IPOPI
INTERNATIONAL
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FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

PIDs AND **THE SKIN**

ABBREVIATIONS

CVID	Common variable immunodeficiency
CGD	Chronic granulomatous disease
IPEX	Immunodysregulation polyendocrinopathy enteropathy X-linked
IPOPI	International Patient Organisation for Primary Immunodeficiency
PGM3	Phosphoacetylglucosamine mutase-3
PID	Primary immunodeficiency
SCID	Severe combined immunodeficiency

Primary immunodeficiencies and the skin (1st edition).

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INTRODUCTION

This booklet explains the range of skin issues that can affect people with primary immunodeficiencies (PIDs) and how they can best be prevented and treated.

Primary immunodeficiencies (PIDs) are rare diseases that occur when certain parts of the immune system are either missing or are not working normally. The immune system is complex and protects the body from infections and other conditions. When the immune system is not working properly, patients with PIDs are more likely to get a variety of different conditions and are more vulnerable to infections, which potentially can be life-threatening.

Most patients can experience skin conditions associated with their PID and sometimes skin infections can be one of the first warning signs of the presence of an underlying PID.

The following sections review the association between skin conditions and PIDs, how they can indicate the presence of an underlying PID, and how they can best be prevented and treated.

PIDs

At present, over 430 different PIDs have been identified ranging from the relatively common (e.g. selective immunoglobulin A deficiency) to the very rare (e.g. severe combined immunodeficiency [SCID]).

PIDs are rare disorders, and while some are more common than others all PIDs can profoundly impact the lives of persons with the condition. PIDs can be diagnosed at any time during the lifespan of a person but the most severe forms of PIDs are usually diagnosed in childhood. That said, others are often recognised during adulthood either because of their later onset or because they have previously been misdiagnosed or have gone undiagnosed.

PIDs can have widely differing presentations, from relatively mild to life-threatening. Some develop over time and worsen as late manifestations or complications appear.

People with PIDs are more susceptible to infections and complications resulting from infections. Often many persons with PIDs go undiagnosed for several years and repeatedly receive treatment with antibacterial drugs but with no permanent cure or positive long-term effect. As different PIDs affect different parts of the immune system a patient's susceptibility to infections depends on which type of PID they have. Respiratory tract infections are commonly associated with antibody deficiencies (e.g. common variable immunodeficiency [CVID]) or complement deficiencies. Lower respiratory tract infections (e.g. pneumonia) are also common with chronic granulomatous disease (CGD), T-cell deficiencies and CD40L deficiencies.

Skin infections are often associated with many PIDs, especially phagocyte cell PIDs (e.g. CGD) combined immunodeficiencies (e.g. SCID, Wiskott-Aldrich syndrome (WAS), CD40L deficiency), CVID and Hyper-IgE syndrome. For some PID patients, skin manifestations may be the presenting lesion that indicates an underlying immunodeficiency.[1]

[1] Lewis DJ, et al. Cutaneous manifestations of genodermatoses and primary immunodeficiency. Dermatol Online J 2019;25:13030

SKIN MANIFESTATIONS OF PIDs

The skin manifestations of PIDs often occur early on in the disease and can signal findings of the underlying immunological condition. Therefore, awareness of associations between skin findings and immune deficiency may aide in the early detection and treatment of serious or life-threatening immunologic defects.

Up to 70% of people with a PID exhibit skin manifestations (such as bacterial, fungal [e.g. candidiasis] or viral infections [e.g. molluscum and warts], or eczema) and these signs may be among the primary presenting symptomatology of a PID.[2,3]

Bacterial and fungal skin infections associated with PIDs may lead to recurrent pyogenic (producing pus) abscesses. Indeed, recurrent, deep abscesses of the skin are one of the ten warning signs for PIDs both in children and in adults: [4]

- ≥4 new ear infections within 1 year
- ≥2 more serious sinus infections within 1 year
- ≥2 months on antibiotics with little effect
- ≥2 pneumonias within 1 year
- Failure of an infant to gain weight or grow normally
- **Recurrent, deep skin or organ abscesses**
- Persistent thrush in mouth or **fungal infection on skin**
- Need for intravenous antibiotics to clear infections
- ≥2 deep-seated infections including septicaemia
- A family history of PID

Children with severe atopy (allergy), eczema and erythroderma (redness and scaling of the skin) should be evaluated for the presence of an underlying PID. The potential underlying PID diagnoses in patients presenting with eczema is shown in the Table.

[2] Erzsebet Bojtor A, et al. [Cutaneous manifestations in primary immunodeficiency diseases. Orv Hetil 2018;159:937-47

[3] Lehman H, Gordon C. The skin as a window into primary immune deficiency diseases: Atopic dermatitis and chronic mucocutaneous candidiasis. J Allergy Clin Immunol Pract 2019;7:788-98

[4] McCusker C, et al. Primary immunodeficiency. Allergy Asthma Clin Immuncol 2018;14(Suppl 2):61

THE POTENTIAL UNDERLYING PID DIAGNOSES IN PATIENTS PRESENTING WITH ECZEMA (ADAPTED FROM SHARMA ET AL 2017) [5]

	Classical Hyper-IgE syndrome (STAT3-Loss of function mutations)	**Hyper-IgE syndrome (Other gene defects)**
Key features	• Early onset eczema • Recurrent cold abscesses • Coarse facies • Skeletal defect	• Eczema • Recurrent severe skin infections by HSV, MCV, HPV • Atopy, asthma
Newborn rash	Yes	No
Molecular defect	*STAT3* gene (loss of function mutations)	• *ERBB2IP, TGFBR1, TGFBR2, CARD11* and *I L6ST* genes (autosomal dominant loss of function mutations) • *ZNF341, IL6ST, IL6R, SPINK5, PGM3, TYK2* and *DOCK8* genes (autosomal recessive loss of function mutations)
Immunological abnormalities	IgE >2,000 IU/ml, absent/ reduced Th17 T cells and pSTAT3 expression, eosinophilia	IgE >2,000 IU/ml, lymphopenia, low IgM and variable IgG, T-cell defect in DOCK8 deficiency
Neurological involvement	Stroke, lacunar infarct	In PGM3 mutation: ataxia, developmental delay, sensorineural hearing loss

DOCK8: dedicator of cytokinesis-8; HPV: human papilloma virus; HSV: Herpes simplex virus; MCV: Molluscum contagiosum virus; PGM3: phosphoglucomutase-3; STAT: signal transducer and activator of transcription; Tyk2: tyrosine kinase-2

	Wiskott-Aldrich syndrome (WAS)	**Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX)**
	• Eczema • Bleeding manifestations • Recurrent infections • Thrombocytopenia, small size platelets, autoimmune diseases	• Eczema • Autoimmune enteropathy • Endocrinopathy (hypo-/hyperthyroidism, Type I diabetes mellitus)
	No	No
	WAS gene mutation	*FOXP3* gene mutation
	Low IgM, normal or low IgG, high IgA and IgE; decreased T-cell number and function	• Neutropenia, high IgE • Normal IgG, IgA and IgM • Low to absent regulatory T cells
	No	No

[5] Sharma D,et al. Approach to a child with primary immunodeficiency made simple. Indian Dermatol Online J 2017;391-405

ECZEMA

Eczema, also known as atopic dermatitis, is a condition that causes the skin to become itchy, red, dry, scaly and inflamed. It can affect small patches of skin or it can be more widespread across the body. People with eczema often also have respiratory allergies, such as allergic rhinitis, asthma or food allergies.

Some PIDs can result in eczema-like skin conditions. In particular, PIDs that cause high levels of IgE in the body commonly cause eczema-like symptoms. These PIDs include autosomal dominant STAT3 (loss of function) deficiency (so called “hyper-IgE syndrome”), combined immunodeficiency (such as Wiskott-Aldrich syndrome, DOCK8 [dedicator of cytokinesis 8] deficiency, phosphoacetylglucosamine mutase-3 [PGM3] deficiency), and several immunodysregulation syndromes such as polyendocrinopathy enteropathy X-linked (IPEX).

Scratching itchy skin in eczema can cause the skin to become broken and this can lead to infections of the skin and even the bloodstream. This is a considerable problem for people with PIDs, who are more susceptible to infections than other people. Skin infections can also cause exacerbations (or ‘flare-ups’) of eczema.

OTHER MANIFESTATIONS

Chronic mucocutaneous candidiasis may indicate an underlying PID such as hyper-IgE syndrome, or the presence of several mutations in genes associated with PIDs, such as STAT2 GOF, IL-17, dectin 1, AIRE and CARD-9.[5]

The presence of warts may be indicative of combined immunodeficiency or WHIM syndrome. Other manifestations may include granulomas, pigment changes and dysplasia of the skin, hair or nails.

MANAGEMENT OF SKIN MANIFESTATIONS OF PIDs

INFECTIONS

Patients with PIDs may require prophylactic treatment for the underlying skin condition. Patients may require both antimicrobials and antifungals to manage and prevent bacterial and fungal skin infections.[3]

Patients, parents and carers must promptly contact their doctor if an infection is suspected to allow prompt diagnosis and treatment. Some infections can be treated at home, but serious infections may need hospital care.

Often a sample (such as pus) will be taken to help doctors identify the infecting organism(s) and choose the best antimicrobial treatment. Identifying the organism is important because treatment can be lengthy or complex in PID and so doctors need to be sure they are giving the correct medications.

Patients with PIDs are sometimes prescribed antimicrobials for long periods of time to protect against infections. This is known as 'prophylaxis'. Doctors consider the benefit/risk balance on an individual patient basis because of possible side effects and the risk of antimicrobial resistance (when microorganisms become resistant to the effects of antimicrobial drugs).

It is possible that people with PIDs may need higher doses or longer courses of antimicrobials than other people because their infections can be harder to treat. Sometimes more than one type of of antimicrobial drug may be needed.

MANAGING ECZEMA

Where possible, any allergic factors (or 'allergens') that trigger eczema should be identified so that these can be avoided. These can include certain fabrics (such as wool), animal dander (skin flakes, like human dandruff), grass pollen, ingredients (such as fragrances) in soaps, detergents or other skincare products, and foods. Possible trigger factors can be investigated using tests on the skin (known as skin prick tests and patch tests) or by blood tests.

Treatments that can be useful for eczema include:

- Regular bathing (using a non-irritating soap), together with the use of moisturiser (or 'emollient') creams or ointments to soothe and hydrate dry skin, especially after bathing.
- Creams or ointments containing corticosteroids can help to reduce itchiness and inflammation. Corticosteroid products should be used carefully according to the instructions provided by the doctor or patient information leaflet.
- Wet wraps (also called occlusive dressings) can be used to hydrate the skin and avoid scratching.
- Oral antihistamine medicines may reduce itching in eczema by blocking the action of histamine, a chemical in the body that is involved in allergic reactions.
- Medicines called calcineurin inhibitors (tacrolimus and pimecrolimus) are sometimes used topically (as creams or ointments) to treat eczema that does not respond to the treatments above. These work by blocking chemicals that cause inflammation.
- In some cases, certain oral medicines (such as corticosteroids, ciclosporin, methotrexate and azathioprine) that affect the immune system are used to treat severe eczema that does not respond to topical treatment.

PSYCHOLOGICAL STRESS

It is important to be aware of the added psychological stress that can sometimes be associated with skin conditions, especially if the condition is visible or during flare-up episodes. Patients affected by this should contact their doctor to discuss how to best manage this and find out about the support services that are available, such as a psychologist, counsellor and stress management. PIDs are otherwise typically 'invisible' conditions.

PREVENTING SKIN INFECTIONS

There are many things that patients with PIDs, parents and carers can do to help prevent skin infections, while maintaining as normal a life as possible. These include good hygiene, such as:

- Washing the hands regularly and carefully, especially before meals and after using the toilet, outdoor activities and playing with pets
- Cleaning and dressing cuts and scrapes
- Catching coughs and sneezes in tissues – this is important both for patients and family members
- Avoid contact with people with infections, where possible.

FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations in 69 countries worldwide, please visit **www.ipopi.org**.

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