Which patients should be evaluated for immunodeficiency ?

Mahshid Movahedi,M.D
Assistant professor of Allergy & Clinical Immunology, TUMS

- **The defect in the immune system can be :**

  - **congenital,** known as **primary immunodeficiency** (due to an intrinsic gene defect),
  - **acquired** (as a result of an underlying disease or treatment) known as **secondary immunodeficiency.**

- Due to the nature of the disease, and the vast array of different defects **(>500 different mutations**) that can lead to the condition, primary immune deficiency is often poorly recognized and diagnosed.

When should we suspect an Immunodeficiency?

- **S- Severe:** can the presenting complaint/recurring infection be life-threatening if untreated?
- **P- Persistent:** does not respond appropriately to conventional treatment?
- **U- Unusual:** is the site of infection and type of microbe unusual? deep tissue infection, opportunistic microbe
- **R- Recurrent:** does the patient have more frequent infections than the average for a person without any immunocompromised features?

10 warning signs for PID in adults and children (Jeffrey Modell)

10 warning signs of PID for children	10 warning signs of PID for adults
≥ 4 new ear infections within 1 year	≥ 2 new ear infections within 1 year
≥ 2 serious sinus infections within 1 year	≥ 2 new sinus infections within 1 year in the absence of allergy
≥ 2 months on antibiotics with little effect	Recurrent viral infections (colds, herpes, warts, and condyloma)
≥ 2 pneumonias within 1 year	1 pneumonia/year for more than 1 year
Failure of an infant to gain weight or grow normally	Chronic diarrhoea with weight loss
Recurrent, deep skin or organ abscesses	Recurrent, deep abscesses of the skin or internal organs
Persistent thrush in mouth or fungal infection on skin	Persistent thrush or fungal infection on skin or elsewhere
Need for intravenous antibiotics to clear infections	Recurrent need for intravenous antibiotics to clear infections
≥ 2 deep-seated infections including septicaemia	Infection with normally harmless tuberculosis-like bacteria
A family history of PID	A family history of PID

Four additional warning signs of inborn errors of immunity.

	Sign
1.	Severe eczema
2.	Allergies
3.	Hematologic and oncologic disorders
4.	Autoimmunity

Non infectious manifestations of IEI

- Patients with inborn errors of immunity (IEI) are susceptible to developing a severe infection-related clinical phenotype, but the clinical consequences of immune dysregulation, expressed with **autoimmunity, atopy**, and **lymphoproliferation** could represent the first sign in a significant percentage of patients.

- Therefore, during the diagnostic work-up patients with IEI are frequently addressed to **different specialists**, including **endocrinologists**, **rheumatologists**, and **allergologists**, often resulting in a delayed diagnosis.

IMMUNODEFICIENCY IN THE ENDOCRINOLOGY UNIT

As a general rule, the finding of **multiple autoimmune endocrinopathies, the early disease onset, the positive familial history for endocrine disorders and autoimmunity** should represent a warning sign for an underlying IEI.

Autoimmune Endocrinopathies :

- **Autoimmune polyendocrine syndrome1 (APS-1)** chronic mucocutaneous candidiasis (CMC) and are prone to the development of different endocrinopathies, mostly Addison's disease and primary hypoparathyroidism. patients can also show autoimmune enteropathy, hepatitis, pancreatitis, and nephritis.

IMMUNODEFICIENCY IN THE HEMATOLOGY AND ONCOLOGY UNIT :

Autoimmune Cytopenia :

- Autoimmune hemolytic anemia
- early chronic immune thrombocytopenia
- Late onset of autoimmune neutropenia
- Multiple cytopenia

(recurrent infections, positive familial history for immune disorders, and impaired serum Immunoglobulin levels and the main lymphocyte subpopulation.)

(**CTLA4, LRBA, STAT3, PI3KCD**)

Lymphoproliferation :

- Lymphadenopathies
- Splenomegaly
- Lymphoid malignancies

(CVID, ALPS, ALPS-like disorders)

Cancer Susceptibility :

- ataxia-telangectasia, Bloom syndrome, Nijmegen breakage syndrome, dyskeratosis congenital
- GATA2 mutations (combined immunodeficiency and susceptibility to myeloid neoplasms)
- IKZF1 mutations (causing hypo gammaglobulinemia and familial lymphoid neoplasms)

- Immune dysregulation, polyendocrinopathy, enteropathy, X-linked **(IPEX) syndrome**. classic triad of enteropathy, eczematous dermatitis, and endocrinopathies, including thyroiditis and type 1 diabetes.

Primary Hypoparathyroidism :

- **22q11.2 deletion syndrome (22q11.2DS),** (neonatal hypocalcemia including cardiac malformations, velo-palatal insufficiency).

IMMUNODEFICIENCY IN THE ALLERGY UNIT :

There is extreme interest in the potential pathogenic links between atopic disorders, autoimmune diseases, and IEI. Severe eczema and newborn erythroderma are the most common presentations of IEI in this clinical context.

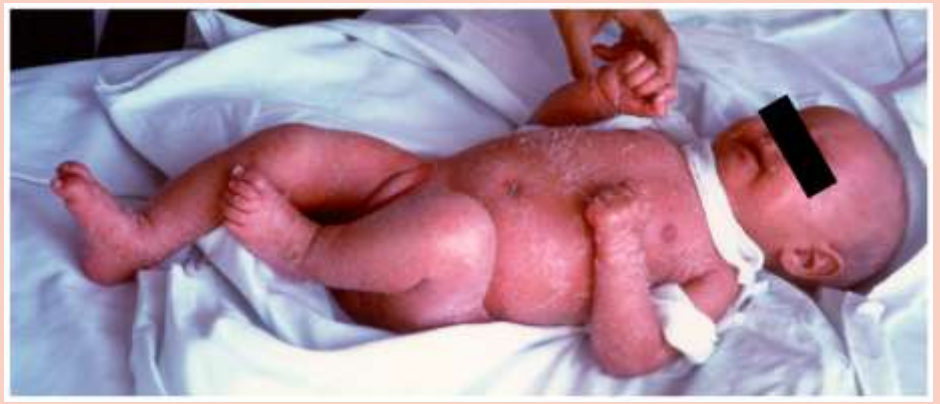
Eczema:

- **Hyper-IgE syndrome (HIES) :** STAT3 loss of function (LOF) and DOCK8 deficiency.

_eczema, elevated eosinophil count, and high serum IgE. increased susceptibility to cutaneous abscesses, CMC, pneumonia, tooth abnormalities, facies with a high palate and increased nasal width, and scoliosis.

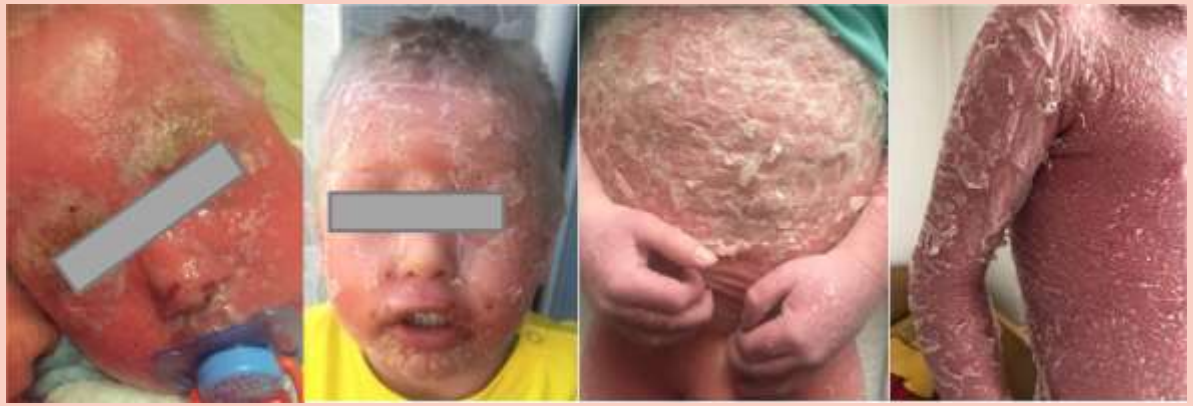
- **Wiskott-Aldrich syndrome (WAS)**
- **IPEX**

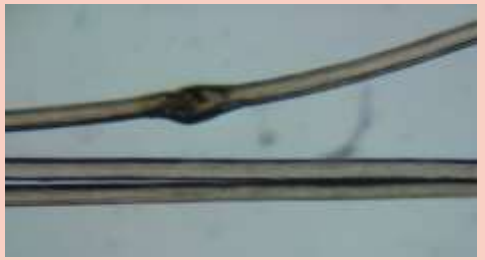
Newborn Erythroderma :



- **Omenn syndrome (OS) :** a subtype of severe combined immunodeficiency featured by the expansion of lymphocytes, peripheral eosinophilia, high serum IgE levels, hepatosplenomegaly, and generalized lymphadenopathy associated with severe, life-threatening infections.

- **Netherton syndrome :** erythroderma, bamboo hair, defective antibody response, and enteropathy.





IMMUNODEFICIENCY IN THE RHEUMATOLOGY UNIT:

Among the **“rheumatologic” manifestations**, sarcoidosis-like phenotype, early-onset systemic autoimmunity (particularly, systemic lupus erythematosus [SLE]), and vasculitis could represent warning signs for IEI.

Granulomatous Disease :

- **granulomatous phenotype of CVID:** pulmonary involvement, which could manifest in the form of granulomatous lymphocytic interstitial lung disease . pulmonary and systemic granulomatous lymphadenopathy.
- **hypomorphic RAG mutations**
- **chronic granulomatous disease (CGD)**

Connective Tissue Diseases and Vasculitis :

- SLE
- Dermatomyositis
- juvenile idiopathic arthritis
- deficiency of adenosine deaminase 2 (DADA2)

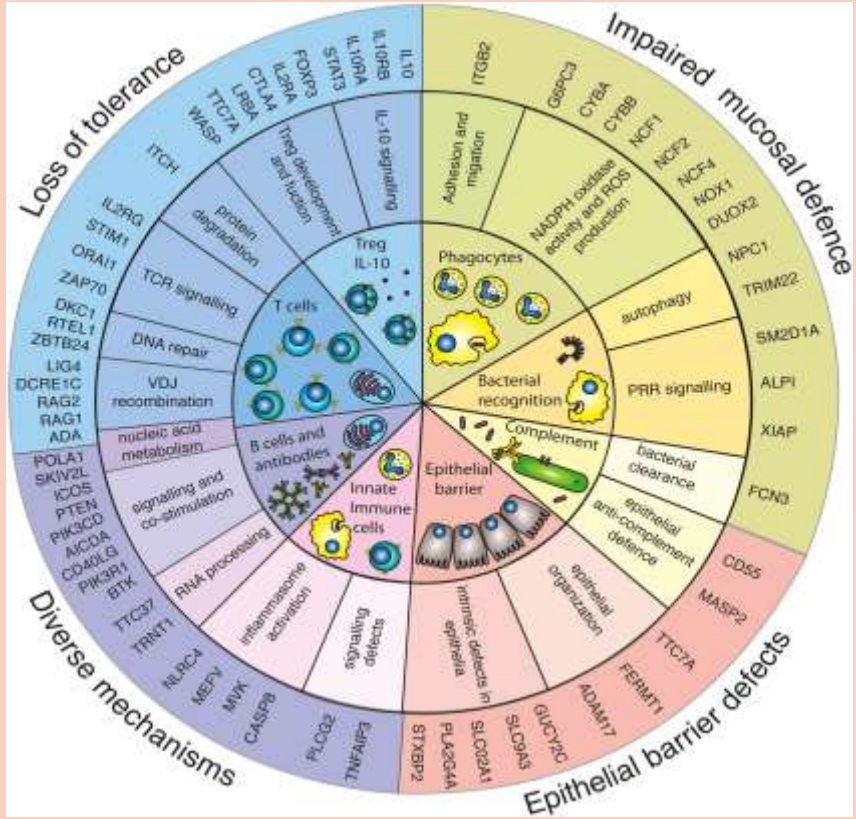
IMMUNODEFICIENCY IN THE GASTROENTEROLOGY UNIT :

- early-onset enteropathy and inflammatory bowel disease (IBD) are the most well-recognized gastrointestinal presentations of IEI.

- CVID, chronic granulomatous disease (CGD), and Treg opathies, X-linked agammaglobulinemia (XLA)

  IgA deficiency (celiac disease), IPEX , ...

Subgroups	Previous classification	Age of onset
Pediatric-onset IBD	Montreal classification A1	<17 yr
	Paris classification A1b	
Early-onset IBD	Paris classification A1a	<10 yr
Very early-onset IBD		<6 yr
Infantile-onset IBD		<2 yr
Neonatal IBD		<28 day of age



If immunodeficiency is suspected :

- 1) First of all, it is important to look through the **history and physical exam.**
- 2) Carry out **CBC ,diff**
- 3) **Test humoral (antibody) immunity**

  - IgG, IgA, IgM, IgE
  - Measure antibody in response to ‘test’ immunization
  - CD flowcytometry (CD19, CD20)

- 4) **Test for cell-mediated immunity :**

➢ Lymphocyte count (ALC)

➢ CD flowcytometry (CD3, CD4,CD8)

➢ In vitro tests of T cell function (LTT)

- 5) **Test for phagocytic cells :**

✓ Neutrophil count

✓ Neutrophil function tests (NBT, DHR)

✓ LADs (CD11, CD15, CD18)

- 6) Test for **complement :**

➢ C3,C4,CH50

- 7) **Definitive tests** :

➢ molecular testing and gene mutations.

Take home massages

1- Delay in diagnosis can leave patients with permanent tissue and organ damage by the time of diagnosis.

2- Try to identify primary immunodeficiencies early to prevent damage and lead to a better prognosis and quality of life for the patient.