Skin disorders are prominent features in primary immunodeficiency diseases: A systematic overview of current data

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ABSTRACT

Background

Primary immunodeficiency diseases (PIDs) are characterized by an increased risk of infections, autoimmunity, autoinflammation, malignancy, and allergic disorders. Skin disorders are also common clinical features in PIDs and may be among the presenting manifestations. Recognition of specific PID-associated skin conditions in combination with other clinical features as described in the currently used warning signs could raise suspicion of an underlying PID.

Objective

We aimed to provide a systematically obtained overview of skin disorders and their prevalence in PIDs. Secondary, the prevalence of *Staphylococcus* (*S.*) *aureus*–associated skin disorders and atopy was reviewed, as these are the most prominent skin features in PIDs.

Methods

A systematic search was performed in EMBASE, MEDLINE, Web of Science, Cochrane, and Google Scholar (up to May 9, 2018). All original observational and experimental human studies that address the presence of skin disorders in PIDs were selected. We rated study quality using the Institute of Health Economics Quality Appraisal Checklist for Case Series Studies.

Results

Sixty-seven articles (5030 patients) were included. Study quality ranged from 18.2% to 88.5%. A broad spectrum of skin disorders was reported in 30 PIDs, mostly in single studies with a low number of included patients. An overview of associated PIDs per skin disorder was generated. Data on S. aureus-associated skin disorders and atopy in PIDs were limited.

Conclusion

Skin disorders are prominent features in PIDs. Through clustering of PIDs per skin disorder, we provide a support tool to use in clinical practice that should raise awareness of PIDs based on presenting skin manifestations.

INTRODUCTION

Primary immunodeficiency diseases (PIDs) represent a heterogeneous group of inherited disorders caused by mutations in genes encoding functional proteins of the immune cells. Based on registries and epidemiologic surveys, it has been suggested that six million people are living with a PID worldwide, whereas only 27.000-60.000 patients have been identified to date.[1] PIDs are usually characterized by recurrent and/or severe infections as well as an increased risk of autoimmunity, autoinflammation, malignancy and allergic disorders.[2-4] Moreover, both infectious and noninfectious skin disorders are common in PIDs and may be among the presenting clinical manifestations.[5-8] *Staphylococcus* (*S.*) *aureus* induced skin infections are the most common infectious skin disorders reported in PIDs, including leukocyte adhesion defects (LAD), chronic granulomatous disease (CGD), severe congenital neutropenia and hyper immunoglobulin (Ig) E syndrome (HIES).[9-11] On the other hand, dermatitis is one of the most prominent noninfectious skin manifestations in PIDs and may be part of the atopic syndrome.[12] Patients with an atopic constitution show next to atopic dermatitis (AD) tendency towards development of food allergies, asthma and rhinoconjunctivitis.[13]

Based on previous narrative reviews without a systematic approach, *S. aureus* skin infections, dermatitis and other skin disorders as well as atopy seem to be all fairly common in patients with a PID, but are also frequently described in the general population.[12] Therefore, it is of importance to realize that presence of specific skin symptoms alone does not necessarily point towards a PID. However, recognition of specific skin conditions in combination with other clinical features suggestive of an immunodeficiency should raise awareness to an underlying PID and may facilitate earlier diagnosis of PIDs.[14]

The aim of this review was to provide a systematically obtained overview of skin disorders and their prevalence in patients with PIDs. Focusing on two prevalent skin disorders in PIDs, the relation between PIDs and *S. aureus*-related skin disorders and atopy will be reviewed in more detail.

MATERIALS AND METHODS

Studies

This review with a systematic approach was conducted and reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines, where applicable.[15] All original observational and experimental human studies were included. We selected both articles reporting skin disorders in patients with PIDs and articles present-

ing a differential diagnosis of a specific skin disorder that includes a PID. No restrictions were made with respect to publication date and language. We excluded case reports (<5 patients), conference abstracts, letters and editorials as the quality of these types of articles can be highly variable. Also articles describing acquired immunodeficiencies, articles reporting skin disorders in PIDs that developed after or during treatment/intervention and articles in which the description of skin disorders in PIDs was not part of the results section were excluded. Data on skin disorders were only extracted if at least five patients per PID were reported.

Study participants

Patients of all ages with a PID according to Picard *et al.*[16] from both hospital setting and general population were included.

Study outcomes

The primary outcome is the presence of skin disorders in PIDs. Secondary outcomes include the prevalence of skin disorders in PIDs, *S. aureus*-associated skin disorders in PIDs, and PIDs associated with an atopic constitution (i.e. atopic dermatitis, food allergy, asthma, rhinoconjunctivitis).

Search strategy

The electronic search was conducted in EMBASE, MEDLINE, Web of Science, Cochrane, and Google Scholar up to May 9th 2018 (Appendix 1). The search was composed of terms of the categories primary immunodeficiency, skin disorder, *Staphylococcus aureus* and atopy supplemented by specific PIDs and skin disorders based on recent literature.[12,17-19]

Study selection and data extraction

All studies identified in the systematic search were screened for relevance by title and abstract. Duplicates and studies that did not meet our inclusion criteria were excluded (Appendix 2). Remaining articles were assessed for eligibility by full text review. Furthermore, a cross-reference check was performed to identify other eligible studies based on the reference lists of all included articles and relevant review articles. Translation of non-English studies was conducted officially. Study selection and data extraction were performed independently by two researchers (JdW and JvV, JdW and RB or JvV and RB). Disagreements were resolved and consensus was reached. If one population was described in different articles, we included the study with the most detailed description of the results. The methodological quality of the individual articles was rated using the Institute of Health Economics (IHE) Quality Appraisal Checklist for Case Series Studies (Appendix 3).[20]

Analysis of data

The prevalence of skin disorders in PIDs was extracted from the included studies. If required, the prevalence was calculated with the available raw data. Because the reported number of patients with a PID was mainly low, the proportion of patients with a PID and skin disorders was descriptively presented. Proportions of skin disorders in PIDs were compared with the prevalence of skin disorders in the general population.[21-26] Data from the general population were based on a birth cohort in Finland (n=1932, age 45-47 years) and a Dermatology outpatient clinic in Turkey (n=11 040, age 1-99 years).[21,22] In addition, a nationwide study of Furue *et al*.[23] reported the prevalence of cutaneous disorders in 67 448 Japanese patients of all ages. In the study of Verhoeven *et al*.[24], the skin disease prevalence per 1000 patient-years in family practices in the Netherlands was converted to a point prevalence in the general population (n=501, age 18-97 years). Finally, two studies from the United States of America and the United Kingdom performed in 1978 and 1976 showed the prevalence of skin disorders in community studies in respectively 20749 (age 1-74 years) and 614 (age 15-74 years) patients.[25,26]

RESULTS

Study characteristics

The literature search identified 15 871 studies. Removal of duplicates resulted in 12 834 studies. Screening on title and abstract yielded 86 full-text articles of which 36 articles remained after full-text screening. Finally, after cross-reference check, a total of 67 articles (5030 patients) were included for further analysis (Figure 1). Skin disorders in patients with PIDs were described in 67 articles, and three articles reported PIDs as part of the differential diagnosis of a specific skin disorder. Fifty-seven studies showed a mean percentage of males of 62.2%. Both children and adults were included with a mean age of 15.8 years, reported in 26 articles. The IHE Quality Appraisal Checklist for Case Series Studies ranged from 18.2% to 88.5% (Table S1).

Skin disorders and their prevalence in primary immunodeficiency diseases

Thirty individual PIDs and their related skin manifestations were found. We categorized the skin disorders in 15 main groups and in 20 more specific subgroups (Table 1). The skin disorders per PID were mainly reported in single studies. Therefore, meta-analysis was not possible. The presence of skin telangiectasia, café au lait macules and hypopigmented macules in ataxia-telangiectasia (AT), skin abscesses in HIES, atopic dermatitis in hypogammaglobulinemia, atopic dermatitis, alopecia (areata), vitiligo and psoriasis in selective IgA deficiency (SIgAD), alopecia, vitiligo and nail dystrophy in autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) and abscesses and granuloma in CGD were

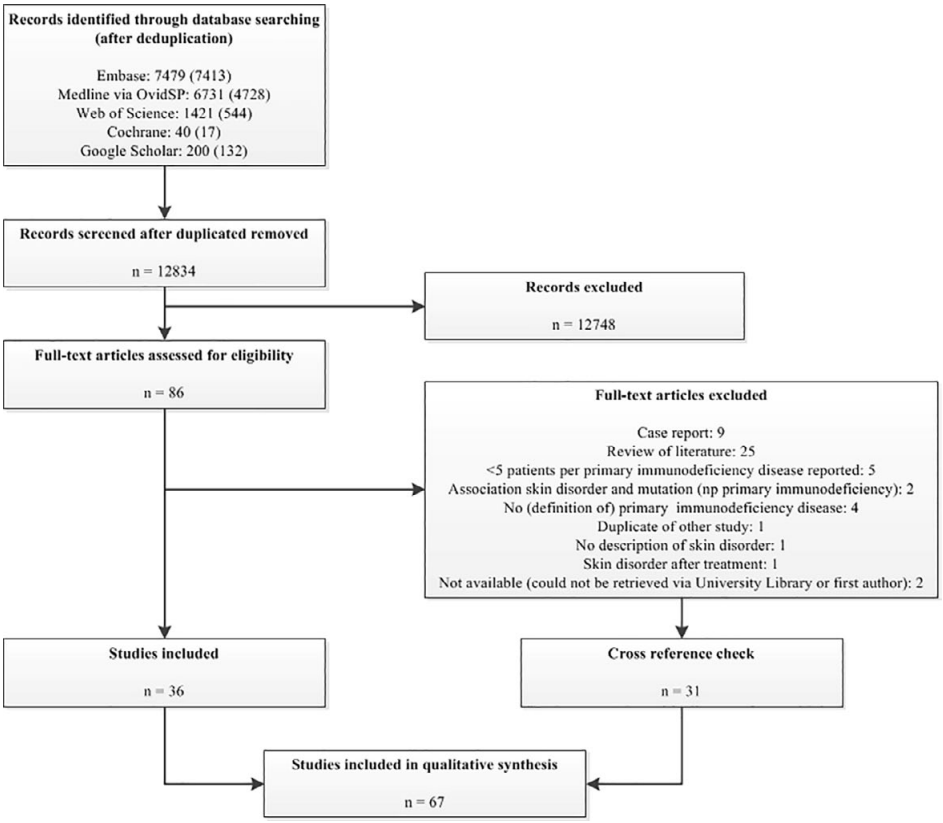

Figure 1. Flow chart of search strategy and study selection

confirmed in at least three articles. All reported skin disorders per PID were used to provide an overview of PIDs per skin disorder group (Figure 2).

Staphylococcus aureus-associated skin disorders in primary immunodeficiency diseases

Skin disorders associated with *S. aureus* in PIDs were reported in six articles (Table S1). In HIES unspecified, 4/7 patients with a papulopustular eruption had a positive *S. aureus* culture.[36] *S. aureus* was also found positive in patients with AD-HIES and a papulopustular rash (2/5), eczematous dermatitis (20/20), cold abscesses (20/20) or wounds (3/4).[39,41] Renner *et al.*[44] described that skin abscesses were frequently due to *S. aureus* infections in autosomal recessive HIES (AR-HIES). In Comèl-Netherton syndrome 8/9 described patients showed recurrent or persistent *S. aureus* skin infections once skin lesions had developed.[49] Lastly, *S. aureus* was isolated in 1/4 patients with CGD and suppurative dermatitis.[80]

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases

Primary immunodeficiency disease					General population
Main groups of skin disorders	**Subgroups of skin disorders**	**Skin disorders as reported in included articles**	**Number of reported cases with skin disorder (proportion)**	**Prevalence of skin disorder (%)**	**Prevalence of skin disorder (%)†**
Immunodeficiencies affecting cellular and humoral immunity					
Severe combined immunodeficiency					
Dermatitis-like lesions		Seborrheic dermatitis	2/9[7]	22.2	2.2-11.7[21-25]
Skin infections	Fungal skin infections	Candidiasis	4/9[7]	44.4	0.6-1.0[22,23]
Omenn syndrome					
Hair abnormalities	Hair loss disorders	Severe alopecia	5/7[27]	71.4	0.4-2.5[21-23]
		Alopecia of eyelashes and eyebrows	3/7[27]	42.9	-
Erythematous skin lesions		Exfoliative erythroderma[a]	7/7[27]	100	0.1[23]
Other skin disorders		Skin induration	6/7[27]	85.7	-
Combined immunodeficiencies with associated or syndromic features					
Ataxia-telangiectasia					
Dermatitis-like lesions		Dermatitis	1/62[6]	1.6	32.4[24]
		Eczema	2/22[28]	9.1	9.0-27.4[21,26]
		Nummular eczema	1/22[28]	4.5	1.9-2.2[21,22]
		Seborrheic rash	2/32[29]	6.3	2.2-11.7[21-25]
Hair abnormalities	Excessive hair growth disorders	Hypertrichosis	7/32[29]	21.9	-
		Hirsutism	2/12[30]	16.7	0.4[22]
	Hair pigmentation disorders	Poliosis	5/12[30]	41.7	-

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease					General population
Skin infections	Fungal skin infections	Oral candidiasis	1/12[30]	8.3	-
		Coccidioidomycosis	1/22[28]	4.5	-
	Viral skin infections	Viral warts	2/32[29], 8/22[28]	6.3-36.4	3.4-4.5[22,23,26]
		Herpes simplex	2/12[30]	16.7	0.8-1.0[22,23]
	Bacterial skin infections	Chronic impetigo	1/22[28]	4.5	0.8-1.6[22,23]
		Impetigo	1/12[30]	8.3	0.8-1.6[22,23]
Erythematous skin lesions		Pinpoint erythematous macules	2/12[30]	16.7	-
Vascular disorders	Telangiectasia	Skin telangiectasia	6/62[6], 16/26[7], 4/12[30]	9.7-61.5	-
		Telangiectasia on cheeks or nose	4/32[29], 18/22[28]	12.5-81.8	-
		Telangiectasia on ears	15/32[29]	46.9	-
		Telangiectasia on back/ shoulders/neck	5/32[29]	15.6	-
	Vasculitis	Allergic vasculitis	1/22[28]	4.5	-
Pigmentation disorders	Hyperpigmentation disorders	Café au lait macules	27/32[29], 3/22[28], 4/12[30]	13.6-84.4	12.4[21]
		Pigmented nevi (>5 mm)	12/32[29]	37.5	-
		Hyperpigmentation	1/62[6]	1.6	-
		Acanthosis nigricans	3/12[30]	25.0	-
	Hypopigmentation disorders	Hypopigmented macules	3/62[6], 14/32[29], 2/12[30]	4.8-43.8	-
		Albinism	1/32[29], 8/22[28]	3.1-36.4	-
		Vitiligo	1/12[30]	8.3	1.2-1.7[21-23]
	Other pigmentation disorders	Blue naevus	1/22[28]	4.5	1.3[21]
		Freckles	1/22[28]	4.5	-
Neoplastic disorders	Others neoplastic disorders	Basal cell carcinoma	1/22[28]	4.5	0.4-0.5[21,23]
		Juvenile melanoma	1/22[28]	4.5	-
Rash		Facial papulosquamous rash	13/32[29]	40.6	-
Nail disorders	Non-infectious nail disorders	Congenital nail dystrophy	2/12[30]	16.7	-
Granulomatous disorders		Skin granulomas	8/8[31]	100	0.3[23]

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease					General population
Other skin disorders		Lichen simplex chronicus	1/32[29]	3.1	3.0[22]
		Sclerodermoid changes	1/22[28]	4.5	-
		Senile keratosis (actinic keratosis)	1/22[28]	4.5	0.4-0.6[21,23]
		Aged skin	2/22[28]	9.1	-
		Shagreen patch	1/12[30]	8.3	-
		Lipoatrophy	1/12[30]	8.3	-
		Hydroa vacciniforme	1/12[30]	8.3	-
		Dermatofibroma	1/12[30]	8.3	0.2-22.2[21,23]
		Purpura	5/26[7]	19.2	-
Wiskott-Aldrich syndrome					
Dermatitis-like lesions		Eczema	5/5[7]	100	9.0-27.4[21,26]
Skin infections	Fungal skin infections	Yeast/fungi	18/154[32]	11.7	-
	Viral skin infections	Varicella	25/154[32]	16.2	-
		HSV I/ HSV II	24/154[32]	15.6	0.8-1.0[22,23]
		Molluscum contagiosum	13/154[32]	8.4	0.8-0.9[22,23]
		Warts	10/154[32]	6.5	3.4-4.5[22,23,26]
	Bacterial skin infections	Impetigo	19/154[32]	12.3	0.8-1.6[22,23]
		Abscesses	19/154[32]	12.3	1.7[22]
		Cellulitis	19/154[32]	12.3	0.9-1.5[22,23]
Vascular disorders	Vasculitis	Henoch-Schönlein purpura	8/154[32]	5.2	-
		Skin vasculitis	12/55[33]	7.8	-
Hyper IgE syndrome unspecified					
Dermatitis-like lesions		Atopic dermatitis	5/6[6], 5/5[34], 28/43[35], 5/8[36]	62.5-100	2.2-12.4[21-24]
		Eczema	30/30[37]	100	9.0-27.4[21,26]
Skin infections	Fungal skin infections	Candida	4/6[6], 25/30[37]	66.7-83.3	0.6-1.0[22,23]
	Bacterial skin infections	Skin abscesses	6/6[6], 36/43[35], 3/8[36], 26/30[37]	37.5-100	1.7[22]
	Other skin infections	Skin infection	3/5[34]	60.0	4.6-43.5[21,25,26]

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease					General population
Ulcers	Oral ulcers	Oral aphthous ulcers	1/5[34]	20.0	0.7[22]
		Oral ulceration	8/11[38]	72.7	0.7[22]
Rash		Newborn rash	35/43[35]	81.4	-
		Maculopapular rash	1/6[6]	16.7	-
		Papulopustular eruption	8/8[36]	100	-
Acne-like lesions		Neonatal acne	6/43[35]	14.0	-
Other skin disorders		Coarse face	3/6[6], 2/8[36]	25.0-50.0	-
Autosomal dominant hyper IgE syndrome					
Dermatitis-like lesions		Eczematous dermatitis	20/21[39]	95.2	32.4[24]
		Eczema	47/82[40], 17/17[41]	57.3-100	9.0-27.4[21,26]
Skin infections	Fungal skin infections	Oral candidiasis	4/21[39]	19.0	-
		Genitalia fungal infection	1/17[41]	5.9	-
	Viral skin infections	Varicella-zoster virus infection	9/21[39]	42.9	-
		Herpes simplex virus infection	4/21[39]	19.0	0.8-1.0[22,23]
		Herpes infection	5/67[40]	7.5	0.8-1.0[22,23]
		Molluscum contagiosum	1/21[39], 1/82[40]	1.2-4.8	0.8-0.9[22,23]
	Bacterial skin infections	Cold abscesses	20/21[39], 9/17[41]	52.9-95.2	1.7[22]
		Skin abscesses	61/82[40]	74.4	1.7[22]
		Cellulitis	15/82[40]	18.3	0.9-1.5[22,23]
		Pustulosis	14/17[41]	82.4	-
		Folliculitis	7/17[41]	41.2	1.1-6.0[21,23]
	Other skin infections	Recurrent skin infections	17/17[41]	100	4.6-43.5[21,25,26]
Ulcers	Oral ulcers	Oral ulcer	1/17[41]	2.4	0.7[22]
Neoplastic disorders	Cutaneous lymphomas	Pilotropic cutaneous T-cell lymphoma	1/21[39]	4.8	-
	Other neoplastic disorders	Squamous cell carcinoma	1/82[40]	1.2	0.3-0.7[23,24]
Rash		Papulopustular rash (<2 months)	14/21[39]	66.7	-

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease					General population
Nail disorders	Infectious nail disorders	Chronic paronychia	8/21[39]	38.1	-
		Onychomycosis	23/82[40], 4/17[41]	23.5-28.0	9.4[21]
Urticaria		Urticaria	13/82[40]	15.9	0.5-8.3[21-23]
Other skin disorders		Lichenification	1/21[39]	4.8	-
		Coarse facies	10/21[39]	47.6	-
		Dry skin	18/21[39]	85.7	-
		Thrush	17/82[40], 6/17[41]	20.7-35.3	-
		Angioedema	9/82[40]	11.0	-
Autosomal recessive hyper IgE syndrome					
Dermatitis-like lesions		Eczema	19/21[42], 7/10[43]	70.0-90.5	9.0-27.4[21,26]
		Atopic dermatitis	7/10[43]	70.0	2.2-12.4[21-24]
Skin infections	Fungal skin infections	Mucocutaneous candidiasis	9/21[42]	42.9	0.6-1.0[22,23]
		Chronic candidiasis of mucosal sites	10/13[44]	76.9	-
	Viral skin infections	Viral warts	13/21[42]	61.9	3.4-4.5[22,23,26]
		Verruca plana	1/10[43]	10.0	3.4-4.5[22,23,26]
		Herpes simplex virus	12/21[42], 8/13[44]	57.1-61.5	0.8-1.0[22,23]
		Recurrent herpes	1/10[43]	10.0	0.8-1.0[22,23]
		Molluscum contagiosum	10/21[42], 4/13[44]	30.8-47.6	0.8-0.9[22,23]
		Severe primary varicella zoster	7/21[42], 2/13[44]	15.4-33.3	-
		Herpes zoster	5/21[42]	23.8	1.4-2.4[22,23]
	Bacterial skin infections	Bacterial skin infection	17/21[42]	81.0	-
		Skin abscesses	11/13[44]	84.6	1.7[22]
		MRSA wound infected eczema	1/10[43]	10.0	-
	Other skin infections	Recurrent stomatitis	1/10[43]	10.0	-
Neoplastic disorders	Cutaneous lymphomas	Cutaneous T-cell lymphoma	1/21[42]	4.8	-
	Other neoplastic disorders	Squamous cell carcinoma	4/21[42]	19.0	0.3-0.7[23,24]
Rash		Severe eczematoid rash	13/13[44]	100	9.0-27.4[21,26]
		Newborn rash	5/21[42]	23.8	-

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease					General population
Other skin disorders		Immune thrombocytopenic purpura	1/10[43]	10.0	-
Nijmegen breakage syndrome					
Skin infections	Fungal skin infections	Candidiasis	6/21[45]	28.6	0.6-1.0[22,23]
	Viral skin infections	Herpes virus lip infection	2/21[45]	9.5	0.8-1.0[22,23]
	Other skin infections	Angular cheilitis	2/21[45]	9.5	0.1-0.3[22,23]
Vascular disorders	Telangiectasia	Cutaneous telangiectasia	3/32[46]	9.4	-
Pigmentation disorders	Hyperpigmentation disorders	Café au lait spots	18/21[46]	85.7	12.4[21]
	Hypopigmentation disorders	Vitiligo	14/21[46]	66.7	1.2-1.7[21-23]
Granulomatous disorders		Skin granuloma	5/35[47]	14.3	0.3[23]
Other skin disorders		Hyperkeratosis	1/21[45]	4.8	-
		Gingivitis	19/21[45]	90.5	-
DiGeorge syndrome					
Rash		Rash	5/5[48]	100	-
Comèl-Netherton syndrome					
Dermatitis-like lesions		Eczema[b]	8/9[49]	88.9	9.0-27.4[21,26]
Hair abnormalities	Hair loss disorders	Severe alopecia	9/9[27]	100	0.4-2.5[21-23]
		Alopecia of eyelashes and eyebrows	5/9[27]	55.6	-
	Other hair abnormalities	Bamboo hair	9/9[49]	100	-
Skin infections	Bacterial skin infections	Recurrent/persistent *S. aureus* skin infections	9/9[49]	100	-
Erythematous skin lesions		Exfoliative erythroderma[c]	9/9[27]	100	0.1[23]
Other skin disorders		Congenital ichthyosis	9/9[49]	100	0.1[22,23]
Predominantly antibody deficiencies					
X-linked agammaglobulinemia					

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease					General population
Dermatitis-like lesions		Dermatitis	4/23[6]	17.4	32.4[24]
Hair abnormalities	Hair loss disorders	Alopecia	1/110[50]	0.9	0.4-2.5[21-23]
Skin infections	Bacterial skin infections	Abscesses	3/23[6]	13.0	1.7[22]
		Furunculosis	2/23[6]	8.7	1.7[22]
		Impetigo	2/23[6]	8.7	0.8-1.6[22,23]
Pigmentation disorders	Hypopigmentation disorders	Vitiligo	0/110[50]	0.0	1.2-1.7[21-23]
Rash		Maculopapular rash	3/23[6]	13.0	-
Psoriasis-like lesions		Psoriasis	0/110[50]	0.0	1.4-8.0[21-26]
Urticaria		Urticaria	2/23[6]	8.7	0.5-8.3[21-23]
Other skin disorders		Pyoderma	1/10[7]	10.0	1.0[22]
		Lichen planus	0/110[50]	0.0	0.3-14.1[21,23,25]
Hypogammaglobulinemia					
Dermatitis-like lesions		Atopic dermatitis	28/28[51], 0/12[52], 46/78[53]	0.0-100	2.2-12.4[21-24]
Common variable immunodeficiency disorder					
Dermatitis-like lesions		Dermatitis	6/28[6]	21.4	32.4[24]
		Atopic dermatitis	9/47[54]	19.1	2.2-12.4[21-24]
		Eczema	4/15[55]	26.7	9.0-27.4[21,26]
Hair abnormalities	Hair loss disorders	Alopecia areata	1/28[6], 1/47[54]	2.1-3.6	0.4-2.5[21-23]
		Alopecia	4/244[50]	1.6	0.4-2.5[21-23]
Skin infections	Fungal skin infections	Candida	4/28[6]	14.3	0.6-1.0[22,23]
		Pseudomembraneous candidiasis	4/15[55]	26.7	-
	Viral skin infections	Recurrent herpes labialis	1/15[55]	6.7	0.8-1.0[22,23]
	Bacterial skin infections	Recurrent skin abscesses	2/31[56]	6.5	1.7[22]
	Other skin infections	Skin infections	7/47[54]	14.9	4.6-43.5[21,25,26]

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease					General population
Ulcers	Oral ulcers	Recurrent aphthosis	5/47[54]	10.6	0.7[22]
		Oral ulcers	9/15[55]	60.0	0.7[22]
		Oral aphthae	10/31[56]	32.3	0.7[22]
Pigmentation disorders	Hypopigmentation disorders	Vitiligo	8/244[50], 2/47[54]	3.3-4.3	1.2-1.7[21-23]
Rash		Maculopapular rash	1/28[6]	3.6	-
Psoriasis-like lesions		Psoriasis	2/244[50], 9/47[54]	0.8-19.1	1.4-8.0[21-26]
Acne-like lesions		Acne	6/47[54]	12.8	0.8-13.1[22-24]
Urticaria		Urticaria[d]	1/28[6]	3.6	0.5-8.3[21-23]
Other skin disorders		Pyoderma	2/5[7]	40.0	1.0[22]
		Lichen planus	1/244[50]	0.4	0.3-14.1[21,23,25]
Selective IgA deficiency					
Dermatitis-like		Dermatitis	5/17[6]	29.4	32.4[24]
		Eczema	2/39[57]	5.1	9.0-27.4[21,26]
		Atopic dermatitis	13/13[51], 4/12[52], 59/102[54], 12/159[58], 12/23[59], 9/123[60], 1/8[61], 9/81[62], 16/347[63]	4.6-100	2.2-12.4[21-24]
		Allergic contact dermatitis	11/347[63]	3.2	1.0-8.5[21-25]
		Seborrheic dermatitis	4/347[63]	1.2	2.2-11.7[21-25]
Hair abnormalities	Hair loss disorders	Alopecia	2/60[50], 1/102[54], 1/8[61]	1.0-12.5	0.4-2.5[21-23]
		Alopecia areata	1/8[64], 1/123[60], 2/347[63]	0.6-12.5	0.4-2.5[21-23]
		Infection related alopecia areata	1/8[64]	12.5	0.4-2.5[21-23]

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease					General population
Skin infections	Fungal skin infections	Candida	2/17[6]	11.8	0.6-1.0[22,23]
		Pseudomembraneous candidiasis	10/39[57]	25.6	-
	Viral skin infections	Recurrent herpes labialis	10/39[57], 2/123[60]	1.6-25.6	0.8-1.0[22,23]
		Herpes simplex	4/347[63]	1.2	0.8-1.0[22,23]
		Herpes zoster	1/347[63]	0.3	1.4-2.4[22,23]
		Molluscum contagiosum	2/347[63]	0.9	0.8-0.9[22,23]
	Bacterial skin infections	Folliculitis	1/17[6]	5.9	1.1-6.0 [21,23]
		Erysipelas recidivans	1/8[64]	12.5	0.1[23]
		Chronic recurrent furunculosis	1/8[64]	12.5	1.7[22]
		Cellulitis	5/347[63]	1.4	0.9-1.5[22,23]
	Other skin infections	Skin infections	2/102[54]	2.0	4.6-43.5[21,25,26]
		Angular stomatitis	1/39[57]	2.6	-
		Scabies	3/347[63]	0.9	0.2-1.5[22,23]
Ulcers	Oral ulcers	Recurrent aphthosis	5/102[54]	4.9	0.7[22]
		Oral ulcers	24/39[57]	61.5	0.7[22]
		Aphthosis recidivans	1/8[64]	12.5	0.7[22]
Erythematous skin lesions		Erythroderma	1/8[64]	12.5	0.1[23]
		Erythema nodosum	1/123[60]	0.8	0.2-0.3[22,23]
Vascular disorders	Vasculitis	Vasculitis	3/7[7]	42.9	-
		Kawasaki disease	1/8[61]	12.5	-
	Other vascular disorders	Raynaud syndrome	1/8[61]	12.5	-
Pigmentation disorder	Hypopigmentation disorders	Vitiligo	1/7[7], 3/60[50], 3/102[54], 1/8[64], 7/159[58], 3/123[60], 1/81[62], 2/347[63]	0.6-14.3	1.2-1.7[21-23]
Psoriasis-like disorders		Psoriasis	0/60[50], 2/102[54], 7/159[58], 1/123[60], 7/347[63]	0.0-4.4	1.4-8.0[21-26]
Acne-like lesions		Acne	6/102[54], 69/347[63]	5.9-19.9	0.8-13.1[22-24]

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease					General population
Urticaria		Urticaria	5/23[59]	21.7	0.5-8.3[21-23]
		Atopic urticaria	4/123[60]	3.3	0.5-8.3[21-23]
		Chronic spontaneous urticaria	17/347[63]	4.9	0.5-8.3[21-23]
Other skin disorders		Lichen planus	0/60[50], 2/159[58]	0.0-1.3	0.3-14.1[21,23,25]
		Immune thrombocytopenic purpura	1/17[6]	5.9	-
		Idiopathic thrombocytopenic purpura	2/123[60]	1.6	-
		Chronic idiopathic thrombocytopenic purpura	1/81[62]	1.2	-
		Epidermolysis bullosa dystrophica	1/8[64]	12.5	-
		Local skin scleroderma	1/123[60]	0.8	-
		Dermatitis herpetiformis	1/123[60]	0.8	0.2-0.3[21,22]
		Ichthyosis and keratoderma of handpalms and footsoles in epileptic patients (Rud syndrome)	1/123[60]	0.8	-
IgM deficiency					
Dermatitis-like lesions		Atopic dermatitis	14/14[51], 11/53[52]	20.8-100	2.2-12.4[21-24]
IgG deficiency					
Dermatitis-like lesions		Atopic dermatitis	11/11[51]	100	2.2-12.4[21-24]
Diseases of immune dysregulation					
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy					
Dermatitis-like lesions		Recurrent and troublesome napkin dermatitis	5/18[65]	27.8	-
Hair abnormalities	Hair loss disorders	Alopecia	2/15[61], 6/18[65], 20/68[66], 6/35[67], 6/22[68]	13.3-33.3	0.4-2.5[21-23]
	Hair pigmentation disorders	Poliosis	1/18[65]	5.6	-

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease					General population
Skin infections	Fungal skin infections	Oral candidiasis	41/68[66]	60.3	-
		Dermal candidiasis	6/68[66], 6/35[67]	8.8-17.1	0.6-1.0[22,23]
		Chronic mucocutaneous candidiasis	18/18[65], 30/35[67]	85.7-100	0.6-1.0[22,23]
		Mucocutaneous candidiasis	21/22[68]	95.5	0.6-1.0[22,23]
		Life-long genital moniliasis	1/18[65]	5.6	-
	Other skin infections	Angular cheilitis	13/18[65]	72.2	0.1-0.3[22,23]
Vascular disorders	Vasculitis	Cutaneous vasculitis	2/68[66]	2.9	-
Pigmentation disorders	Hypopigmentation disorders	Vitiligo	1/15[61], 2/18[65], 9/68[66], 13/35[67], 6/22[68]	6.7-37.1	1.2-1.7[21-23]
		Halo naevi	1/18[65]	5.6	0.8[21]
Nail disorders	Infectious nail disorders	Ungual candidiasis	33/50[66]	66.0	-
		Candidal paronychia and/or onychomycosis	13/18[65]	72.2	9.4[21]
		Nail candidiasis	12/35[67]	34.3	-
	Non-infectious nail disorders	Nail dystrophy	26/50[66], 6/35[67], 4/22[68]	17.1-52.0	-
Urticaria		Urticarial eruption	23/35[67]	8.6	0.5-8.3[21-23]
		Urticarial rash	2/22[68]	9.1	0.5-8.3[21-23]
Other skin disorders		Oral thrush	35/35[67]	100	-
Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome					
Dermatitis-like		Atopic dermatitis	7/10[69]	70.0	2.2-12.4[21-24]
		Severe eczema	5/14[70]	35.7	9.0-27.4[21,26]
		Mild eczema	4/14[70]	28.6	9.0-27.4[21,26]
		Eczema	5/5[71], 2/5[72]	40.0-100	9.0-27.4[21,26]
Hair abnormalities	Hair loss disorders	Alopecia[e]	2/14[70]	14.3	0.4-2.5[21-23]

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease					General population
Skin infections	Fungal skin infections	Chronic mucocutaneous candidiasis	4/5[71]	80.0	0.6-1.0[22,23]
	Viral skin infections	HSV skin infection	1/5[71]	20.0	0.8-1.0[22,23]
		Herpes zoster	1/5[71]	20.0	1.4-2.4[22,23]
	Bacterial skin infections	Staphylococcal superinfection of eczema	1/5[71]	20.0	-
	Other skin infections	Cheilitis	4/10[69]	40.0	0.1-0.3[22,23]
Erythematous skin lesions		Exfoliative erythroderma	2/10[69]	20.0	0.1[23]
Nail disorders	Infectious nail disorders	Onychodystrophy[f]	2/10[69]	20.0	-
		(Peri-)onyxis	1/10[69]	10.0	-
Psoriasis-like lesions		Psoriasiform rash	2/10[69]	20.0	1.4-8.0[21-26]
Other skin disorders		Palmar keratoderma	1/10[69]	10.0	-
		Inflammatory oedema (lips and perioral) or Quincke oedema	3/10[69]	30.0	-
		Mild xerosis	1/14[70]	7.1	-
		Acrodermatitis enteropathica	1/5[71]	20.0	-
Adenosine deaminase 2 deficiency					
Dermatitis-like lesions		Eczema	5/9[73]	55.6	9.0-27.4[21,26]
Ulcers	Oral ulcers	Oral aphthae	3/9[73]	33.3	0.7[22]
	Other ulcers	Livedoid vasculopathy/ulcers	1/9[73]	11.1	-
Erythematous skin lesions		Erythema nodosum	2/9[73], 1/8[74]	12.5-22.2	0.2-0.3[22,23]
Vascular disorders	Vasculitis	Cutaneous vasculitis	3/9[73]	33.3	-
		Polyarteritis nodosa	1/9[73]	11.1	-
	Other vascular disorders	Raynaud's phenomenon	1/8[74]	12.5	-
Neoplastic disorder	Other neoplastic disorders	AML chloroma	1/9[73]	11.1	-
Rash		Rash	3/9[73]	33.3	-
Urticaria		Urticaria-like rash	1/8[74]	12.5	0.5-8.3[21-23]

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease					General population
Other skin disorders		Livedo reticularis	3/9[73], 6/8[74]	33.3-75.0	0.1[23]
		Livedo racemose	1/9[73]	11.1	0.1[23]
		Aspecific skin induration	4/9[73]	44.4	-
Congenital defects of phagocyte number or function					
Leukocyte adhesion defect unspecified					
Skin infections	Bacterial skin infections	Cellulitis	2/6[6]	33.3	0.9-1.5[22,23]
		Folliculitis	2/6[6]	33.3	1.1-6.0[21,23]
Other skin disorders		Periodontitis	2/6[6]	33.3	-
Leukocyte adhesion defect type 1					
Skin infections	Fungal skin infections	Candida infection	8/15[75]	53.3	0.6-1.0[22,23]
	Bacterial skin infections	Skin abscesses	12/15[75]	80.0	1.7[22]
		Cellulitis	4/15[75]	26.7	0.9-1.5[22,23]
Ulcers	Oral ulcers	Oral ulcers	13/15[75]	86.7	0.7[22]
Other skin disorders		Gingivitis	9/15[75]	60.0	-
Chronic granulomatous disease					
Dermatitis-like lesions		Dermatitis	nm/429[76], nm/39[77]	-	32.4[24]
		Eczema	8/48[78]	16.7	9.0-27.4[21,26]
Skin infections	Bacterial skin infections	Abscesses	23/34[6], nm/429[76], nm/39[77], 1/48[78], 156/368[79], 11/49[80]	2.1-67.6	1.7[22]
		Folliculitis	5/34[6]	14.7	1.1-6.0[21,23]
		Impetigo	3/34[6], 16/95[80]	8.8-16.8	0.8-1.6[22,23]
		Cellulitis	18/368[79]	4.9	0.9-1.5[22,23]
		Furunculosis	nm/429[76]	-	-
		Pustular eruption	10/48[78]	20.8	-
	Other skin infections	Chronic cutaneous infections	1/6[81]	16.7	4.6-43.5[21,25,26]
		Cutaneous/subcutaneous infections	22/48[78], 43/84[82]	45.8-51.2	4.6-43.5[21,25,26]
		Skin infection	59/130[80]	45.4	4.6-43.5[21,25,26]

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease					General population
Ulcers	Oral ulcers	Oral ulceration	7/9[38], 2/6[81]	33.3-77.8	0.7[22]
	Other ulcers	Nose ulcers	5/34[6]	14.7	-
Vascular disorders	Vasculitis	Kawasaki disease	2/48[78]	4.2	-
Nail disorders	Infectious nail disorders	Paronychia	2/34[6]	5.9	-
Granulomatous disorders		Granuloma	2/11[61], nm/429[76], 4/48[78]	8.3-18.2	0.3[23]
Acne-like lesions		Acne	nm/429[76]	-	0.8-13.1[22-24]
Urticaria		Urticaria	1/48[78]	2.1	0.5-8.3[21-23]
Other skin disorders		Discoid lupus erythematosus[9]	30/340[79]	8.8	0.1-0.3[21,22]
		Thrush	11/48[78]	22.9	-
Severe congenital neutropenia					
Skin infections	Fungal skin infections	Mucocutaneous candidiasis	5/18[83]	27.8	0.6-1.0[22,23]
	Bacterial skin infections	Cutaneous abscesses	10/18[83]	55.6	1.7[22]
	Other skin infections	Cutaneous infections	7/18[83]	38.9	4.6-43.5[21,25,26]
Ulcers	Oral ulcers	Oral ulcers	13/18[83]	72.2	0.7[22]
Papillon-Lefèvre syndrome					
Nail disorders	Noninfectious nail disorders	Nail changes (mainly slight thickening of nails)	13/47[84]	27.7	3.3-3.4 [24,26]
Psoriasis-like lesions		Extensive psoriasiform plaques	3/47[84]	6.4	1.4-8.0[21-26]
Other skin disorders		Punctate hyperkeratosis on palms and soles	8/47[84]	17.0	-
		Well-demarcated hyperkeratosis of knees and elbows	23/47[84]	48.9	-
		Ichthyosis	2/47[84]	4.3	0.1[22,23]
GATA2 deficiency					
Neoplastic disorders	Other neoplastic disorders	Cutaneous melanoma	1/71[85]	1.4	0.1-1.2[21,23]

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease					General population
Defects in intrinsic and innate immunity					
Chronic mucocutaneous candidiasis					
Skin infections	Other skin infections	Perleche (angular cheilitis)	3/7[6]	42.9	0.1-0.3[22,23]
Other skin disorders		Thrush[h]	7/7[6]	100	-
Autoinflammatory disorders					
PLCG2 associated antibody deficiency and immune dysregulation					
Ulcers	Other ulcers	Neonatal-onset ulcerative lesions (cold-sensitive regions)	8/36[86]	22.2	2.0[23]
Erythematous skin lesions		Recurrent red papules and patches	1/36[86]	2.8	-
Pigmentation disorders	Hypopigmentation disorders	Vitiligo	1/36[86]	2.8	1.2-1.7[21-23]
Granulomatous disorders		Granulomatous inflammation	4/36[86]	11.1	0.3[23]
Urticaria		Cold urticaria	36/36[86]	100	0.5-8.3[21-23]
Muckle-Wells syndrome					
Ulcers	Oral ulcers	Oral ulcers	7/29[87]	24.1	0.7[22]
Pigmentation disorders	Hyperpigmentation disorders	Hyperpigmented, sclerotic and hypertrichotic plaques	6/6[88]	100	-
Rash		Skin rash	15/15[87]	100	-
Urticaria		Attacks of recurrent urticaria	2/6[88]	33.3	0.5-8.3[21-23]
		Urticaria	8/8[89]	100	0.5-8.3[21-23]
		Cold-induced urticaria	14/29[87]	48.3	0.5-8.3[21-23]
Other skin disorders		Weals caused by cold	16/16[90]	100	-
Neonatal onset multisystem inflammatory disease					
Urticaria		Urticaria	8/8[89]	100	0.5-8.3[21-23]

Table 1. Skin disorders and their prevalence in primary immunodeficiency diseases (continued)

Primary immunodeficiency disease				General population
Complement deficiencies				
C2 deficiency				
Urticaria	Chronic urticaria	2/47[91]	4.3	0.5-8.3[21-23]
Other skin disorders	Subacute cutaneous lupus erythematosus	2/47[91]	4.3	0.3[22]
	Dermatitis herpetiformis	1/47[91]	2.1	0.2-0.3[21,22]

Abbreviations: nm, not mentioned. †Data from the general population were based on a birth cohort in Finland (n=1932, age 45-47 years) and a Dermatology outpatient clinic in Turkey (n=11 040, age 1-99 years).[21,22] In addition, a nationwide study of Furue *et al*.[23] reported the prevalence of cutaneous disorders in 67 448 Japanese patients of all ages. In the study of Verhoeven *et al*.[24], the skin disease prevalence per 1000 patient-years in family practices in the Netherlands was converted to a point prevalence in the general population (n=501, age 18-97 years). Finally, two studies from the United States of America and the United Kingdom performed in 1978 and 1976 showed the prevalence of skin disorders in community studies in respectively 20749 (age 1-74 years) and 614 (age 15-74 years) patients.[25,26 A-H]See Figure S1.

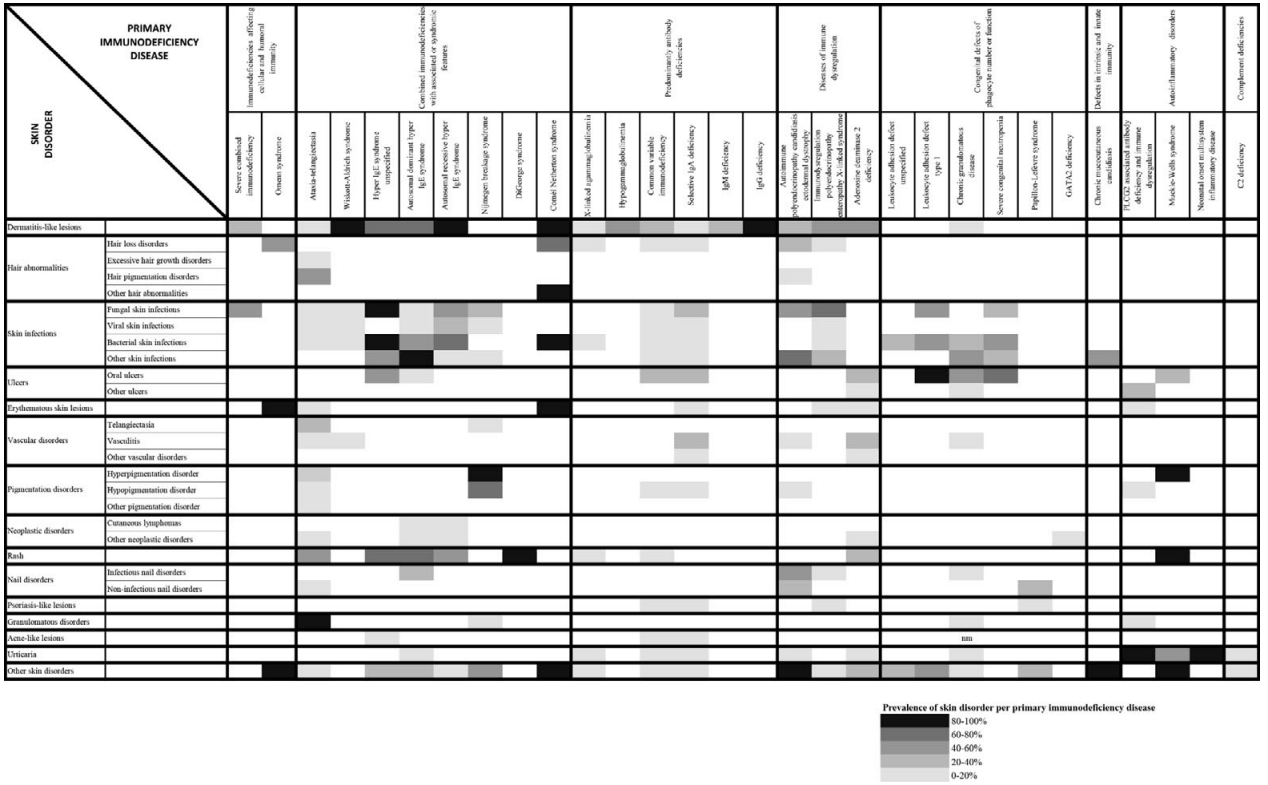

Figure 2. Differential diagnosis of primary immunodeficiency diseases per skin disorder

Abbreviations: nm, not mentioned†. † The exact prevalence of acne-like lesions in chronic granulomatous disease was not reported in the included article. The prevalence of skin disorders per primary immunodeficiency disease was based on the reported proportion of patients with the skin disorders in the total group of patients with the primary immunodeficiency disease. In case of multiple studies reporting a skin disorder in a primary immunodeficiency disease, the general prevalence was calculated by dividing the total number of affected patients (skin disorder) by the total number of patients with the primary immunodeficiency disease.

Primary immunodeficiency diseases associated with atopy

The prevalence of at least two atopic symptoms (i.e. eczema, food allergy, asthma and/or rhinoconjunctivitis) in PIDs was described in 17 articles (Table S1). Cohen *et al.*[30] found no atopy in patients with AT. In HIES unspecified, AD-HIES and AR-HIES, all of the atopic symptoms, if reported, were present in about half of the patients.[35,39-43] Renner *et al.*[49] described the presence of atopy in most Comèl-Netherton patients. The number of patients with eczema, food allergy, asthma, and rhinoconjunctivitis were presented in two studies with hypogammaglobulinemia patients.[52,53] Eight studies reported the prevalence of atopy in a total of 398 patients with SIgAD, in which 11.6% (46/398) patients had eczema, 3.4% (9/263) had food allergy, 37.1% (43/116) had asthma, and 20.0% (55/275) had rhinoconjunctivitis.[52,58-60,62] In IgM-deficient patients, eczema, asthma, and rhinoconjunctivitis were prevalent symptoms.[52] Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX) patients were mainly positive for eczema.[70] Eight of 48 CGD patients had eczema and one out of 18 had rhinoconjunctivitis.[78] Finally, Aderibigbe *et al.*[86] have shown that one to three out of eight patients with Phospholipase C Gamma 2 (PLCG2) gene associated antibody deficiency and immune dysregulation (PLAID) had eczema, food allergy, asthma, and/or rhinoconjunctivitis.

DISCUSSION

This review demonstrates that skin disorders are common symptoms in both children and adult patients with PIDs based on data from 67 systematically selected studies. Only a few PIDs related to *S. aureus*-associated skin disorders or atopy were reported in mainly single studies.

This is the first review using a systematic approach without limitations on skin disorders or PIDs. Therefore, we managed to obtain a complete spectrum of skin disorders in PIDs. A recent study of Ettinger *et al.*[92] that focused on PIDs and the respective gene defects included an overview of PIDs per skin disorder in a nonsystematic approach. Although some PIDs are characterized by skin disorders, such as telangiectasia in AT and granuloma in CGD, the novelty of this review is showing an overview of all skin disorders in PIDs including skin disorders of which an association with a PID was not yet known.

Furthermore, we succeeded in composing an overview of PIDs per skin disorder that could serve as a valuable support tool for PID awareness in clinical practice and for registries. In the Netherlands, the diagnostic delay in PIDs (i.e. time period between the date of onset of first symptoms and the date of diagnosis) ranges from 0 to 14.5 years and is dominated by the defects in innate immunity (14.5 years), HIES (10.5 years) and hypogammaglobulinemia

(10.0 years).[93] Moin *et al.*[6] and Berron-Ruiz *et al.*[7] reported that in, respectively, 31.8% and 78.9% of the PIDs the cutaneous alterations preceded and were the basis for the clinical immunological diagnosis. Increased attention for these cutaneous manifestations as signal function of PIDs in combination with presence of the current warning signs for the suspicion of PIDs might improve earlier diagnosis of PIDs. These warning signs include (a) four or more new ear infections within 1 year; (b) two or more serious sinus infections within 1 year; (c) two or more months on antibiotics with little effect; (d) two or more pneumonias within 1 year; (e) failure of an infant to gain weight or grow normally; (f) recurrent, deep skin or organ abscesses; (g) persistent thrush in mouth or fungal infection on skin; (h) need for intravenous antibiotics to clear infections; (i) two or more deep-seated infections including septicemia; and (j) a family history of PID.[94] In addition, narrowing the number of eligible PIDs through clustering of skin disorders could further reduce the diagnostic delay in PIDs. Using the multi-stage diagnostic protocol of de Vries[4] or the phenotypic approach for PID classification and diagnosis by Bousfiha *et al.*[95], the diagnosis of suspected PIDs or PID-classes based on clinical symptoms could be confirmed with laboratory tests. For example, a first diagnostic step in case of a supposed antibody deficiency or neutropenia could be blood count and differentiation, IgG, IgA, IgM and IgE. In case of a possible combined immunodeficiency disease, these tests should be supplemented by lymphocyte subpopulations.

Our review has some limitations. First of all, exclusion of case reports describing fewer than five cases in our analysis might have resulted in loss of information about skin disorders in rare PIDs. However, the quality of case reports is highly variable, potential publication bias plays a role, and thus, exclusion of these case reports might have improved the reliability of this review. Furthermore, through the addition of selected PIDs and skin disorders to our electronic search we could have caused a selection bias. Although we used a cross-reference check, we cannot exclude that we might have missed some articles. Thirdly, demonstrating that specific skin disorders are characteristic for PIDs was not possible. We could only compare the presence of a number of skin disorders in patients with a PID with the prevalence of skin disorders in the general population based on six studies varying in publication year and age of the studied population.[21-26] However, most of these skin disorders were more prevalent in patients with a PID compared with the general population. Lastly, the reliability of the description of skin disorders might be questioned since in only 27 of the 67 included articles the department of Dermatology was involved. Probably, the described skin disorders were not all diagnosed by a dermatologist, but by an immunologist or pediatrician. Moreover, the majority of studies did not use skin biopsy to confirm the diagnosis of the cutaneous manifestations histopathologically. In severe combined immunodeficiency (SCID) patients, it was shown by Denianke *et al*.[96] that clinically comparable skin lesions could demonstrate different histopathological images, possibly due an altered

immune system. Subsequently, the reported clinical diagnosis of skin disorders reported in articles included in this review might not correlate with the corresponding histopathological diagnosis as well.

Because most PIDs are rare, reliable prevalence of skin disorders in PIDs can only be obtained by reporting skin disorders on an international basis. The international PID database of The European Society for Immunodeficiencies (ESID) registers, among others, data on warning signs of PIDs. These warning signs give only attention to infectious skin disorders. Noninfectious cutaneous symptoms are not included. Based on data of this review we suggest to start to collect more detailed data on all skin disorders in the ESID registry.

Future research is needed to validate these data and support an association between specific cutaneous symptoms and PIDs. Given the low number of articles reporting *S. aureus*-associated skin disorders and atopy in PIDs, more data have to be collected to further improve earlier recognition of PIDs. In addition, data on *S. aureus*-associated skin disorders might provide new treatment options for skin disorders, such as targeted therapy directed against *S. aureus*.

Conclusion

This review with a systematic approach shows that skin disorders are a prominent feature in PIDs. Earlier diagnosis of PIDs can be facilitated by recognition of specific skin conditions as signal function of PIDs in combination with the current warnings signs for PIDs or by recognizing PID specific clusters of skin conditions. We provide a support tool to use in clinical practice that should raise awareness of PIDs based on the presenting skin manifestations. Limited data are available on *S. aureus*-associated skin disorders and atopy in PIDs.

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Table S1. Study characteristics per study

	Country	Patients			IHE Quality Appraisal[a]	Primary immunodeficiency disease	*Staphylococcus aureus*[b]	Atopy[c]
		N	% Male	Mean age (y)				
Gernez 2018[40]	USA	85	58.8	27.3 (med)	5.5/11	Autosomal dominant hyper IgE syndrome	-	47/82 eczema, 31/82 food allergy
Nguyen 2018[85]	USA	71	32.4	-	4.5/11	GATA2 deficiency	-	-
Sahin 2018[74]	Turkey	8	75.0	16.9	7.5	Adenosine deaminase 2 deficiency	-	-
Zhou 2018[80]	China	169	95.9	-	10.5/13	Chronic granulomatous disease	1/4 suppurative dermatitis	-
Azizi 2017[50]	Iran	471	67.3	16.0 (med)	7.5/11	X-linked agammaglobulinemia Common variable immunodeficiency Selective IgA deficiency	-	-
Broides 2017[43]	Israel	10	-	6.4	4.5/11	Autosomal recessive hyper IgE syndrome	-	10/10 eczema, 1/10 food allergy, 4/10 asthma
Deripapa 2017[47]	Russia	35	45.7	13.4 (med)	8.5/13	Nijmegen breakage syndrome	-	-
Erkoçoğlu 2017[62]	Turkey	81	-	10.4	7.5/13	Selective IgA deficiency	-	9/81 eczema, 1/81 food allergy, 28/81 asthma, 22/81 rhinoconjunctivitis
Magen 2017[63]	Israel	347	54.2	24.1	8.5/11	Selective IgA deficiency	-	16/347 eczema
Muşabak 201[56]	Turkey	31	61.3	28 (med)	8/11	Common variable immunodeficiency	-	-
Wolach 2017[82]	Israel	84	79.8	-	5.5/11	Chronic granulomatous disease	-	-
Wu 2017[41]	China	17	47.1	11.8	7.5/11	Autosomal dominant hyper IgE syndrome	3/4 wounds	17/17 eczema, 2/17 food allergy

Table S1. Study characteristics per study (continued)

	Country	Patients			IHE Quality Appraisal[a]	Primary immunodeficiency disease	*Staphylococcus aureus*[b]	Atopy[c]
		N	% Male	Mean age (y)				
Wu 2017[78]	China	48	91.7	5.8	5.5/11	Chronic granulomatous disease	-	8/48 eczema, 1/18 rhinoconjunctivitis
Zaidi 2017[68]	India	22	-	14 (med)	7/11	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy	-	-
Altun 2016[52]	Turkey	*258*	58.5	59.3 mo	4.5/11	Hypogammaglobulinemia	-	0/12 eczema, 7/12 asthma, 8/12 rhinoconjunctivitis
						Selective IgA deficiency		4/12 eczema, 3/12 asthma, 8/12 rhinoconjunctivitis
						IgM deficiency		11/53 eczema, 19/53 asthma, 35/53 rhinoconjunctivitis
Baris 2016[72]	Turkey	30	83.3	10.6	6.5/11	Immunodysregulation, polyendocrinopathy, enteropathy X-linked syndrome	-	2/5 eczema
Blazina 2016[61]	Slovenia	247	59.5	20	8/11	Selective IgA deficiency	-	-
						Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy		
						Chronic granulomatous disease		
Ferre 2016[67]	USA	35	45.7	13.4 (med)	8.5/11	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy		
Mehr 2016[89]	Australia	18	66.7	12 (med)	7.5/11	Muckle-Wells syndrome	-	-
						Neonatal onset multisystem inflammatory disease		
Sobolewska 2016[87]	Germany	37	43.2	-	4.5/11	Muckle-Wells syndrome	-	-

Table S1. Study characteristics per study (continued)

	Country	Patients			IHE Quality Appraisal[a]	Primary immunodeficiency disease	*Staphylococcus aureus*[b]	Atopy[c]
		N	% Male	Mean age (y)				
Szczawińska-Popłonyk 2016[53]	Poland	78	53.8	17 mo	5/11	Hypogammaglubulinemia		46/78 eczema, 40/78 food allergy
Van Montfrans 2016[73]	The Netherlands, Belgium	9	77.8	17.3	10/13	Adenosine deaminase 2 deficiency	-	5/9 eczema
Aderibigbe 2015[86]	USA	36	-	-	7/11	PLCG2 associated antibody deficiency and immune dysregulation	-	1/8 eczema, 3/8 food allergy, 3/8 asthma, 2/8 rhinoconjunctivitis[d]
Gualdi 2015[54]	Italy	47 (CVID), 102 (SIgAD)	57.4 (CVID), 54.9 (SIgAD)	23.4 (CVID), 8.6 (SIgAD)	9/13	Common variable immunodeficiency	-	9/47 eczema
						Selective IgA deficiency		59/102 eczema
Aghamohammadi 2014[34]	Iran	75	58.7	2 (med)	11.5/13	Hyper IgE syndrome unspecified	-	5/5 eczema
Celiksoy 2014[51]	Turkey	160	61.3	1.2 (med)	11.5/13	Hypogammaglobulinemia	-	28/28 eczema
						Selective IgA deficiency		13/13 eczema
						IgM deficiency		11/11 eczema
						IgG deficiency		14/14 eczema
Greenberger 2013[29]	Israel	32	59.4	11.8	7.5/11	Ataxia-telangiectasia	-	-
Uzel 2013[71]	USA	5	80.0	9.9	10/13	Immunodysregulation, polyendocrinopathy, enteropathy X-linked syndrome	-	5/5 eczema
Chu 2012[42]	USA	21	47.6	15.9	4.5/11	Autosomal recessive hyper IgE syndrome	-	19/21 eczema, 14/21 food allergy, 10/21 asthma

Table S1. Study characteristics per study (continued)

	Country	Patients			IHE Quality Appraisal[a]	Primary immunodeficiency disease	*Staphylococcus aureus*[b]	Atopy[c]
		N	% Male	Mean age (y)				
Olaiwan 2011[39]	France	21	52.4	19	5/11	Autosomal dominant hyper IgE syndrome	2/5 papulopustular rash, 20/20 eczematous dermatitis, 20/20 cold abscesses	20/21 eczema, 5/21 asthma or rhinoconjunctivitis
Aghamohammadi 2009[59]	Iran	23	65.2	8 (med)	8/13	Selective IgA deficiency	-	12/23 eczema, 7/23 food allergy, 12/23 asthma, 8/23 rhinoconjunctivitis
Gregorek 2009[45]	Poland	21	52.4	11.2 (med)	6/11	Nijmegen breakage syndrome	-	-
Halabi-Tawil 2009[69]	France	10	100	-	5.5/11	Immunodysregulation, polyendocrinopathy, enteropathy X-linked syndrome	-	7/10 eczema
Renner 2009[49]	Germany	9	66.7	6 (med)	6/11	Comèl-Netherton syndrome	8/9 recurrent or persistent skin infections	9/9 atopy: 8/9 eczema, 7/9 food allergy, 2/9 asthma, 5/9 rhinoconjunctivitis
Van den Berg 2009[76]	The Netherlands	429	81.8	-	7/11	Chronic granulomatous disease	-	eczema
Gambineri 2008[70]	Italy	14	-	range 0-19	7/11	Immunodysregulation, polyendocrinopathy, enteropathy X-linked syndrome	-	11/14 eczema, 1/14 food allergy, 1/14 asthma
Movahedi 2007[75]	Iran	15	66.7	4 (med)	6.5/11	Leukocyte adhesion defect type I	-	-
Rezaei 2007[83]	Iran	18	55.6	8.8	6/11	Severe congenital neutropenia	-	-
Collins 2006[65]	Ireland	18	38.9	14.6	8.5/13	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy	-	-
El-Darouti 2006[88]	Egypt	6	33.3	23.2	2/11	Muckle-Wells syndrome	-	-

Table S1. Study characteristics per study (continued)

	Country	Patients			IHE Quality Appraisal[a]	Primary immunodeficiency disease	*Staphylococcus aureus*[b]	Atopy[c]
		N	% Male	Mean age (y)				
Moin 2006[6]	Iran	210	58.1	-	5/11	Ataxia-telangiectasia	-	1/62 eczema
						Hyper IgE syndrome unspecified		5/6 eczema
						X-linked agammaglobulinemia		4/23 eczema
						Common variable immunodeficiency		6/28 eczema
						Selective IgA deficiency		5/17 eczema
						Leukocyte adhesion defect		-
						Chronic granulomatous disease		-
						Chronic mucocutaneous candidiasis		-
Eberting 2004[35]	USA	43	37.2	23	5/11	Hyper IgE syndrome unspecified	-	28/43 eczema, 22/43 asthma, 14/43 rhinoconjunctivitis
Haas 2004[90]	Germany	16	43.8	-	6.5/13	Muckle-Wells syndrome	-	-
Markert 2004[48]	USA	5	100	-	9/13	DiGeorge syndrome	-	-
Renner 2004[44]	Germany, USA	13	30.1	-	10/13	Autosomal recessive hyper IgE syndrome	skin abscesses (frequently)	13/13 eczema
Dupuis-Girod 2003[33]	France	55	100	-	5/11	Wiskott-Aldrich syndrome	-	-
Ullbro 2003[84]	Sweden	47	44.7	10 (med)	9/13	Papillon-Lefèvre syndrome	-	-
Chamlin 2002[36]	USA	8	75.0	-	4/11	Hyper IgE syndrome unspecified	4/7 papulopustular eruption	5/8 eczema

Table S1. Study characteristics per study (continued)

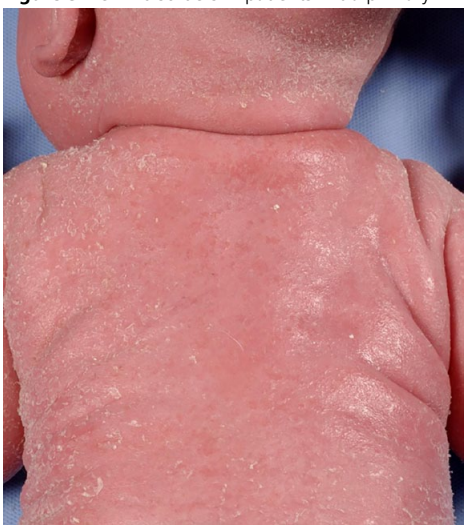
	Country	Patients			IHE Quality Appraisal[a]	Primary immunodeficiency disease	*Staphylococcus aureus*[b]	Atopy[c]
		N	% Male	Mean age (y)				
Hiel 2001[46]	The Netherlands	55	56.4	-	3/11	Nijmegen breakage syndrome	-	-
Berron-Ruiz 2000[7]	Mexico	130	-	range 0-17	3/11	Severe combined immunodeficiency	-	-
						Ataxia-telangiectasia		-
						Wiskott-Aldrich syndrome		5/5 eczema
						X-linked agammaglobulinemia		-
						Common variable immunodeficiency		-
						Selective IgA deficiency		-
Liese 2000[77]	Germany	39	94.9	-	6/11	Chronic granulomatous disease	-	eczema
Lipsker 2000[91]	France	47	-	-	5/11	C2 deficiency	-	-
Pruszkowski 2000[27]	France	51	47.1	-	5/11	Omenn syndrome	-	-
						Comèl Netherton syndrome		
Winkelstein 2000[79]	USA	368	85.9	-	5/11	Chronic granulomatous disease	-	-
Grimbacher 1999[37]	USA	30	33.3	26.5	5.5/11	Hyper IgE syndrome unspecified	-	30/30 eczema
Koskinen 1996[58]	Finland	159	-	-	8/13	Selective IgA deficiency	-	12/159 eczema, 5/159 food allergy, 17/159 rhinoconjunctivitis
Sullivan 1994[32]	USA	154	100	11	7/11	Wiskott-Aldrich syndrome	-	-
Porter 1993[55]	England	15	86.7	range 3-14	4.5/11	Common variable immunodeficiency	-	4/15 eczema
Porter 1993[57]	England	39	71.8	range 2-13	4.5/11	Selective IgA deficiency	-	2/39 eczema
Patrizi 1992[60]	Italy	142	57.0	6.0	6.5/13	Selective IgA deficiency	-	9/123 eczema

Table S1. Study characteristics per study (continued)

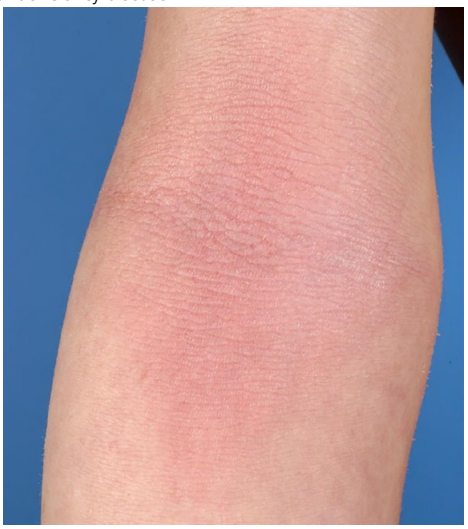
	Country	Patients			IHE Quality Appraisal[a]	Primary immunodeficiency disease	*Staphylococcus aureus*[b]	Atopy[c]
		N	% Male	Mean age (y)				
Paller 1991[31]	USA	8	25.0	10.5	4.5/11	Ataxia-telangiectasia	-	-
Ahonen 1990[66]	Finland	68	54.4	follow-up to age 10 mo-53 y at end of study	10/13	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy	-	-
Charon 1985[38]	USA	27	44.4	20.3	3.5/11	Hyper IgE syndrome unspecified Chronic granulomatous disease	-	-
Cohen 1985[81]	USA	6	66.6	range 17-32	4/11	Chronic granulomatous disease	-	-
Cohen 1984[30]	USA	12	-	-	4.5/11	Ataxia-telangiectasia	-	0/12 atopy
Göring 1981[64]	Germany	8	-	-	3.5/11	Selective IgA deficiency	-	-
Reed 1966[28]	USA	22	63.6	13.4	6/11	Ataxia-telangiectasia	-	2/22 eczema

Abbreviations: N, number of patients; y, year; mo, months; med, median; CVID, common variable immunodeficiency; sIgAD, selective IgA deficiency; IHE, Institute of Health Economics. [a]Prospective studies could reach a maximum score of 13 points and retrospective studies could reach a maximum score of 11 points according to the Institute of Health Economics Quality Appraisal Checklist for Case Series Studies. [b]Number of patients with positive *Staphylococcus aureus* culture / number of patients with reported skin disorder. [c]Number of patients with atopic disorder / number of patients included in the study. [d]Number of patients with atopic disorder / number of patients with a history of cold urticaria (subgroup in original study).

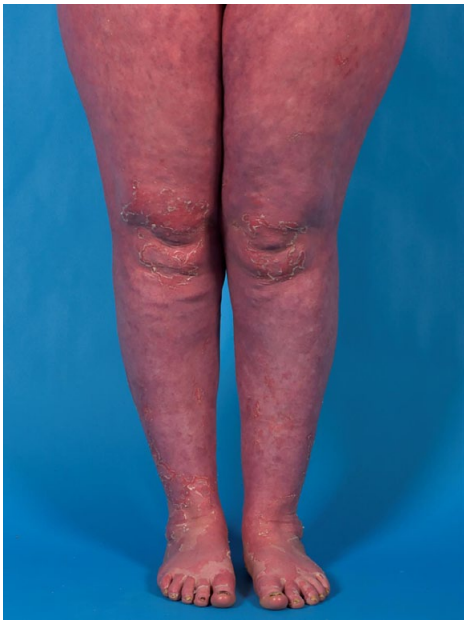
Figure S1. Skin disorders in patients wit a primary immondeficiency disease



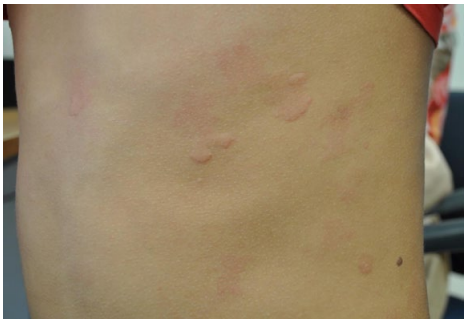
a. Exfoliative erythroderma in Omenn syndrome



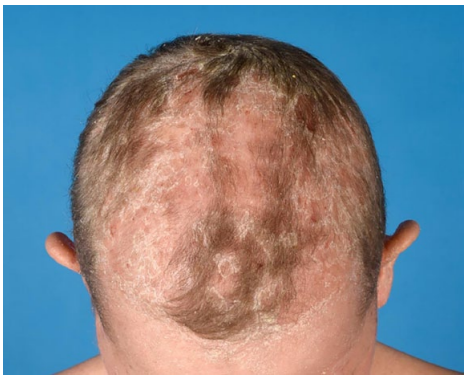
b. Dermatitis in Comèl Netherton syndrome



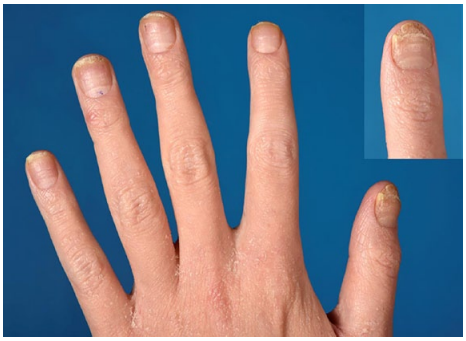
c. Exfoliative erythroderma in Comèl Netherton syndrome



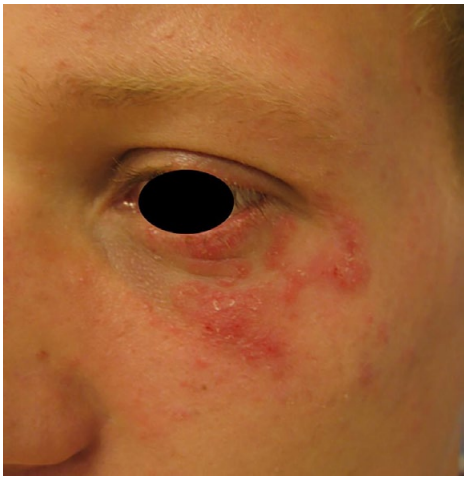
d. Urticaria in common variable immunodeficiency



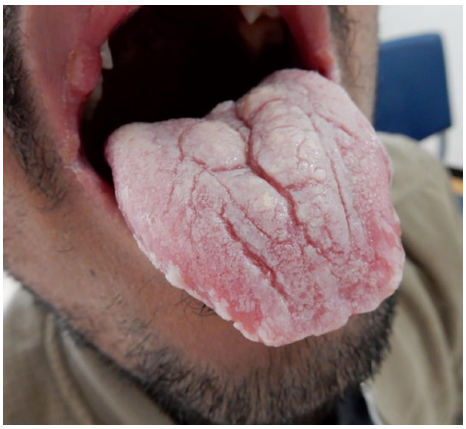
e. Alopecia in immunodysregulation polyendocrinopathy enteropathy X-linked syndrome



f. Onychodystrophy in immunodysregulation polyendocrinopathy enteropathy X-linked syndrome



g. Discoid lupus erythematosus in chronic granulomatous disease



h. Thrush in chronic mucocutaneous candidiasis

Appendix 1. Selected terms of primary immunodeficiency disease and skin disorder used for the electronic search

Primary immunodeficiency disease	Skin disorder
Agammaglobulinemia	Abscess
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy	Albinism
Ataxia-telangiectasia	Basal cell carcinoma
Chediak-Higashi syndrome	Café-au-lait
Chronic granulomatous disease	Candidiasis
Chronic mucocutaneous candidiasis	Carcinoma
Common variable immunodeficiency	Decubitus
DiGeorge syndrome	Depigmentation disorder
Griscelli syndrome	Dermatitis
Hermansky-Pudlak syndrome	Ecthyma
Hyper IgE syndrome	Eczema
Hyper IgM syndrome	Erythroderma
Hypogammaglobulinemia	Granuloma
Idiopathic CD4+ lymphocytopenia	Hyperkeratosis
IgA deficiency	Hyperpigmentation
IgM deficiency	Hypopigmentation
Interleukin-1 receptor-associated kinase-4 deficiency	Infection
Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome	Lupus erythematosus
Leukocyte adhesion defect	Lymphoma
Comèl-Netherton syndrome	Melanoma
PLCG2 associated antibody deficiency and immune dysregulation	Panniculitis
Severe combined immunodeficiency	Pigment disorder
Transporter-associated-with-antigen deficiency	Pyoderma
Warts, hypogammaglobulinemia, immunodeficiency and myelokathexis syndrome	Small vessel vasculitis
Wiskott-Aldrich syndrome	Squamous cell carcinoma
X-linked agammaglobulinemia	Ulcer
	Verruca
	Vitiligo
	Wart

Appendix 2. Inclusion and exclusion criteria for selecting studies for this review

Types of studies

Inclusion criteria

- Original observational and experimental human studies which assess the presence of skin disorders in patients with a primary immunodeficiency disease.
- Original observational and experimental human studies which report a differential diagnosis of a specific skin disorder that includes a primary immunodeficiency disease.

Exclusion criteria

- Case reports (<5 patients per primary immunodeficiency disease), conference abstracts, letters, editorials and review articles.
- Studies reporting only a genetic mutation (suggestive for a primary immunodeficiency disease) instead of a primary immunodeficiency disease as clinical diagnosis.
- Studies reporting skin disorders in primary immunodeficiency diseases that developed after and/or during treatment or intervention.
- Studies in which the description of skin disorders in primary immunodeficiency diseases was not part of the results section.

Participants

Inclusion criteria

- Patients of all ages with a primary immunodeficiency disease according to Picard et al. both in hospital setting and the general population.[16]

Exclusion criteria

- Patients with an acquired immunodeficiency.

Controls

- No controls.

Outcome measures

- Primary: An overview of the presence of skin disorders described in patients with a PID, in order to compose a differential diagnosis of primary immunodeficiency diseases per skin disorder.
- Secondary: The prevalence of skin disorders in primary immunodeficiency diseases, S. aureus associated skin disorders in primary immunodeficiency diseases and primary immunodeficiency diseases associated with an atopic constitution (i.e. atopic dermatitis, food allergy, asthma, rhinoconjunctivitis).

Appendix 3. Quality assessment score

Institute of Health Economics (IHE) Quality Appraisal Checklist for Case Series Studies

Stars indicate the points allocated if the item criterion is met.[20] A maximum score of 13 can be allocated in each article.

Criteria that are not applicable are excluded.

Study objective

1. **Was the hypothesis/aim/objective of the study clearly stated?**
   Yes: The hypothesis/aim/objective of the study was clearly reported (includes patients, intervention and outcome). ★
   Partial: Only one or two components (patients, intervention, or outcome) were included. ★
   No: The hypothesis/aim/objective was not reported.

Study design

2. **Was the study conducted prospectively?**
   Yes: It was clearly stated that the study was conducted prospectively. ★
   Unclear: Unclear or no information was provided.
   No: The study clearly stated it was a retrospective study.

3. **Were the cases collected in more than one centre?**
   Yes: Cases were collected in more than one centre (multicentre study). ★
   Unclear: Unclear where the patients came from.
   No: Cases were collected from one centre.

4. **Were patients recruited consecutively?**
   Yes: There was a clear statement or it was clear from the context that the patients were recruited consecutively; or the study stated that all eligible patients were recruited. ★
   Unclear: No information was provided about the method used to recruit patients in the study.
   No: The study clearly stated that patients were not recruited consecutively; or the patients were recruited based on other criteria such as access to intervention determined by the distance or availability of resources.

Study population

5. **Were the characteristics of the patients included in the study described?**
   Yes: All of the most relevant characteristics of the patients were reported (for example, number, age, gender, ethnicity, severity of disease/condition, comorbidity, or etiology). ★
   Partial: Some, but not all, of the most relevant characteristics were reported. ½★
   No: Only the number of patients was reported.
   Note: Assessor(s) should decide which aspects are important before using the checklist.

6. **Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?**
   Yes: Both inclusion and exclusion criteria were reported. ★
   Partial: Either the inclusion or exclusion criteria were reported. ½★
   No: Neither inclusion nor exclusion criteria were reported.
   Note: Assessor(s) should decide which aspects are important before using the checklist.

7. **Did patients enter the study at a similar point in the disease?**
   Yes: It was clear from the baseline data presented in the study (for example, tables of patients' characterises) that the majority (at least 80%) of patients entered the study at a similar point in terms of the duration and severity of the disease/condition and the presence of co-morbidities/complications. ★
   Unclear: There was no baseline information on patients' characteristics to make a judgment.
   No: There was a wide range in the severity of the disease/condition and co-morbidities/complications in patients at baseline.
   Note: Assessor(s) should decide which aspects are important before using the checklist. It might be useful to discuss with specialists to determine the most important aspects that should be considered.

Outcome measures

10. Were relevant outcome measures established a priori?
Yes: All relevant outcome measures were stated in the introduction or methods section. ★
Partial: Some, but not all, of the relevant outcome measures were stated in the introduction or method section. ½★
No: None of the relevant outcome measures were stated in the introduction or method section.

12. Were the relevant outcomes measured using appropriate objective/subjective methods?
Yes: All relevant outcomes were measured with appropriate methods. These measures can be objective (for example, gold standard tests or standardized clinical tests), subjective (for example, self-administered questionnaires, standardized forms, or patient symptoms interview forms), or both. ★
Partial: Some, but not all, relevant outcomes were measured with appropriate methods. ½★
No: The methods used to measure the relevant outcomes were inappropriate.
Note: Assessor(s) should decide which methods are appropriate before using the checklist.

Results and conclusions

15. Was follow-up long enough for important events and outcomes to occur?
Yes: It was clear from the information provided that the follow-up period was long enough for the majority (at least 80%) of patients, to allow for important events and outcomes (for example, changes in clinical status, adverse events) to occur. ★
Unclear: The length of follow-up was not clearly reported.
No: It is clear from the information provided that the follow-up period was not long enough to allow for important events and outcomes to occur.
Note: Assessor(s) should define the appropriate duration of follow-up for each outcome of interest (for example, short-term and long-term adverse events).

16. Were losses to follow-up reported?
Yes: The number or proportion of patients lost to follow-up was clearly reported; the authors reported outcome results on all patients initially included; or the number lost to follow-up can be subtracted from the number of patients enrolled and the number of patients included in the final analysis. ★
Unclear: There was a discrepancy between the number or proportion of patients reported in tables, figures, and text.
No: The number or proportion of patients lost to follow-up was not reported.

19. Were the conclusions of the study supported by the results?
Yes: The conclusions of the study were supported by the evidence presented in the results and discussion sections. ★
Unclear: Unclear conclusion statement that makes it difficult to link the presented evidence to conclusions.
No: The conclusions were not supported by the evidence presented in the results and discussion sections.

Competing interests and sources of support

20. Were both competing interests and sources of support for the study reported?
Yes: Both competing interests and sources of support (financial or other) received for the study were reported; or the absence of any competing interest and source of support was acknowledged. ★
Partial: Either the competing interest or source of support was reported. ½★
No: Neither competing interests nor sources of support were reported.