INTRODUCTION

Primary immunodeficiency diseases (PID) are a group of disorders caused by genetic defects in the immune system that lead to immune dysfunction [1]. The most frequent manifestations of PID are severe recurrent infections that are caused by unusual organisms and are difficult to cure [2,3]. Among other manifestations of PID, there are autoimmune diseases, allergic disorders, and malignancy.

Allergic disorders are often manifested by atopy which typically can be present as atopic dermatitis (eczema), allergic rhinitis (hay fever) or asthma. The majority of allergic diseases are immunoglobulin IgE mediated [4]. At present, almost half of the world’s population suffers from allergic diseases. The prevalence of allergic disorders has rapidly increased in recent years but is significantly underestimated in some countries [5].

In patients with the normal function of the immune system, infections lead to Th1 and Th2 type of immune responses. This also causes the development of Tregs, which support a balance between Th1 and Th2 immune responses, and prevent their harmful effects. In the cases of absent or poor Tregs check, the patients become more susceptible to allergic or autoimmune diseases [4].

Physicians’ awareness concerning PID is poor among physicians of different specialties [6], though an early diagnosis of these diseases is very important for preventing the development of complications and improving the quality of life of the children with PID. Allergic manifestations of skin are often early findings of PID [7]. Thus, it is very important to recognize allergic reactions as possible manifestations of PID.

The purpose of this study was to collect and systematize data on PID, associated with allergic or allergic-like manifestations for improving the early diagnosis of PID.

The novelty of the study is in the complex assessment of allergic and allergic-like manifestations in children with PID.

ALLERGIC MANIFESTATIONS OF PRIMARY IMMUNODEFICIENCY DISEASES AND ITS TREATMENT APPROACHES

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ABSTRACT

Allergic manifestations are one of the clinical signs of primary immunodeficiency diseases (PID). In this review, the common allergic manifestations of PID are summarized, and their main differential characteristics and treatment approaches are outlined. Allergic manifestations occur more often in patients with combined immunodeficiencies with or without associated or syndromic features. In patients with PID they usually are present in the 1st year of life, may be among the first symptoms of PID, and are commonly manifested by eczema and increased immunoglobulin IgE levels. Often the skin barrier function is not impaired in patients with eczema and PID, although some diseases (such as Comel-Netherton syndrome) do affect skin barrier function. There is usually no correlation between IgE levels and the severity of allergic skin manifestations. Allergic-like manifestations in PID patients include urticaria-like rash and angioedema. Urticaria-like rash is associated with autoinflammatory disorders, which are commonly accompanied by fever, and caused by a neutrophilic infiltrate in the dermis. Angioedema in hereditary angioedema patients is caused by high bradykinin production. Early differentiation of allergic manifestations in PID from atopic dermatitis and other atopic conditions is very difficult; however, it is very important because it influences on treatment methods. A multidisciplinary approach to the management of PID patients, with the involvement of immunologists, allergists, and formulation of appropriate treatment improve the prognosis and quality of life of the PID patients.

Keywords: Allergic manifestations, Primary immunodeficiencies, Treatment approaches.

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ALLERGIC MANIFESTATIONS OF PID

PID are classified into nine major groups: Combined immunodeficiencies without non-immunologic phenotypes; combined immunodeficiencies with syndromic features; predominantly antibody deficiencies; diseases of immune dysregulation; congenital defects of phagocyte number, function, or both; defects of innate immunity, autoinflammatory disorders; complement deficiencies; and phenocopies of PID [2].

In the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency classification [2], allergic manifestations are mentioned for 11 diseases (Table 1) and allergic-like manifestations for 6 diseases (Table 2). While mammalian sterile 20-like 1 (MST1) deficiency is included in this classification, its allergic manifestations were not listed (Table 3).

Clinical symptoms of dedicator of cytokinesis 8 (DOCK8) deficiency include atopic dermatitis, allergies, cutaneous viral infections, cutaneous staphylococcal abscesses, recurrent sinopulmonary infections, and malignancy [8,9]. Laboratory findings indicate elevated serum IgE levels, hypo-IgM, T cell lymphopenia, and eosinophilia [9]. The DOCK8 gene mutation was discovered in 2009 [10], allowing to isolate it as a separate nosological form, since it was previously known as autosomal recessive hyper-IgE syndrome [11]. The authors reported about 21 patients with confirmed DOCK8 deficiency they had followed for 20 years [9]. Dermatitis in patients with DOCK8 deficiency occurred in 91% of cases and was characterized by severe course. Substantial food and environmental allergies were registered in 71% of DOCK8-deficient patients, while nearly 50% had asthma [9].

Another study reported a case of moderate atopic dermatitis, food allergy to cow’s milk protein and hen eggs, and extensive molluscum contagiosum in a 3-year-old patient with DOCK8 deficiency [12].
Table 1: Primary immune deficiencies associated with allergic manifestations (according to the classification from the international union of immunological societies expert committee for primary immunodeficiency)

| Disease                                           | Inheritance | Allergic manifestations                                      | Laboratory findings                                                                 | Other clinical manifestations                                                                 |
|--------------------------------------------------|-------------|----------------------------------------------------------------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Combined immunodeficiencies                      |             |                                                                |                                     |                                                                                             |
| DOCK8 deficiency                                 | AR          | Severe atopy, increased IgE, hypereosinophilia.                | Decreased impaired T-lymphocyte proliferation, decreased, low CD27+memory B cells, low IgM, low NK cells with impaired function | Recurrent infections; extensive cutaneous viral and bacterial (staph.) infections, susceptibility to cancer |
| Omenn syndrome                                  |             | Erythroderma, eosinophilia, increased IgE.                    | Restricted T cell repertoire, and impaired function, B cells normal or decreased, serum Ig decreased | Adenopathies, hepatosplenomegaly                                                                |
| Combined immunodeficiencies with associated or syndromic features |             |                                                                |                                     |                                                                                             |
| WAS                                             | XL          | Eczema often increased IgE.                                   | Progressive decrease, abnormal lymphocyte responses to anti-CD3, decreased IgM: antibody to polysaccharides particularly decreased; often increased IgA | Thrombocytopenia with small platelets; lymphoma; autoimmune disease; IgA nephropathy; bacterial and viral infections. |
| WIP deficiency                                  | AR          | Eczema increased IgE.                                         |                                     | Recurrent infections; thrombocytopenia. WAS-like phenotype.                                   |
| AD- Hyper-IgE syndrome (Job's syndrome)          | AR          | Eczema, elevated IgE;                                          | Normal Th-17 and T follicular helper cells decreased, switched and non-switched memory B cells are reduced; BAFF level increased, specific antibody production decreased | Distinctive facial features (broad nasal bridge), osteoporosis, fractures, scoliosis, delay of shedding of primary teeth, hyperensible joints, bacterial infections (skin and pulmonary abscesses, pneumatoceles) due to Staphylococcus aureus, candidiasis, anerysm formation |
| Tyk2 deficiency                                 | AR          | Elevated IgE.                                                 | Multiple cytokine signaling defect                                                   | Susceptibility to intracellular bacteria (Mycobacteria, Salmonella), fungi, and viruses. |
| Comel-Netherton syndrome                         | AR          | Atopic diathesis, elevated IgE.                               | Switched and non-switched B cells are reduced, elevated IgA, antibody variably decreased | Congenital ichthyosis, bamboo hair, increased bacterial infections, failure to thrive Growth-hormone insensitive dwarfism, dysmorphic features, lymphohytic interstitial pneumoniitis, autoimmunity |
| STAT5b deficiency                                | AR          | Eczema                                                        | Modestly decreased T-cell.                                                          | Growth-hormone insensitive dwarfism, dysmorphic features, lymphohytic interstitial pneumoniitis, autoimmunity |
| Predominantly antibody deficiencies              | Variable    | May have allergies                                            | IgA decreased/absent                                                                | Usually asymptomatic; may have recurrent infections; or autoimmune disease |
| Selective Igk deficiency                         |             |                                                                |                                     |                                                                                             |
| Diseases of immune dysregulation                 |             |                                                                |                                     |                                                                                             |
| IPEX, immune dysregulation, polyendocrinopathy   | XL          | Eczema, Elevated IgE.                                         | Lack of (and/or impaired function of) CD4+CD25+FOX3+regulatory T cells (Tregs), elevated IgA | Autoimmune enteropathy, early-onset diabetes, thyroiditis, hemolytic anemia, thrombocytopenia. |
| Enteropathy X-linked Autoinflammatory disorders  |             |                                                                |                                     |                                                                                             |
| PLAID                                           | AD          | Cold urticaria                                                 | Mutations cause activation of IL-1 pathway, hypogammaglobulinemia                    | Recurrent sinopulmonary infections, skin granuloma.                                           |

DOCK8 deficiency impacts immune cell function, migration, and affects innate and adaptive immune responses [13]. It also causes persistence of B cells in germinal centers, early T-cell death, and decreased natural killer cell cytotoxicity [14]. The median IgE levels in DOCK8 deficiency were 5201 IU, low IgM levels observed in 62% of patients, and lymphopenia in 20% of patients, mainly due to low CD4+ and CD8 T-cell number [15].

**Omenn syndrome**

Omenn syndrome is another severe combined immunodeficiency that is manifested by allergic symptoms. It is an autosomal recessive disease characterized by erythroderma, desquamation, alopecia, chronic diarrhea, failure to thrive, lymphadenopathy, eosinophilia, hepatosplenomegaly, and elevated serum IgE levels [16]. The disease is caused by mutations in the RAG1 or RAG2 genes [17]. Omenn syndrome is an inflammatory condition caused by multiple genetic abnormalities, which can significantly impair T-cell development in the thymus. It is a genetically heterogeneous condition, meaning that patients with similar phenotypes may have different underlying genetic defects. It was linked to mutations in ARTEMIS, ADA, ILR2, ILR7, CHD7, DNA ligase 4, and other novel homozygous mutations [18,19].

Omenn syndrome is associated with the virtual absence of B cells, low IgG, IgA, and IgM levels [20]. The presence and expansion of oligoclonal autoreactive T cells lead to lymphocytosis [21]. Activated and antigen-
Rash
MUTATIONS OF 55-KDA TNF RECEPTOR

Neonatal onset rash
LABORATORY FINDINGS

Defect in cryopyrin, involved in
ALLERGIC MANIFESTATIONS

Atopic dermatitis, multiple
Eczematous dermatitis [59]

Other clinical manifestations

Non-pruritic
DEFECT IN CRYOPYRIN, INVOLVED IN

Defect in cryopyrin, involved in
Urticaria

Wiskott-Aldrich syndrome (WAS)

Defect in cryopyrin, involved in
Leukocyte apoptosis and NF-xB signaling

Defect in cryopyrin, involved in
Leukocyte apoptosis and NF-xB signaling and IL-1 processing

Defect in cryopyrin, involved in
Leukocyte apoptosis and NF-xB signaling and IL-1 processing

Mutations of 55-kDa TNF receptor

Mutations in nucleotide binding site of

SNHL, amyloplakosis

Arthritis, chills, fever, and
leukocytosis is after exposure to cold

Chronic meningitis, and arthropathy
with fever and inflammation

Recurrent fever, seborrhea, and ocular
or joint inflammation

Uveitis, granulomatous synovitis,
camptodactyly, and cranial
neuropathies; 30% of the patients
develop Crohn's disease

Spontaneous activation of the
complement pathway with consumption of
C4/C2 spontaneous activation of the
contact system with generation of
bradykinin from high molecular weight
kininogen

Allergic manifestations of this disease are well known and well
understood. Eczema usually has widespread involvement, but
primarily appears on the face, scalp, in the flexures, and diaper area. It is
followed by progressive lichenification. Eczema can be complicated by
secondary infections such as cellulitis and abscess and gets better with
age [24]. Eczema can be associated with other IgE-mediated allergic
diseases, such as urticaria, food allergies, and asthma.

DEFICIENCY IN THE WAS PROTEIN (WASP)-INTERACTING PROTEIN (WIP DEFICIENCY)

Deficiency in the WIP deficiency is a novel autosomal recessive PID [25]. Clinical features of WIP deficiency are similar to WAS, but the WAS sequence and mRNA levels are normal. WAS protein (WASP) cannot be detected in the cells of these patients. WASP is almost completely complexed with the WIP deficiency [25]. Clinical features of these patients. WASP is almost completely complexed with the WIP deficiency [25]. Clinical features of these patients. WASP is almost completely complexed with the WIP deficiency [25]. Clinical features of these patients. WASP is almost completely complexed with the WIP deficiency [25]. Clinical features of these patients. WASP is almost completely complexed with the WIP deficiency [25]. Clinical features of these patients. WASP is almost completely complexed with the WIP deficiency [25]. Clinical features of these patients. WASP is almost completely complexed with the WIP deficiency [25]. Clinical features of these patients. WASP is almost completely complexed with the WIP deficiency [25]. Clinical features of these patients. WASP is almost completely complexed with the WIP deficiency [25]. Clinical features of these patients. WASP is almost completely complexed with the WIP deficiency [25]. Clinical features of these patients. WASP is almost completely complexed with the WIP deficiency [25].

HYPER-IGE SYNDROME (JOBS SYNDROME)

Hyper-IgE syndrome is an autosomal dominant disease (AD-HIES).
Allergic manifestations of this disease are well known and well
described [27]. The disease is characterized by eczema, recurrent
bacterial infections (skin and pulmonary abscesses, pneumatoceles),
mucocutaneous candidiasis, elevated serum IgE levels, and

- Table 2: Primary immunodeficiencies associated with allergic-like manifestations

| Disease               | Inheritance | Allergic-like manifestations | Laboratory findings | Other clinical manifestations |
|-----------------------|-------------|------------------------------|---------------------|------------------------------|
| Autoinflammatory disorders |            |                              |                     |                              |
| MWS                   | AD          | Urticaria                    | Defect in cryopyrin, involved in leukocyte apoptosis and NF-xB signaling and IL-1 processing | SNHL, amyloplakosis          |
| FCAS                  | AD          | Non-pruritic urticaria       | Defect in cryopyrin, involved in leukocyte apoptosis and NF-xB signaling and IL-1 processing | Arthritis, chills, fever, and leukocytosis is after exposure to cold |
| NOMID or CINCA        | AD          | Neonatal onset rash          | Defect in cryopyrin, involved in leukocyte apoptosis and NF-xB signaling and IL-1 processing | Chronic meningitis, and arthropathy with fever and inflammation |
| TRAPS                 | AD          | Rash                         | Mutations of 55-kDa TNF receptor leading to intracellular receptor retention or decreased soluble cytokine receptor available to bind TNF | Recurrent fever, seborrhea, and ocular or joint inflammation |
| Blau syndrome         | AD          | Rash                         | Mutations in nucleotide binding site of CARD15, possibly disrupting interactions with lipopolysaccharides and NF-xB signaling | Uveitis, granulomatous synovitis, camptodactyly, and cranial neuropathies; 30% of the patients develop Crohn's disease |
| Complement deficiencies |            |                              |                     |                              |
| C1 inhibitor deficiency | AD        | HAE                          | Spontaneous activation of the complement pathway with consumption of C4/C2 spontaneous activation of the contact system with generation of bradykinin from high molecular weight kininogen | SNHL, amyloplakosis          |

- Table 3: Other primary immunodeficiencies associated with allergic manifestations

| Disease               | Inheritance | Allergic manifestations | Laboratory findings | Other clinical manifestations |
|-----------------------|-------------|-------------------------|---------------------|------------------------------|
| PGM3 deficiency       | AR          | Atopic dermatitis, multiple allergies, and asthma elevated IgE level | Cytopenia, mostly lymphopenia and neutropenia. | Recurrent infections, neurologic abnormalities |
| MST1 deficiency       | AR          | Eczematous dermatitis [59] | Decreased/increased proportion of terminal differentiated effector memory cells (TEMRA), low naive T cells, restricted T cell repertoire in the TEMRA population, and impaired T cells | Recurrent bacterial, viral, and candida infections; intermittent neutropenia; EBV-driven lymphoproliferation; lymphoma; congenital heart disease, autoimmune cytopenias; HPV infection. |

Stimulated T helper 2 (T2) cells produce high levels of interleukin 4 (IL-4) and IL-5. These cytokines cause eosinophilia and elevated IgE levels [17].

Wiskott-Aldrich syndrome (WAS)

Wiskott-Aldrich syndrome can also be manifested by eczema and increased IgE levels [2]. Eczema in patients with WAS is a feature of the clinical triad which also includes microthrombocytopenia and recurrent infections [22]. WAS is an X-linked disorder. The genes associated with WAS are on the short arm of the X chromosome (Xp11.22-p11.23). At present, there are more than 300 identified unique mutations resulting in WAS; this produces a wide variability of clinical symptoms [23]. The majority of the mutations are missense mutations, followed by nonsense, splice-site, and short deletion mutations.

Eczema was registered in 80% of the patients with WAS [22]. It is often identified during the 1st month of life and fits the diagnostic criteria for atopic dermatitis. The eczema usually has widespread involvement, but primarily appears on the face, scalp, in the flexures, and diaper area. It is followed by progressive lichenification. Eczema can be complicated by secondary infections such as cellulitis and abscess and gets better with age [24]. Eczema can be associated with other IgE-mediated allergic diseases, such as urticaria, food allergies, and asthma.
eosinophilia [2]. The severity of the disease can vary. AD-HIES is associated with heterozygous mutations of signal transducer and activator of transcription three genes (STAT3; 17q21.31) [27].

Neonatal rash is among first clinical features of this disorder. The skin barrier function in the AD-HIES patient is not impaired, in contrast with the AD patients that experience changes of skin barrier function [28]. AD-HIES affects not only the immune system but also connective tissue, skeleton, and dental development [29]. Distinct facial features are a characteristic feature of this syndrome. Increased risk of autoimmune and lymphoproliferative diseases is also associated with this disease.

Increased IgE levels up to 2000 U/ml are common in patients with AD-HIES, often higher than 5000 U/ml. Despite the high levels of IgE, the patients with AD-HIES suffer from a deficiency of allergic sensitization [27]; this can be explained by a normal skin barrier function and confirm its significance in the development of allergic sensitization.

In a study, the patients with STAT3 mutations experienced weakened allergic reactions, in particular, food allergies and anaphylaxis [30]. Since eczema can be among the early symptoms in patients with AD-HIES, timely differentiation of HIES from atopic dermatitis is difficult, extremely important due to the differences in treatment [31].

Human tyrosine kinase 2 (Tyk2) deficiency
Human tyrosine kinase 2 (Tyk2) deficiency was initially registered in a Japanese patient as a syndrome with elevated IgE and with susceptibility to intracellular infections [2,32]. Another study reported a Turkish patient with Tyk2 deficiency without hyper-IgE syndrome [33]. Additional six patients from different countries with Tyk2 deficiency suffered from mycobacterial and viral infections without hyper-IgE syndrome [34]. Tyk2 deficiency leads to multiple cytokine signaling defects, first of all to impaired production of IFN-α/β and IL-12 that causes susceptibility to intracellular infections [34]. The leukocytes and fibroblasts respond normally to IL-6, which can explain normal IgE levels in these patients. The main clinical manifestations of Tyk2 deficiency are mycobacterial and/or viral infections.

Comel-Netherton syndrome
Comel-Netherton syndrome is an autosomal recessive genodermatosis. Skin manifestations in these patients appear at birth or during the 1st week of life. Typical ailments include congenital ichthyosiform erythroderma, atopic diathesis, and a hair-shaft abnormality known as trichorrhexis invaginata [35].

Skin inflammation, leading to scaling and exfoliation, and erythroderma, an atopic diathesis complicated by infections, sepsis, and dehydration are the disorders that can be life threatening. Dehydration caused by corticosterone barrier dysfunction can cause extensive metabolic abnormalities and hypernatremia [36].

Mutations of the both copies of serine proteinase inhibitor of kazal type 5 (SPINKS) gene cause Comel-Netherton syndrome [37]. SPINK5 products, such as lymphoepithelial kazal-type-related inhibitor (LEKTI), and tissue kallikreins (KLKS) balance serine proteinase/inhibitors in skin and effect skin barrier function and desquamation [38]. SPINK5 mutations result in truncated LEKTI; thus, LEKTI in patients with Comel-Netherton syndrome can be of different length, depending on the location of mutations. Clinical manifestations correlate with LEKTI domain deficiency in patients with Comel-Netherton syndrome [38]. The studies have also proved that deregulated epidermal proteinase activity is linked to atopic dermatitis [39]. These studies point to new targets for treatment intervention.

Food allergy, especially to peanuts, eggs, and fish often persists in patients with Comel-Netherton syndrome. The majority of patients have an atopic predisposition, with a family history of asthma, atopic dermatitis or hay fever. Serum IgE levels are typically increased, sometimes exceeding 10,000 IU/mL [39]. Specific IgE antibodies to environmental and food allergens can be detected, and hypereosinophilia can be present in the patients.

STAT5b deficiency
STAT5b deficiency is an autosomal recessive disorder. It is characterized by short stature and recurrent pulmonary infections: Bacterial pneumonia or opportunistic infections (hemorrhagic Varicella, herpes zoster, and Pneumocystis jirovecii) [40-42]. Other clinical signs include dysmorphic features and a high-pitched voice. Short stature develops in these patients since STAT5b is involved in growth hormone induced signaling [41]. In addition, STAT5b is involved in the intracellular signaling cascade of IL-2 and IFN-gamma and causes immunodeficiency, typically T cell lymphopenia. Immune dysregulation is also manifested by eczema and autoimmunity.

Selective IgA deficiency
Selective IgA deficiency is the most common PID. The patients may be asymptomatic, have recurrent infections, or autoimmune diseases. Patients with selective IgA deficiency can also suffer from allergic disorders [43,44]. The incidence of allergic manifestations ranges from 13% [45] to 54% [46] of patients. There is a significant relationship between allergy incidence and patient's age. It is more commonly present among younger patients [45]. Other studies reported that low IgA levels are associated with atopic diseases not only in children but also in adults [47,48]. Allergy in patients with selective IgA deficiency is manifested by asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, urticaria, drug allergy, and food allergy [46].

Immune dysregulation, polyendocrinopathy, and enteropathy X-linked (IPEX) syndrome
Immune dysregulation, polyendocrinopathy, and enteropathy X-linked (IPEX) syndrome is caused by inheritable mutations in the forkhead box protein 3 (FOXP3) gene and is characterized by the development of multiple autoimmune disorders [49]. FOXP3 Treg cells have inhibitory functions and are responsible for immune homeostasis and tolerance to self- and non-self-antigens [49]. Impaired function of FOXP3+ regulatory T cells leads to autoimmune disorders that usually are manifested by enteropathy, early-onset diabetes, thyroiditis, hemolytic anemia, and thrombocytopenia [2]. Severe diarrhea due to autoimmune enteropathy typically begins in the first few months of life and causes failure to thrive. Patients with IPEX syndrome frequently suffer from eczema. Autoimmune enteropathy and eczema are the main features of disease presence after 1 month of age [50]. They are often associated with increased IgE levels and eosinophilia in children with IPEX syndrome [51].

PLCγ2-associated antibody deficiency and immune dysregulation (PLAID)
PLCγ2-associated antibody deficiency and immune dysregulation (PLAID) belong to the group of autoinflammatory disorders and is characterized by cold urticaria, recurrent bacterial infections, autoimmunity, and skin granuloma development [52]. Cold urticaria in PLAID patients is common, and develops rapidly, within minutes after contact with cold; it resolves after warming up. Skin rash in cases of physical urticaria is caused by mast cell activation and mediator release [53,54]. Sometimes prolonged cold contact can cause anaphylaxis [52]. The patients frequently have a family history of atopy [53].

Phosphoglucomutase 3 (PGM3) deficiency
Phosphoglucomutase 3 (PGM3) deficiency was described in 2014 as an autosomal recessive disease associated with atopic dermatitis, recurrent infections, and increased IgE levels [55-57] (Table 3). Atopic dermatitis is a common manifestation; it was observed in all 17 registered patients with PGM3 deficiency [55,56]. Other allergic manifestations such as asthma and multiple allergies can also be present [57]. Neurologic abnormalities, such as developmental delay
and low IQ, ataxia, dysarthria, myoclonus, and sensorineural hearing loss, are common for these patients [57].

**MST1 deficiency**

Mammalian sterile 20-like (MST1) deficiency is an autosomal recessive disease, characterized by bacterial, viral, and candida cutaneous infections, and structural cardiac anomalies [57,58]. Eczema-like skin lesions beginning in the 1st year of life and mild erythematous skin lesions were registered in 3 patients with MST1 deficiency from a single family [59].

**ALLERGIC-LIKE MANIFESTATIONS OF PID**

Some autoinflammatory disorders are characterized by rash, mostly of urticaria-like type (Table 3). This group includes cryopyrin-associated periodic syndromes (CAPS), represented by three diseases caused by a defect in the same gene CIAS1/NLRP3 coding for the protein cryopyrin (NALP3): Muckle-Wells syndrome (MWS), neonatal-onset multisystem inflammatory disease or chronic infantile neurologic, cutaneous, and articular syndrome (NOMID/CINCA), and familial cold autoinflammatory syndrome (FCAS) [60,61].

Rash in cases of CAPS is caused by a neutrophilic infiltrate in the dermis and is unrelated to mast cell degranulation [60]. Deficit of cryopyrin, involved in leukocyte apoptosis and NF-kB signaling and IL-1 processing, is detected in patients with CAPS [2]. All autoinflammatory conditions associated with periodic fever, joint pain, and other systemic manifestations can also be present. The severity and clinical signs vary for each of these diseases. NOMID/CINCA is the most severe condition, while FCAS is considered the mildest form [60].

MWS, also known as an urticaria-deafness-amyloidosis syndrome, is an autosomal dominant disease, which causes sensorineural deafness and recurrent hives, and can lead to amyloidosis. NOMID/CINCA is also characterized by progressive hearing loss, but in cases of MWS, it develops later. Cognitive and physical disability, bone and joint deformities, and short stature are evidenced in NOMID/CINCA [62]. Typically in FCAS, but less often in MWS, the symptoms are exacerbated by cold and are self-limited within 12–24 hs [61]. In NOMID/CINCA, the rash is present early: After birth or within the first few days or weeks of life. Typically, the rash is not irritating, but in some cases, it may be itchy [60].

Despite the differences in the pathogenesis of allergic rash and rash in patients with autoinflammatory disorders, in both instances, these manifestations look alike and require differential diagnosis. Such patients often come to see an allergist. FCAS can be considered as cold urticaria, which is an allergic reaction to cold temperatures that develops after a few minutes of cold exposure but is never associated with fever and joint pain.

TNF receptor-associated periodic syndrome (TRAPS) is caused by a mutation of the TNFRSF1A gene and characterized by episodic flares that last for 3 weeks or longer with fever, migrated rash, abdominal pain, joint pain, periorbital edema, and conjunctivitis [63]. Rash is one of the most frequent manifestations of TRAPS, and its occurrence varies from 55% [64] to 63% [63] of patients.

Blau syndrome (BS) is caused by the mutation in CARD15/NOD2 gene and characterized by early onset granulomatous arthritis, uveitis, and skin rash [65]. Clinical manifestations also include fever, malignant systemic and pulmonary hypertension, granulomatous large-vasculitis and granulomatous inflammation of the liver, kidneys, and lungs.

Skin rash is an early symptom, usually the first manifestation, appearing in the 1st year of life, often at the age of 1 month [66]. It is manifested by a symmetric dark red, slightly scaly, maculopapular, eczematoid-like or lichenoid-like rash with localization first on the face and spreading to the trunk and extremities; it resolves spontaneously [67].

C1 inhibitor deficiency, also called hereditary angioedema (HAE), is characterized by recurrent episodes of angioedema, without urticaria or pruritus [68]. The skin and mucosal tissues of upper respiratory and gastrointestinal tracts are often affected [69]. The swelling is self-limited, although when involves upper respiratory tract, especially larynx, it can lead to fatal asphyxiation.

Enormous production of bradykinin, a vasodilator mediator, causes the clinical manifestations of HAE [70]. In HAE, histamine and other mast cell mediators are not directly involved as they are in allergic and urticarial reactions, so antihistamines are not effective.

The above discussion proves that the variability of clinical manifestations in PID patients requires a multidisciplinary approach to their management [71] with the involvement of immunologists, allergists, and other specialists.

**TREATMENT APPROACHES**

Treatment approaches to the allergic manifestations in PID patients and allergic disorders are often different.

Common general treatment strategies of PID include antibiotics, intravenous or subcutaneous immunoglobulin (IVIG/SCIG), and hematopoietic stem cell transplantation (HSCT).

The treatment of allergic symptoms includes corticosteroids (topical, or nasal; or oral, or systemic) and/or local application of calcineurin inhibitors (tacrolimus and pimecrolimus) [72]. Although PID are often associated with viral, bacterial, and candida infections, it is a challenge to treat atopic dermatitis and other allergic manifestations by means of these drugs, considering their immunosuppressive action. These medications are not recommended for long-term use or treatment of large surface areas. Skin and other infections should be carefully examined. In cases of skin superinfection with Staphylococcus aureus in patients with PID and eczema, systemic antibiotics, and antiseptic arrangements are used just as in cases of general atopic dermatitis [73].

Long-Term use of emollients for the treatment of skin allergic manifestations is helpful in AD-HIES, WAS, Comel-Netherton syndrome, and other syndromes associated with eczema [74].

Patients with AD-HIES often require medication to control pruritus. Diphenhydramine or a longer-acting antihistamine such as loratadine, fexofenadine, desloratadine, or cetirizine can be used for this purpose [75].

HSCT is established as the treatment of choice in patients with combined immunodeficiencies (DOCK8 deficiency, Omenn syndrome, MST1 deficiency, WAS, and WIP deficiency) [76], and the main method of treatment in patients with IPEX syndrome [77,78]. Cutaneous improvement in the first 6 months after transplant was reported [9,76]. IVIG is the treatment of choice in Netherton's syndrome [79]. This therapy also results in relieving skin manifestations.

Immunosuppression with cyclosporine is recommended for dermatitis and eosinophilia treatment in patients with Omenn syndrome [80]. Interleukin gamma can be used to control IL-4 and IL-5 production in these patients.

Anti-inflammatory effect of Vitamin D3 supplementation has been proved in patients with asthma [81].

Gene therapy is being investigated to treat IPEX syndrome, Omenn syndrome, and WAS [77,78,82].

Other approaches are used for the treatment of autoinflammatory disorders. Biologic agents that target interleukin-1 are effective for treating CAPS [60,62]. Anakinra is approved for patients with NOMID/CINCA, rilonacept, and canakinumab - for patients with FCAS and MWS.
CONCLUSIONS

Allergic manifestations are one of the clinical signs of PID. They take place more often in patients with combined immunodeficiencies with or without associated or syndromic features.

Allergic manifestations in patients with PID usually are present in the 1st year of life, they can be among the first symptoms of PID and are commonly manifested by eczema and increased IgE levels.

Often the skin barrier function is not impaired in patients with eczema and PID, although some diseases (Comel-Netherton syndrome) have a negative impact on skin barrier function.

There is usually no correlation between IgE levels and severity of allergic skin manifestation.

Allergic-like manifestations in PID patients include urticaria-like rash and angioedema. Urticaria-like rash is associated with autoinflammatory disorders, which are commonly accompanied by fever, and caused by a neutrophilic infiltrate in the dermis. Angioedema in HAE is caused by high production of bradykinin.

Early differentiation of allergic manifestations due to PID from atopic dermatitis and other atopic conditions is very difficult, although it is very important because it influences on the choice of treatment methods.

A multidisciplinary approach to the management of PID patients with involvement of immunologists, allergists, and prescription of appropriate treatment improve the prognosis and quality of life of PID patients.

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AUTHOR’S CONTRIBUTIONS

Concept, collection of data, writing the article, and critical review of the article has been carried out by Oksana Boyarchuk.

CONFLICTS OF INTEREST

The author hereby declares that there are no conflicts of interest in this research.

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