

Eczema and Urticaria as Manifestations of Undiagnosed and Rare Diseases



Molly J. Youssef, MD^a, Yvonne E. Chiu, MD^{b,c,*}

KEYWORDS

- Eczema • Urticaria • Nutritional deficiencies • Immunodeficiency syndromes
- Autoinflammatory syndromes • Mycosis fungoides

KEY POINTS

- Autoinflammatory syndromes should be suspected in a child with recurrent bouts of urticaria associated with other symptoms of inflammation (fever, arthritis, serositis, hepatosplenomegaly, ocular, and/or neurologic involvement).
- Immunodeficiency syndromes often present with a neonatal eczematous eruption along with recurrent infections, chronic lymphadenopathy, and/or failure to thrive.
- In a child with a chronic dermatitis that is unresponsive to treatment, biopsy may be warranted to rule out mycosis fungoides (MF).
- Nutritional deficiencies are important to consider in children presenting with recalcitrant dermatitis, often with characteristic locations and/or other clinical features.

INTRODUCTION

Eczema and urticaria are common cutaneous eruptions seen in children. In the vast majority of cases, they are skin-limited disorders that run a benign course. In rare instances, they may signify a more serious underlying disease such as an immunodeficiency or an autoinflammatory syndrome. This review highlights the signs and symptoms that should alert the clinician to suspect something more concerning.

ECZEMA

Eczematous eruptions are characterized by scaly pink papules and plaques, often with associated pruritus. The most common eczematous eruption of childhood is

Disclosure Statement: The authors have no conflicts of interest to disclose.

^a Department of Dermatology, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, WI 53226, USA; ^b Section of Pediatric Dermatology, Department of Dermatology, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, WI 53226, USA;

^c Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI, USA

* Corresponding author. Department of Dermatology, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, WI 53226.

E-mail address: ychiu@mcw.edu

Pediatr Clin N Am 64 (2017) 39–56

<http://dx.doi.org/10.1016/j.pcl.2016.08.004>

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atopic dermatitis, which affects nearly 13% of children in the United States.¹ Nearly two-thirds of children with atopic dermatitis have onset of skin manifestations before 1 year of age but typically after 2 months of age.² Atopic dermatitis has a predilection for the face, scalp, and extensor extremities in infants and young children, whereas flexural sites are more common in older children and adults. A personal or family history of atopy is also a clue for the diagnosis. Although eczema is often equated with atopic dermatitis, there are several other eczematous eruptions of the skin.

Because atopic dermatitis is such a common condition in childhood, it is important to recognize unusual clinical presentations that may indicate the need for further investigation. Many of the childhood diseases associated with eczematous eruptions benefit tremendously from early diagnosis. Some unusual, but very important, causes of eczema in childhood include:

- Primary immunodeficiencies:
 - Autosomal-dominant hyper-IgE syndrome (AD-HIES),
 - Dedicator of cytokinesis 8 gene (DOCK8) deficiency,
 - Phosphoglucomutase 3 (PGM3) deficiency,
 - Wiskott–Aldrich syndrome (WAS),
 - Severe combined immunodeficiency (SCID),
 - IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome), and
 - Netherton syndrome (NS).
- MF.
- Nutritional deficiencies:
 - Pellagra,
 - Kwashiorkor,
 - Zinc deficiency, and
 - Biotin deficiency.

Primary Immunodeficiencies

Eczematous dermatitis is a significant clinical feature of many primary immunodeficiency disorders. When severe and widespread eczema develops at birth or in the early neonatal period and is associated with recurrent or severe infections, chronic lymphadenopathy, significantly increased IgE levels, persistent eosinophilia, recalcitrant oral thrush, or failure to thrive, an evaluation for an underlying immunodeficiency may be warranted.³ The specific clinical manifestations of primary immunodeficiencies with associated eczematous dermatitis are listed in [Table 1](#). For many of these conditions, hematopoietic stem cell transplantation is the treatment of choice, although gene therapy and enzyme replacement are novel treatments under development for some immunodeficiency disorders.

Autosomal-dominant hyperimmunoglobulin E syndrome

AD-HIES is an immunodeficiency syndrome caused by dominant negative mutations in the signal transducer and activator of transcription 3 (STAT3) gene. STAT3 regulates processes involving cell growth and inflammation, with mutations in STAT3 leading to failure of T helper 17 cell differentiation and reduced IL-17 production.^{4,5} AD-HIES is characterized by eczematous eruptions, skin abscesses, recurrent sinopulmonary infections, mucocutaneous candidiasis, and malignancies. The rash commonly presents within the first few weeks of life, which is earlier onset than is typical for atopic dermatitis. The eruption tends to start on the face and scalp. It may be papulopustular at onset but within the first year of life, an eczematous dermatitis develops

Table 1
Features of primary immunodeficiencies associated with eczematous dermatitis

Disease	Gene	Inheritance	Clinical Features	Lab Abnormalities
AD-HIES	<i>STAT3</i>	AD, less commonly sporadic	• Cold abscesses • Recurrent sinopulmonary infections • Mucocutaneous candidiasis • Coarse facies • Minimal trauma fractures • Scoliosis • Joint hyperextensibility • Retained primary teeth • Coronary artery tortuosity or dilation • Lymphoma	• High IgE (>2000 IU/μL) • Eosinophilia
DOCK8 deficiency	<i>DOCK8</i>	AR	• Severe mucocutaneous viral infections • Mucocutaneous candidiasis • Atopic features (asthma, allergies) • Squamous cell carcinoma • Lymphoma	• High IgE • Eosinophilia • With or without decreased IgM
PGM3 deficiency	<i>PGM3</i>	AR	• Neurologic abnormalities • Leukocytoclastic vasculitis • Atopic features (asthma, allergies) • Sinopulmonary infections • Mucocutaneous viral infections	• High IgE • Eosinophilia
WAS	<i>WASP</i>	XLR	• Hepatosplenomegaly • Lymphadenopathy • Atopic diathesis • Autoimmune conditions (especially hemolytic anemia) • Lymphoreticular malignancies	• Thrombocytopenia (<80,000/uL) • Low mean platelet volume • Eosinophilia is common • Lymphopenia • Low IgM, variable IgG

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Table 1
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Disease	Gene	Inheritance	Clinical Features	Lab Abnormalities
SCID	Variable, depends on type	XLR and AR most common	• Recurrent, severe infections • Failure to thrive • Persistent diarrhea • Recalcitrant oral candidiasis • Omenn: lymphadenopathy, hepatosplenomegaly, erythroderma	• Lymphopenia common • Variable patterns of reduced lymphocyte subsets (T, B, natural killer cells) • Omenn: high lymphocytes, eosinophilia, high IgE
IPEX	FOXP3	XLR	• Severe diarrhea (autoimmune enteropathy) • Various autoimmune endocrinopathies (especially diabetes mellitus, thyroiditis) • Food allergies	• High IgE • Eosinophilia • Various autoantibodies
Netherton syndrome	SPINK5	AR	• Hair shaft abnormalities • Erythroderma • Ichthyosis linearis circumflexa • Food allergies • Recurrent gastroenteritis • Neonatal hypernatremic dehydration • Upper and lower respiratory infections	• High IgE • Eosinophilia

Abbreviations: AD, autosomal dominant; AD-HIES, autosomal-dominant hyper-IgE syndrome; AR, autosomal recessive; DOCK8, dedicator of cytokinesis 8 gene; Ig, immunoglobulin; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; PGM3, phosphoglucomutase 3; SCID, severe combined immunodeficiency; WAS, Wiskott–Aldrich syndrome.

with varying severity (Fig. 1). The presence of *Staphylococcus aureus* seems to be a provoking factor and cutaneous infections are common.⁶⁻⁸ These patients may suffer from recurrent cold abscesses, most often secondary to *S aureus* and lacking typical features of warmth and erythema. All patients with AD-HIES have elevated serum IgE, usually with peak levels of greater than 2000 IU/ μ L, and eosinophilia is almost always present.⁸ Children with severe atopic dermatitis may have greatly increased IgE levels and eosinophilia, so this feature alone is not diagnostic of AD-HIES. Craniofacial, musculoskeletal, dental, and vascular abnormalities can be extremely useful for diagnosing AD-HIES.^{9,10} AD-HIES is also associated with an increased risk of malignancy, most commonly non-Hodgkin lymphoma.⁷

Dedicator of cytokinesis 8 gene deficiency

Mutations in the DOCK8 gene were discovered to be responsible for an autosomal-recessive form of hyper-IgE syndrome.¹¹ DOCK8 deficiency shares many similar clinical features with AD-HIES, including elevated serum IgE levels, eosinophilia, eczematous dermatitis, staphylococcal skin and sinopulmonary infections, and risk of lymphoma. However, unlike the neonatal pustular eruption that often occurs in AD-HIES, patients with DOCK8 deficiency tend to develop an eczematous rash in the classic atopic dermatitis areas. The eruption may begin beyond the neonatal period. In a study by Chu and colleagues,¹² the incidence of newborn rash was 24% in the DOCK8-deficient cohort, in contrast with 81% of patients with AD-HIES, although the DOCK8-deficient cohort had more severe dermatitis. Other distinguishing features of DOCK8 deficiency include the presence of multiple food and environmental allergies, asthma, and an increased risk of squamous cell carcinoma. Furthermore, nearly all patients with DOCK8 deficiency develop extensive, recurrent and treatment-resistant cutaneous viral infections owing to herpes simplex virus, varicella zoster virus, human papilloma virus, and/or molluscum contagiosum. DOCK8 deficiency has been shown to impair the development and survival of mature natural killer (NK) cells, which would contribute to the host susceptibility to viral infections.¹³

Phosphoglucomutase 3 deficiency

PGM3 deficiency is another autosomal-recessive form of hyper-IgE syndrome owing to a mutation in the PGM3 gene that results in dysfunction of the glycosylation pathway. This condition shares similar features with both AD-HIES and DOCK8 deficiency, including the development of eczematous dermatitis of variable severity. Neurologic impairment and leukocytoclastic vasculitis are unique features of PGM3 deficiency.¹⁴



Fig. 1. Early papulopustular rash on the face of an infant with hyper-IgE syndrome. (From Olaiwan A, Marie-Oliveria C, Fraitag S, et al. Cutaneous findings in sporadic and familial autosomal dominant hyper-IgE syndrome: a retrospective, single-center study of 21 patients diagnosed using molecular analysis. *J Am Acad Dermatol* 2011;65:1169; with permission.)

Wiskott–Aldrich syndrome

WAS is an X-linked recessive condition characterized by thrombocytopenia and small dysfunctional platelets, recalcitrant eczematous dermatitis, and recurrent bacterial infections. It almost exclusively occurs in males with few reports of females affected.¹⁵ WAS is secondary to loss-of-function mutations in the WAS protein (WASP) gene, which plays a role in lymphoid development and thereby affects both B and T lymphocyte function.¹⁶ Owing to thrombocytopenia and platelet dysfunction from birth, patients often present initially with spontaneous bleeding, such as epistaxis or bloody stools. The dermatitis usually begins within the first few months of life and is indistinguishable from atopic dermatitis, but may be more generalized and/or severe. The face, scalp, and flexural areas are typically affected and secondary bacterial infections are common. Owing to the bleeding diathesis, excoriated areas are more likely to demonstrate serosanguinous crust, petechiae, and purpura. Recurrent bacterial infections, especially with encapsulated organisms, begin in infancy as maternal antibodies wane. Most children with WAS also develop autoimmune or inflammatory disease over time. Hemolytic anemia is the most common, but other conditions reported in patients with WAS include autoimmune neutropenia, painful cutaneous small vessel vasculitis, arthritis, cerebral vasculitis, inflammatory bowel disease, and renal disease.¹⁷ In 1 study, nearly 25% of WAS patients developed malignancies including lymphoma and myelodysplasia.¹⁸

Severe combined immunodeficiency

SCID describes a group of disorders that arise from a variety of genetic defects and result in absent lymphocyte development and function. The most common types of SCID include an X-linked recessive form involving IL2RG mutations with loss of T and NK cell development, and an autosomal-recessive form involving RAG1 or RAG2 mutations with resultant loss of T-cell and B-cell development. Adenosine deaminase–SCID accounts for approximately 15% of cases, with deficiency of intracellular enzyme adenosine deaminase leading to the accumulation of metabolic precursors that are toxic to lymphocytes.¹⁹ Infants tend to present between 3 and 6 months of life as maternal antibodies wane, although screening for SCID as part of the newborn panel has been more recently implemented in many states and leads to earlier diagnosis.²⁰ Typical features of SCID include recurrent and/or severe infections, persistent diarrhea, failure to thrive, and recalcitrant oral candidiasis. Infants may also develop a generalized dermatitis, which may be seborrheic or exfoliative. Omenn syndrome is a variant of SCID caused by deficiency of RAG protein, and nearly all infants with Omenn syndrome present with extensive skin inflammation or erythroderma (**Fig. 2**). Other common features of Omenn syndrome include hepatosplenomegaly, lymphadenopathy, alopecia, eosinophilia, and elevated IgE levels.^{7,19}

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome

IPEX syndrome is an X-linked recessive disorder owing to a mutation in the FOXP3 transcription factor resulting in abnormal development of T-regulatory cells.^{21,22} Affected males typically present during the first months of life with severe watery diarrhea owing to autoimmune enteropathy, various autoimmune endocrinopathies (eg, early onset diabetes mellitus, thyroiditis), and chronic dermatitis. The dermatitis in infancy tends to be eczematous and is usually widespread affecting the trunk, lower extremities, and face. It is often recalcitrant to standard treatments and may be complicated by frequent staphylococcal superinfections and sepsis. Other reported cutaneous manifestations of IPEX syndrome include psoriasiform dermatitis, erythroderma, urticaria, alopecia, onychodystrophy, and cheilitis.^{23,24} The majority



Fig. 2. Generalized exfoliative dermatitis in a 2-month-old boy with Omenn syndrome. (From Hsu C, Lee JY, Chao S. Omenn syndrome: a case report and review of literature. *Dermatologica Sinica* 2009;29:51; with permission.)

of patients with IPEX have markedly elevated IgE and eosinophils, and a variety of autoantibodies.²⁵

Netherton syndrome

NS is an autosomal-recessive condition with a triad of ichthyosis, atopic diathesis, and hair shaft deformities. It is caused by mutations in the SPINK5 gene, which encodes a serine protease inhibitor and mutations ultimately leads to reduced desmosomal proteins.^{26,27} NS typically presents in the neonatal or early infantile period with generalized ichthyosiform erythroderma. The scaly erythroderma tends to improve with age, but the majority of patients with NS will develop ichthyosis linearis circumflexa starting in toddler or early childhood years and appearing as migratory, serpiginous, and polycyclic scaly lesions with a characteristic peripheral double-edged scale.²⁸ Infants may also develop recurrent acute gastroenteritis, failure to thrive, and hypernatremic dehydration. NS has a classic hair shaft abnormality called trichorrhexis invaginata, resulting in easily broken hairs that appear as “bamboo hair” or “ball and socket” abnormalities under magnification. A recent study identified many immunologic abnormalities in patients with NS, including reduced memory B cells, skewed Th1 phenotype, impaired antibody amplification and class-switching, decreased NK cell cytotoxicity, and elevated proinflammatory cytokine levels.²⁹ These findings

have led some to suggest that NS should be considered a primary immunodeficiency and helps to explain why patients with NS are susceptible to staphylococcal skin infections, respiratory infections, and sepsis. The majority of patients with NS also demonstrate an atopic diathesis with pruritic atopic dermatitis, food allergies, rhinitis, and/or asthma.²⁹

Malignancy

Mycosis fungoides

MF is a type of primary cutaneous T-cell lymphoma and is predominantly a disease of older adults, with pediatric MF accounting for less than 5% of all MF cases. The clinical presentation of MF in children is quite variable and may occur at any age, even as early as infancy.³⁰ Hypopigmented MF is a variant that occurs most commonly in children, especially those with darker skin types. Children with hypopigmented MF present with hypopigmented macules and patches, which are often round and may have slight overlying scale. The lesions are usually asymptomatic and occur in sun-protected areas. Hypopigmented MF can easily be mistaken for postinflammatory hypopigmentation secondary to atopic dermatitis or other inflammatory conditions. MF in children may also present as erythematous, scaly papules and plaques, which can be pruritic and very closely mimic atopic dermatitis. There may be subtle clues of MF, such as poikilodermatous changes, atrophy, and telangiectasia. Frequently, it is the chronicity and recalcitrance to therapy that prompts skin biopsy and leads to the diagnosis of MF, often years after the lesions developed. Fortunately, most cases of pediatric MF represent very early stage disease without involvement of lymph nodes, viscera, or blood. It tends to follow an indolent course and progression to advanced-stage MF during childhood is rare.^{30–32} Common treatment options for MF in children include phototherapy and topical steroids.

Nutritional Deficiencies

Nutritional deficiencies are important to consider in children presenting with recalcitrant dermatitis. Even children with adequate access to food can develop nutritional deficiencies secondary to chronic medical conditions, parental nutritional ignorance, food allergen avoidance, or restrictive diets. Identification of nutritional deficiencies is life saving for some children, and the conditions are often easily treatable.

Pellagra

Pellagra is a disorder resulting from a severe cellular deficiency of niacin, owing to inadequate dietary nicotinic acid or its precursor essential amino acid, tryptophan. Pellagra now rarely occurs in developed countries owing to dietary availability of niacin, but those with malabsorptive states, restrictive eating behaviors, and poor social circumstances (eg, homelessness) remain at particular risk. This condition is characterized by the classic triad of dermatitis, diarrhea, and dementia. The dermatitis begins as a well-demarcated scaling erythema, with similar appearance to a sunburn, on areas exposed to sunlight, heat, friction, or pressure. The face, neck, dorsal hands and arms, feet, and inguinal area are commonly affected; in infants, the diaper area is often involved. There may be associated burning sensation, pruritus, and/or tenderness. “Casal’s necklace” is a term used for a characteristic red eruption with well-defined borders on the lower neck. Vesicles and bullae may be present. Over time, the erythema transitions to a dusky brown-red color, and later stages may demonstrate hyperkeratosis, scaling, fissuring, and shellaclike shiny appearance. Oral involvement, such as glossitis, cheilitis, aphthous ulcers, and fissuring, occurs in one-third of patients. Gastrointestinal manifestations may include diarrhea, poor

appetite, nausea, vomiting, and abdominal pain. Neuropsychiatric disturbances can range broadly—from headache and irritability to confusion and psychosis. Measurement of urinary metabolites of niacin (N_1 -methylnicotinamine and/or pyridine) can aid in the diagnosis of pellagra.^{33,34}

Secondary pellagra occurs when adequate amounts of niacin are consumed in the diet, but other conditions interfere with its absorption or processing. Hartnup disease is a rare autosomal-recessive disorder caused by a mutation in the SLC6A19 gene, which encodes a transporter of neutral amino acids.³⁵ Loss of function of this transporter leads to inability to resorb tryptophan and other amino acids by the small intestine and renal tubules. Hartnup disease is often diagnosed in children between the ages of 3 and 9 years and manifests as a pellagralike cutaneous eruption and neurologic abnormalities (predominantly cerebellar ataxia). Diagnosis can be achieved by analysis of urine amino acids, and treatment consists of prolonged high doses of oral nicotinic acid.³⁶

Kwashiorkor

Severe protein deficiency is most often seen in children of developing countries secondary to poverty and limited access to protein-containing foods. In higher income countries, protein deficiency is more commonly owing to food allergen avoidance and other restrictive diets, nutritional ignorance, and malabsorptive conditions.³⁷ The substitution of rice milk as a dietary staple for infants has become a common cause of protein deficiency in the United States.³⁸ The presence of protein deficiency without significant total caloric deficit results in a condition called kwashiorkor, with typical features including edema, hypoalbuminemia, and rash. The eruption appears as an erythematous, crusted, erosive, and desquamative dermatitis. The dermatitis tends to have an overlying reddish-brown scale with sharply marginated, raised edges that may seem to be “pasted-on” or similar to “flaky paint.” The flexures, face, perioral area, and diaper area are most frequently affected, which differs from the rash on sun-exposed sites seen in pellagra. The edema seen in kwashiorkor tends to be prominent on the face, feet, and abdomen. Affected children often demonstrate mental status changes such as irritability or apathy. Treatment of children with kwashiorkor involves gradual introduction of a high-protein diet with careful attention to electrolyte imbalances and hydration status.³⁷

Zinc deficiency

Zinc deficiency often manifests with an eczematous dermatitis but in characteristic locations that help to establish the diagnosis. Acrodermatitis enteropathica is an autosomal-recessive inherited disorder with mutations in SLC39A, which results in dysfunction of an intestinal zinc transporter, with subsequent severe zinc deficiency. Breastfeeding-related zinc deficiency can occur secondary to maternal mutations resulting in poor secretion of zinc into breastmilk, or in premature infants exclusively breastfed without zinc supplementation. In addition, there is a risk of zinc deficiency in patients with malabsorption as seen in inflammatory bowel disease and cystic fibrosis, as well as children receiving parenteral nutrition without zinc additive.^{39,40} Whether zinc deficiency is congenital or acquired, it may present with a triad of diarrhea, acral and periorificial dermatitis, and alopecia. The dermatitis consists of eczematous pink scaly plaques, which can become vesicular, bullous, pustular, or desquamative. The lesions develop over the anogenital and periorificial areas, extensor extremities, scalp, fingers, and toes (**Fig. 3**). Secondary infection with *Candida albicans* is common on the face and may also lead to paronychia of the digits. Infants with zinc deficiency may demonstrate growth delay, poor feeding, apathy, and/or irritability.



Fig. 3. The rash of zinc deficiency on the thighs and genitals of a breastfed infant.

Diagnosis is based on clinical suspicion and low serum zinc levels. Both acrodermatitis enteropathica and acquired forms of zinc deficiency are treated with zinc supplementation, and infants often show dramatic improvement of their symptoms within days.^{40,41} Findings resembling acrodermatitis enteropathica have also been described in patients with biotin deficiency and certain organic acid disorders.

URTICARIA

Urticaria is owing to localized edema in the superficial dermis, leading to the characteristic pink or pale elevated swellings called wheals. Wheals may vary in size from a few millimeters to several centimeters. Urticarial lesions may assume an annular, polycyclic, or serpiginous pattern with clearing of the central region and coalescence of the wheals. Urticaria is classically pruritic and transient with individual wheals lasting less than 24 hours. Acute urticaria, defined as urticaria occurring for less than 6 weeks, is a common self-limited hypersensitivity response in children that is often secondary to infection, medications, or food allergies. However, chronic urticaria can be a manifestation of rare autoinflammatory syndromes and a clue to an underlying disorder.

Autoinflammatory syndromes are a rare category of inherited disorders characterized by recurrent fevers and episodic inflammation of multiple organ systems. Unlike autoimmune diseases, which exhibit autoreactive T lymphocytes or autoantibodies, the persistent inflammation in autoinflammatory syndromes is owing to aberrant regulation of the innate immune system where cytokine signaling pathways are activated in the absence of a recognizable infection.^{42,43} Autoinflammatory syndromes should be suspected in a child with recurrent bouts of urticaria lasting months to years. The urticarial outbreaks are associated with other symptoms of inflammation such as fever, arthritis, serositis, hepatosplenomegaly, and ocular and/or neurologic involvement (Table 2). Infection or malignancy should be excluded through appropriate investigations.

Atypical urticaria are a common presenting feature in several autoinflammatory syndromes that present in childhood, including:

- Cryopyrin-associated periodic syndromes (CAPS)
 - Familial cold autoinflammatory syndrome
 - Muckle-Wells syndrome
 - Chronic infantile neurologic cutaneous articular syndrome/neonatal-onset multisystem inflammatory disease

Table 2
Febrile autoinflammatory diseases causing urticaria in children

Disease	Gene (Protein)	Inheritance	Attack Length	Timing of Onset	Cutaneous Features	Extracutaneous Clinical Features
FCAS	<i>NLRP3</i> (cryopyrin)	AD	Brief; Minutes-3 d	Neonatal or infantile	Cold-induced urticaria	• Arthralgia • Conjunctivitis • Headache
Muckle-Wells syndrome	<i>NLRP3</i> (cryopyrin)	AD	1–3 d	Neonatal, infantile, childhood (can be later)	Widespread urticaria	• Arthralgia/arthritis • Sensorineural hearing loss • Conjunctivitis/episcleritis • Headache • Amyloidosis
Chronic infantile neurologic cutaneous articular syndrome/ neonatal-onset multisystem inflammatory disease	<i>NLRP3</i> (cryopyrin)	AD	Continuous flares	Neonatal or infantile	Widespread urticaria	• Deforming osteoarthropathy, epiphyseal overgrowth • Sensorineural hearing loss • Dysmorphic facies • Chronic aseptic meningitis, headaches, papilledema, seizures • Conjunctivitis/uveitis, optic atrophy • Growth retardation • Developmental delay • Amyloidosis
HIDS	<i>MVK</i> (mevalonate kinase)	AR	3–7 d	Infancy (<2 y)	• Intermittent morbilliform or urticarial rash • Aphthous mucosal ulcers • Erythema nodosum	• Arthralgia/arthritis • Cervical lymphadenopathy • Severe abdominal pain • Diarrhea/vomiting

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Table 2
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Disease	Gene (Protein)	Inheritance	Attack Length	Timing of Onset	Cutaneous Features	Extracutaneous Clinical Features
						• Headache • Elevated IgD and IgA antibody levels • Elevated urine mevalonic acid during attacks
Tumor necrosis factor receptor-associated periodic syndrome	<i>TNFRSF1A</i> (TNFR1)	AD	>7 d	Childhood	• Intermittent migratory erythematous macules and edematous plaques overlying areas of myalgia, often on limbs • Periorbital edema	• Migratory myalgia • Conjunctivitis • Serositis • Amyloidosis
Systemic onset juvenile idiopathic arthritis	Polygenic	Varies	Daily (quotidian)	Peak onset at 1–6 y	• Nonfixed erythematous rash, may be urticarial • With or without Dermatographism • With or without Periorbital edema	• Polyarthritits • Myalgia • Hepatosplenomegaly • Lymphadenopathy • Serositis
PLAID	PLCG2	AD	N/A	Infancy	• Urticaria induced by evaporative cooling • Ulcers in cold-exposed areas	• Allergies • Autoimmune disease • Recurrent sinopulmonary infections • Elevated IgE antibody levels • Decreased IgA and IgM antibody levels • Often elevated antinuclear antibody titers

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; Ig, immunoglobulin; PLAID, PLC γ 2-associated antibody deficiency and immune dysregulation; SoJIA, systemic onset juvenile idiopathic arthritis.

- Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)
- Tumor necrosis factor receptor-associated periodic syndrome
- Systemic onset juvenile idiopathic arthritis
- PLC γ 2-associated antibody deficiency and immune dysregulation (PLAID)

Cryopyrin-associated Periodic Syndromes

CAPS are a group of autoinflammatory syndromes caused by mutations in cryopyrin, also called NLRP3 (nucleotide-binding domain and leucine-rich repeat containing family, pyrin domain-containing 3).⁴⁴ When stimulated by various danger-associated molecular patterns and pathogen-associated molecular patterns, NLRP3 associates with other proteins to form the inflammasome, resulting in increased release of active IL-1 β . Mutations in NLRP3 result in constitutive inflammasome activity and subsequent IL-1 β secretion.

In the CAPS, a rash is usually the first notable symptom. The rash is typically migratory and resembling urticaria, but it is often nonpruritic and can be painful. The rash commonly has diurnal variation with minimal rash in the morning, gradual increase in severity throughout the day, and worst rash in the evening.⁴³ In familial cold autoinflammatory syndrome, the urticarial eruption is unique in that it occurs approximately 1 to 2 hours after exposure to cold temperature.^{45,46} In addition to an urticarial eruption, all forms of CAPS are characterized by recurrent fevers and joint inflammation, usually presenting in infancy. The majority of individuals with Muckle-Wells syndrome suffer from a sensorineural hearing loss, whereas chronic infantile neurologic cutaneous articular syndrome/neonatal-onset multisystem inflammatory disease is the most severe of the cryopyrinopathies with neurologic abnormalities (including sensorineural hearing loss) and deforming osteoarthropathies. In addition, the development of secondary amyloidosis occurs in approximately 25% of patients with Muckle-Wells syndrome and chronic infantile neurologic cutaneous articular syndrome/neonatal-onset multisystem inflammatory disease. Amyloid deposition in the kidneys can lead to renal failure and is an important factor in overall prognosis.^{42,46} Interestingly, the severity of clinical disease does not predict association with amyloidosis.⁴³ Treatment of CAPs is focused on decreasing IL-1 β activity through the use of anakinra (IL-1 receptor antagonist), rilonacept (IL-1 trap), and canakinumab (IL-1 β monoclonal antibody).^{47–49}

Hyperimmunoglobulinemia D with Periodic Fever Syndrome

HIDS is an autosomal-recessive disease associated with mutations in the MVK gene. These mutations result in decreased activity of mevalonate kinase, resulting in decreased isoprenoid production and ultimately, increased IL-1 β release.⁵⁰ Inflammatory symptoms begin within the first 1 to 2 years of life, often triggered by vaccinations. Cutaneous manifestations occur in two-thirds of patients with HIDS, and may include morbilliform and urticarial eruptions, as well as erythema nodosum (Fig. 4). Importantly, about one-half of patients develop aphthous ulcers in the mouth and/or genitals, which often leads to an incorrect diagnosis of Behçet disease.⁵¹ Abdominal pain is also a common feature of HIDS.

Tumor Necrosis Factor Receptor-associated Periodic Syndrome

Caused by mutations in the TNFR1 gene, tumor necrosis factor receptor-associated periodic syndrome is unique in that febrile attacks are longer lasting, often 1 to 6 weeks.^{52,53} Skin manifestations can resemble urticaria and include migratory erythematous macules or patches, edematous dermal plaques, serpiginous or annular



Fig. 4. Urticarial eruption on the trunk and extremities in a patient with hyperimmunoglobulinemia D with periodic fever syndrome. (From Brydges S, Athreya B, Kastner DL. Periodic fever syndromes in children. In: Cassidy JT, Petty RE, editors. Textbook of pediatric rheumatology. 5th edition. Philadelphia: Elsevier Saunders; 2005. p. 642–60; with permission.)

lesions, and periorbital edema.⁴² Often there is a warm, tender erythematous swollen plaque that arises on the limbs near the trunk and migrates distally (Fig. 5). Skin lesions typically correlate with underlying myalgias.⁴⁵ Secondary amyloidosis may occur in 10% to 15% of patients.

Systemic-Onset Juvenile Idiopathic Arthritis

Systemic onset juvenile idiopathic arthritis is a polygenic autoinflammatory syndrome. Although it is officially classified as a subtype of juvenile idiopathic arthritis, it shares many similarities with the hereditary autoinflammatory syndromes.⁵⁴ The condition is characterized by daily high spiking fevers in association with an inflammatory arthritis lasting longer than 6 weeks.⁵⁵ In contrast with other forms of JIA, the diagnosis of systemic onset JIA requires an additional extraarticular finding, which may include hepatomegaly, splenomegaly, lymphadenopathy, serositis, or an evanescent rash. The rash typically consists of salmon pink or erythematous macules and urticarial plaques, with possible associated dermatographism, involving the trunk, neck, and extremities. The face, palms, and soles are almost always spared. The urticarial eruption with systemic onset juvenile idiopathic arthritis varies throughout the day; it tends to be worst in evening hours, correlating with fever spikes and arthritis flares.^{42,44,46}

PLC γ 2-associated Antibody Deficiency and Immune Dysregulation

PLAID is a recently described entity that may represent a distinct type of autoinflammatory syndrome with an associated immunodeficiency.⁵⁶ PLAID is an autosomal-dominant condition caused by a mutation in PLCG2, leading to the development of urticaria in early childhood.⁵⁷ The urticaria are typically induced by evaporative cooling; ulcers in cold-exposed areas are also seen. Patients with this condition also develop autoimmune disease and recurrent sinopulmonary infections. Some patients with PLAID have a more pronounced inflammatory syndrome with pneumonitis, colitis, eye inflammation, arthralgias, and blistering skin lesions.^{58,59} Immunologic abnormalities include elevated IgE, decreased IgA and IgM, and decreased circulating B cells and NK cells.



Fig. 5. Migrating erythematous plaques during an inflammatory attack in a patient with tumor necrosis factor receptor-associated periodic syndrome. (From van der Hilst JCH, van der Meer JWM, Drenth JPH. Autoinflammatory fever syndromes. In: Rich R, Fleisher T, Shearer E, et al, editors. Clinical immunology: principles and practice. 3rd edition. Philadelphia: Elsevier/Mosby; 2008. p. 899–908; with permission.)

SUMMARY

Eczema and urticaria may occasionally be the presenting complaint in a child with an underlying rare disease. Immunodeficiency syndromes should be suspected when eczema is associated with neonatal onset, recurrent infections, chronic lymphadenopathy, or failure to thrive. Nutritional deficiencies and MF are also in the differential diagnosis for a child with a recalcitrant eczematous eruption. Autoinflammatory syndromes should be suspected in a child with chronic urticaria, fever, and other systemic signs of inflammation. Even though these disorders are rare, early recognition of these disorders allows for appropriate treatment and decreased morbidity for the child.

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