examination:** She had generalized wasting and bilateral crepitations on auscultation. She had arthritis involving small joints of the hands and both knees.

**On evaluation:**

CBC—Hb: 9.7 gm/dL, TC: 11700/mm$^3$, and PC: 632000/mm$^3$.

ESR: 43.

CT thorax: Suggestive of bronchiectasis.

Serum IgG: 260 mg/dL (639–1439), IgA: 10 (70–312), and IgM: 44 (56–352).

CD 19 count: Normal.

**Genetic test:** Negative.

**Diagnosis:** Common variable immunodeficiency with inflammatory arthritis.

Treatment: She was treated with a course of steroids, after which arthritis became passive. She is on monthly immunoglobulin (IVIG) replacement.

**Common variable immunodeficiency**

- Characterized by low levels of protective antibodies and increased risk of infections.
- Autoimmunity is known to occur in 1/3rd of cases.
- Genetic cause is known in about 10% of cases.
- Usually presents in adulthood.
- Males and females are equally affected.
- Acquired cause of agammaglobulinemia.
- Treatment—intravenous immunoglobulin 400–600 mg/kg/month.

## Case 4

A 7-year-old girl presented with complaints of chronic diarrhea for 3 months. In the past, she had several episodes of lower respiratory infections and recurrent oral thrush. She also had autoimmune thyroiditis, diagnosed at 5 years of age, and was being treated with thyroxine.

**On examination:** Onychomycosis affecting multiple nails and bilateral coarse crepitations.

**On evaluation:**

CBC—Hb: 7 gm/dL, TC: 7000 cells/mm3, and PC: 550000/mm3.

CT thorax: Suggestive of early bronchiectasis changes.

Anti TPO antibody: 50 IU/mL (<12).

Immunoglobulin levels and lymphocyte subset analysis: Normal.

**Genetic test:** Pathogenic heterozygous variant in *STAT1* gene.

**Diagnosis:** STAT1 gain of function (AD) with chronic mucocutaneous candidiasis and autoimmune thyroiditis.

**STAT1 gain of function mutation**

- Rare genetic disorder presenting with chronic mucocutaneous candidiasis (CMC).
- Viral, bacterial, and fungal infections.
- Autoimmune manifestations are common—hypothyroidism, autoimmune enteropathy, etc.
- Caused by mutation in *STAT1 GOF*.
- Inherited as an autosomal dominant disease.
- Treatment includes JAK3 inhibitors and hematopoietic stem cell transplant.

Message: Endocrinopathy with recurrent infections—think of IEI.

## Conclusion

- Disorders of immune dysregulation characteristically predispose patients to autoimmune manifestations and infections.
- Autoimmunity can be a presenting manifestation or can occur during the evolution of the disease in patients with IEI.
- Errors of immunity should be ruled out in children presenting with polyautoimmunity and polyendocrinopathy.

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