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REVIEW

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Syndromic immunodeficiencies: a pediatrician's perspective on selected diseases

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Abstract
Background: Syndromic immunodeficiencies are a genetically and pathophysiologically heterogeneous group of inborn errors of immunity. These are characterized by multiple extra immune clinical symptoms and a wide range of immunological phenotypes with increased susceptibility to infections, autoimmune phenomena, immune dysregulation, organ-specific pathology, and malignancy.
Objective: To increase the pediatricians' awareness of this multifaceted group of primary immunodeficiencies in children.
Methods: A comprehensive review of genetic background and clinical symptomatology of syndromic immunodeficiencies as well as current diagnostic approach and treatment modalities.
Results: From the pediatrician's perspective, an early-life diagnosis of syndromic immunodeficiencies, which is frequently indispensable for successful life-saving immunocorrection, poses a diagnostic challenge. Increased pediatricians' awareness to recognize signs and symptoms of these diseases in affected children is of paramount importance. Current advances in molecular biotechnology and immunogenetics, resulting in the implementation of newborn screening and new-generation sequencing, provide informative tools for definitive diagnosis and, in many new disease entities, for their definition and genotype–phenotype delineation and correlation.
Conclusions: A broad spectrum of clinical phenotypes in children with syndromic primary immunodeficiencies requires pediatrician's special attention, that is, individualized multidisciplinary approach under the supervision of a clinical immunologist.

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Introduction

The syndromic primary immunodeficiencies (syndromic PIDs) are a group of inborn errors of immunity in which the development of other organs and systems is affected. The genetic background of syndromic PIDs is highly diverse, ranging from chromosomal aberrations involving abnormal expression of a large number of structural and regulatory genes (such as *trisomy 21* in Down syndrome [DS], and *4p* deletion in Wolf–Hirschhorn syndrome) to monogenic diseases associated with genes encoding molecules playing a role in receptor–ligand interactions, intracellular signal transduction, or a cell-cycle regulation (e.g., *Signal Transducer and Activator of Transcription* 3 [*STAT3*], loss-of-function [LOF] mutation in the autosomal dominant [AD] hyper-IgE syndrome [HIES]) or even epigenetic regulation (such as defective deoxyribonucleic acid [DNA] methylation in immunodeficiency, centromeric instability, and facial dysmorphism [ICF] syndrome). According to the data available in the European Society for Immunodeficiencies (ESID) registry, syndromic PIDs, also known as other well-defined PIDs, constitute as much as 16% of all PID diseases in the European pediatric population.[1] A multitude of developmental, anatomical, and functional abnormalities accompany this PID category of diseases; predominantly, facial dysmorphism, oral and dental abnormalities, cardiovascular malformations, ectodermal and skeletal features as well as neurodevelopmental delay have been observed in affected children. Therefore, syndromic PIDs encompass a variety of extra immune phenotypes, which commonly predominate in the patient's clinical presentation and, from the clinician's perspective, they may constitute important warning signs, crucial for the recognition.[2,3] Several new syndromes have been identified recently with their genotype–phenotype correlations, and coexisting immune deficiencies have been delineated, such as polymerase delta (POLD 1, POLD2) deficiency syndrome,[4] deficiency of adenosine deaminase 2 (DADA2),[5] or cell division cycle 42 (CDC42) deficiency.[6–9] The immunodeficiency in syndromic PIDs is, in fact, very heterogeneous, thus reflecting a variable genetic background of different disease entities. The long quest to implement a newborn screening toward immunodeficiencies is also aimed at an early diagnosis of the children with syndromic PIDs, who have a profound inability to mount an appropriate generation of T and B cells. Nonetheless, it must be highlighted that increased susceptibility to infections in syndromic PIDs not only results from the impaired immune response to pathogens but also from nonimmune anatomical and functional disorders, such as cleft palate, defective swallowing, tracheomalacia, structural lung disease, increased pulmonary blood flow, neuromuscular diseases, skeletal deformations, and mental retardation significantly contribute to the severity of infections and create a vicious circle of infection and inflammation.

In this review, we focus on clinical symptomatology and the background of several syndromic PIDs from the pediatricians' perspective in order to increase the awareness of this disease category in clinical practice. However, it is worth noting that the selection of syndromes associated with PIDs in this review is arbitrary in some sense because many other genetic syndromes are accompanied by an impaired immune response. *In the latest update on the classification of human inborn errors of immunity, as many as 58 immunodeficiencies with associated or syndromic features have been reported.*[10] The vast majority of children affected by this category of PIDs require multidisciplinary care under the supervision of pediatrician and clinical immunologist. Therefore, immunodeficiency syndromes, most frequently associated with dysmorphism and multiorgan anatomical and functional abnormalities, have been selected for a broader discussion in this review.

Down syndrome

The most common genetic disease caused by a chromosomal anomaly is Down syndrome caused by trisomy 21, which occurs in infants at a frequency of 1:600 (1:900 in the United States), so the worldwide incidence is approximately 1:750 live births.[11,12]

Despite the progressive improvement in medical care and treatments, the life expectancy of individuals with DS is still less than 50 years,[13] because DS is associated with many complex medical conditions. Individuals with DS intend to have major health problems caused by immunological impairment and increased susceptibility to viral and bacterial respiratory tract infections, predisposition to autoimmune disorders (e.g., celiac disease, diabetes mellitus, hypothyroidism) and an increased risk of different types of hematological malignancies.[11,12,14] Furthermore, DS patients present with characteristic dysmorphic features and various anatomical malformations, such as upper and lower airway abnormalities (deformation of the middle ear, macroglossia, tracheomalacia, structural lung disease), congenital cardiac anomalies (most frequently atrioventricular septal defect) as well as gastrointestinal (gastroesophageal reflux, enteric aganglionosis [Hirschprung disease]) and orthopedic (neuromuscular scoliosis) problems.[11] These nonimmunological, anatomical, and functional disorders are important predisposing factors to recurrent infections, which in the vast majority affect the respiratory system. Infections such as pneumonia, bronchiolitis, and croup constitute approximately 55% of all hospital admissions in DS-affected children.[11] DS infants have a higher rate of hospitalization and a more severe course of bronchiolitis because of respiratory syncytial virus (RSV) infection.[11]

The increased susceptibility to infections, predisposition to autoimmune phenomena, and a high risk of malignant transformation reflect impaired immunocompetence in DS. The majority of DS subjects intend to have smaller thymus with an abnormal structure, which implies that lymphopenia, a leading cause of immunological impairment in this group, is found in more than 90% of affected patients. The consequences of this abnormal thymic anatomy and function include immune dysregulation with increased expression of cytokines, tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ), and reduced range of different T and B lymphocyte subsets.[11,12,15] Reduced level of T cell receptor (TCR) excision circles (TREC), which constitute DNA by-products of the T lymphocyte receptor recombination, reflects diminished production of new T cells in the thymus, defective thymic output, and T cell differentiation, and finally, a decreased T lymphocyte help to B cells.[15] An impaired B cell pattern with defective B cell

memory and impaired molecular maturation of immunoglobulin A (IgA) and M (IgM) correlate with immune deficiency in the B cell compartment.[16,17] A decreased antibody response to immunization, caused by IgG and IgA hypergammaglobulinemia, specifically with high levels of IgG1 and IgG3 and low levels of IgG2 and IgG4, was also observed in children with DS from their early years.[15] Furthermore, the defective T and B cell functions and coexisting defects in the components of innate immunity, such as complement pathway, toll-like receptors (TLR) as well as dysregulated pro- and anti-inflammatory cytokine IL-6 and IL-10 production, contribute to a combination of immunodeficiency and immune dysregulation.[18,19]

It may be assumed that not only the alterations of the humoral and cellular parameters are the cause of the immune impairment observed in subjects with DS, but also gene dosage imbalance caused by the presence of a supernumerary chromosome 21 may play a role. It has been shown that differentially expressed genes that might be of pathogenic importance for the development of immunological alterations are observed in DS patients. The overexpression of the *superoxide dismutase* (*SOD1*) and the *integrin subunit beta 2* (*ITGB2*) genes significant to neutrophil function or dysregulation in the *regulator of calcineurin 1* (*RCAN1*) gene mediating the inflammatory response of activated T cells has been postulated to contribute to disrupted innate and adaptive response in DS.[11] Altered expressions of several genes with relevant functions in immune cells and involved in immune and inflammatory pathways, but located on chromosomes other than 21, such as *CD19*, *CD28*, *IL-6*, and *IL-10*, have been demonstrated, supporting the hypothesis that secondary transcriptional changes throughout the genome also occur as a result of trisomy 21.[14]

The evaluation of the occurrence of frequent adult malignancies is permitted due to the life expectancy of individuals with DS. A high incidence of leukemia from the early years in children with DS contributes to the perception that DS is considered to take an active part in increasing the risk of malignancy, with gastric, liver, or testicular cancers occurring with increased frequency in DS.[13] Therefore, an important take-home message for clinicians regarding diagnosing and monitoring DS patients is to increase awareness about clinical phenotype with combined immunodeficiency (CID) as a risk factor for possible serious complications in the form of autoimmune, autoinflammatory, and malignant diseases.

DiGeorge syndrome

22q11.2 deletion syndrome or DiGeorge syndrome (DGS), also known as velocardiofacial (VCF) syndrome, is the most common chromosomal microdeletion disorder, with an estimated prevalence in the range of 1:3000 to 1:6000 live births.[20] The disease can be inherited in an AD manner; however, only about 10% of DGS children inherit it from an affected parent, and the vast majority of cases occur *de novo* through nonhomologous meiotic recombination in a small pericentromeric region of the chromosome 22, leading to haplo insufficiency of about 106 genes. However, heterozygosity alone does not explain the genetic mechanism of the highly variable phenotypes, and many novel genetic and epigenetic factors can influence severity of the disease. Structurally, the 22q11.2 region is a very complex area of the human genome involving protein-coding and noncoding genes, whose mutations lead to numerous known diseases (such as *PRODH*, associated with type 1 hyperprolinemia (PRODH1), *SNAP29*, associated with cerebral dysgenesis, neuropathy, and ichthyosis, or *GP1BB*, associated with Bernard–Soulier platelet anomaly). The most highlighted gene relevant for the phenotype of DGS is *TBX1* as its abnormality results in conotruncal cardiac anomalies and abnormal thymicorganogenesis.[21]

DiGeorge syndrome is characterized by a very broad phenotypic range of symptomatology, determined by variable genetic modifiers.[22] Typical conditions in DGS result from the disorders of growth of the third and fourth pharyngeal arches in embryonic development, leading to multiorgan dysfunctions. Common disorders include cardiovascular malformations, such as conotruncal heart disease in the form of pulmonary artery stenosis or tetralogy of Fallot, aortic arch type B, persistent truncus arteriosus, or ventricular septal defect. A broad constellation of findings also includes developmental disabilities, cleft palate, laryngeal and esophageal dysfunctions, endocrinopathies (hypoparathyroidism and hypothyroidism), renal malformation, and facial dysmorphism with hooded eyelids, bulbous nasal tip, short philtrum, small mouth, and low-set ears.[22,23] These cardiovascular, neurological, and endocrine developmental disorders superimpose immunodeficiency and immune dysregulation with atopic and autoimmune phenomena in DGS.[24,25] As 22q11.2 deletion syndrome is a multisystem condition, and less common manifestations may be overlapping with other diseases (e.g., scoliosis, microcephaly, sensorineural hearing loss, and coloboma), in children presenting with atypical features, it is crucial to consider a secondary diagnosis resulting from carrying two unrelated genetic diagnoses, including cystic fibrosis; coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear abnormalities (CHARGE) syndrome; SCID; or glucose-6-phosphate dehydrogenase (G6PD) deficiency.[26]

Thymic hypoplasia or a complete aplasia is of paramount importance for T cell functions, and deletions in *T-box* 1 (*TBOX1*) in 22q11.2 are major determinants of T cell development. The impaired thymic output of T cells and T cell lymphopenia, deficiency in T CD4+ helper cells, closely related to deletion breakpoints, and a compromised follicular T cells help B cells in germinal centers to limit B cell differentiation and formation of switched memory B cells. This leads to decline of antibody production and impaired response to vaccines, which is observable in approximately 75% of affected patients.[20,27-30] Both constellation of nonimmune findings and a broad range of immune phenotype with T and B cells immunodeficiency create an increased susceptibility to sinopulmonary viral and bacterial infections.

The most profound T cell deficiency occurs in DGS with athymia, also named as complete DGS (cDGS); its prevalence has been estimated to be 1.5% of all children with 22q11.2 deletion syndrome.[31] The immunological phenotype of cDGS is either associated with severe T cell deficiency or with the oligoclonal expansion of T cells with

a memory phenotype. This confers not only a lack of protective immunity against pathogens but also contributes to immune dysregulation manifesting as rashes, enteropathy, and lymphadenopathy. Profound T cell lymphopenia is a common feature of cDGS and severe combined immunodeficiency (SCID), but it needs to be highlighted that the underlying defect is thymic aplasia in the first, and a defect in the development of hematopoietic lineage in the latter condition. Therefore, hematopoietic stem cell transplantation (HSCT), which provides a post-thymic T cell population, may not lead to an effective immune reconstitution in cDGS. Thymus transplantation approach has recently emerged as a promising treatment option of cDGS, enabling thymopoiesis and naïve T cell generation with a broad TCR repertoire.[31]

CHARGE syndrome

Acronym CHARGE describes a syndrome that consists of coloboma of the eye, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, and ear anomalies. Incidence of CHARGE association is estimated to be 1 in 15,000–17,000 live births.[32] The genetic cause of CHARGE syndrome is usually a LOF mutation in the *chromodomain-helicase DNA-binding 7* (*CHD7*) gene, which can be found in over 90% of patients with CHARGE syndrome.[32,33] The spectrum of clinical phenotypes in CHARGE syndrome is variable and a typical combination of six cardinal features corresponds with its AD inheritance. However, recent discoveries of *CHD7* pathogenic variants have largely expanded the clinically recognizable features of the syndrome, adding microphthalmia, sensorineural hearing loss, autism, delay in neurodevelopmental, palatal defects, esophageal atresia, parathyroid maldevelopment and hypocalcemia, and pituitary endocrinopathy to its broad range of symptoms.[34]

The phenotype of *CHD7* haploinsufficiency not only encompasses the constellation of symptoms suggested by the CHARGE acronym but immune system disorders are also noted in the syndrome. *CHD7* is a chromatin-remodeling protein essential for differentiation of multipotent cells responsible for thymus organogenesis; therefore, mutation in the *CHD7* gene can result in T cell lymphopenia and immunodeficiency,[35] which occur in 80% of patients with CHARGE syndrome.[36] Except for the decreased thymic output, reflected by low T lymphocyte excision circle (TREC) numbers, and reduced number of T cells, it has been hypothesized that abnormal development and function of thymic epithelial cells, which are indispensable for appropriate T cell education and maturation, affect T cell-dependent immune response.[36] Interestingly, NK cell and B cell numbers are normal in almost all affected children,[36,37] but in some patients abnormal generation of class-switched memory B cells,[36] low serum immunoglobulin (Ig) levels, and abnormal response to vaccines[38] are observed. Immunodeficiency in CHARGE syndrome is characterized by a wide scale of severity from asymptomatic, slight fluctuations in T cell levels to a rare mortality condition resembling SCID, and the intensity of immunodeficiency-related symptoms depends on the degree of thymic dysfunction.[38,39]

All pediatric patients affected with CHARGE syndrome suffer from recurrent infections, most frequently of the respiratory tract. The most common infection is otitis media, which occurs in as many as 65% of patients. Both immunodeficiency and anatomical anomalies of the palate, middle and external ear, and also cranial nerve defects, which affect swallowing, are important factors facilitating the development of infections.[39] Atopic disorders, such as asthma, allergic rhinitis, and atopic dermatitis, occur in as many as 65% of CHARGE patients,[40] as a result of an impaired regulatory T cell (Treg) number or function due to abnormal thymic T cell development.[41] Because of potential immune system disorders, it is recommended to evaluate all children with a diagnosis of CHARGE syndrome for immunodeficiency, especially when infections are frequent. Early diagnosis of the syndrome is of paramount importance to introduce therapy adjusted to the severity of immune deficiency.

Ataxia telangiectasia

Ataxia telangiectasia (A-T), also known as Louis-Bar or Boder–Sedgwick syndrome, is an autosomal recessive (AR) genomic instability syndrome, resulting from the mutation of *ataxia-telangiectasia mutated* (*ATM*) gene. The gene, localized at 11q22.3-23.1, encodes for a high molecular weight, predominantly a nuclear serine/threonine protein kinase, which is a member of the large phosphatidylinositol-3-kinase (PI3K)-related protein kinase (PIKK) family. The ATM kinase also plays important cytoplasmic roles, phosphorylating numerous protein substrates, and in mitochondrial respiration and energy metabolism. The enzyme is involved in maintaining the cell-cycle homeostasis, and coordinates the cellular signaling pathways in response to DNA double-strand breaks (DSBs), genotoxic and oxidative stress.[42–45] The prevalence of A-T has been estimated to range between 1 in 40,000 and 1 in 100,000 live births.[46] The impact of genetic background on the cellular nature of A-T is pleiotropic and the phenotype of the disease is complex and heterogeneous, varying among affected patients based on the severity of ATM mutations.[47] A-T is a multisystem disease characterized by neurodegeneration with progressively debilitating cerebellar ataxia, postural instability, decreased ability to walk, choreoathetosis, tremors, including rhythmic and nonrhythmic movements that complicate intended movements, dysarthria as well as problems with cough and swallowing. The vision is not impaired in A-T, but affected children experience impaired coordination of eye movements and visual fixation, such as oculomotor apraxia, nystagmus, or strabismus. The extended A-T phenotype also includes dermatological manifestations, such as oculocutaneous telangiectasia and cutaneous granulomas, hormonal dysfunction, for example, growth retardation, insulin-resistant diabetogenic response, and premature aging as well as infertility because of gonadal dysgenesis resulting from defective meiotic recombination.[47,48] The pathophysiology of chronic airway and lung disease in the form of recurrent wheezing, bronchiectasis, and interstitial lung disease is complex, and aspiration, defective clearance of the airways, progressive

chest muscle weakness, and impaired ability to mount an effective immune response to pathogens are major contributing factors. The etiology of respiratory tract infections in early childhood is usually viral, and in later childhood, common bacterial pathogens, such as *Streptococcus pneumoniae*, *Hemophilus influenza*, or *Staphylococcus aureus*, are frequent causes of pneumonia in A-T patients. Over time, colonization with mucoid *Pseudomonas aeruginosa* is found; however, opportunistic pulmonary infections are not reported.[49] Combined humoral and cellular immunodeficiency with immune dysregulation occurs in approximately 67% of affected patients, a predisposition to lymphoid malignancies, and sensitivity to ionizing radiation is a marker of chromosomal instability and impaired molecular mechanisms of the ATM kinase response to DNA damage.[50] The ATM kinase plays an important role in the processes of lymphocyte development, which rely on DNA double-strand break repair, such as V(D)J recombination, which is critical for successful rearrangement of their antigen receptor genes and class switch recombination (CSR) of immunoglobulin genes.[51] The CID in children affected with A-T is therefore associated with impaired lymphocyte neogenesis, low circulating T and B cell numbers, decreased antigen receptor repertoire diversity, and impaired formation of T cell-dependent memory B cells. Humoral immunodeficiency in A-T includes antibody production defect, most frequently IgA deficiency, IgG2 and IgG4 subclass deficiency, and impaired response to vaccination, whereas cellular immunodeficiency is characterized by low T helper cell numbers and reduced lymphoproliferative response to antigens and mitogens.[52] Three immunological phenotypes have been distinguished among A-T children: normal immunoglobulin levels, selective IgA deficiency, and class-switch recombination defects.[53] The latter group of patients, with a "hyper-IgM phenotype" is characterized by an elevated IgM level, which is, alike high alpha-fetoprotein (AFP) level, a marker for a more severe immune dysfunction, dysregulation, and autoimmune phenomena, increased infection risks and progressive liver disease.[54-56]

Immunodeficiency in A-T is associated with a high risk of malignancies, most frequently B cell non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), and T cell acute lymphoblastic leukemia (ALL), which occur at a high rate and at early age, and shorten the survival.[56]

A broad spectrum of clinical phenotypes with numerous infectious and variable noninfectious complications, as well as organ-specific pathologies in A-T, requires pediatrician's special attention, multidisciplinary approach, and careful management of affected children.

Nijmegen breakage syndrome

Nijmegen breakage syndrome (NBS) is an AR syndrome belonging to the same group of chromosomal instability disorders as A-T, ICF syndrome,[57] DNA ligase 4 (LIG4) deficiency,[58] Artemis,[59] and Cernunnos/XLF[60] deficiencies, associated with defective nonhomologous end-joining (NHEJ) mechanism that repairs DNA double-strand breaks.[61] Cells derived from NBS patients show radiosensitivity to ionizing radiation with associated disorders of cell-cycle control, spontaneous chromosomal aberrations, and telomere loss. Whereas reparation of damaged DNA leads to mutagenesis and carcinogenesis, a very high predisposition to malignant transformation is a cardinal feature of this syndrome that shortens survival.[61]

Nijmegen breakage syndrome is associated with mutations in the *NBN* (*Nibrin*) gene located on chromosome 8q21 and encoding Nibrin protein (NBN protein). Nibrin protein is a member of the nuclear protein hMRE11/RAD50 complex, implicated in the repair of DNA double-strand breaks and recombination, and is also essential for cell cycle regulation and checkpoint arrest, thus ensuring chromosomal integrity and mitochondrial homeostasis. The majority of patients affected with NBS are of Slavic origin and carry a major Slavic founder mutation 657del5 in exon 6 of the *NBN* gene. An unexpectedly high frequency of heterozygotes, estimated to occur with a frequency 1:177, has been found in Czech, Polish, and Ukrainian populations, which may be a contributing factor to the high risk of malignancies, in particular breast cancer, B cell chronic lymphocytic leukemia, and T cell prolymphocytic leukemia.[62]

Microcephaly without any visible neurological defects, CID connected with recurrent infections, and a high risk of malignancy, especially of lymphoid origin, are the most important clinical features of this syndrome. Many external features such as dysmorphic facial appearance, impaired somatic development, or mild growth retardation are more noticeable with age. Receding and sloping forehead, receding mandible, prominent midface with long nose and philtrum, or upward slanting palpebral fissures are the main features of facial dysmorphism in NBS.[63] Girls are affected by premature gonadal failure and hypoplasia of the uterus and ovaries.

Inseparable complications of the syndrome are respiratory tract infections, such as pneumonia, acute or recurrent bronchitis and sinusitis, otitis media, chronic rhinitis as well as urinary tract infections and gastroenterocolitis.[64] A chronic structural airway disease with bronchiectasis, lung fibrosis,[63] and pulmonary granulomatosis[65] has also been noted in sporadic cases. Chronic and severe viral infections caused by hepatotropic viruses, such as hepatitis B (HBV) and C (HCV) viruses, and by lymphotropic Epstein-Barr virus (EBV) or cytomegalovirus (CMV) may result from a profound immunodeficiency, characteristic for NBS. Autoimmune diseases encompassing autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenic purpura (ITP), thyroiditis, arthritis, and celiac disease also constitute an important clinical problem.[64]

Malignancies are the most important complications that shorten the survival of patients affected with NBS, and only about half of NBS patients reach adult age. Over 40% of patients by the age of 20 years develop malignant diseases, most of them of hematopoietic origin, with B and T cells non-Hodgkin lymphomas or acute T cell leukemia being the most common.[66] Treatment of malignancies in NBS is extremely difficult because of the cytotoxic effect of chemotherapy and radiotherapy, and an increased number of patients have so far successfully went through hematopoietic stem cell transplantation.[67]

Immunodeficiency is an integral part of the broad constellation of clinical symptomatology in children affected with NBS, and is observed in about 74% of patients. Combined humoral and cellular immunodeficiency is

characterized by inadequate immunoglobulin production and class switch recombination defect, resulting from bone marrow failure and B and T cells lymphopenia, and defective T cell-dependent response to antigens with ineffective T cell help B cells to promote memory B cell generation.[68,69] The management of NBS-affected children is often unsuccessful because of the systemic nature of the disease and associated severe complications worsening their long-term prognosis.

Hyper-IgE syndromes

Hyper-IgE syndromes (originally named Job's syndrome) encompass a group of PIDs characterized by a classical triad of symptoms, such as high serum-IgE level, eczema, and recurrent pulmonary infections. These symptoms are present most commonly, but the clinical phenotypes of patients affected with HIES are highly variable. The first definition of the disease was provided in 1966, when "cold abscesses" were described in two red-haired girls, and since that time many discoveries in the field of molecular biology and immunogenetics have shed light on the diverse etiology and pathophysiology of HIES, leading to further definition of the disease and delineation.

Taking into account both clinical characteristics and genetic background, HIES includes AD LOF mutations in *STAT3* and AR mutations in *dedicator of cytokinesis 8* (*DOCK8*), *tyrosine kinase 2* (*TYK2*), and *phosphoglucomutase 3* (*PGM3*) genes.[70] Over the last decade, other monogenic disorders with similar phenotypes have been reported, such as mutations in *caspase recruitment domain family, member 11* (*CARD11*),[71] *zinc finger protein 341* (*ZNF341*),[72] *epidermal growth factor (EGF) receptor binding (ERB) B2 interacting protein* (*ERBB2IP*, *ERBIN*),[73] and *interleukin 6 signal transducer* (*IL6ST*) genes.[74,75] Whereas AR mutations in *DOCK8*, *TYK2*, and *PGM3* deficiencies would be better classified as CIDs due to their cytoskeletal and glycosylation defects of T cells, it has been suggested to reserve the term HIES for the most common AD form due to *STAT3* deficiency.[76] The *STAT3* signaling protein is widely expressed in immune and nonimmune cells and is involved in host defense, tissue, and vascular remodeling as well as wound healing, consistent with its multisystem clinical phenotype. *STAT3* plays a role in signal transduction from multiple pro- and anti-inflammatory cytokine (among others IL-6, IL-10, IL-17, IL-21, and IL-22) receptors to the nucleus, and thus mediates various pathways, accounting to both excessive and decreased inflammatory response.[76-78]

A broad phenotypic range of symptoms in AD-HIES reflects the widespread role played by *STAT3* in both immune system and the skeletal, vascular, and dental systems.[76-78] Eczematoid rashes are early signs and a hallmark of AD-HIES. It may appear in neonates in the form of a papulopustular or eczematoid eruption on the face, neck, scalp, axillae, and diaper area, which may over time evolve into generalized eczematoid dermatitis or erythroderma, complicated by staphylococcal skin abscesses and boils, not showing features of inflammation, and by mucocutaneous candidiasis.[79] Eczema is also a cardinal feature of *DOCK8* or *PGM3*-related HIES. The differentiation of HIES from severe atopic dermatitis and other immunodeficiencies associated with eczema, such as Wiskott–Aldrich syndrome, Omenn syndrome, Comel–Netherton syndrome, or immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), is challenging for pediatricians, dermatologists, and allergologists. Furthermore, in infants and young children, due to lack of constellation of other consistent findings, a clinical diagnosis could be misleading.[80]

Recurrent pneumonia, predominantly associated with *STAT3*–HIES, is most frequently caused by *Staphylococcus aureus* and *Aspergillus fumigatus*or *scedosporium*, resulting in parenchymal lung damage, pneumatoceles formation, and airway structural remodeling with development of bronchiectasis, which, in turn, predispose to colonization with a wide spectrum of pathogens, such as *Pseudomonas aeruginosa* and nontuberculous *mycobacteria*.[81-83]

Connective tissue abnormalities typically belong to the clinical presentation of *STAT3*–HIES and include congenital skeletal anomalies, scoliosis, joint hyperextensibility, primary teeth retention, and coronary arterial malformations and aneurysms.[76-78,81,84] Dysmorphic facies, which could be puzzling symptoms in puberty or adulthood, but not overt in early childhood, include deep-set eyes, coarse and asymmetric face, broad nasal bridge, fleshy nasal tip, and increased interalar distance. Less frequently, this appearance could be accompanied with midline anomalies, such as cleft palate, tongue, and lingula as well as unilateral body hypertrophy.

In spite of plenty of symptoms described in affected patients, the clinical presentation is not always suggestive and recognition of HIES in children is challenging because most of the symptoms do not occur in every patient, their full expression may not be present in young children, and misdiagnoses of frequent childhood allergic diseases could show overlapping symptomatology.[77] Therefore, in young children, a clinically relevant National Institute of Health (NIH) HIES scoring system may not be a sufficient informative tool helpful in diagnosing HIES and requires young age corrections.

A markedly elevated serum-IgE is considered a major laboratory finding in both AD- and AR-HIES. IgE levels start rising right after the birth, but a diagnostic threshold of IgE > 2000 IU/mL may not be reached in very young patients, and thus the age-adjusted value of 10 times the age-appropriate level has been suggested in affected infants. IgE levels are characterized by timely fluctuations, which do not strictly correlate with clinical symptoms and the severity of infections. Blood and tissue eosinophilia is also commonly present, but without a relationship with elevation in IgE, these parameters reflect high sensitivity and low specificity for HIES.[76,77]

The immune system disorders in AD-HIES occurring in virtually all affected patients are composite and result from IL-6-mediated *STAT3* dysfunction. This further leads to impaired activation of the transcription factor retinoic acid-related gamma T (RORγT), a master regulator of differentiation of T cells to a pro-inflammatory Th17 subtype. Consequently, failure to stimulate epithelial cells to produce chemokines and stimulate chemotaxis and phagocytosis by IL-17A and IL-17F, and to produce defensins by IL-22, contributes to an increased susceptibility to infections with extracellular bacteria and fungi.[85,86] Lack of optimal *STAT3* signaling results in impaired B cell maturation and

survival, somatic hypermutation, memory B cell development, IgG1, IgG3, and IgA production, and antibody affinity maturation.[87] Aberrant function of *STAT3* predisposes affected patients to a higher risk of malignancies, in particular non-Hodgkin's lymphoma. Autoimmune diseases, such as vasculitis, membranoproliferative glomerulonephritis (MPGN), and systemic lupus erythematosus (SLE), have been reported in several patients.[76]

Symptomatology of AR-HIES is also variable and there are some symptoms more relevant to a particular mutation. For example, patients with *DOCK8* mutations are more vulnerable to viral, such as human papillomavirus (HPV) and fungal infections, and have a greater risk of malignant transformation. These patients neither present systemic nonimmunological skeletal, dental, vascular, and dysmorphic features attributed to *STAT3* deficiency nor develop pulmonary pneumatoceles.[88] In PGM3 deficiency, affected patients manifest eczema and recurrent infections as well as nonimmunological symptoms such as dysmorphic features, neurological impairment, and skeletal dysplasia.[89]

Characteristic clinical manifestations of syndromes associated with PIDs are summarized in Table 1. In Table 2, the most important immune system abnormalities, and consequently their clinical phenotypes are displayed.

Diagnostic tools

Although signs and symptoms of syndromic PIDs usually appear early in life and most of the syndromes are recognized in young children, in some cases the diagnosis can be delayed, particularly in children lacking classical clinical phenotypes or presenting a puzzling gradual development of the syndrome-specific symptomatology. In the countries where live attenuated vaccines (LAV), such as Bacille Calmette–Guerin (BCG) and an oral poliomyelitis vaccine (OPV), belong to the routine vaccination programs, the risk of life-threatening vaccine-associated complications, such as BCG-itis and poliomyelitis, in immunocompromised children is a considerable problem.[90] To reduce significant morbidity of PID patients, development and progression of infection-associated irreversible organ damage, and immune-mediated organ-specific pathology, as well as to improve survival and quality of life, an early diagnosis strategy with the implementation of a large-scale newborn screening (NBS) has been adopted.[91] The methods used for the detection of PIDs associated with T and/or B cell lymphopenia are based on the measurements of episomal excision products of lymphocyte receptors, TRECs, and kappa deleting recombination excision circles (KRECs). While TREC is a common screening approach, providing a good combination of sensitivity and specificity, and a satisfactory cost-effectiveness ratio, the role of KREC remains debatable.[91] Initially designed to detect SCID and X-linked agammaglobulinemia (XLA), characterized in their classic forms by severe T and B cell deficiencies, NBS also proved effective to identify syndromic PIDs, such as, but not limited to, trisomy 21, A-T, DGS, CHARGE or Noonan syndrome[92-97] and congenital lipomatous overgrowth, vascular malformations, epidermal nevi and spinal abnormalities (CLOVES syndrome),[98] B cell lymphoma/leukemia 11B (*BCL11B*)[99], or exostosin-like 3 (*EXTL3*)[100] mutations, associated with T and B cell lymphopenia.[101] Syndromic PIDs, characterized by reduced numbers of TREC copies and identified in NBS are summarized in Table 3.

The next step of the comprehensive diagnostic approach is a flow cytometric immunophenotyping, which is an essential tool for the evaluation of multiple components of the immune system. It plays both a confirmatory role in patients in whom a PID was assessed based on NBS and enables establishing an individual immunophenotype and a PID diagnosis in those patients in whom lymphopenia was not detected in NBS; it also serves for monitoring of the dynamics within the lymphocyte compartments. Flow cytometry is also used for evaluating different functional processes of the innate and adaptive immune response, such as lymphocyte proliferation assays, assessment of radiosensitivity, and the putative diagnosis-specific test release of extra- and intracellular signaling molecules, cytokines, and transcription factors facilitate the PID diagnosis.[102-105] While flow cytometric analysis is an irreplaceable informative tool assessing the innate and adaptive immune response, its results can only be considered in conjunction with other tests according to diagnostic protocols, such as serum immunoglobulin levels, vaccine-specific antibody titers, autoantibodies, complement components, granulocyte phagocytosis, and oxidative burst as well as disease-specific tests, such as AFP in A-T or calcium-phosphorus homeostasis in DGS.[106]

Whereas the field of pediatric PIDs is expanding, the spectrum of phenotypic and immunological features ascribed to PIDs is also advancing dynamically, and PIDs are no longer considered monogenic diseases following Mendelian modes of inheritance. Introduction of next-generation sequencing (NGS) methods has significantly changed the understanding of genetic backgrounds of PIDs. The immunophenotypic variability and complexity reflect the multigenic and somatic causes of many disease entities.[107] Recent advances in new technologies of molecular analysis, meeting pediatricians' and pediatric immunologists' expectations, in particular, whole-exome sequencing (WES), have been increasingly engaged in establishing a definitive diagnosis of a wide spectrum of new disease entities in affected children.[10,108-111]

Preventive measures and therapeutic options: current status and future perspectives

It being the fact that inactivated and LAV are the mainstay of active immunization in pediatrics, protecting against viral and bacterial diseases, in patients affected by PIDs, they pose the risk of vaccine-related infectious complications. Severe, life-threatening infections following LAV, such as BCG, OPV, measles vaccine (MeV), and an oral rotavirus vaccine (ORV), have been reported in PID patients and ascribed to a variety of disturbances of immune response, such as defective production of interferons, T and B cells deficiency and dysfunction, and NK cell deficiency.[112-114] From the pediatrician's perspective, an early PID diagnosis afforded by NBS is important to avoid live viral and bacterial vaccines. A pediatrician's awareness is also required in case of newborns and infants having a positive family history of PIDs to postpone all live vaccines until the child has

Table 1 Major clinical phenotypes, including anatomical abnormalities and organ dysfunctions, in children with syndromic PIDs.

Syndrome	Dysmorphic features	Cardiovascular	Respiratory	Neurological	Cutaneous	Endocrine/metabolic	Gastrointestinal
Down syndrome	Flat face, short midface, almond-shaped eyes, flat nasal bridge, macroglossia, short stature	Atrioventricular septal defect, tetralogy of Fallot	Structural lung disease, tracheo- and bronchomalacia, lung fibrosis, short Eustachian tube, narrow ear canal	Developmental delay, decreased muscle tone	Dry skin	Hypothyroidism, diabetes mellitus	Celiac disease, duodenal atresia, imperforated anus
DiGeorge syndrome	Hooded eyelids, hypertelorism, bulbous nasal tip, short philtrum, small mouth, cleft palate, small mandible, low-set ears, short stature, vertebral anomalies, polydactyly, renal agenesis, cryptorchidism, microphthalmia, coloboma	Conotruncal heart anomalies: pulmonary stenosis, tetralogy of Fallot, ventricular septal defect, interrupted aortic arch type B	Laryngomalacia, laryngeal atresia, asthma	Developmental delay, cognitive disorders, speech impairment, psychiatric illness		Hypoparathyroid gland hypoplasia with hypocalcemia, hypothyroidism	Hirschprung disease, imperforated anus, intestinal malrotation, tracheoesophageal atresia
CHARGE syndrome	Coloboma, cleft lip and palate, short stature, genital anomalies, dysplastic kidneys	Ventricular septal defect	Choanal atresia, external and inner ear anomalies	Cranial nerve anomalies, hearing loss, decreased muscle tone, autism, developmental delay		Hypothyroidism, gonadotropin or growth hormone deficiency	
Noonan syndrome	Hypertelorism, coloboma, low-set ears, pectus carinatum/excavatum, craniosynostosis, short stature, skeletal malformations, renal abnormalities, cryptorchidism	Pulmonary valve stenosis, ventricular septal defect, atrioventricular canal, hypertrophic cardiomyopathy	Otitis media	Mild developmental delay, language impairment	Café-au-lait spots, solar lentigines, keratosis pilaris	Growth hormone deficiency and resistance, delayed puberty	Intestinal malrotation, immature gut motility
Ataxia telangiectasia (A-T)			Structural lung disease, interstitial and granulomatous lung disease, restrictive lung disease, impairment of pulmonary function	Progressive cerebellar ataxia, ocular apraxia, choreoatetosis, decreased muscle tone, tetraparesis, dysarthria, ineffective chewing, swallowing, and coughing, cognitive problems, depression, psychosocial problems	Oculocutaneous telangiectasia, granulomatosis, café-au-lait spots, solar lentigines	Diabetes mellitus, hypogonadotropic hypogonadism, hyperthyroidism	Failure to thrive, gastroesophageal reflux, constipation, nonalcoholic liver cirrhosis

Nijmegen breakage syndrome (NBS)	Microcephaly, sloping forehead, prominent midface with long nose and philtrum, receding mandible, upward slanting palpebral fissures, syn- and clinodactily, short stature, skeletal anomalies, renal hypoplasia		Interstitial and granulomatous lung disease	Mental retardation, impaired cognitive functions, and brain malformations	Cutaneous granulomatosis	Growth retardation, hypergonadotropic hypogonadism	Anal atresia
DNA Ligase IV (LIG4) deficiency	Microcephaly, facial dysmorphism with prominent midface, long nose, micrognathia, long ears, protruding tongue, skeletal malformations			Mental retardation	Cutaneous telangiectasia, warts	Primary ovarian failure	Failure to thrive, anorexia
STAT3-hyper-IgE syndrome (HIES)	Coarse face, hypertelorism, prominent forehead and chin, increased interalar width, arched palate, cleft lip and palate, dental anomalies, scoliosis, joint hyperextensibility, craniosynostosis, Chiari type 1 malformation	Cardiovascular arterial malformations, coronary artery tortuosity, aneurysms	Structural lung disease, bronchiectasis, bronchopleural fistula, parenchymal lung damage, pneumatoceles, asthma	Focal white matter hyperintensities	Eczematoid rash, erythroderma, porous skin, furunculosis		Gastroesophageal reflux, gastrointestinal dysmotility, rectal prolapse

Table 2 The spectrum of immune deficiencies associated with syndromic PIDs.

Syndrome	Pathophysiology	Adaptive immunity	Innate immunity	Immunophenotype
Down syndrome	-Overexpression of genes found in chromosome 21: superoxide dismutase (*SOD1*) and integrin beta-chain2 (*ITBG2*), or CD18 significant for neutrophil functions, *RCAN1* (regulator of calcineurin 1) inhibiting signal transduction mediated by NFAT (nuclear factor of activated T cells) -Accelerated immunosenescence -Zinc deficiency	-Thymic hypoplasia and reduced recent thymic emigrants and T cell turnover (corresponding with low TREC numbers) -Altered thymic selection and regulatory Treg cell generation -Reduced T CD4+ and CD8+ cell numbers -Defective T cell response to stimulation with mitogens -Increased apoptosis of B cells -Defect in differentiation of B cells and reduced number of switched-memory cells -Suboptimal antibody response to immunizations	-Defect in neutrophil functionality, reduced phagocytic activity -Increased numbers of nonclassical (CD14dimCD16+) monocytes with overexpression of toll-like receptors TLR4 and TLR2 -Greater numbers of $\gamma\delta$ T cells -Downregulation of C1QA, C1R, C3, and C6 complement factors and type 1 interferonopathy -Abnormal cytokine profile: increased levels of proinflammatory IL-2, IL-6, TNF-α, and anti-inflammatory IL-10, IL-1Ra	-Recurrent infections: pneumonia, structural and interstitial lung disease, otitis media, periodontitis -Autoimmune disorders: celiac disease, hypothyroidism, arthritis, diabetes mellitus -Proinflammatory phenotype with neuroinflammation, Alzheimer's disease -Hematological malignancies: ALL
DiGeorge syndrome	-*22q11.2* deletion is associated with large blocks of low copy repeats (LCR) and segmental duplications, leading to genetic complexity -*TBX1* gene in the LCR22A–LCR22B region underlie the morphogenesis of pharyngeal arch and thymic development and lymphopoiesis -*DGCR6* gene negatively regulates *TBX1* expression -*RREB1* gene encodes a zinc finger transcription factor, regulating RAS-responsive elements -CRK-like proto-oncogene, adaptor protein (*CRKL*) gene is involved in the occurrence of conotruncal cardiac anomaly and NK cell dysfunction -Premature thymic involution and immune aging	-Alterations in size and architecture of the thymus and defective thymocyte development -Reduced thymic output reflected by low TREC numbers -Low naïve T CD4+ and CD8+ cells and skewing toward a memory phenotype -Impaired generation of follicular Th cells and germinal centers formation -Impaired development of thymic and peripheral Treg cells -Progressive decrease of thymic expression of autoimmune regulator (AIRE) -B cell deficiency and antibody production defects	-NK cell dysfunction -Neutropenia	-Recurrent infections: pneumonia, sinusitis, and interstitial and structural lung disease -Autoimmune phenomena: hypothyroidism, celiac disease, thrombocytopenia, neutropenia, and juvenile idiopathic arthritis -Atopy, asthma -Immune dysregulation: pulmonary granulomatosis
CHARGE syndrome	*CHD7* pathogenic variants are associated with impaired tissue-specific regulation of gene expression. Both *CHD7* and *TBOX1* genes expressed in the pharyngeal arches may share role in impaired thymic development	-T cell lymphopenia due to impaired thymic organogenesis, low thymic output correlating with low TREC numbers, decreased T CD4+ cells, impaired T cell response to antigenic stimulation -Impaired B cell differentiation, disturbed memory B cell generation, antibody deficiency, defective response to vaccination	-Low numbers of NK cells	-Recurrent infections: bronchiolitis, pneumonia, sinusitis, otitis media, dermatitis, and sepsis -Atopic disorders: asthma and eczema

Noonan syndrome	-Mutations in genes involved in the RAS GTPase MAPK (mitogen-activated protein kinase) signaling pathway, playing essential roles in controlling cellular developmental processes -Increased gene dosage in 12q24	-T cell lymphopenia early in life, low TREC numbers -Lymphatic vessels dysplasia, generalized lymphedema, intestinal and pulmonary lymphangiectasia, chylothorax	-Overactivation of monocytes and secretion of proinflammatory cytokines	Malignancies: -Myeloproliferative disorders: juvenile myelomonocytic leukemia (218C>T mutation in the *PTPN11* gene), B-cell ALL -Embryonal tumors: rhabdomyosarcoma, neuroblastoma, and also Sertoli cell tumor, glioma, astrocytoma -Autoimmune hepatitis
Ataxia telangiectasia	-Inactivation of protein kinase ATM results in defective DNA damage signaling, genomic instability, abnormal gene transcription and expression, cytoskeletal abnormalities, mitochondrial dysfunctions, aberrant checkpoint controls, hypersensitivity to ionizing radiation, inefficient energy metabolism and response to oxidative stress -Dysfunction in V(D)J recombination -Premature aging of the immune system -Chromosomal translocations in the regions of chromosomes 7 and 14 that are associated with TCR and heavy-chain immunoglobulin coding regions	-Embryonic or absent thymus with T cell lymphopenia, low T CD4+ cells early in life -Abnormal T cell and B cell neogenesis corresponding with low TREC and KREC levels -Abnormal TCR surface expression -Defective T cell lymphoproliferative response to antigenic and mitogenic stimulation -Deficiency in T cell helps B cells, resulting in antibody deficiency, impaired class-switching and somatic hypermutations -Ineffective antibody response to immunization	-Neutropenia -Overactivation of macrophages with proinflammatory cytokine milieu and defective IL-10 suppressive activity	-Infectious complications: sinusitis, pneumonia, bronchiectasis, restrictive lung disease, interstitial lung disease, pulmonary granulomatosis -Immune dysregulation: cutaneous granulomas, nonmalignant lymphoproliferation, vasculitis -Autoimmune disorders: thrombocytopenia, arthritis, vitiligo, diabetes mellitus -Malignancies: hematopoietic cancers: leukemias and lymphomas, also breast and gastrointestinal cancers
Nijmegen breakage syndrome (NBS)	-*NBN* gene mutation abrogates formation of a complex with MRE11 and RAD50, resulting in defect in DNA DSBs, genomic instability, disturbed V(D)J and class-switch recombination -Immunosenescence -High incidence of rearrangements in chromosomes 7 and 14, correlating with encoding the TCR and immunoglobulin heavy chain	-Lymphopenia due to impaired early T-cell and B-cell development -Low T CD4+ cell counts and impaired T cell help in B cells, memory B cell generation, GC formation, immunoglobulin production, class switch recombination -Defective T-cell lymphoproliferative response to antigens and mitogens -Impaired humoral response to immunizations	-Neutropenia -Macrophage activation, inflammatory immune phenotype	-Recurrent sinopulmonary infections, interstitial lung disease, structural lung disease, otitis media, urinary tract infections -Autoimmune disorders: hemolytic anemia -Immune dysregulation: cutaneous granulomatosis, granulomatous lung disease -Malignancies, predominantly of lymphoid origin: B-cell and T-cell non-Hodgkin lymphoma, ALL, Hodgkin disease, acute myeloblastic leukemia, brain tumors: medullosarcoma, perianal rhabdomyosarcoma

(Continued)

Table 2 (Continued)

Syndrome	Pathophysiology	Adaptive immunity	Innate immunity	Immunophenotype
DNA LIG4 deficiency	-LIG4 deficiency causes disturbances in DNA double-strand breaks repair through NHEJ pathway and leads to cellular apoptosis, mutagenesis, radiosensitivity, and disrupted V(D)J recombination -Progressive bone marrow failure and combined B and T cell immune deficiency	-Severe T cell and B cell lymphopenia resulting in SCID or CID phenotype, low TREC numbers, restricted TCR repertoire -Profound antibody deficiency	-Neutropenia -Low NK cells	-Infections: pneumonia, sepsis, otitis, sinusitis, structural lung disease, urinary tract infections -Autoimmune disease: pancytopenia, psoriasis, hypothyroidism, sclerosing cholangitis -Hematological malignancies: B cell lymphoma, ALL
STAT3-hyper-IgE syndrome	-LOF mutations in *STAT3* cause defects in signal transduction and secretion of pro- and anti-inflammatory cytokines (e.g., IL-6, IL-10, IL-11, IL-17, IL-21, IL-22, and IL-23) -Failure of RORγT transcription factor activation leads to disturbed differentiation of Th17 cells and secretion of IL-17 and IL-22 -Disrupted stimulation of epithelial cells by IL-17F to produce chemokines -Impaired stimulation of epithelial cells by IL-22 to produce β-defensins	-Decreased memory T cells and low Th17 cells -Lack of optimal B cell differentiation and memory B cell generation, disturbed somatic hypermutations and antibody affinity maturation -High IgE levels with frequently decreased IgA and ineffective antigen-specific antibody response to encapsulated bacteria	-Impaired epithelial cells activity: defect in upregulation of antimicrobial peptides production in epithelial cells -Suboptimal activation of PMN cells with disturbed chemotaxis and phagocytosis -Eosinophilia -Neutropenia	-Severe and chronic bacterial, viral, and fungal infections: Recurrent pneumonia, chronic lung disease with impaired healing, interstitial and parenchymal destruction, mucocutaneous candidiasis, abscesses -Immune dysregulation with both excessive and decreased inflammatory response, severe eczema and erythroderma -Autoimmunity -Increased risk of tumorigenesis: Hodgkin and non-Hodgkin lymphoma
DOCK8-hyper-IgE syndrome	-Impaired activation of small RHO-family GTPase, CDC42 in DOCK8 deficiency, resulting in defective cytoskeletal rearrangement and abnormal immune cell trafficking	-CID immunophenotype with T cell and NK cell lymphopenia -A survival defect of Dock8-deficient B cells, T cells, and Treg cells -Impaired T cells help B cells in germinal centers, impaired antibody affinity maturation, and response to vaccinations -High IgE and decreased IgM levels	-Impaired dendritic cell migration and IFN-γ production -Impaired migration of macrophages -Defective NK cell toxicity and IFN-γ production -Eosinophilia	-Increased susceptibility to viral and fungal infections, mucocutaneous candidiasis, chronic cutaneous and respiratory tract infections, abscesses, and cellulitis -Severe allergy: atopic dermatitis, asthma, food allergy -Malignancies: lymphoma, squamous cell carcinoma
PGM3-hyper-IgE syndrome	Common defect in the glycosylation pathway of proteins in intracellular and extracellular compartments	-Possible SCID phenotype with profound T cell lymphopenia	-Eosinophilia -Neutropenia	-Recurrent severe respiratory and gastrointestinal infections -Atopic disease: eczema, asthma

Table 3 Syndromic PIDs identified in newborn screening.

Abnormal TRECs
Down syndrome
DiGeorge syndrome
CHARGE syndrome
Ataxia telangiectasia
NBS
ICF deficiency
Noonan syndrome
Hyper-IgE syndrome
Wiskott–Aldrich syndrome
CLOVES syndrome
EXTL3 deficiency
BCL11B deficiency
Rac Family Small GTPase 2 (RAC2) deficiency
LIG4 deficiency
DCLRE1C deficiency (*Artemis)*
Cernunnos/XLF deficiency

been fully tested to rule out a serious T cell immunodeficiency. This recommendation is particularly important for pediatricians and patients living in the regions where newborn TREC screening is not fully implemented.[115] Further decisions about the enactment of vaccination program must be individualized, particularly in children with such syndromic PIDs as DS or DGS, depending on the degree of immune response impairments. An important prophylactic measure is to vaccinate all family members and close contacts, avoiding OPV and using an inactivated poliomyelitis vaccine (IPV), and also maintaining active immunization in the population to achieve herd immunity.[115]

There is also increasing evidence on the beneficial effects of immunoglobulin replacement therapy in an advancing spectrum of PIDs and syndromes associated with primary immune deficiencies. In primary antibody deficiencies, such as XLA or common variable immunodeficiency (CVID), a life-long immunoglobulin supplementation is the principle of prophylaxis against infections. However, in some syndromic immunodeficiencies, not limited to humoral, but also with cellular deficiencies, such as *STAT3*-HIES or DOCK8 deficiency, a beneficial effect of intravenous (IVIg) or subcutaneous (SCIg) immunoglobulins with reduction in the number of episodes of pneumonia and skin infections, could be expected.[116,117] While there is a lack of clear disease-specific guidelines about IVIg/SCIg therapy in other syndromes associated with PIDs, for example, DS, DGS, A-T, or NBS, the decision about starting the treatment should be based on individual clinical and immunological indications. Improvement and satisfaction in quality of life with decreased incidence rates of infection have been achieved in patients receiving a self-administered home-based SCIg therapy under the supervision of a pediatrician and clinical immunologist.[118,119]

Another widely recommended option of protection against infection in patients with PIDs is antibiotic prophylaxis, which may be recommended as primary therapy or in combination with immunoglobulin replacement. Owing to a high rate of bacterial multiorgan complication, among syndromic PIDs, *STAT3*–HIES is a specific indication. In PIDs with predominating T cell defects, prophylaxis against *Pneumocystis jiroveci* is required with cotrimoxazole.[120] Like other preventive measures in syndromic PIDs, antibiotic prophylaxis is individually recommended depending on the clinical course of immunodeficiency, infection pattern, dysregulated inflammatory response, and organ-specific complications such as bronchiectasis.[121] Among causative pathogens, respiratory viruses, such as rhinovirus and adenovirus, play an important role, which in turn, alter local immune responses and promote bacterial superinfections with *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.[121] Clear guidelines addressed to pediatricians regarding current practices for the prevention of infection in children with syndromic PIDs, including the application of viable and nonviable vaccines and chemotherapeutics, based on current evidence[89,115,122-126] are summarized in Table 4.

The clinical and immunological phenotypic heterogeneity with infections, atopy, autoimmunity, autoinflammation, and lymphoproliferation with a highly diverse genetic background of syndromic PIDs makes it difficult to define a universal rational therapy and poses the requirement for an individual therapeutic approach. The progress in understanding the pathophysiology of PIDs has led to guidelines adjusted to disease-specific programs regarding indications to immune reconstitution with HSCT, conditioning regimens, and long-term outcomes. For several syndromic PIDs, such as SCID, DOCK8 deficiency, LRBA deficiency, and IPEX, HSCT is considered a curative option, and for DNA double strand break (DSB) repair disorders or DADA2, it is considered a partially curative, whereas for some of them, such as for DGS, it remains controversial.[127]

Advances in the understanding of molecular mechanisms of PIDs related to hyperinflammation and immune dysregulation have led to targeted precision medicine-based therapeutic approaches with biological agents and small molecules, such as proinflammatory cytokine receptor antagonists, fusion proteins, humanized monoclonal antibodies, binding proteins, or small molecule inhibitors.[128,129] Looking at the future, new perspectives of treatment tools engaging technologies of genome editing and gene delivery will be opened in selected monogenic PIDs.[130,131]

Conclusion

From a pediatrician's perspective, syndromic immunodeficiencies are a very heterogeneous group of inherited disease entities characterized by a broad phenotypic range of symptoms and a constellation of findings, accompanied by high variability of immunological disorders. This means a frequent pediatrician confrontation with children lacking classical hallmarks of many conditions associated with immune system impairment and manifesting predominantly nonimmunological symptoms, thus widening a spectrum of possible diagnoses. Noninfectious phenomena, such as autoimmunity, immune dysregulation, organ-specific pathology, and malignancy, could be a prevailing symptomatology in clinical phenotypes of affected children. Therefore, syndromic immunodeficiencies pose a diagnostic challenge in

Table 4 Guidelines for pediatricians on prevention of infections in syndromic PIDs.

		Vaccinations	
Syndromic PID	Prevention of infections	Recommended	Contraindicated
Down syndrome	-Sinopulmonary infections Trimethoprim-sulfamethoxazole 6 mg/kg 1-2x daily 3x/week or azithromycin 10 mg/kg 1x daily 3x/week	Inactivated influenza vaccine Inactivated polio vaccine Live viral vaccines (measles/mumps/rubella (MMR), varicella vaccine) can be safely given in mild combined immunodeficiency (CD4+ count >400) 13-valent conjugated, followed by 23-valent polysaccharide pneumococcal vaccine Tetravalent conjugate meningococcal plus monovalent serotype B vaccines *Haemophilus influenza* type B vaccine	Viable influenza vaccine Oral polio vaccine Rotavirus vaccine MMR vaccine in advanced combined immunodeficiency In children receiving immunoglobulin therapy (IVIg, SCIg), live viral vaccines are contraindicated for 3-11 months
DiGeorge syndrome	-Sinopulmonary infections Trimethoprim-sulfamethoxazole 6 mg/kg 1-2x daily 3x/week or azithromycin 10 mg/kg 1x daily 3x/week -Severe T-cell lymphopenia *Pneumocystis jiroveci* prophylaxis: Trimethoprim-sulfamethoxazole 6 mg/kg 1-2x daily 3x/week Fluconazole 3 mg/kg 1x daily Respiratory syncytial virus prophylaxis: Palivizumab (children <2 years with CD4+ count <200)	Inactivated influenza vaccine Inactivated polio vaccine Human papilloma virus (HPV) vaccine Live viral vaccines (MMR, varicella vaccine) can be safely given in mild combined immunodeficiency (CD4+ count >400) 13-valent conjugated, followed by 23-valent polysaccharide pneumococcal vaccine Tetravalent conjugate meningococcal plus monovalent serotype B vaccines *Haemophilus influenza* type B vaccine	BCG Viable influenza vaccine Oral polio vaccine Rotavirus vaccine MMR vaccine in advanced combined immunodeficiency In children receiving immunoglobulin therapy (IVIg, SCIg), live viral vaccines are contraindicated for 3-11 months
CHARGE syndrome	-Sinopulmonary infections Trimethoprim-sulfamethoxazole 6 mg/kg 1-2x daily 3x/week or azithromycin 10 mg/kg 1x daily 3x/week	Inactivated influenza vaccine Inactivated polio vaccine Live viral vaccines (MMR, varicella vaccine) can be safely given in mild combined immunodeficiency (CD4+ count >400) 13-valent conjugated, followed by 23-valent polysaccharide pneumococcal vaccine Tetravalent conjugate meningococcal plus monovalent serotype B vaccines *Haemophilus influenza* type B vaccine	Viable influenza vaccine Oral polio vaccine Rotavirus vaccine MMR vaccine in advanced combined immunodeficiency In children receiving immunoglobulin therapy (IVIg, SCIg), live viral vaccines are contraindicated for 3-11 months
Noonan syndrome	-Sinopulmonary infections Trimethoprim-sulfamethoxazole 6 mg/kg 1-2x daily 3x/week or azithromycin 10 mg/kg 1x daily 3x/week	Inactivated influenza vaccine Inactivated polio vaccine Live viral vaccines (MMR, varicella vaccine) can be safely given in mild combined immunodeficiency (CD4+ count >400) 13-valent conjugated, followed by 23-valent polysaccharide pneumococcal vaccine Tetravalent conjugate meningococcal plus monovalent serotype B vaccines *Haemophilus influenza* type B vaccine	Viable influenza vaccine Oral polio vaccine Rotavirus vaccine MMR vaccine in advanced combined immunodeficiency In children receiving immunoglobulin therapy (IVIg, SCIg), live viral vaccines are contraindicated for 3-11 months
Ataxia telangiectasia	-Sinopulmonary infections Trimethoprim-sulfamethoxazole 6 mg/kg 1-2x daily, 3x/week or azithromycin 10 mg/kg 1x daily 3x/week -Bronchiectasis Azithromycin 10 mg/kg 1x daily 3x/week Chronic *Pseudomonas aeruginosa* colonization: inhaled tobramycin	Inactivated influenza vaccine Inactivated polio vaccine HPV vaccine 13-valent conjugated, followed by 23-valent polysaccharide pneumococcal vaccine Tetravalent conjugate meningococcal plus monovalent serotype B vaccines *Haemophilus influenza* type B vaccine	BCG Viable influenza vaccine Oral polio vaccine Rotavirus vaccine MMR vaccine In children receiving immunoglobulin therapy (IVIg, SCIg), live viral vaccines are contraindicated for 3-11 months

(Continued)

Table 4 (Continued)

Syndromic PID	Prevention of infections	Vaccinations	
		Recommended	Contraindicated
Nijmegen breakage syndrome	-Sinopulmonary infections Trimetoprim-sulfamethoxazole 6 mg/kg 1-2x daily 3x/week, or azithromycin 10 mg/kg 1x daily 3x/week -Recurrent viral infections Acyclovir	Inactivated influenza vaccine Inactivated polio vaccine HPV vaccine	BCG Viable influenza vaccine Oral polio vaccine Rotavirus vaccine MMR vaccine In children receiving immunoglobulin therapy (IVIg, SCIg), live viral vaccines are contraindicated for 3–11 months
DNA LIG4 deficiency	-Long-term antibiotic, antiviral, and antifungal chemoprophylaxis Azithromycin 10 mg/kg 1x daily 3x/week Acyclovir Fluconazole 3 mg/kg 1x daily	Inactivated influenza vaccine Inactivated polio vaccine 13-valent conjugated, followed by 23-valent polysaccharide pneumococcal vaccine Tetravalent conjugate meningococcal plus monovalent serotype B vaccines *Haemophilus influenza* type B vaccine	BCG Viable influenza vaccine Oral polio vaccine Rotavirus vaccine MMR vaccine In children receiving immunoglobulin therapy (IVIg, SCIg), live viral vaccines are contraindicated for 3–11 months
STAT3-hyper-IgE syndrome	-Sinopulmonary infections Trimethoprim-sulfamethoxazole 6 mg/kg 1-2x daily 3x/week or azithromycin 10 mg/kg 1x daily 3x/week -Staphylococcal skin abscesses Anti-staphylococcal penicillin, e.g., flucloxacillin 12, 5-25 mg/kg 4x daily or trimethoprim-sulfamethoxazole 6 mg/kg 1-2x daily 3x/week -Bronchiectasis Azithromycin 10 mg/kg 1x daily 3x/week Chronic *Pseudomonas aeruginosa* colonization: inhaled tobramycin -Pneumatoceles *Aspergillus prophylaxis*: itraconazole 5 mg/kg 1x daily	Inactivated influenza vaccine Inactivated polio vaccine 13-valent conjugated, followed by 23-valent polysaccharide pneumococcal vaccine Tetravalent conjugate meningococcal plus monovalent serotype B vaccines *Haemophilus influenza* type B vaccine	BCG Viable influenza vaccine Oral polio vaccine Rotavirus vaccine MMR vaccine In children receiving immunoglobulin therapy (IVIg, SCIg), live viral vaccines are contraindicated for 3–11 months
DOCK8-hyper-IgE syndrome	-Sinopulmonary infections Trimetoprim-sulfamethoxazole 6 mg/kg 1-2x daily 3x/week or azithromycin 10 mg/kg 1x daily 3x/week -Recurrent viral infections Acyclovir	Inactivated influenza vaccine Inactivated polio vaccine HPV vaccine 13-valent conjugated, followed by 23-valent polysaccharide pneumococcal vaccine Tetravalent conjugate meningococcal plus monovalent serotype B vaccines *Haemophilus influenza* type B vaccine	BCG Viable influenza vaccine Oral polio vaccine Rotavirus vaccine MMR vaccine In children receiving immunoglobulin therapy (IVIg, SCIg), live viral vaccines are contraindicated for 3–11 months
PGM3-hyper-IgE syndrome	-Sinopulmonary infections Trimethoprim-sulfamethoxazole 6 mg/kg 1-2x daily 3x/week or azithromycin 10 mg/kg 1x daily 3x/week -Bronchiectasis Azithromycin 10 mg/kg 1x daily 3x/week Chronic *Pseudomonas aeruginosa* colonization: inhaled tobramycin	Inactivated influenza vaccine Inactivated polio vaccine 13-valent conjugated, followed by 23-valent polysaccharide pneumococcal vaccine Tetravalent conjugate meningococcal plus monovalent serotype B vaccines *Haemophilus influenza* type B vaccine	BCG Viable influenza vaccine Oral polio vaccine Rotavirus vaccine MMR vaccine In children receiving immunoglobulin therapy (IVIg, SCIg), live viral vaccines are contraindicated for 3–11 months

pediatric practice. To increase awareness in pediatricians regarding this group of immunodeficiencies in children, a comprehensive diagnostic approach and useful informative diagnostic tools are required. In an early comprehensive diagnosis of syndromes associated with PIDs, pediatrician's role by careful history and physical examination must be highlighted. This group of PIDs requires particular long-term systematic individualized multidisciplinary care of a pediatrician, primary physician, endocrinologist, neurologist, pulmonologist, and psychologist, under the supervision of a clinical immunologist.

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Author contributions

ASzP was responsible for the design and intellectual content of the review; coordinated and supervised data collection, and drafted the final manuscript. KB, MD, AD, DG, KWa, and KWr were responsible for data collection and drafted the initial manuscript. These six authors equally contributed to this work.

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