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Neutropenia and Primary Immunodeficiency Diseases

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Primary immunodeficiency diseases (PID) are a heterogeneous group of congenital disorders of the immune system leading to recurrent infections, autoimmunity, malignancies, and hematological disorders. This review focuses specifically on inherited disorders associated with neutropenia, which may occur in isolation or as a feature of more complex immune disorders. It has been known for a long time that defined immunodeficiency syndromes, such as CD40L deficiency, WHIM syndrome, or Chédiak Higashi syndrome, may be associated with neutropenia even though the mechanisms are poorly understood. In some PID, neutropenia may result from chronic viral infection or from autoimmunity. Recently, the identification of several novel genetic defects (e.g., p14-deficiency, HAX1-deficiency, AK2-deficiency) has shed light on the pathophysiology of congenital neutropenia. This review summarizes the clinical, immunological, and genetic features of congenital neutropenia syndromes.

Keywords susceptibility to infection, neutrophil granulocytes, mutation, neutropenia, primary immunodeficiency diseases, severe congenital neutropenia

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INTRODUCTION

Primary immunodeficiency diseases (PID) are inherited disorders that predispose individuals to recurrent infections which are due to common or unusual microorganisms [1–3]. More than 150 different types of PID have already been reported [1, 2]. Autoimmune disorders and malignancies are common in many types of PID. In addition, some are associated with hematological disorders such as neutropenia, anemia, or thrombocytopenia [4–6]. Neutropenia, which is defined as a reduction in the absolute neutrophil count (to less than 1,500/mm^3 in Caucasians) [7], is a common hematological manifestation encountered in these patients. It could be associated with viral infections, an autoimmune disease, or have a genetic basis [4, 8, 9]. The latter group, which may be seen in only some types of PID, comprises a genetically heterogeneous group of diseases ranging from isolated severe congenital neutropenia to complex inherited disorders associating neutropenia, lymphoid immunodeficiency, and hypopigmentation (Table 1) [10–12].

The aim of this review is, therefore, to describe these PID that are associated with inherited forms of neutropenia.

SEVERE CONGENITAL NEUTROPENIA

Severe congenital neutropenia (SCN, OMIM#202700) is a rare primary immunodeficiency disease with a bone marrow maturation arrest of granulocytic differentiation at the promyelocyte-myelocyte stage [4, 13–15]. This results in a persistent severe neutropenia, and an increased risk of recurrent severe infections and predisposition to acute myeloid leukemia and myelodysplasia [12, 15, 16)].

Patients with this condition are characterized by early onset recurrent bacterial infections usually by the age of 1 year [4, 13, 17]. Although superficial or systemic bacterial infections in infancy are the hallmark of SCN, fungal infections may also occur [18]. Oral cavity and mucous membranes are the most frequent sites of involvement, which could be manifested as mouth ulcers and periodontitis. The skin is also a common site of manifestation with rash, ulcerations, and abscesses being reported frequently in the SCN patients. In children, frequent aphthous stomatitis and gingival hyperplasia may result in loss of permanent teeth [13]. Also, splenomegaly is a common finding in these patients being detected in one-fifth of SCN patients before treatment with granulocyte colony-stimulating factor (G-CSF) and up to half of them through 10 years of treatment [13]. Recently, neurological disorders,

TABLE I Primary Immunodeficiency Diseases Which Could Be Associated with Congenital Neutropenia

Diseases	Genetic defects	Inheritance	Associated features
Severe congenital neutropenia	*ELA2*	AD	Myelodysplasia
	HAX1	AR	Neurological disorders; increased immunoglobulin levels
	WASP	XL	Myelodysplasia; monocytopenia; decreased number of lymphocytes; reverse CD4/CD8 lymphocyte ratio; decreased number of NK cells; defective lymphocyte proliferative responses
	G6PC3	AR	Cardiac and urogenital malformations
	GFI1	AD	Decreased number of B-lymphocytes; increased number of CD4+ T-lymphocytes and monocytes
	GCSFR	AD	G-CSF refractory neutropenia
Cyclic neutropenia	*ELA2*	AD	Cyclic anemia and monocytopenia; neutrophils functional deficiency
Shwachman-Diamond syndrome	*SBDS*	AR	Exocrine pancreatic insufficiency; chondrodysplasia; myelodysplasia; impaired mobility, migration, and chemotaxis of neutrophils
Chédiak-Higashi syndrome	*LYST*	AR	Partial oculocutaneous hypopigmentation; progressive neurologic defects; giant lysosomes; defective NK cell activity, T lymphocytes cytotoxicity, neutrophil chemotaxis, coagulation defects
Griscelli syndrome, type 2	*RAB27A*	AR	Partial oculocutaneous hypopigmentation; defective NK and T-lymphocytes activities
Hermansky-Pudlak syndrome, type 2	*AP3B1*	AR	Oculocutaneous hypopigmentation; defective NK cell activity, T-lymphocytes cytotoxicity, neutrophil dysfunction, coagulation defects
p14 deficiency	*P14 (MAPBPIP)*	AR	Partial oculocutaneous hypopigmentation; short stature; increased number of B-lymphocytes; decreased IgM levels; defective T lymphocyte cytotoxic activity

(Continued on next page)

TABLE I Primary Immunodeficiency Diseases Which Could Be Associated with Congenital Neutropenia *(Continued)*

Diseases	Genetic defects	Inheritance	Associated features
WHIM (warts, hypogammaglobulinemia infections, myelokathexis) syndrome	*CXCR4*	AD	Warts; decreased number of B- and T-lymphocytes, especially CD4+ T-lymphocytes; decreased immunoglobulin levels
CD40 ligand deficiency	*CD40L*	XL	Increased or normal IgM level; decreased other isotypes
Agammaglobulinemia with absent B-cells	*BTK*	XL	Profoundly decreased or absent number of B-lymphocytes; decreased levels of all immunoglobulin isotypes
	IGHM	AR	
	IGLL1	AR	
	CD79A	AR	
	CD79B	AR	
	BLNK	AR	
PNP (Purine nucleoside phosphorylase) deficiency	*PNP*	AR	Neurological impairment; autoimmune phenomena; decreased number of total lymphocytes and T-cells; normal or decreased levels of immunoglobulin isotypes
ALPS (autoimmune lymphoproliferative syndrome)	*TNFRSF6*	AD, AR	Autoimmune phenomena; chronic non-malignant lymphoproliferation; CD4-CD8- double negative T-cells in blood or lymph node; defective lymphocyte apoptosis in vitro
	TNFSF6	AD, AR	
	CASP10	AD	
	CASP8	AD	
	NRAS	AD	
Cartilage hair hypoplasia	*RMRP*	AR	Disproportionate short-limbed short stature; metaphyseal chondrodysplasia; hypoplastic hair; macrocytic anemia; decreased number of T-lymphocytes; deficiency of cell-mediated immunity; impaired lymphocyte responses to mitogens
Glycogen storage disease Ib	*G-6PT1*	AR	Hypoglycemia, growth retardation, hepatomegaly; impaired mobility, phagocytosis, and chemotaxis of neutrophils
Barth syndrome	*TAZ1*	XL	Short stature; skeletal myopathy; dilatative cardiomyopathy

TABLE I Primary Immunodeficiency Diseases Which Could Be Associated with Congenital Neutropenia *(continued)*

Diseases	Genetic defects	Inheritance	Associated features
Dyskeratosis congenita	*DKC1*	XL	Reticulate skin pigmentation; nail dystrophy; leukoplakia of the oral mucosa; aplastic anemia; decreased number of T-lymphocytes; defective functions of T-lymphocytes
Reticular dysgenesis	*AK2*	AR	Early fatal septicemia; sensorineural deafness; complete deficiency of lymphocytes; thymus hypoplasia; lack of innate and adaptive humoral and cellular immune functions
Cohen syndrome	*COH1*	AR	Short stature hypotonia; microcephaly; mental retardation

including developmental delay, mental retardation, epilepsy, and decreased cognitive function, are reported in some SCN patients [19–21]. Other associated findings such as cardiac and urogenital malformations can also be seen in some patients with congenital neutropenia [22].

It has become apparent that congenital neutropenia is a monogenic disorder that may be caused by multiple genetic defects [10, 11, 23]. Mutations in the gene-encoding neutrophil elastase 2 (*ELA2*, OMIM*130130) account for approximately half of SCN cases [24, 25] (our observation). It is seen in both autosomal dominant and sporadic forms of the disease [14, 24, 26]. Neutrophil elastase is a serine protease, exclusively expressed in neutrophils and monocytes and is stored in the primary granules of neutrophils [27]. While it is still unclear how heterozygous mutations in *ELA2* cause SCN, three hypotheses have been proposed that could explain the relationship between *ELA2* mutations and neutropenia. First, mutations in this gene, which code neutrophil elastase as a protease, may lead to malfunction of the protein and result in aberrant proteolysis [28]. Model of unfolded protein response is the second proposed mechanism [29, 30], in which mutations in the *ELA2* gene result in structural perturbations in the neutrophil elastase protein. This subsequently leads to accumulation of misfolded neutrophil elastase in the endoplasmic reticulum, which triggers the unfolded protein response and ultimately apoptosis of

neutrophil precursors [31]. Third, aberrant intracellular trafficking of mutated *ELA2* may explain the resultant neutropenia [28, 32, 33]. Whatever the mechanism would be, the final effect is accelerated apoptosis of myeloid progenitor cells of the patients [29, 34].

Recently, mutations in the HS-1-associated protein X (*HAX1*, OMIM*605998) gene have been shown to cause autosomal recessive SCN, also known as Kostmann syndrome (OMIM#610738) [35]. HAX-1, a mitochondria-targeted protein, is critical for maintaining the inner mitochondrial membrane potential and protects myeloid cells from apoptosis [36–38]. Mutations in the *HAX1* gene may affect two transcript variants which may have distinct functions in the blood and brain. Interestingly, it has been shown that patients who carry mutations affecting both transcript variants are prone to develop neurological symptoms in addition to neutropenia [19, 20]. This human phenotype resembles, in certain aspects, the phenotype of HAX1-deficient mice who show increased apoptosis in neurons [39].

Mutations in the gene-encoding Wiskott-Aldrich syndrome protein (*WAS*, OMIM*300392) result in X-linked neutropenia [40]. The Wiskott-Aldrich syndrome protein (WASp) is a key regulator of actin polymerization in hematopoietic cells [41]. Mutations of WASp also cause the classic Wiskott-Aldrich syndrome (WAS) and X-linked thrombocytopenia (XLT). However, unlike the mutations in WAS and XLT, which lead to reduced or completely absent WASp levels and/or activity, the mutations in X-linked neutropenia result in enhanced gene activity [40, 42]. It has been suggested that the hyperactivated and dysregulated actin polymerization caused by these mutations may induce defective mitosis and cytokinesis and subsequently result in suppression in granulopoisis [43]. In addition to neutropenia, decreased levels of monocytes, decreased T-cells CD4+/CD8+ ratios, and reduced numbers of natural killer cells have been reported in X-linked neutropenia. Some patients show disturbances in lymphocytic functions, including reduced phagocytic ability and proliferation [42, 44].

Mutations in the gene glucose-6-phosphatase catalytic subunit 3 (G6PC3, OMIM*611045) have recently been identified in a group of autosomal recessive SCN patients with additional organ involvement, including cardiac and urogenital malformations and increased venous marking [22]. G6PC3 is a ubiquitously expressed protein located in the endoplasmic reticulum and catalyzes dephosphorylation of glucose-6-phosphate. Similar to patients with mutations in *ELA2* or *HAX1*, there was a paucity of mature neutrophils in the bone marrow and an

increased susceptibility to apoptosis in primary hematopoietic cells and fibroblasts of the affected patients. Mechanistically, deficiency of G6PC3 leads to an increased endoplasmic reticulum stress and an increased activity of GSK3β, a switch factor in controlling a variety of cellular functions, Wnt-signaling, and apoptosis [45].

Heterozygous mutations in the protooncogene growth factor-independent 1 (*GFI1*, OMIM*600871) gene are also associated with SCN [46]. An increased population of immature and undifferentiated neutrophils and monocytes are present on the peripheral blood of these patients [46] as well as in *GFI1*-knockout mice [47, 48].

Mutations in the granulocyte colony-stimulating factor receptor (*GCSFR*, OMIM*138971) gene are present in a number of SCN patients [13, 14, 49]. These mutations are detected in approximately 80% of the SCN patients who developed acute myeloid leukemia [14, 50] and seem to play a role for leukemogenesis in these patients. Mutations in *GCSFR* are somatic and thought to be acquired during life. In addition to acute myeloid leukemia, *GCSFR* mutations are not restricted to patients developing MDS/AML, they can also be found in SCN patients developing acute lymphoid leukemia and chronic myeloid leukemia [51].

Despite progress in elucidating causative genes in SCN, in many patients no mutation can be found, suggesting that additional and as yet unknown genes play a role in the pathophysiology of SCN. Also, a small group of patients have been described with mutations in other genes (e.g., *PRDM5* and *PFAAP5*) [52, 53]. Genetic studies are under way to discover further genes controlling the survival of neutrophils in these patients.

CYCLIC NEUTROPENIA

Cyclic neutropenia (OMIM#162800) is a rare blood disorder in which profound oscillations of circulating neutrophil counts occur. Neutropenia is seen for 3–6 days with an average cycle lasting 21 days [54–56]. In bone marrow cells from these patients, a defective proliferative response to haematopoietic factors, including G-CSF, has been documented [57, 58].

Patients with this condition encounter severe infections during the neutropenic phases [17]. As in congenital neutropenia, the infections usually affect the mucosal sites, such as oral cavity, upper respiratory tract, or rectal mucosa [17]. When the neutrophil counts increase, the infections and accompanying symptoms usually disappear. However,

severe infections can be life threatening. For example, necrotizing enterocolitis (typhlitis) is a threat to these patients and if not diagnosed promptly may progress to acute perforation of the bowel with bacteremia and septic shock [15].

Other hematologic abnormalities frequently associated with this condition include leukopenia, which occurs in most situations together with neutropenia and also anemia and thrombocytopenia [17, 55].

Cyclic neutropenia may be sporadic or transmitted in an autosomal dominant inheritance pattern. Mutations in *ELA2* (OMIM*130130), the same gene involved in the majority of cases with SCN, are found in the majority of patients with cyclic neutropenia [59]. It remains unknown why mutations in *ELA2* may cause either SCN or cyclic neutropenia.

SHWACHMAN-DIAMOND SYNDROME

Shwachman-Diamond syndrome (SDS, OMIM#260400) is a congenital bone marrow failure syndrome, which is characterized hematologically by varying degrees of cytopenia and a marked propensity to develop myelodysplastic syndrome and acute myelogenous leukemia [60, 61].

Neutropenia is the most common hematologic finding occurring constantly in about one-third of the patients and intermittently in the remaining two-thirds [62]. Besides low neutrophil counts, neutrophils of patients with SDS often exhibit qualitative abnormalities such as impaired mobility, migration, and chemotaxis, which may account for the severe infections seen in patients without marked neutropenia [63–65]. Furthermore, anemia as well as thrombocytopenia develops in about 40% of patients during the course of the disease [63]. In addition to hematologic abnormalities, SDS patients also suffer from exocrine pancreatic insufficiency, broad spectrum of skeletal abnormalities, growth retardation, dental caries, neurodevelopmental delay, and hepatic dysfunction [62, 66, 67].

The disease is transmitted through an autosomal recessive pattern. The *SBDS* (Shwachman-Bodian-Diamond syndrome) gene (OMIM*607444) is mutated in the majority of SDS patients [68]. *SBDS* is expressed widely in human tissues and promotes spindle stability and chromosome segregation [69]. It has been proposed to be involved in both ribosomal and non-ribosomal processes [70], and the mutation of this gene contributes to bone marrow failure and leukemogenesis [69].

CHÉDIAK-HIGASHI SYNDROME

Chédiak-Higashi syndrome (CHS, OMIM#214500) is a rare lysosomal storage disorder in which neutropenia is associated with other defects of the immune system including natural killer cells, T-cells, granulocytes and monocytes [71, 72]. This results in a severe immune deficiency and an increased susceptibility to infections.

Patients with CHS are also characterized by variable oculocutaneous hypopigmentation, bleeding diathesis, and progressive neurologic defects [73, 74] (Table 2). Also, a life-threatening lymphoproliferative syndrome characterized by diffuse lymphohistiocytic infiltration of the major organs is a common manifestation in these patients [75]. The diagnostic feature of the disease on the subcellular level is enlarged vesicles of lysosome origin in all cell types, including blood cells. The latter finding provides an easy clue to rapid diagnosis [76].

CHS is an autosomal recessive disorder and is derived from mutations in the gene lysosomal trafficking regulator gene (*LYST,* OMIM*606897) [77]. The CHS protein encoded by this gene has been shown to regulate lysosome-related organelle size and movement, and abnormal functioning of this protein results in mistrafficking and defective exocytosis of intracellular proteins. This mechanism may be responsible for the impaired chemotactic responses and cell-killing defects observed in NK cells and cytotoxic T cells of CHS patients [78]. However, its exact role in neutropenia has not yet been determined [79].

GRISCELLI SYNDROME TYPE 2

Griscelli syndrome type 2 (GS2, OMIM#607624) is a rare immunodeficiency disorder characterized by variable cellular immunodeficiency and mild neutropenia in addition to hypopigmentation of skin and hair [80, 81].

Besides GS2, there are two other types of GS (types 1 and 3) which are all common in a silver-gray colored hair and an abnormal accumulation of end stage melanosomes in the center of melanocytes [80, 81]. However, immunological defects are only associated with GS2 and defects in the central nervous system that are common in the other 2 types are not observed in these patients. Also, most patients with GS2 develop an uncontrolled and life-threatening activation of T-lymphocytes and macrophages [80].

Mutations in the gene RAS-associated protein (*RAB27A,* OMIM*603868) are responsible for this autosomal recessive disorder

TABLE II Characteristics of the Immunodeficiency Syndromes with Hypopigmentation

	Chédiak-Higashi syndrome	Griscelli syndrome type 2	Hermansky-Pudlak syndrome type 2	p14 deficiency
Hypopigmentation	Variable	Variable	Prominent	Prominent
Gene defect	*LYST*	*RAB27A*	*AP3B1*	*P*14
Hair shaft findings	Distributed regular melanin granules	Large irregular melanin granules	Normal or distributed small clumps of pigment	–
Prominent facial features	–	–	+	+
Neutropenia	+	+/–	+	+
Immunodeficiency	+	+	+	+
Bleeding disorder	+	–	+	–
Giant intracellular granules	+	–	–	–
Hemophagocytic lymphohistiocytosis	+	+	+/–	–
Neurological disorder	+	–	–	–
Pulmonary fibrosis	–	–	+/–	–
Developmental delay	+/–	–	+/–	–
Short stature	–	–	–	+

[82]. *RAB27A*, a small GTPase protein, has been demonstrated to be a key regulator of secretion in cells with secretory lysosomes such as cytotoxic T-lymphocytes [83]. The azurophilic granules of neutrophils in these patients are not able to release myeloperoxidase which may account for the defective bacterial killing observed in these patients [84]. However, no mechanism can directly explain the neutropenia in this group of patients.

HERMANSKY-PUDLAK SYNDROME TYPE 2

Hermansky-Pudlak syndrome type 2 (HPS2, OMIM#608233) is a rare lysosomal trafficking disorder associated with immunodeficiency. HPS2 is part of the heterogeneous groups of disorders known as Hermansky-Pudlak syndromes (HPS); however, unlike other types of HPS, only this type is associated with recurrent infections due to chronic neutropenia and other deficiencies in the innate immune system [85–89]. In addition to chronic neutropenia and/or neutrophil dysfunction, patients with this disorder reveal NK cell and CD8 cell cytotoxicity [90]. In contrast to patients with GS2 or CHS, they typically do not present with macrophage activation syndromes, suggesting that the defect in cytotoxicity may be less severe.

Other clinical manifestations of this disorder, which is in common with other types of HPS, are oculocutaneous hypopigmentation and prolonged bleeding time due to defects in platelet aggregation [91]. Some patients develop lung fibrosis and inflammatory colitis over time. The life-threatening lymphoproliferative syndrome characterized by diffuse lymphohistiocytic infiltration of multiple tissues, which is common in CHS and GS2, has also been reported in one patient with HPS2 carrying also a monoallelic mutation in *RAB27A* [92] (Table 2).

HPS2 is an autosomal-recessive disease caused by mutations in the gene encoding the b3A subunit of the heterotetrameric adaptor protein AP-3 complex (*AP3B1*, OMIM*603401) [89]. Most mutations result in complete absence of b3A protein expression, which subsequently disrupts the whole AP-3 complex and degrades all other subunits. The AP-3 complex has been shown to have a critical role in protein sorting to the secretory lysosomes [93]. Secretory lysosomes are present in a few cell types, such as melanocytes, CTLs, NK cells, and neutrophils [92]. Therefore, it seems that the diverse clinical manifestations of the disease could be attributed to a common pathway such as altered trafficking of proteins to the plasma membrane instead of secretory lysosomes. Neutrophil elastase has been suggested to be dependent on the AP-3 complex in order to be stored in the primary granules of

neutrophils, and mutations in this complex misdirect neutrophil elastase to the plasma membrane [32, 33]. Evidence for this model comes from analysis of neutrophils from HSP2 patients, which have reduced intracellular content of neutrophil elastase [32]. Therefore, it seems that the pathopysiologic mechanisms for neutropenia in SCN, CN, and HPS2 share similarities. A reduced level of neutrophil elastase in primary granules could thus be explained either by reduced production (as seen in SCN and CN) or mistrafficing (as seen in HPS2). However, the clinical and morphologic aspect in these patient groups is quite distinct and other pathways may also be involved.

p14 DEFICIENCY

p14 deficiency (OMIM#610798) is a recently discovered immunodeficiency disorder characterized by severe neutropenia associated with defects in other components of the immune system, including reduced numbers of B cell subsets and defective function of cytotoxic T cells [94]. p14-Deficient neutrophils also show ineffective degradation of ingested bacteria. However, neutrophil maturation in the bone marrow has been shown to be intact, and no increased susceptibility to apoptosis has been observed in the neutrophils.

The clinical phenotype of patients with this disorder includes oculocutaneous hypopigmentation, short stature, coarse facial features, and recurrent bronchopulmonary infections [94, 95] (Table 2).

The disorder is transmitted through an autosomal recessive pattern. In the original family reported, the disease is caused by a homozygous point mutation in the 3′-untranslated region of the gene that encodes p14 (*P*14, OMIM*610389) [94]. This mutation allows for residual protein expression. Complete deficiency of p14 appears to be incompatible with normal development, since mice with a complete deletion of p14 are not viable [96]. p14 is an endosomal adaptor protein and is specifically required to regulate endosomal traffic and cellular proliferation. Deficiency of this protein leads to an abnormal maturation and function of specialized lysosomes in cytotoxic T cells, melanocytes, and neutrophils. The exact mechanism leading to neutropenia remains to be defined.

WHIM

WHIM denotes a rare immunodeficiency syndrome associating warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM, OMIM#193670) [97]. Myelokathexis is the term used to describe that

neutrophils are retained in the bone marrow and not released into the peripheral blood stream [98]. Other functions of neutrophils, such as phagocytosis and bactericidal activity, are normal [99, 100]. The bone marrow of these patients shows hyperplasia of myeloid cells and degenerative changes in mature neutrophils, such as condensed nuclei connected by long, stringy filaments and multiple small cytoplasmic vacuoles suggesting apoptosis (this is what "myelokathexis" means) [101]. In addition to neutropenia, other defects in the immune system such as global hypogammaglobulinaemia and reduced numbers of both B and T cells are observed in these patients.

The defects in the immune system result in recurrent upper respiratory tract infections (sinusitis, tonsillitis, otitis media, pneumonia) caused by common pathogens; however, the clinical course is relatively benign and responds well to antibiotic therapy [97, 99]. The affected patients show a specific susceptibility to HPV-induced warts with variable clinical presentations ranging from individuals with relatively few or no warts to those who are afflicted with extensive cutaneous verrucosis, including genital condyloma acuminata with dysplastic changes [97, 102]. Complex congenital heart defects have also been reported in these patients [97, 102].

The inheritance pattern of WHIM is autosomal dominant. This syndrome is caused by heterozygous mutations of a chemokine receptor gene *CXCR4* (OMIM*162643), leading to increased signaling [103]. CXCR4 and its ligand, the stromal cell-derived factor-1 (CXCL12/SDF-1), play a central role in bone marrow homing and trafficking of hematopoietic progenitor cells, mobilization of lymphocytes, and release of developing neutrophils from the bone marrow [104–107]. Under physiologic control, this interaction is temporary, and it has been shown that proteases such as neutrophil elastase disrupt this interaction and prevent CXCR4 from over activation [108]. Therefore, sustained intracellular signaling and increased responsiveness of CXCR4 to SDF-1 observed in WHIM neutrophils might strongly impair the release of mature neutrophils from the bone marrow and account for the myelokathexis and neutropenia observed in patients with WHIM.

CD40 LIGAND DEFICIENCY

CD40 ligand deficiency or X-linked Hyper-IgM syndrome (XHIGM, OMIM#308230) is a rare and severe primary immunodeficiency disease leading to low levels of IgG, IgA, and IgE, normal or elevated IgM level in serum, and defective immunoglobulin class switch recombination [109, 110]. Neutropenia occurs in approximately two-thirds of patients

with XHIGM and has been shown to be associated with gingivitis and oral ulcers [111]. From a clinical point of view, it is important to note that bacterial infections and congenital neutropenia may be the lead symptoms of CD40L deficiency [112].

Typically, patients present during the first two years of life; however, in some patients the disease may not be manifested until adulthood. The respiratory and gastrointestinal tracts are usually the first sites of infection. The fact that opportunistic microorganisms, such as pneumocystis species or cryptosporidium, are often seen suggest that T-cell deficiency may be of critical importance in CD40L deficiency. Patients are at risk for chronic organ dysfunction (such as bronchiectasis, sclerosing cholangitis, etc.) and the development of neoplasms, especially lymphoma and carcinomas affecting the liver, pancreas, and biliary tract [111, 113, 114].

The mutated gene responsible for this X-linked disorder encodes the CD40 ligand (*CD40L*, CD154, OMIM*300386), expressed on T-cells. This mutation affects the crosstalk between T- and B-cells [115]. The CD40L–CD40 interaction is essential in T cell-dependant B cell proliferation and antibody isotype switching [116]. However, the association between neutropenia and CD40L defects remains obscure. Some authors suggest that autoantibodies against neutrophils may be the cause. However, convincing evidence is still lacking. Other proposed mechanisms are defective myeloid differentiation causing maturational arrest [109, 117] or a defect in the release of mature granulocytes from the marrow to the peripheral blood [118].

AGAMMAGLOBULINEMIA WITH ABSENT B-CELLS

Agammaglobulinemia with absent B-cells is a predominantly antibody deficiency, characterized by profoundly decreased or absence of circulating B-lymphocytes and markedly decreased serum levels of all immunoglobulin isotypes. Although the disease is first described as X-linked agammaglobulinemia (XLA), subsequently autosomal recessive forms of disease were described [119]. Affected patients typically present with early onset recurrent bacterial infections during the first year of life [120, 121]. In up to 20% of patients, low counts of neutrophil granulocytes are seen as well [122] but usually only prior to initiation of immunoglobulin replacement therapy [123, 124].

Absence of B-cell immunity in this disorder predisposes patients to the development of recurrent bacterial infections, especially in the respiratory and gastrointestinal tracts [120–122, 125]. Arthritis was also commonly reported in these patients, while a pyogenic cause has been

isolated in a minority of cases [126]. The clinical manifestations of patients with an autosomal recessive form of the disease resemble those of XLA; albeit, apparently in more severe phenotypes [119]. Approximately one-third of reported patients with an autosomal recessive form of the disease had also experienced neutropenia during the course of the disease [127, 128].

Mutations in the gene, Bruton's tyrosine kinase (*BTK*, OMIM+300300), a member of the Tec family of kinases, which is required for the proper maturation of B-cell precursors in the bone marrow, is responsible for XLA [129, 130]. In a very limited number of patients with agammaglobulinemia, mutations in the μ heavy chain (*IGHM*, OMIM*147020), Igα (*CD79A*, OMIM*112205), Igβ (*CD79B*, OMIM*147245), λ5 (*IGLL1*, OMIM*146770), and B cell linker protein (*BLNK*, OMIM+604515) genes have been explained, which lead to autosomal recessive forms of the disease [127, 128, 131–135]. Decreased numbers of granulocyte precursors have been noted in the bone marrow of patients with XLA, suggesting that the *BTK* mutations may play a direct role in the maturation of the myeloid cells [136, 137]. However, neutropenia is also seen in other variants of agammaglobulinemia with absent B-cells, which suggests in indirect mechanism such as decreased production of cytokines.

PNP DEFICIENCY

Purine nucleoside phosphorylase (PNP) deficiency is a combined immunodeficiency, characterized by a triad of recurrent infections, autoimmunity, and neurologic abnormalities. Autoimmune phenomena, such as neutropenia, are accompanied by defects in both T- and B-cell immunity [138, 139].

The combined immunodeficiency results in severe and unusual infections, especially gastrointestinal and respiratory infections, which usually occur during the first year of life [138, 140]. However, some patients develop significant infections later in life, and some may experience only mild symptoms during the course of disease [140, 141]. Neurologic abnormalities such as nonprogressive cerebral palsy, spastic paresis, or tonus abnormalities are common in PNP deficiency [140, 141]. Autoimmune phenomena can be detected in one-third of the patients [139, 142]. Along with neutropenia, patients with this disorder may manifest other autoimmune phenomena such as hemolytic anemia, immune thrombocytopenic purpura, arthritis, pericarditis, and systemic lupus erythematosus [138, 140]. Among metabolic abnormalities, hypouricemia and reduced uric acid excretion are typically present in these patients [138].

PNP deficiency is an autosomal recessive disorder caused by mutations in the gene encoding PNP (PNP, OMIM+164050). PNP is a key enzyme in the purine salvage pathway, which catalyzes the phosphorylation of substrates such as inosine to hypoxanthine [143]. Thus, mutations in this pathway result in accumulation of abnormally high levels of purine metabolites that are believed to cause lymph toxicity in patients with PNP deficiency [144, 145]. The reason why such accumulation may cause neutropenia, however, is not understood.

ALPS

Autoimmune lymphoproliferative syndrome (ALPS, OMIM#601859) is a genetically heterogeneous disorder in which defects in the Fas-mediated apoptosis results in autoimmune phenomena and lymphoproliferation [95, 146]. An increase in a normally rare population of T cells that do not express CD4 or CD8, but do express the alpha-beta form of the T-cell antigen receptor, is present in the peripheral blood of the patients [147]. Also a group of these patients show a polyclonal increase in serum immunoglobulin levels as well as an increase in serum IL-10 levels [148].

Lymphoproliferation with combined lymphadenopathy and massive splenomegaly as well as autoimmune manifestations, especially autoimmune haemolytic anemia, immune-mediated thrombocytopenia, and neutropenia, are most common manifestations of the patients [95, 146, 149]. Neutropenia predisposes the patients to bacterial infections, which may be the first clinical presentation. Long term side effects include the onset of haematological malignancies [146].

ALPS can be inherited with both autosomal dominant and autosomal recessive forms. Mutations of these genes *FAS* (*TNFRSF6,* OMIM*134637), *FASL* (*TNFSF6,* OMIM*134638), Caspase 8 (*CASP8*, OMIM*601763) and Caspase 10 (*CASP10*, OMIM*601762), which are the members of the pathway crucial for lymphocyte apoptosis induction, have been implicated as etiologic factors in the development of ALPS [150–153]. Since ALPS involved defective inhibition of autoreactive T- and B-cells, neutropenia is most likely of autoimmune pathophysiology.

CARTILAGE HAIR HYPOPLASIA

Cartilage hair hypoplasia (CHH, OMIM#250250) is a multi-organ disorder in which neutropenia is estimated to be present in about one-quarter of patients [154]. Besides neutropenia, patients with this disorder have abnormalities in other components of the immune

system. These include lymphopenia, delayed hypersensitivity, impaired in vitro responsiveness of lymphocytes to mitogens, and defective humoral immunity [155–158].

Patients with CHH also present with disproportionate short-limbed short stature, metaphyseal chondrodysplasia, hypoplastic hair, macrocytic anemia, neuronal dysplasia of intestine (expressed as malabsorption or Hirschsprung disease), limited elbow extension, ligamentous laxity, and predisposition to cancer [159, 160].

CHH is an autosomal recessive disorder caused by mutations in the RNase mitochondrial RNA processing (*RMRP*, OMIM*157660) gene [161]. The *RMRP* gene encodes the untranslated RNA subunit of the ribonucleoprotein endoribonuclease, RNase MRP, which is involved in ribosome assembly and cell-cycle regulation. *RMRP* defects disrupt the normal cellular proliferation and regulation of the cell cycle which may underlie the combined immunodeficiency and increased risk of malignancies. The exact mechanism leading to neutropenia is not well understood.

GLYCOGEN STORAGE DISEASE TYPE Ib

Glycogen storage disease type Ib (GSDIb, OMIM#232220) is a rare metabolic disorder in which most patients encounter severe neutropenia during their course of disease. The pattern of neutropenia is usually intermittent; however, no clear cyclical course has been identified. In addition to neutropenia, the neutrophils of these patients show abnormal functions which include impaired mobility, chemotaxis, phagocytosis, calcium flux activities, and respiratory burst [162, 163].

Patients with GSD-Ib manifest a complex phenotype characterized by metabolic symptoms caused by hypoglycemia, hyperlactacidemia, hyperlipidemia, and hyperuricemia, growth retardation, hepatomegaly, nephromegaly, osteopenia, and frequent occurrences of inflammatory bowel disease. Although neutropenia causes susceptibility to bacterial infections, the metabolic issues are more life-threatening in these patients.

Although the neutropenia results in frequent infections of different organs of the body, most patients die of metabolic derangement [164].

The autosomal-recessive disorder is caused by a deficiency in the glucose-6-phosphate (G6P) transporter (*G6PT*, OMIM*602671) [165]. G6PT is a part of the glucose-6-phosphatase (G6Pase) complex which transport G6P into the endoplasmic reticulum lumen and hydrolyze it to glucose [166, 167]. Similar to G6PC3-deficiency, mutations in the G6P-transporter disrupt the endogenous production of glucose in the

endoplasmic reticulum. This may result in an abnormal homeostasis of the endoplasmic reticulum which subsequently activates the unfolded protein response (UPR) [168, 169]. Finally the persistent activation of the UPR leads to the apoptosis of the neutrophils and neutropenia [169].

BARTH SYNDROME

Barth syndrome (OMIM#302060) is a multisystem mitochondrial disorder including various degrees of neutropenia, heart failure, skeletal myopathy, growth retardation, and cognitive impairment [170, 171]. Elevated urinary excretion of 3-methylglutaconic acid and hypocholesterolemia may be seen [172].

Neutropenia may lead to chronic aphthous stomatitis, which is usually due to Candida infections and is a common sequel of neutropenia [172]. Functional abnormality, such as directed motility and killing activity, has not been reported in these patients [173].

The X-linked recessive disease is caused by mutations in the *TAFAZZIN* gene (OMIM*300394) [174]. Tafazzin is a phospholipid acyltransferase, involved in remodeling cardiolipin, a specific mitochondrial phospholipid. Mutations in its gene result in changes in cardiolipin composition and also a consistent decrease in its total concentration in many tissues and organs, such as heart, skeletal muscle, granulocytes, and fibroblasts. As cardiolipin is a specific mitochondrial phospholipid, it is proposed that abnormal characteristics of this protein may lead to changes in mitochondrial architecture and function [172]. However, the mechanism responsible for neutropenia has not been revealed yet [175].

DYSKERATOSIS CONGENITA

Dyskeratosis congenita (DC) is an inherited multisystem syndrome in which neutropenia is most often accompanied by cytopenia of other lineages; however, isolated neutropenia is present in around 10% of patients [176, 177]. Immunological abnormalities are also described in a subgroup of patients and include abnormal (reduced or elevated) immunoglobulin levels and defects in the number and functions of T-lymphocytes [177].

Besides hematologic and immunologic features, patients with this condition are usually manifested by cutaneous findings, such as abnormal pigmentations, hyperhidrosis, and loss of dermatoglyphics; nail dystrophy, oral leukoplakia, and hair abnormalities, but developmental

delay, pulmonary fibrosis, short stature, esophageal webs, neurological abnormalities, and dental caries and loss could also be seen [177]. An increased frequency of malignancies, particularly of head, neck, and gastrointestinal origin are also reported in these patients [176, 177].

DC has a heterogeneous pattern of inheritance in which X-linked recessive (OMIM#305000), autosomal dominant (OMIM#127550), and autosomal recessive (OMIM#224230) forms have been recognized. The majority of patients inherit the X-linked form, caused by mutations in the *DKC1* (OMIM*300126) gene encoding the nucleolar protein dyskerin, which is also found to be more severe than other forms and results in an earlier onset age [178]. Two genes (*TERC*, OMIM*602322 and *TERT*, OMIM+187270), which encode the RNA component and enzymatic component of telomerase, respectively, have shown to be responsible for the autosomal dominant variant, while *NOP10* (OMIM*606471) gene, a component of H/ACA snoRNP complexes such as telomerase, is responsible for the autosomal recessive mode of inheritance [179–181]. These gene products are involved in the telomere maintenance pathway [179]. Therefore, the pancytopenia observed in DC seems to be the result of premature shortening of telomeres leading to decreased potential of hematopoietic stem cells to proliferate [182].

RETICULAR DYSGENESIS

Reticular dysgenesis (RD, OMIM#267500) is a rare form of severe combined immunodeficiency in which severe neutropenia is associated with absent numbers of lymphocytes, hypoplasia of the thymus and other lymphoid tissues [183]. Patients with this condition lack both innate and adaptive (humoral and cellular) immune responses [183]. The bone marrow of these individuals show a characteristic maturation arrest in the myeloid lineage at the stage of promyelocyte [184]. However, erythropoiesis and thrombopoiesis usually remain intact.

Patients experience severe septicemia within the first days of life. The disease could also be accompanied with bilateral sensorineural deafness.

The disease is transmitted through an autosomal recessive mode of inheritance. Recently, mutations in the gene encoding the mitochondrial energy metabolism enzyme adenylate kinase 2 (*AK2*, OMIM*103020) have shown to be responsible for RD [185]. *AK2* is selectivity expressed in neutrophil and leukocyte differentiation pathways and also in the vascularis region of the inner ear, which explains the clinical manifestations of the disease [185, 186].

COHEN SYNDROME

Cohen syndrome (OMIM#216550) is a disorder with heterogeneous clinical manifestations in which neutropenia is associated with hypotonia, microcephaly, mental retardation, short stature, obesity, and characteristic facial features including short philtrum, prominent upper central incisors, and prominent nasal root [187]. Neutropenia may only be present in an intermittent course. Severe infections are unusual in Cohen syndrome; however, gingivitis, periodontitis, and cutaneous infections due to neutropenia may be seen [188–190].

The disorder is transmitted through an autosomal recessive pattern and mutations in the *COH1* gene (OMIM*607817) have been identified as the cause of this disorder [191]. The protein encoded by this gene is a potential transmembrane protein which is presumably involved in vesicle-mediated sorting and intracellular protein transport [191, 192]. However, there is no clear explanation of how *COH1* mutations can cause the clinical symptoms including neutropenia in Cohen syndrome.

TREATMENT OF NEUTROPENIA

Severe congenital neutropenia causes life-threatening bacterial infections. Before the G-CSF era, most patients died within the first years of life [13, 14, 17]. After the introduction of G-CSF, the episodes of infections were reduced and survival and quality of life of the patients were improved [193–195]. At present, G-CSF is the first choice of treatment for these patients. Most patients respond to a daily dose of 3–5 microgram/kg s.c. and develop normal counts of circulating neutrophils.

In the bone marrow, G-CSF acts on myeloid progenitor cells enhancing proliferation and differentiation. Apoptosis is reduced. In addition, GCSF acts on mature myeloid cells [196]. In sum, this results in the production of more neutrophils [197, 198] and a delay in their apoptosis [199, 200].

However, some patients do not respond to G-CSF therapy. These patients are candidates for a curative treatment approach by transplantation of allogeneic hematopoietic stem cells. Bone marrow transplantation is also indicated in those patients who develop a clonal hematopoietic disorder such as myelodysplastic syndrome or acute myeloid leukemia. Also, a group of patients treated with G-CSF acquire mutations in the G-CSF receptor, which predisposes them to leukomogenesis [51, 201]. In these patients in whom G-CSF does not result in a clinical benefit, hematopoietic stem cell transplantation is the only currently available treatment [202]. Following transplantation, a

substantial number of patients normalize their peripheral blood counts and may not require further G-CSF treatment.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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