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REVIEW

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Primary Immunodeficiencies Associated with Atopic Dermatitis

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ABSTRACT

Atopic dermatitis is the most common skin disease seen during childhood. Other allergic diseases may accompany atopic dermatitis and increased IgE and peripheral blood eosinophilia are common findings. Patients with atopic dermatitis who do not respond to standard treatment measures should be reassessed for differential diagnosis. Early-onset, treatment resistant severe atopic dermatitis with recurrent infection history apart from the infections occurring due to defective skin integrity are the warning signs for an underlying primary immunodeficiency. Clinicians should always remember that atopic dermatitis may be the first finding of an underlying primer immunodeficiency in patients. The sooner the diagnosis is made, the more likely it will be to avoid complications and morbidity.

Keywords: Atopic dermatitis, primary immunodeficiency, diagnosis

INTRODUCTION

Atopic dermatitis, which is the most common chronic skin disease, is the result of epithelial barrier dysfunction. The prevalence during childhood is 10-20% (1). Itchy, erythematous lesions and edema are seen in the acute phase whereas lichenification is the characteristic feature of the chronic period. Other allergic diseases such as food allergy, allergic rhinitis or asthma may accompany or occur in the following years since atopic dermatitis is the initial point of the atopic march in most of the patients. Increased IgE and peripheral blood eosinophilia are common findings (2).

The treatment approach for atopic dermatitis should comprise many aspects including removal of allergens and irritants, moisturisation of the skin, suppression of inflammation with topical antiinflammatory agents, and taking measures to prevent itching and infections (3) (Figure 1). Patients with atopic dermatitis who do not respond to standard treatment measures should be reassessed for the differential diagnosis; all systems should be reevaluated, and the past medical history and family history should be questioned in detail.

Early-onset, treatment resistant severe atopic dermatitis with a recurrent infection history apart from the infections occurring due to defective skin integrity are the warning signs for an underlying primary immunodeficiency (PID) (4). The PIDs associated with atopic dermatitis include Omenn Syndrome, IPEX Syndrome, Wiscott-Aldrich Syndrome, Netherton Syndrome, autosomal dominant hyper IgE Syndrome (AD-HIES) [signal transducer and activator of transcription 3 (STAT3)deficiency], autosomal recessive (AR)-HIES [dedicator of cytokinesis 8 (DOCK 8)], tyrosine kinase 2 (TYK2), phosphoglucomutase 3 (PGM3) deficiencies (5-8). Apart from these, atopic dermatitis may be seen in the course of STK4 deficiency, incomplete DiGeorge Syndrome or any other form of combined immunodeficiencies.

Since eczematous skin lesions may be the presenting sign, patients with severe AD should be investigated for PIDs. Early diagnosis of PIDs has prime importance for timely and effective treatment of the patients. Delay in diagnosis is related with an increase in the morbidity and complications, and a decrease in the quality of life (3).

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The objective of this review is to provide comprehensive information about primary immunodeficiencies with atopic dermatitis and their differential diagnosis. A table summarizing the diseases and distinguishing features is given below (Table I).

Omenn Syndrome

Omenn Syndrome is a rare form of severe combined immunodeficiency. It is characterized by exfoliative erythroderma, desquamatous alopecia, chronic diarrhea, failure to thrive, hepatosplenomegaly, lymphadenopathy, eosinophilia and high IgE levels. There is a predisposition for opportunistic infections (10).

A wide variety of hypomorphic mutations in V (D)J recombination genes (RAG1, RAG2, RMRP, Artemis etc.) and other SCID genes may cause the clinical picture (11). It classically presents in the first age. T-cell lymphopenia and impaired T cell function are present in the lymphocyte subgroup analysis by flow cytometry. In most cases B cells are absent and accordingly IgA, G, M levels are low. High IgE levels and eosinophilia seen in the course of disease may be due toabnormal release of IL-4 and IL-5 from activated T cells and exaggerated Th2 response (12, 13).

Treatment of infections and prevention of opportunistic infections should be targeted. The definitive and curative treatment is hematopoetic stem cell transplantation (HSCT) (14).

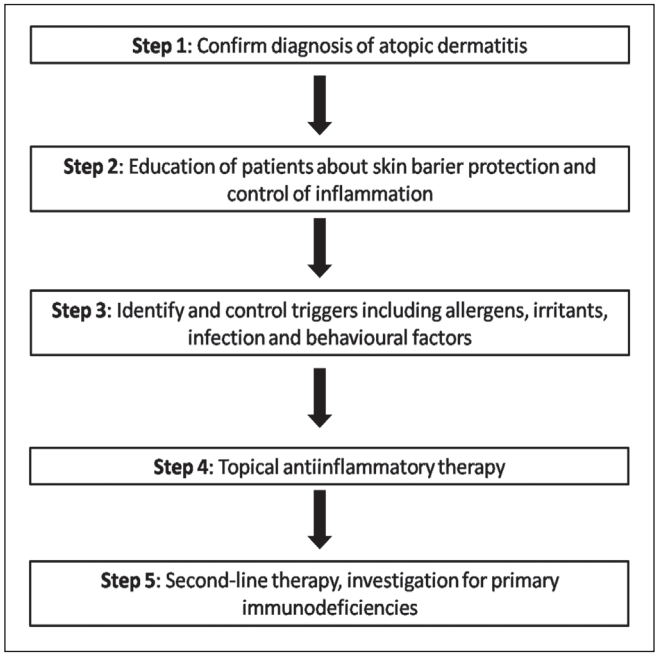

Figure 1. Approach to patient with atopic dermatitis, modified from (9).

IPEX Syndrome

IPEX is an acronym for immune dysregulation, polyendocrinopathy, enteropathy, X-linked. The disease classically presents in infancy (male infants) and is characterized by multiple endocrinopathies, severe chronic enteropathy, dermatitis, anemia, and thrombocytopenia.

FOXP3 is a member of forkhead box P (FOXP) family of transcription factors and essential for Treg cell function (15). Treg cells, which clearly have a critical role in central tolerance and in inhibiting autoimmune diseases and self reactivity, are responsible for clinical findings seen in the IPEX syndrome. Life-threatening chronic diarrhea due to an autoimmune enteropathy, autoimmune endocrinopathy (neonatal type 1 diabetes or thyroiditis) are classical findings of the illness. Autoimmunity of all types affecting many organ systems (autoimmune hepatitis, autoimmune cytopenia, interstitial lung disease) may occur.

IgE-mediated severe food allergies are also common. While atopic dermatitis is present during early infancy, skin findings such as alopecia universalis, diffuse erythema may be seen over time (16).

Laboratory findings include IgE and IgA elevation and peripheral blood eosinophilia. Autoantibody positivity is a common finding. Flow cytometric analysis of lymphocyte subsets may show lack of CD4 + CD25 + Treg cells.

Main part of the treatment is supportive therapy (treatment of diabetes, blood transfusions, dietary modifications, parenteral nutrition). Intensive immunosupression with steroid, cyclosporine, tacrolimus, infliximab etc. is frequently used to control immune dysregulation leading to autoimmune disease and allergic inflammation. The only curative treatment is HSCT with limited success and considerable morbidity and mortality especially when it is not performed in the early ages (17-19).

Wiscott-Aldrich Syndrome

Wiscott-Aldrich Syndrome is characterized by eczema, microthrombocytopenia, eosinophilia, recurrent infections and increased risk of autoimmunity and malignancy. As an X-linked disorder, it is seen almost exclusively in males. WAS gene encodes a protein which is involved in

cytoskeletal reorganization and actin polymerization and its absence impacts immunologic synapse formation (20).

Since mutation in the WAS gene result in a wide spectrum of clinical phenotypes, identification of the type of mutation (termination, frameshift, missense) by molecular diagnosis is crucial for predicting the phenotype of the disease and giving chance for prenatal diagnosis.

All cell types originating from the hematopoietic stem cell may be affected due to the mutation in the WAS gene. Impaired function of T, B, NK cells leads to combined immunodeficiency; small platelets and thrombocytopenia ends with tendency to bleeding. Inadequate Treg function and intrinsic loss of B cell tolerance may result in increased autoimmunity. Predisposition to malignancies such as primarily B-cell lymphoma, is also a common feature of the disease (20).

Table I. Primary Immunodeficiencies associated with atopic dermatitis.

	Additional manifestations to AD	Mutated gene	Function of the gene	Differentiating laboratory features	Treatment
Omenn syndrome	Hepatosplenomegaly, lymphadenopathy, diarrhea, failure to thrive	SCID genes	V(D)J recombination, T and B cell development and function	Lymphopenia, hypogammaglobulinemia, eosinophilia, high IgE	HSCT
IPEX syndrome	Chronic diarrhea, multiple endocrinopathies, alopecia universalis	FOXP3	Functional differentiation of Tregs	IgE and IgA elevation and peripheral blood eosinophilia lack of CD4 + CD25 + Treg cells. Autoantibody positivity	Supportive therapy, immunomodulatory agents, HSCT
Wiscott-Aldrich syndrome	Recurrent sinopulmonary infections, bleeding disorder, autoimmunity, increased malignancies	WAS	Actin cytoskeleton remodeling	Thrombocytopenia, microplatelets (low MPV), high IgE and IgA	Supportive care, HSCT, gene therapy?
Netherton syndrome	Bamboo hair, food allergy, asthma, angioedema, recurrent infections of respiratory and gastrointestinal system	SPINK5	Epithelial barrier integrity via serine protease inhibitor	High IgE, spesific IgE positivity for food allergens	IVIG
AD HIES-STAT3	Cold abscess with S. aureus affecting skin and internal organs, recurrent lung infections complicating with pneumatoceles, coarse facial features, hypermobility of joints, retained primary teeth, vascular malformations	STAT3	intracellular signal transduction pathway of many cytokines	Very high IgE (>2000IU/ml)	IVIG, antimicrobial prophylaxis, HSCT?
DOCK8 deficiency	Cutaneous viral infections, food allergy, asthma, increased risk of malignancy	DOCK8	cell adhesion, migration, cell structure, rearrangement of the cytoskeleton	Lymphopenia, low IgM, high IgE	HSCT
TYK2 deficiency	Early-onset atopic dermatitis-like skin lesions, skin abscesses, oral candidiasis, recurrent sinopulmonary infections, cutaneous viral infections increased risk of infections with BCG and non-typhi Salmonella	TYK2	signal transduction between type 1 IFN and cytokine receptors and STAT transcription factors	Normal or slightly elevated IgE levels	Supportive care, HSCT?
PGM3 deficiency	Psychomotor retardation, myoclonus, recurrent EBV and sinopulmonary infections complicated with bronchiectasis	PGM3	N-glycan biosynthesis	Lymphopenia, neutropenia, high IgE	Supportive care, HSCT?

In laboratory evaluation IgA and IgE levels are elevated, eosinophilia is present, platelet count and MPV is low. Antibody response to vaccinations is impaired.

Conventional treatment and supportive therapy with prophylactic antimicrobials (TMP-SMX, acyclovir), platelet transfusions, irradiation of blood products and testing for CMV and IVIG replacement therapy should be done. Immunosuppressive agents are needed to control autoimmune manifestations. Some patients may need splenectomy to control bleeding. The curative treatment is HSCT. Gene therapy is an alternative and promising therapy under investigation (21, 22).

Netherton Syndrome

Netherton syndrome is a rare AR disorder of cornification presenting with congenital ichthyosiform erythroderma, specific hair shaft abnormality termed trichorrhexis invaginata and allergic manifestations. There is mutation in the SPINK5 gene encoding a multidomain serine protease known as lymphoepithelial Kazal-type 5 inhibitor (LEKT1). LEKT1 functions as a 'super' serine protease inhibitor and its absence leads to epithelial barrier dysfunction (23, 24). The skin findings, scaling erythroderma, starts early in life and creates a high risk for life-threatening complications such as hypernatremic dehydration, sepsis and failure to thrive. The easily broken hair, defined as trichorrhexis invaginata or bamboo hair, is a pathognomonic feature of the disease (25, 26).

Food allergy, hay fever, angioedema, anaphylaxis and asthma may also be seen in the course of the disease. There is increased risk for respiratory and gastrointestinal system infections (27).

The treatment is mostly symptomatic but there are also reports regarding IVIG replacement therapy improving skin integrity and decreasing frequency of infections (27).

Table II. AD-HIES NIH scoring system (5).

Clinical findings/points	0	1	2	3	4	5	6	7	8	9	10
Highest Serum IgE (IU/mL)	<200		200-500		501-1000				1001-2000		>2000
Skin abscesses	None		1-2		3-4				>4		
Pneumonia	None		1		2		3		>3		
Parenchymal lug disease	Absent						Bronchiectasis		Pneumatocele		
Retained primary teeth	None	1	2	3					>3		
Scoliosis	<10°		10-14°		14-20°				>20°		
Fractures with minimal trauma	None				1-2				>2		
Highest eosinophil count	<700				700-800		>800				
Characteristic face	Absent			Mildly		Present					
Midline anomaly	Absent					Present					
Newborn rash	Absent					Present					
Eczema (worst)	Absent	Mild		Moderate	Severe						
URI/year		3		4-6	>6						
Candidiasis	None	Oral		Fingernails		Systemic					
Other serious infections	None				Severe						
Fatal infection	Absent				Present						
Hyperextensibility	Absent				Present						
Lymphoma	Absent				Present						
High palate	Absent			Present							
Young-age correction	>5 yr			2-5 yr		1-2 yr		≤1 yr			

Score >40: likely to carry AD-HIES phenotype, 20-40: inconclusive, <20: unlikely.

AD HIES-STAT3 Deficiency

AD-HIES or Job Syndrome with broader array of clinical features is characterized by atopic dermatitis-like skin rash, cold abscess (skin and visceral organs) mainly associated with S. aureus, recurrent pulmonary infections, pneumatocele and bronchiectasis formation, skeletal anomalies such as scoliosis, hyperextensibility in joints, retention of primary teeth, characteristic facial appearance, mucocutaneous candidiasis and high IgE levels (> 2000 IU / mL, often> 20,000 IU / mL) (28). Multisystem involvement including craniofacial, dental, musculoskeletal, neurological and vascular anomalies, in addition to skin rash and IgE elevation, is distinctive feature for AD-HIES (29, 30) and is included in the scoring of the disease which was devised by US National Institutes of Health (NIH) (Table II). The existing HIES scoring systems may skip the patients with younger ages since all the findings of scoring does not appear or present yet in infancy and early childhood. For this reason, Schimke et al. Suggested that the diagnostic work-up should be initiated if any of the 7 items from the scoring system exists: abscesses of the internal organs, other severe infections, pneumatoceles, nail or mucocutaneous candidiasis, bone fractures without significant trauma, scoliosis and a family history of HIES even if total score is low (31). There is increased risk for non-Hodgkin lymphoma (32).

The dominant negative mutations in the STAT3 gene cause the disease. Since the STAT3 gene encodes a cytoplasmic protein that is involved in the intracellular signal transduction pathway (JAK-STAT) of a number of cytokines (IL 6, 10, 11, 21, 22), both pro- and anti-inflammatory responses are affected and immune dysregulation occurs.

Table III. Comparison of clinical and laboratory features of different genetic defects causing HIES (modified from (46).

	AD-HIES STAT3 mutations	AR-HIES DOCK8 mutations	AR-HIES TYK2 mutations	AR-HIES PGM3 mutations
Sinopulmonary infections	+++	+++	+++	+++
Cutaneous viral infections	-	+++	+++	++
Mucocutaneous candidiasis	+++	++	+	+
Susceptibility to mycobacteria	-	-	+++	-
Abscesses with S. aureus	+++	++	++	++
Newborn rash	+++	-	++	-
Eczema	++	+++	+	+++
Asthma	-	++	-	+++
Food allergies	-	+++	-	+++
Malignancy risk	+	++	-	++
Coarse facial features	+++	-	-	-
Skeletal abnormalities (Scoliosis)	+++	-	-	++
Retained primary teeth	+++	-	-	-
Hyperextensible joints	+++	-	-	-
Vascular aneurysms	+++	-	-	+/-
Vasculitis	-	-	-	++
Developmental delay	-	-	-	++
Elevated IgE	+++	++	+	+++
Eosinophilia	++	+++	-	+++
Decreased IgM	-	++	-	-
T cell lymphopenia	-	+++	**variable**	**++(mostly CD8)**
Decreased Th17 cells	+++	++	-	-
Reversed CD4/CD8 ratio	-	-	-	++
Expansion of Th2 cells	++	+++	-	+++

Laboratory findings include high IgE levels, decrease in Th17 cells and cytokines, and deterioration in T and B cell subgroups. There is poor response to both protein and polysaccharide immunisations (33).

Supportive care should be provided to control pruritus and eczamatoid dermatitis and long-term antibiotic prophylaxis is recommended for the prevention and treatment of infections. IVIG replacement is required to control infections and diminish pulmonary complications in patients with lowered immunoglobulin levels or significantly lowered vaccine responses (34, 35). Further studies are needed to assess the role of omalizumab treatment in HIES (36). HSCT was performed in selected patients but did not demonstrate long term benefit (37).

AR HIES

DOCK8 Deficiency

DOCK8 deficiency is a combined immunodeficiency characterized by recurrent viral and bacterial infections, severe atopy, early onset malignancies (6). The hallmark of the disease is the tendency for cutaneous infections with a variety of viruses such as herpes (HSV), herpes zoster (VZV), disseminated Varicella (VZV), molluscum contagiosum (MCV) (38).

50-80% of patients have allergies to food or environmental allergens, and 30% have asthma (39). Facial paralysis, hemiplegia, cerebral aneurysms and CNS vasculitis are among the common findings of the patients (6). There is an increased risk of malignancies; including HPV-associated squamous cell carcinoma, EBV-associated Burkitt lymphoma, diffuse large B-cell lymphoma (39).

DOCK8 is an important protein involved in cell adhesion, migration, cell structure and in the rearrangement of the cytoskeleton. Mutations in the DOCK8 gene by autosomal recessive trait usually affect the cells of the immune system. T cell differentiation and survival are deteriorated (38). Susceptibility to cutaneous viral infections may be due to an inability of CD8+ T cells to effectively enter the skin.

Laboratory findings include slightly elevated IgE levels, significantly low IgM levels, peripheral eosinophilia. T cell counts are low, antibody responses to vaccinations are absent.

DOCK8 deficiency should be treated with HSCT in the early phases of the disease before the development of complications (40, 41).

TYK2 Deficiency

TYK2 deficiency was formerly one of the AR-HIES forms since early-onset atopic dermatitis-like skin lesions, skin abscesses, oral candidiasis, recurrent sinopulmonary infections, cutaneous viral infections are common findings seen in the course of the disease. Also there is an increased risk of infections with BCG and non-typhi Salmonella (8). Since TYK2 gene encodes a protein that functions in the signal transduction between type 1 IFN and cytokine receptors and STAT transcription factors, the disease hasa similar phenotype with AD-HIES regarding infectious complications and immunological findings (42). The IgE levels are either normal or slightly elevated. TYK2 deficiency is one of the reasons of mendelian susceptibility to mycobactrial diseases.

PGM3 Deficiency

PGM3 deficiency is characterized by atopic dermatitis, atopy of any kind, autoimmunity, elevated IGE levels, myoclonus and neurocognitive impairment secondary to dysmyelinization, recurrent EBV infections and sinopulmonary infections and bronchiectasis (43, 44).

The common findings in the defined patients are psychomotor retardation and developmental delay.

Since PGM3 has a central role in the synthesis of uridine diphosphate N-acetylglucosamine which is essential for N-glycan production, the deficiency of PGM3 results in a glycosylation defect. Many proteins of the immune system such as immunoglobulins, adhesion molecules, complement and cytokines are glycosylated and glycosylation is required for their function therefore PGM3 deficiency may lead to a severe form of immunodeficiency.

The laboratory findings include high IgE, neutropenia, eosinophilia. Proliferation and differentiation of T cells affected and the production of Th2 and Th17 cytokines is deteriorated. T and B cell lymphopenia and reversal of CD4/CD8 ratio are seen (44, 45). Clinical and laboratory features and distinctive properties of genetic defects causing HIES syndrome are shown in Table III.

CONCLUSION

Clinicians should always keep in mind that atopic dermatitis may be the first finding of an underlying primary immunodeficiency. In a patient with atopic dermatitis, the presence of recurrent, atypical, invasive infections and autoimmunity, disease in other organ systems, and the inability to control atopic dermatitis with standard treatment measures should be warning signs for primary immunodeficiencies. The sooner the diagnosis is made, the more likely it will be to avoid complications and morbidity.

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