REVIEW

Educational paper

Syndromic forms of primary immunodeficiency

Rogier Kersseboom · Alice Brooks · Corry Weemaes

Abstract The syndromic primary immunodeficiencies are disorders in which not only the immune system but also other organ systems are affected. Other features most commonly involve the ectodermal, skeletal, nervous, and gastrointestinal systems. Key in identifying syndromic immunodeficiencies is the awareness that increased susceptibility to infections or immune dysregulation in a patient known to have other symptoms or special features may hint at an underlying genetic syndrome. Because the extraimmune clinical features can be highly variable, it is more difficult establishing the correct diagnosis. Nevertheless, correct diagnosis at an early age is important because of the possible treatment options. Therefore, diagnostic work-up is best performed in a center with extensive expertise in this field, having immunologists and clinical geneticists, as well as adequate support from a specialized laboratory at hand. This paper provides the general pediatrician with the main clinical features that are crucial for the recognition of these syndromes.

Keywords Syndromic immunodeficiency · Primary immunodeficiency · Genetics · DNA repair disorders · 22q11 deletion syndrome

Abbreviations

WAS	Wiskott–Aldrich syndrome
CHH	Cartilage–hair hypoplasia
NBS	Nijmegen breakage syndrome
A-T	Ataxia telangiectasia
ICF syndrome	Immunodeficiency centromeric instability and facial dysmorphisms syndrome
HIES	Hyper-IgE syndrome
DS	Down syndrome
syndromic PID	Syndromic primary immunodeficiencies
SCID	Severe combined immunodeficiency
BMT	Bone marrow transplantation
HSCT	Hematopoietic stem cell transplantation

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Introduction

The syndromic primary immunodeficiencies (syndromic PID) are disorders in which not only the immune system but also other organ systems are affected. In contrast to other primary immunodeficiencies, more often features other than the immune-defect are the presenting symptoms. Nevertheless, patients with syndromic PID may present with recurrent infections as well. In many malformation and/or mental retardation syndromes, increased rates of infections are assumed to result mainly from anatomical problems, failing physiological mechanisms, and institutionalization. In contrast, syndromic PID have an intrinsic abnormality of the immune system that increases susceptibility to infections. Within the IUIS classification system, syndromic PID are mainly found in the category of "other well defined immunodeficiency syndromes" but are present in many other categories as well [54]. We advocate using the name "syndromic PID" because it lays more emphasis on the extraimmune phenotype, which, in fact, can be prominent.

Syndromic PID can be caused by single gene disorders, metabolic aberrations, and chromosomal abnormalities, and

for some, the genetic basis has not yet been unraveled. In general, the genetic defects in syndromic PID impact on important cellular processes thereby affecting multiple cell lines and organ systems. In DNA repair disorders (ataxia telangiectasia, Bloom syndrome, and Nijmegen breakage syndrome), all cells are affected resulting in severe growth retardation, neurological disease in some, increased susceptibility to malignancy, and predisposition to infections. Immunodeficiency likely results from aberrant DNA repair in lymphocytes during the somatic recombination events, such as V(D)J recombination (the process of antigen receptor diversification by combining different gene segments) and class switch recombination (the process of immunoglobulin isotype switching) that are necessary to generate the enormous range of specificities of antigen receptors [79]. In other syndromic PID such as hyper-IgE syndrome, Wiskott–Aldrich syndrome or hypohidrotic ectodermal dysplasia with immune-deficiency, signaling molecules are affected that transmit signals from a variety of receptors in different cell types thereby resulting in features in several organ systems.

This paper provides the general pediatrician with the main clinical features that are crucial for the recognition of syndromic PID [49]. In addition, a short overview of current diagnostic and therapeutic options is given. In Table 1, an overview is provided that helps making a differential diagnosis starting from several lead symptoms such as, e.g., facial dysmorphisms, growth failure, and skin problems. For the general diagnostic approach, readers are referred to the first paper in this educational series (de Vries and Driessen).

Ataxia telangiectasia

Ataxia telangiectasia (A-T; OMIM 208900) is an autosomal recessive disorder caused by mutations in the *ATM*-gene, a protein kinase that is involved in DNA repair [66]. Clinical features are progressive cerebellar ataxia, oculocutaneous telangiectasias, immunodeficiency, and increased susceptibility to malignancies, particularly lymphomas and leukemias [70]. Ataxia develops shortly after learning to walk and begins as truncal ataxia but, within several years, involves peripheral coordination as well. Neurological disturbances also include extrapyramidal symptoms (Fig. 1a-1). From about 10 years on, most children become wheelchair-bound for the remainder of their lives. The hallmark feature of A-T "oculocutaneous telangiectasias" usually appears at about 4 to 6 years of age (Fig. 1a-2).

Most patients suffer from recurrent respiratory infections. Systemic bacterial, severe viral, and opportunistic infections are uncommon in A-T. In patients with classical A-T, both humoral and cellular immunity are disturbed with IgA, IgG2, and IgG4 deficiency as most common manifestations [55]. However, 10% of A-T patients present with decreased serum IgG and IgA with normal or raised IgM levels, resulting in more severe infections, thus showing a phenotype reminiscent of hyper-IgM syndrome [52]. Antibody responses to tetanus and diphtheria toxoid show protective levels, but the majority has a specific polysaccharide antibody deficiency. T cells have been found to be decreased in a considerable fraction of patients, with a specific reduction in the numbers of naïve CD4+ cells (CD4+CD45RA+ cells) and naïve CD8+ cells (CD8+CD45RA+ cells). NK cell numbers are elevated [67].

In recent years, it was recognized that some patients present with a milder form of A-T, atypical A-T. Although affected patients had extrapyramidal symptoms (even in childhood), ataxia was less severe or even absent and patients were not wheelchair-bound and had normal immunoglobulins [73, 82]. Whereas classical A-T is characterized by loss of function, atypical A-T cases typically have some residual ATM kinase activity left.

Diagnosis of A-T can be suspected from the combination of clinical features, a slight increase in blood α-fetoprotein in the majority of patients and from typical cytogenetic aberrations. Standard karyotyping of peripheral blood lymphocytes can be difficult because lymphocytes are less responsive to mitogenic stimuli resulting in few metaphases. When successful, a 7;14 translocation can be found in 5–15% of lymphocytes. More commonly, a radiosensitivity assay of lymphoblasts or fibroblasts is used to confirm A-T.

> In all patients with classical Ataxia teleangiectasia, teleangiectasias are absent in the first years of life. Ataxia develops shortly after learning to walk.

Nijmegen breakage syndrome

Nijmegen breakage syndrome (NBS; OMIM 251260) is a rare autosomal recessive disorder first described in 1981 by Weemaes et al. in two brothers with microcephaly, small stature, facial dysmorphisms, and immunodeficiency [83]. NBS is more common in Eastern European and Slavic populations due to a relatively high carrier frequency. In 1998, the gene causing NBS was discovered, and it was shown that mutations in the *NBS1*-gene resulted in loss of NBS1 and deficient DNA repair [81].

Table 1 Considerations on the differential diagnosis in patients presenting with:

Disease	T cells	B cells	Serum Ig	Associated features	Molecular defect
MICROCEPHALY					
DNA ligase IV deficiency	↓	↓	↓	Growth retardation, dysmorphisms, radiation sensitivity	*DNA ligase IV*
Cernunnos deficiency	↓	↓	↓	*Intrauterine and postnatal* growth retardation, radiation sensitivity	*Cernunnos*
Nijmegen breakage syndrome	↓	N ↓	Often IgA↓ IgG2 ↓	Bird-like face, radiation sensitivity	*NBS1 (NBN)*
Rad 50 deficiency	N	N		Radiation sensitivity	*RAD50*
Bloom syndrome	N	N	reduced	*Intrauterine and postnatal* growth retardation, sun-sensitive erythema, short stature	*recQ-like helicase BLM*
Hoyeraal–Hreidarsson syndrome	N ↓	N ↓	variable	Cerebellar hypoplasia, *intrauterine* growth retardation, pancytopenia	*DKC1*
GROWTH DEFECT					
Dysproportional					
Cartilage–hair hypoplasia	↓	N	normal or reduced	Short-limbed dwarfism, sparse hair	*MRMP*
Schwachman-Diamond syndrome	N	N	normal	Pancytopenia, exocrine pancreatic insufficiency	*SBDS*
Proportional					
Bloom syndrome	N	N	reduced	*Intrauterine and postnatal* growth retardation, sun-sensitive erythema, short stature	*recQ-like helicase BLM*
Nijmegen breakage syndrome	↓	N ↓	Often IgA↓ IgG2 ↓	Bird-like face, radiation sensitivity	*NBS1 (NBN)*
Cernunnos	↓	↓	↓	*Intrauterine and postnatal* growth retardation, radiation sensitivity	*Cernunnos*
FACIAL DYSMORPHISMS					
ICF syndrome	N ↓	N ↓	Hypogammaglobulinemia	Centromeric instability, infections	*DNMT3B/?*
Bird-like face					
Nijmegen breakage syndrome	↓	N ↓	Often IgA↓ IgG2 ↓	Bird-like face, radiation sensitivity	*NBS1 (NBN)*
Cernunnos	↓	↓	↓	*Intrauterine and postnatal* growth retardation, radiation sensitivity	*Cernunnos*
Ligase IV deficiency	↓	↓	↓	Growth retardation, dysmorphisms, radiation sensitivity	*DNA ligase IV*
Down syndrome (e.g. trisomy 21)	N	N	N-reduced	Dysmorphisms	Chromosomal disorder
22q11 Deletion	↓	N	N-reduced	Conotruncal malformation, velopharyngeal insufficiency	Chromosomal disorder
Hyper-IgE syndrome AD	Th17 ↓	N	IgE ↑	Distinctive facial features, fractures, scoliosis, retained primary dentition	*STAT3*
Hyper-IgE syndrome AR	Th17 N-↓	N	IgE ↑	Some have distinctive facial features, susceptibility to viral infections and mycobacterial infections	*DOCK8, TYK2*
SKIN DISORDERS					
Omenn syndrome	restricted	N ↓	Decreased, IgE ↑	Erythroderma, SCID	*RAG1/2, Artemis, ADA, unknown.*
Atopic Dermatitis					
Wiskott–Aldrich Syndrome	N ↓	N	IgM ↓, IgA↑, IgE ↑	Microthrombocytopenia	*WAS*
Hyper-IgE syndrome AD	Th17 ↓	N	IgE ↑	Distinctive facial features, fractures, scoliosis, retained primary dentition	*STAT3*

Table 1 (continued)

Disease	T cells	B cells	Serum Ig	Associated features	Molecular defect
Hyper-IgE syndrome AR	Th17 N -↓	N	IgE ↑	Some have distinctive facial features, susceptibility to viral infections and mycobacterial infections	*DOCK8, TYK2*
STAT5b deficiency	↓	N	Normal	Growth hormone insensitive dwarfism	*STAT5b*
Comél-Netherton syndrome	N	↓	IgE↑ IgA↑ antibodies ↓	Congenital ichthyosiform erythroderma, trichorrhexis invaginata, and an atopic diathesis	*SPINK5*
Anhydrotic ectodermal dysplasia					
NEMO	N-↑		60% IgG ↓, sometimes hyper-IgM	May have distinctive facial features, conical incisors, hypohydrosis	*NEMO*
IκBα deficiency	Naïve T cells ↑		IgM ↑↑ IgG ↓	Conical teeth	*IκBα*
Ca^{2+} channel deficiency	N	N-↑	N-↑	Severe immunodeficiency, muscular hypotonia, severely impaired T cell function	*STIM-1, ORAI-1*
Chronic mucocutaneous Candidiasis	N	N	Normal	Defect in Th17 cells	*CARD9, Dectin-1*
Hypopigmentation					
Chediak Higashi	N	N	Normal	Low NK cells, partial albinism, encephalopathy	*LYST*
Griscelli Syndrome	N	N	Normal	Partial albinism, encephalopathy in some	*RAB27A*
Warts					
WHIM		↓	Hypogammaglobulinemia		*CXCR4*
ATAXIA					
Ataxia telangiectasia	↓	N-↓	Often IgA↓ IgG2 ↓	Ocular telangiectasia, radiation sensitivity	*ATM*
Ataxia telangiectasia like disease	↓	N		Radiation sensitivity	*MRE11*

Characteristic clinical features include microcephaly, growth retardation, bird-like facial features, combined immunodeficiency, and a strong predisposition for lymphoid malignancies (Fig. 1b) [32, 83]. All patients have microcephaly and short stature, their body length being below the 10th centile in all cases. In about 75%, microcephaly is already present at birth. The facial appearance is characterized by a receding forehead, prominent midface with long nose and long philtrum, receding mandible, upward slanting of palpebral fissures, epicanthic folds, large ears with dysplastic helices, and sparse hair. The distinctive facial features may not be present before the age of 3 years. Commonly clinodactyly and/or syndactyly may be found. In almost all patients, skin pigmentary changes can be observed. Although mental development was normal in 22 out of 55 patients (40%), about 28 out of 55 patients (50%) had borderline to mild retardation, while five out of 55 patients (10%) were moderately mentally retarded [32]. In a minority of cases, congenital malformations are found. Predisposition to lymphoid malignancy is strong.

Patients suffer from repeated infections, most frequently recurrent airway and ENT infections followed by recurrent urinary tract infections [32]. Commonly, IgG and IgA deficiency is found and less frequently IgA deficiency is accompanied by IgG2 and/or IgG4 deficiency, while IgM deficiency is rare [32]. Often, the percentage of T cells is decreased, due to low numbers of CD4+ T cells. Especially naïve CD4+ cells (CD4+CD45RA+ cells) have been shown to be reduced. The frequency of CD8+ cells usually does not appear to be affected [32, 46]. NK cells are normally present. In vitro responses of lymphocytes to mitogenic stimuli such as phytohemagglutinin (PHA) are decreased in most patients.

Diagnosis can be suspected from standard karyotyping of peripheral blood lymphocytes, revealing inversions and translocations involving chromosomes 7 and 14 in 10–50% of metaphases. Furthermore, radiosensitivity of fibroblasts or lymphocytes may be increased.
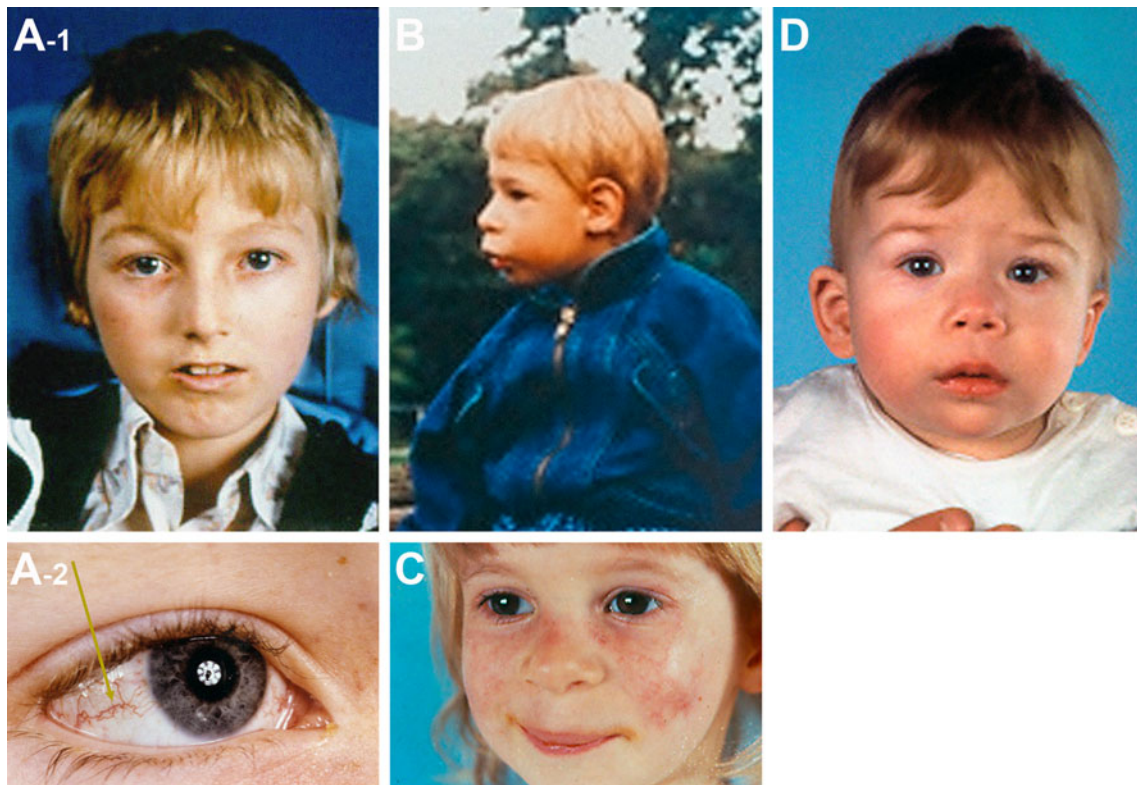
Fig. 1 Photographs highlighting several important clinical features from four classical syndromic PID, which can be diagnosed by cytogenetic studies. (**a**-*1*, **a**-*2*) Ataxia telangiectasia: note the conjunctival telangiectasias and the rather expressionless facies; (**b**) Nijmegen breakage syndrome: note the microcephaly, the prominent midface with long nose and long philtrum, receding mandible, large ears, and sparse hair; (**c**) Bloom syndrome: note the butterfly rash on the cheeks; (**d**) ICF syndrome: note the epicanthic folds, flat broad nasal bridge with ocular hypertelorism, and low-set ears

Of note, microcephaly and radiosensitivity have also been found in some other syndromic immunodeficiencies such as Cernunnos/XLF and Ligase IV deficiency. Patients with Cernunnos/XLF deficiency (OMIM 611291) have growth retardation, microcephaly, dysmorphic features, and urogenital malformations. Their immunodeficiency is characterized by mild-to-severe B and T cell lymphopenia, whereas NK cells are unaffected [6]. Patients with Ligase IV deficiency (OMIM 606593) are characterized by microcephaly, growth retardation, a bird-like face, pancytopenia, and may have a severe combined immunodeficiency (SCID) phenotype as well [56, 78].

Prenatal onset of growth deficiency and microcephaly, and increased susceptibility to infections may point at DNA repair disorders such as Nijmegen breakage syndrome and Bloom syndrome.

Bloom syndrome

Bloom syndrome (OMIM 210900) is an autosomal recessive disorder caused by inactivating mutations in the *Blm*-gene, a RecQ-helicase involved in DNA repair [19]. Although Bloom syndrome is very rare, it is found more frequently in Ashkenazi Jewish populations. Patients present with severe prenatal and postnatal growth retardation, microcephaly, and sun-sensitive erythematous lesions (SLE-like butterfly rash) that are mostly found on sun-exposed regions of the face (Fig. 1c) [24]. In infancy, vomiting and diarrhea are common problems. Importantly, Bloom syndrome patients have a significantly increased risk for one or multiple malignancies. The tumor types and sites involved resemble that in the general population, although onset is much earlier. In the first two decades of life, predominantly, leukemia and non-Hodgkin's lymphoma are found. Later in life, epithelial cancers from the colon and upper respiratory tract occur more frequently.

Immunodeficiency is highly variable and usually not severe, although most patients experience recurrent airway

and ENT infections. Left untreated, this can result in bronchiectasis. Immunoglobulin levels (especially IgM) are decreased in most patients. T, B, and NK cells are present in normal numbers, but in vitro responses of lymphocytes to mitogens can be decreased [84].

Diagnosis can be suspected from standard karyotyping showing quadriradial configurations and increased numbers of spontaneous chromatid breaks and gaps. A very specific confirmatory cytogenetic test evaluates the number of sister chromatid exchanges per metaphase, which is highly increased in Bloom syndrome patients.

> Classic cytogenetic tests such as standard karyotyping of mitogen stimulated lymphocytes and evaluation of the frequency of sister chromatid exchanges can be very helpful in diagnosing Ataxia telangiectasia, Nijmegen breakage syndrome, Bloom syndrome and ICF syndrome.

ICF syndrome

Immunodeficiency, centromeric instability, and facial dysmorphisms syndrome (ICF-syndrome; OMIM 242860) is an autosomal recessive disease characterized by facial dysmorphisms, immunodeficiency, and branching of chromosomes 1, 9, and 16 after PHA stimulation of lymphocytes [42]. In about half of the patients, mutations in the *DNMT3B*-gene, a gene involved in DNA methylation, can be found [29, 30, 88]. Facial dysmorphism, including epicanthic folds, hypertelorism, flat nasal bridge, and low-set ears, are very frequent findings (Fig. 1d) [29]. Malignancies have been described infrequently [68].

Recurrent airway and ENT infections are very common, but opportunistic infections were described in several patients as well. Although hypogammaglobulinemia up to agammaglobulinemia have been shown to be present in nearly all patients, B and T cell numbers and subpopulations are generally normal.

Diagnosis can be confirmed by standard karyotyping of mitogen-stimulated lymphocytes revealing formation of multiradiate chromosomes 1, 9, and 16.

Life expectancy is poor, especially in patients with severe infections in infancy or chronic gastrointestinal problems and failure to thrive. Allogeneic stem cell transplantation has been successfully employed although long-term results are not yet available [23].

Wiskott–Aldrich syndrome

Wiskott–Aldrich syndrome (WAS; OMIM 301000) is a rare X-linked recessive condition that was first recognized in 1937 by Alfred Wiskott, a German pediatrician, who described a family with three boys suffering from the "classical triad" microthrombocytopenia, recurrent infections, and atopic eczema [57]. WAS is caused by mutations in the WAS-gene which is located on Xp11.22. Although only males present with the full spectrum of Wiskott–Aldrich syndrome, incidentally, females with mild microthrombocytopenia have been reported caused by skewed X-inactivation [3, 53]. WAS includes a spectrum of disorders including classical WAS, X-linked thrombocytopenia (XLT), intermittent XLT, and X-linked congenital neutropenia.

During the first years of life, the main health problem in classical WAS is thrombocytopenia, resulting in intermittent mucosal bleeding, bloody diarrhea, and intermittent or chronic petechiae and purpura [74]. Microthrombocytopenia is mostly congenital and life-threatening bleeding can be precipitated by serious infections. About 80% of classical WAS patients also have mild-to-severe eczema (Fig. 2a). In addition, in classical WAS, infections are often severe with susceptibility to bacterial, viral (VZV and HSV), and even opportunistic organisms (*Pneumocystis jiroveci*). At least 40% of those who survive the early complications develop one or more autoimmune conditions such as autoimmune hemolytic anemia, vasculitis, neutropenia, arthritis, renal disease, and inflammatory bowel disease [16, 69, 74]. Importantly, individuals with WAS have a 13% risk of developing lymphomas especially when autoimmune disease is present [74]. Although patients with XLT do have microthrombocytopenia, eczema and immune dysfunction are mild in comparison to classical WAS.

In patients with classical WAS, both humoral and cellular immunity are disturbed with lymphocyte numbers decreasing over time, resulting in mild-to-more-severe lymphopenia [57, 76]. IgM is mostly decreased, whereas IgG remains generally within normal limits. In contrast, IgA and IgE can be elevated. Furthermore, serological responses to polysaccharide antigens are markedly depressed, indicative of a specific polysaccharide antibody deficiency.

Although WAS can be readily recognized on the basis of the clinical triad this constellation is present in only 25% of patients with classical WAS at diagnosis [74]. As microthrombocytopenia with increased bleeding tendency is the most common symptom of WAS, WAS should be considered in each such case. Diagnosis can be confirmed by a combination of an assay capable of detecting WASP protein and genetic testing. Differential diagnosis includes Omenn syndrome and hyper-IgE syndrome, which may also present
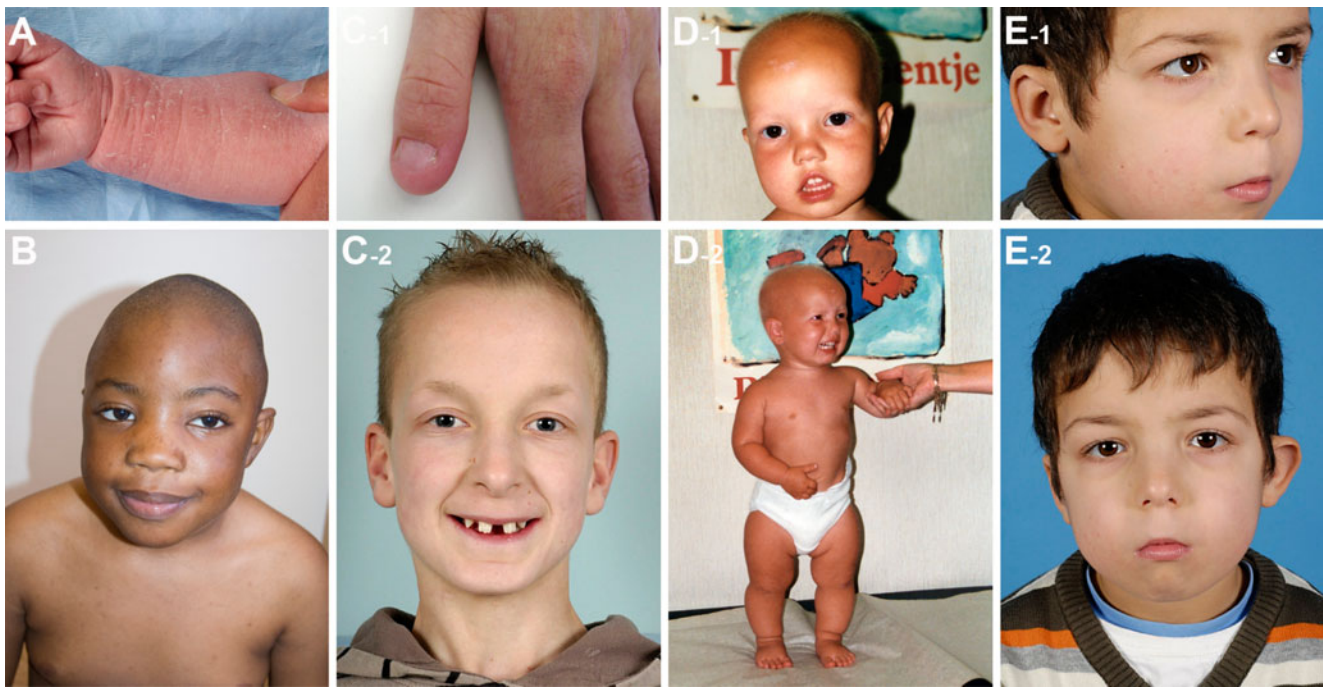
Fig. 2 Dysmorphic features in other syndromic PID. (a) Wiskott–Aldrich syndrome: note the dry skin with eczema; (b) hyper-IgE syndrome: note the broad nasal bridge, wide fleshy nasal tip, and mild prognathism; (c-1, c-2) Hypo-/anhidrotic ectodermal dysplasia with immunodeficiency: note the high square forehead and ectodermal dysplasia with dry skin, nail dysplasia, and conical wide spaced teeth;

(d-1, d-2) Cartilage–hair hypoplasia: note the disproportional short stature associated with fine and sparse hair; (e-1, e-2) 22q11.2 deletion syndrome: note the mild hypertelorism, downslanting of palpebral fissures, hooded eyelids, hypoplasia of the alae nasi, prominent nose with squared nasal root and narrow alar base, and small square low-set ears

with eczema and severe infections but are not accompanied by microthrombocytopenia.

> Microthrombocytopenia is the most distinctive feature of Wiskott-Aldrich syndrome, whereas the classical triad including microthrombocytopenia, recurrent infections and atopic eczema is present in only one fourth of patients.

Hyper-IgE syndrome

The hyper-IgE syndrome (HIES) was first described in 1966 by Davis and Wedgwood, which named it the "Job syndrome", after the biblical figure Job who was covered with sore boils [13]. The classical description of HIES is a triad of: (a) recurrent staphylococcal skin abscesses without typical features of inflammation called "cold abscesses", (b) recurrent pneumonia with pneumatocele formation, and (c) highly elevated levels of serum IgE. More recently, the genetic basis was unraveled showing genetic heterogeneity with both autosomal dominant (AD) and autosomal recessive (AR) forms of HIES. AD HIES is caused by dominant negative variants in the *STAT3*-gene (OMIM 147060) [34, 48]. AR HIES has been shown to be caused by mutations causing loss of tyrosine kinase 2 (*TYK2*) (OMIM 611521) or dedicator Of cytokinesis 8 (*DOCK8*) (OMIM 243700). Most reported cases of AR HIES were due to *DOCK8* loss explaining 16 out of 20 families that were described [20], while *TYK2* loss has been described only twice worldwide [20, 47, 86].

AD HIES is characterized by typical dysmorphic features such as facial asymmetry, prominent forehead, deep-set eyes, broad nasal bridge, wide fleshy nasal tip, high-arched palate, and mild prognathism that become apparent in late puberty (Fig. 2b) [26]. Furthermore, patients may manifest skeletal abnormalities including failure or delay of shedding primary teeth, pathologic fractures, and scoliosis [26]. Patients may present with early-onset atopic dermatitis-like eczema, which is resistant to treatment. Immunologically, AD HIES is characterized by high serum IgE levels, eosinophilia, chronic mucocutaneous candidiasis, and severe recurrent airway and ENT infections with *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influen-*

zae, and occasionally, *Aspergillus*. Pneumatoceles develop in approximately 75% of patients.

Features such as dysmorphisms and skeletal problems are variably associated with AR HIES, while pneumatocele formation was infrequently seen in patients with *DOCK8*- or *TYK2*-mutations [20]. Furthermore, patients may suffer from asthma, allergies, central nervous system symptoms, and autoimmune phenomena. In addition to the immunological features that are found in AD HIES, patients with AR HIES demonstrate unusual susceptibility to various viruses resulting in recurrent serious molluscum contagiosum and herpes simplex infections, while patients with TYK2-associated HIES also demonstrated increased susceptibility to mycobacteria [20, 47, 90].

Importantly, AD HIES and a significant subgroup of AR HIES (DOCK8) have been associated with early-onset squamous-cell carcinoma and lymphoma in some patients.

Although it is clear that immune-defects underlie the HIES phenotype, no straightforward simple quantitative changes in B and T cell numbers and immunoglobulin levels have been described, besides high levels of IgE and eosinophilia to distinguish HIES from other diseases. However, in early childhood, normal IgE levels cannot definitely rule out HIES as these may increase at a later age as well. In older patients, IgE levels may become normal again [26].

HIES can be suspected from the typical clinical picture and diagnosis can be confirmed by mutational screening of STAT3, TYK2, or DOCK8. Clinical suspicion can be increased by following the NIH scoring system, which especially helps identifying patients with *STAT3*-associated HIES [27, 87]. Interestingly, a recent study showed that 25 patients with a clinical diagnoses of HIES (including patients with AD HIES and AR HIES), all had impaired T_H17 responses, suggesting that this test may be used as a first confirmation of a clinical suspicion of HIES [1]. As such, it is now incorporated into the NIH scoring system [87]. Differential diagnosis with severe atopic dermatitis can be difficult in the first years of life, even more because high levels of serum IgE (up to ~25.000 U/ml) may be present. WAS, characterized by severe intractable eczema of neonatal onset, can be differentiated by testing for microthrombocytopenia.

> Normal IgE levels cannot definitely rule out HIES.

> One should include Hyper-IgE syndrome, but also parasitic infections and atopic dermatitis in the differential diagnosis of high IgE levels.

Hypo-/anhidrotic ectodermal dysplasia with immune-deficiency

Hypo-/anhidrotic ectodermal dysplasia with immune-deficiency (HED-ID; OMIM 300291) is characterized by diminished or absent sweat glands, thin and sparse hair, conical incisors, nail dysplasia, hypodontia, and immunodeficiency (Fig. 2c-1 and 2c-2). Most cases of HED-ID are caused by hypomorphic mutations in the *NEMO*-gene [nuclear factor κB (NF–κB) essential modulator], which is located on the X-chromosome [14]. As the disease follows an X-linked recessive inheritance pattern, mostly males are affected, although affected females have been described. More severe mutations in *NEMO* result in incontinentia pigmenti, an ectodermal dysplasia without immunodeficiency that presents exclusively in females. Hypermorphic mutations in *IκBα* causes an autosomal dominant type of HED-ID and has been reported twice [11, 35]. HED-ID is one of the many different ectodermal dysplasias encompassing more than 200 conditions involving a combination of disorders of hair, nails, teeth, and sweat glands. Some children with HED-ID manifest a more severe phenotype with osteopetrosis and lymphedema (OL-EDA-ID; OMIM 300301).

From early childhood on, affected patients may suffer from unusually severe, life-threatening, and recurrent bacterial infections of the lower respiratory tract, skin, soft tissues, bones, digestive tract, leading to bronchiectasis, chronic lung disease, intractable diarrhea, and failure to thrive. The commonly implicated pathogens are *S. pneumoniae*, *S. aureus*, *Pseudomonas*, *H. influenzae*, and mycobacteria, but pathogens such as *P. jiroveci* and *Candida* (causing opportunistic infections) have been described as well [7, 31]. Also, increased susceptibility to HSV may predispose to HSV encephalitis [50]. Severity and spectrum of features may vary strongly. More recently, cases of HED-ID have been described with few ectodermal features but increased susceptibility to infections [50, 58].

Immunologically, it can be difficult to suspect HED-ID from routine immunological assessment as findings are generally non-specific. T and B cell numbers are mostly normal but can be increased (especially naïve CD4+ CD45RA+ T cells) [31, 35]. In addition, immunoglobulin levels may vary. However, in a retrospective study, 24 out of 41 (59%) of HED-ID patients had hypogammaglobulinemia. Some of the latter group also had increased IgM levels and thus demonstrated a phenotype reminiscent of hyper-IgM syndrome. Other possibly distinctive features were a specific polysaccharide antibody deficiency (in 13 out of 16 patients), a specific antibody response defect (in 18 out of 28 patients) and an elevated IgA level (in 13 out 35 patients) [31]. More specific in vitro tests evaluating NF–κB activation after specific stimuli such as TNFα and anti-CD40 may prove useful in the future.

Diagnosis is primarily based on the combination of clinical features, including infectious problems and ectodermal dysplasia, and can be confirmed by molecular genetic testing of *NEMO* or *IκBα*. As the clinical picture may be highly variable from typical patients to patients without ectodermal dysplasia with recurrent pneumococcal infections, setting the right diagnosis can be very difficult. Differential diagnosis includes several ectodermal dysplasias (OMIM 612782 and 612783) [22], hyper-IgM syndrome, and milder forms of SCID.

Cartilage–hair hypoplasia

Cartilage–hair hypoplasia (CHH; OMIM 250250), also known as metaphyseal chrondodysplasia McKusick type, is a rare autosomal recessive short-limb dwarfism syndrome associated with fine and sparse hair, defective cellular immunity, and predisposition to several cancers (e.g., non-Hodgkin's lymphoma and basal cell carcinoma; Fig. 2d-1 and 2d-2) [75]. The syndrome is caused by mutations in the *RMRP*-gene [62]. Incidence is higher in genetic isolates such as in Finland and in the old-order Amish communities in the USA [63]. The radiologic features include metaphyseal dysplasia with shortened tubular bones, bowed femora with rounded distal epiphyses, disproportionally long fibula, and cone-shaped epiphyses of the hand. Severity is variable, and radiographic changes are often inconspicuous in the first few years, although often, growth failure and sparse hair can be seen [36]. Other less frequent clinical features include defective erythropoiesis, bone marrow aplasia, and Hirschsprung disease [80, 85].

Defective immunity is a major feature in CHH. An increased tendency to infections (mainly bacterial pneumonias) is present in 40–50%, predominantly in the first 2 years of life [64]. Early studies described CHH patients who suffered from fatal complications of varicella [39]. In some, severe autoimmune features have been described including autoimmune hemolytic anemia and autoimmune enteropathy [5]. Morbidity and mortality are both directly the consequence of immune dysfunction [41].

In CHH, usually, only cellular immunity is involved, but sporadically, both cellular and humoral immunity show defects. One third of the patients show lymphopenia, and over 80% show abnormal lymphocyte proliferation upon stimulation with mitogens. IgA and/or IgG subclass deficiency is present in more than one third of CHH patients [40].

In view of possible deficient immunity, it is recommended that all affected CHH patients are carefully monitored for signs of increased susceptibility to infections during the first 2 years of life. Several studies suggest that many individuals with CHH can safely receive live vaccines, although these should be avoided in CHH patients who clearly have SCID [64].

> As metaphyseal abnormalities on radiographs may be absent in infancy, Cartilage-Hair Hypoplasia should be considered in all patients with a small stature and unexplained lymphopenia.

22q11.2 deletion syndrome/Shprintzen syndrome/DiGeorge syndrome

The 22q11.2 deletion syndrome (OMIM 192430), the most common human deletion syndrome, is characterized by a plethora of clinical features [65]. *TBX1*, one of the genes located in the deleted region, is considered to be the major gene involved. DiGeorge syndrome (historically referring to patients with heart, thymus, and parathyroid gland abnormalities) and Shprintzen syndrome/Velo-Cardio-Facial syndrome (characterized by cleft palate or velopharyngeal insufficiency, congenital heart malformations, and a typical facial Gestalt) not only share clinical features but also a common deletion. For this reason, "22q11 deletion syndrome" is the preferred nomenclature to describe these clinical entities associated with this deletion. Conotruncal heart malformations (50–80%), such as tetralogy of Fallot or interruption of the aortic arch form the most common group of congenital malformations. The face is typically characterized by hooded eyelids, a bulbous nasal tip with hypoplastic alae nasi and small ears (Fig. 1i, j) [65]. Psychomotor development is often delayed, and an increased incidence of psychosis is reported [25].

Recurrent ENT infections are the most common immunological feature. A fraction of 22q11 patients also develop autoimmune diseases such as juvenile rheumatoid arthritis and hematologic autoimmune disease [12, 15]. Although infectious problems are mild to moderate in the majority of patients, an estimated 80% of 22q.11.2 deletion patients have low T cells. Remarkably, there is a slower decrease of T cells compared with age-related control individuals [43]. In addition to T cell abnormalities, IgA deficiency [71], impaired responses to vaccines, and frank hypogammaglobulinemia have been described. Subtle defects in the B cell compartment such as decreased proportions of memory B cells have also been reported [43]. Only 1% of patients lack T cells due to aplasia of the thymus, which has classically been described as DiGeorge syndrome. This specific subset of patients is at risk for serious infections and requires irradiated blood products to prevent graft versus host disease.

Therefore, at diagnosis T cell characterization and evaluation of serum immunoglobulin levels is recommended.

> The immune status should be checked in infants with 22q11.2 deletion syndrome before administering blood products, in order to determine if irradiation of the blood is indicated.

Down syndrome

Down syndrome is the most common chromosomal disorder and is commonly caused by trisomy 21. It is generally thought that changes in expression levels of multiple genes on chromosome 21 and secondary on other chromosomes are causative of the phenotype ("the gene dosage hypothesis"). Studies in patients with partial trisomy have pointed at certain regions on chromosome 21 for disorders such as leukemia and congenital heart disease, but have not yet shown linkage to a particular region with respect to increased susceptibility to infections [37]. More likely, subtle differences in expression of multiple genes are involved, affecting a variety of cell types thereby resulting in immune imbalance [60, 72].

Infections of especially the lower respiratory tract contribute significantly to morbidity and mortality in patients with Down syndrome [89]. Also, upper respiratory tract infections are more common than in children without trisomy 21 [33]. Specifically, it was recently shown that Down syndrome is an independent risk factor for severe lower respiratory tract infections with respiratory syncytial virus with an OR of 12,6 [4, 44]. To what extent an underlying immunological defect is causative remains a matter of discussion, as multiple other causes may influence infection rate as well (e.g., more frequent institutionalization, aspiration). Several differences in B, T, and NK cell numbers have been reported in children with Down syndrome as well as changes in immunoglobulin levels and granulocyte function, which have not been consistent and mostly cannot be interpreted simply as a cause of immunodeficiency [8, 9, 38, 45, 61, 77]. As such, most findings in routine immunological screening, at the moment, do not contribute to identifying those children at risk for recurrent infections and do not provide a therapeutic value. An interesting exception to this was the recent observation that MBL deficiency increases susceptibility to respiratory tract infections in Down syndrome patients, which may be used to identify patients at risk for infectious disease such as RSV [51].

> Down syndrome patients may be at increased risk for recurrent infections, careful follow-up should identify those patients in need of supportive measures.

Discussion

In this report, we provided an overview of some of the most important syndromic immunodeficiencies. Key in identifying syndromic immunodeficiencies is the awareness that increased susceptibility to infections or immune dysregulation in a patient known to have other pathology may hint at an underlying genetic syndrome. Other organ systems frequently found to be involved are the ectodermal, skeletal, nervous, and gastrointestinal systems. Clinical features not directly associated with the immune defect may be prominent and be the first presentation. For this, Table 1 is providing a differential diagnosis on the basis of several key features. On the other hand, syndromic immunodeficiencies may present with serious infections as well, with extraimmune symptoms arising at a later time point.

Clinical presentation and coming to a diagnosis Microcephaly with recurrent infections may point at one of the several DNA repair or DNA maintenance disorders. Small stature and intrauterine growth retardation may be important clues to the correct diagnosis because disorders such as Cernunnos deficiency, Bloom syndrome, and Hoyeraal Hreidarsson syndrome frequently have proportional growth retardation, which is already present at birth. Severe difficulty to treat "eczema" and microthrombocytopenia in a male makes the diagnosis of WAS almost certain. Patients with chromosomal aberrations such as 22q11 deletion syndrome most likely present with other features such as facial dysmorphisms, cardiac defects, or velopharyngeal insufficiency because the immune-defect is mostly mild. Thorough examination of the mucocutaneous surface for atopic dermatitis, ectodermal dysplasia, candidiasis, hypopigmentation, or warts may be very helpful in delineating the specific syndrome.

Opportunistic infections with cryptococcal or invasive fungal infections, are rarely seen in most syndromic immunodeficiencies but may be present in WAS, ICF syndrome, Hoyeraal–Hreidarsson syndrome, HED-ID, HIES, and Cartilage–hair hypoplasia. In A-T and NBS, opportunistic infections have never been described. In Chediak–Higashi syndrome and Griscelli syndrome severe immune dysregulation such as hemophagocytic

lymphohistiocytosis has been reported to occur more frequently.

An increased risk for malignancy has been reported in multiple syndromic immunodeficiencies. In DNA repair disorders like A-T, NBS, and Bloom syndrome there is a high risk for malignancy, and patients are mostly at risk for leukemias, lymphomas, and solid tumors later in life. Treatment may be difficult, because conventional radiation dosages are dangerous, radiomimetic drugs may have to be avoided and other cytostatics have to be used at reduced dosages. Therefore, patients need a specific therapeutic approach. Also in WAS, CHH, and HIES, there is an increased risk for malignancies (mainly lymphomas), which warrants careful follow-up irrespective of the immunological status and extending beyond pediatric age.

Early diagnosis is essential for adequate treatment and follow-up Because of the complex pathology in many of these syndromes, follow-up in a multidisciplinary team is warranted. In general, immunological surveillance is the same as in other primary immunodeficiencies (see the first paper in this educational series by de Vries et al.). Inactivated vaccines can be administered without problem, but care should be taken with administering live-attenuated vaccines. Patients at risk for opportunistic or other infections may be treated with prophylactic antimicrobial agents. For more severe humoral immunodeficiency, immunoglobulin substitution is indicated. As some of the immunodeficiency syndromes have a poor prognosis due to a severe course of the disease, conservative treatment with supporting measures may not be sufficient. For several diseases such as HED-ID, severe WAS, and CHH, bone marrow transplantation has been employed with great success [5, 10, 17, 57, 59].

Bone marrow transplantation has improved prospects for many patients with a syndromic PID For WAS boys who received BMT from a matched healthy sibling or closely matched unrelated donor before the age of 5 years had a greater than 85% probability of being cured [57]. In a recent European collaborative survey, 16 patients with CHH and immunodeficiency underwent HSCT, mostly at a young age [5]. Overall survival was 62,5%, and surviving patients had good reconstitution of the immune system with autoimmunity resolved post-transplantation. Analogous to other patient groups, the outcome with matched-related donors was significantly better than haploidentical bone marrow transplantation. In Cernunnos/XLF deficiency, Ligase IV deficiency, Hoyeraal–Hreidarsson syndrome, ICF syndrome, and NBS, successful bone marrow transplantation has been reported, but long-term studies are not yet available [2, 18, 21, 28]. One of the remaining hopes is that BMT may also decrease the risk for malignancy. As bone marrow transplantation can have severe side effects, the decision to

transplant is strongly dependent on the type of disorder, long-term prognosis, severity in which the patient is affected, age of the patient, and availability of an adequate donor.

Genetic counseling is appropriate in all syndromic immunodeficiencies Early diagnosis can be very important as stringent follow-up may identify clinical problems at an earlier stage and may make treatment easier. As many syndromic immunodeficiencies may have an atypical presentation, it is advisable to involve clinical geneticists at an early stage. The clinical geneticist can also help in counseling the parents and helping them adapt to the situation. Moreover, it is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents with a previous affected child or to young adults who are affected or at risk of being carriers. Obviously, the optimal timing for counseling on the recurrence risk, clarification of carrier status, and discussion of the availability of prenatal testing is before a new pregnancy is conceived.

Conflict of interest All authors declare no conflict of interest.

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