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Chapter

Neutropenia in Primary Immunodeficiency Diseases

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Abstract

Phagocytes including neutrophil granulocytes and macrophages are important cells of the innate immune system whose primary function is to ingest and destroy microorganisms. Neutrophils help their host fight infections by phagocytosis, degranulation, and neutrophil extracellular traps. Neutrophils are the most common type of circulating white blood cells and the principal cell type in acute inflammatory reactions. A total absence of neutrophils or a significant decrease in their number leads to severe immunodeficiency that renders patients vulnerable to recurrent infections by *Staphylococcus aureus* and Gram-negative bacteria being the most life-threatening. Neutropenia may be classified as mild, moderate or severe in terms of numbers in the peripheral blood, and intermittent, cyclic, or chronic in terms of duration. Besides well-known classic severe congenital neutropenia, chronic neutropenia appears to be associated with an increasing number of primary immunodeficiency diseases (PIDs), including those of myeloid and lymphoid lineage. A comprehensive overview of the diverse clinical presenting symptoms, classification, aetiological and genetic etiologies of chronic isolated and syndromic neutropenia is aimed to be reviewed.

Keywords: immune system, neutropenia

1. Introduction

Inborn errors of immunity, traditionally called primary immunodeficiency diseases (PIDs) are a group of genetic defects that interfere with a component of the human immune system. Over the past decade, substantial knowledge has been gained regarding the genetic abnormalities involved in the pathogenesis of PIDs. More than 400 distinct disorders with 430 gene defects have been reported in the 2019 International Union of Immunological Societies (IUIS) phenotypical classification of human inborn errors of immunity [1]. Despite developmental changes in normal values for white blood cell counts during childhood and discrepancies in the mean value of neutrophil counts observed in people from different ethnicities, an absolute neutrophil count of less than 1500/μL is accepted as neutropenia. Absolute neutrophil count (ANC) is determined by multiplying the total leukocyte count by the percentage of segmented neutrophils and bands in the peripheral blood. Neutropenia may be defined as mild neutropenia, with an ANC of 1000–1500/μL; moderate neutropenia, with an ANC of 500–1000/μL; severe neutropenia, with an ANC <500/μL or agranulocytosis (ANC <200/μL). Neutropenia is defined to be chronic if it lasts longer than 3 months. Neutropenia may be chronic, intermittent,

or cyclic. Peripheral neutrophil granulocyte counts show sinusoidal variation with 21 days in cyclic neutropenia.

Neutropenia is a common hematological manifestation of several PIDs with diverse genetic defects varying from congenital defects of phagocytes, to combined immunodeficiencies, and is often discovered in the course of an evaluation for acute infection. Congenital neutropenias associated with primary immunodeficiency diseases range from isolated severe congenital neutropenia to complex inherited disorders that comprise intellectual disabilities, organ abnormalities, facial dysmorphism or skin hypopigmentation. In IUIS classification, congenital defects of phagocytes are listed in two main groups; I. Defects of phagocyte number (neutropenia), and II. Functional defects of phagocytes [1]. In addition to the IUIS classification, chronic or intermittent neutropenia can be observed in other inborn errors of immune system, such as X-linked agammaglobulinemia, CD40L deficiency, reticular dysgenesis, WHIM syndrome, or in diseases of immune dysregulation. Defective myeloid cell differentiation, defective release of granulocytes from the bone marrow, enhanced apoptosis, or increased destruction of peripheral blood granulocytes are the main pathophysiological mechanisms underlying chronic severe or intermittent neutropenia in PID patients [1–3]. Primary immunodeficiency disorders associated with chronic or intermittent neutropenia are listed in **Table 1**.

Neutropenia increases host susceptibility to bacterial and fungal infections, primarily from their endogenous flora in the gut, mouth and skin as well as from nosocomial organisms, and usually presents with infections of mucous membranes, gingiva, and skin. *Staphylococcus aureus*, Gram-negative bacteria, and fungi are the most common pathogens. The most common presenting features of neutropenia are fever, aphthous stomatitis, and gingivitis. Recurrent gingivitis with multiple dental caries may lead to teeth loss. The spectrum of infections varies from localized cellulitis, furunculosis, perirectal inflammation, sinusitis, and otitis media to more severe infections such as pneumonia, colitis, intestinal perforation with peritonitis, deep tissue abscess, and sepsis. Patients with severe congenital neutropenia develop severe bacterial infections in the first year of life. In some cases, inherited neutropenia may predispose to acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).

1.1 Primary genetic defects of severe congenital neutropenia

Severe congenital neutropenia (SCN) comprise multiple hereditary syndromes, with or without extrahaematopoietic manifestations. It is characterized by an arrest in myeloid maturation at the promyelocyte-myelocyte stage and an absence of mature neutrophils in the bone marrow. Regardless of the molecular etiology, congenital neutropenia is rare with an estimated prevalence of <1/100,000 [4–6]. Patients are prone to recurrent infections such as otitis, sinusitis, gingivitis, stomatitis, skin infections, pneumonia, deep abscesses, and septicemia beginning in their first months of life. Furthermore, SCN patients have an increased risk of malignant transformation, AML, or MDS.

Mutations in numerous genes have been identified in SCN [1, 4, 5]. The prevalence of some genetic subtypes of SCN is dependent on ethnicity. Autosomal dominant heterozygous mutations of *ELANE* or *ELA2*, encoding neutrophil elastase, a serine protease that is stored in the azurophilic granules, are the most prevalent cause of SCN in Caucasians [7–9]. *ELANE* mutations lead to accelerated apoptosis as a result of abnormal protein folding in the endoplasmic reticulum and altered function through mutant neutrophil elastase mislocalization. ELANE deficiency is also responsible for cyclic neutropenia, which is characterized by regular

	Inheritance	Gene	Pathogenic mechanism	Clinical and laboratory features in addition to neutropenia
Severe Congenital Neutropenia				
Neutrophil elastase deficiency	AD, sporadic	ELANE / ELA2	Activation of the unfolded protein response (UPR), apoptosis of myeloid progenitor cells	Leukemia and myelodysplastic syndrome predisposition
HAX1 deficiency	AR	HAX1	Destabilization of mitochondrial membrane potential, abgrogated G-CSFR signaling, enhanced apoptosis of myeloid and neuronal cells	Leukemia and myelodysplastic syndrome predisposition, mental retardation, seizures
Glucose-6-phosphatase deficiency	AR	G6PC3	Impaired intracellular glucose homeostasis, dysglycosylation and UPR lead to enhanced apoptosis of myeloid cells	Thrombocytopenia, visible superficial veins, congenital heart defects, uropathy, cryptorchidism
X-linked neutropenia	XL	WASP	Disturbed actin polymerization, altered cytoskeletal responses, defective mitosis and cytokinesis	Lymphopenia, leukemia predisposition
Jagunal homolog 1 deficiency	AR	JAGN1	Aberrant N-glycosylation of multiple proteins, elevated apoptosis	CSF3 hypo/un-responsiveness
GFI1 deficiency	AD	GFI1	Impaired neutrophil differentiation, lymphoid immunodeficiency	Monocytosis, lymphopenia
SEC61A1 deficiency	AD	*SEC61A1*	Disturbed protein translocation, and dysregulation of the UPR	Recurrent sinopulmonary infections, skin abscess, oral aphthosis and enteritis
Bi-allelic CSF3R deficiency	AR	CSF3R	Transmembran GCSF receptor/intracellular signaling	CSF3 unresponsiveness
Somatic mutation of CSF3R	No genetic inheritance	CSF3R		
Disorders of molecular trafficking				
Chediak-Higashi syndrome	AR	LYST	Defective biogenesis of lysosomes, cytotoxic granules and melanosomes	Partial oculocutaneous albinism, recurrent infections, fever, hepatosplenomegaly, bleeding tendency, neurological dysfuntions, giant lysosomes (leukocytes), hair shaft anomaly

	Inheritance	Gene	Pathogenic mechanism	Clinical and laboratory features in addition to neutropenia
Griscelli syndrome type IIb	AR	RAB27a	Defective priming of cytotoxic granules and melanosomes	Recurrent infections, fever, hepatosplenomegaly, specific hair shaft anomaly
Cohen syndrome	AR	COH1, VPS13B	Altered vesicle sorting and transport	Psychomotor retardation, microcephaly, facial dysmorphism, hypotonia, joint laxity, obesity, retinochoroidal dsytrophy
Hermansky-Pudlak syndrome	AR	AP3P1	Defective endosome formation and lysosomal protein sorting,in immune cells	Recurrent infections, pulmonary fibrosis
VPS45 deficiency	AR	VPS45	Defective endosomal trafficking leads to impaired differentiation and motility and increased apoptosis of myeloid and mesenchymal cells	Myelofibrosis, nepromegaly, hepatomegaly, mental retardation
P14 deficiency	AR	LAMTOR2	Aberrant distribution of late endosomes, defective MAPK and ERK signaling, diminished phagocytosis	Growth delay, short stature, oculocutaneous hypopigmentation, partial albinism, coarse facial features
Disorders of molecular processing				
Shwachman-Diamond syndrome	AR	SBDS	Mitotic spindle destabilization, genomic instability, enhanced apoptosis	Exocrine pancreas deficiency, metaphyseal dysplasia, mental retardation, cardiomyopathy
Dyskeratosis congenita	XL	DKC1	Dysfunctional telomere maintenance	Skin pigmentation, nail dysplasia, oral leucoplakia, pulmonary fibrosis, stenosis of the oesophagus, liver diseas
	AD	TERC		
	AR	TERT		
Metabolic diseases				
Glycogen storage disease type 1b	AR	SLC37A4	Impaired intracellular glucose homeostasis	Hypoglycemia, fasting hyerlacticacidemia, hepatomegaly
Barth syndrome	XL	TAZ1	Mitochondrial dysfunction, destabilization of mitochondrial respiratory chain complexes, increased apoptosis in myeloid cells	Cardiomyopathy, endomyocardial fibrosis

	Inheritance	Gene	Pathogenic mechanism	Clinical and laboratory features in addition to neutropenia
Pearson syndrome	Mitochondrial	Deletion of mtDNA	Variably sized mtDNA deletion, variable heteroplasmy, and mosaicism lead to metabolic disorder/energy failure and apoptosis in affected tissues	Bone marrow failure, vacuoles in erythroid precursors, exocrine pancreas insufficiency, hepatopathy, nephropathy, endocrinopathy, neuromuscular degeneration
Other PID diseases				
X-linked agammaglobulinemia	XL	BTK	unclear	Recurrent bacterial infections, hypogammaglobulinemia, absent B cells
Hyper IgM syndrome	AR	CD40	Abrogated CD40LG:CD40-signalling, autoimmunity	Class-switch recombination deficiency, combined immunodeficiency oppurtunistic infections, biliary tract and liver disease, Cryptosporidium infections, intermittent neutropenia
	XL	CD40L		
WHIM syndrome	AD	CXCR4	Constitutively activated CXCR4 impairs chemokinesis of neutrophils, dendritic cells and B cells from the bone marrow	Warts, hypogammaglobulinemia, immunodeficiency, myelokathexis
Reticular dysgenesis	AR	AK2	Defective mitochondrial adenine nucleotide homeostasis, enhanced apoptosis	Lymphopenia (T-B-NK- SCID), deafness
GATA2 deficiency	AD	GATA2	Complex ontogenic dysregulation of hematopoiesis and vascularization, reduced numbers of hematopoietic stem cells	Sensoryneural deafness, lymphoedema, pulmonary alveolar proteinosis
STK4/MST1 deficiency	AR	STK4	Disturbed mitochondrial membrane potential, enhanced apoptosis	Intermittent neutropenia, bacterial, viral (HPV, EBV, molluscum), candidal infections, lymphoproliferation, combined immunodeficiency, congenital heart defects
Cartilage-Hair hypoplasia	AR	RMRP	Defective ribosome assembly, aberrant cell cycle control and telomere function	Short-limbed dwarfism, metaphyseal dysostosis, sparse hair, autoimmunity, lymhopenia, bone marrow failure, lymphoma predisposition

Table 1.
Inheritance patterns, pathogenic mechanisms and important hematological or extrahematopoietic features of primary immunodeficiency diseases associted with neutropenia.

oscillations with the ANC ranging from normal to <200/μL with a periodicity of the 21 days (±4 days) cycle [9]. Recessive disorders, such as *HAX1, G6PC3*, *JAGN1* are usually diagnosed in consanguineous families. Mutations in *TAZ* (Barth syndrome) and *WAS* have X-linked inheritance [4, 5, 10, 11]. Digenic or multigenic mutations have been also reported in SCN patients [12]. Some mutations are linked to the geographic origin [10, 13–15]. Autosomal recessive (AR) *HAX1* mutations account for about 15% of SCN patients, mostly from consanguineous Kurdish patients from the Middle East. AR *G6PC3* mutation has a high prevalence (25%) in Israel among Arameans [13, 16].

Several genetic defects have been identified as being responsible for SCN and there is currently no clear genotype–phenotype correlation for this syndrome. Patients with *ELANE*, germline *CSF3R* mutations and *WAS*/X-linked severe congenital neutropenia usually present without extrahaematopoietic manifestations [10, 13, 14].

Homozygous mutations in the antiapoptotic gene *HAX1*, encoding ubiquitously expressed HCLS1-associated protein X-1 protein, are the defects identified in classic Kostmann syndrome [10]. HAX1 is critical for the maintenance of inner mitochondrial membrane potential and is an important regulator of myeloid homeostasis. There are 2 HAX-1 isoforms. HAX1 mutations affecting both isoforms (mainly p.Q190X and p.R86X) cause SCN frequently accompanied by neurological involvement (mental retardation, developmental delay, and seizures). Mutations affecting only one isoform (mainly p.W44X in Turkish patients) lead to SCN without neurological symptoms [14].

GFI1 (Growth factor independent 1) is a zinc finger transcription factor important in myeloid and lymphoid differentiation. Dominant-negative GFI1 mutations cause a severe maturation arrest of myeloid cells [4, 13].

Inactivating, X-linked mutations in *WAS,* the Wiscott–Aldrich syndrome gene, are responsible for the classical immune deficiency, microthrombocytopenia, autoimmunity, bleeding diathesis, and predisposition to lymphoma. Apart from classic Wiscott–Aldrich syndrome, XLN is a rare familial form of SCN caused by autosomal dominant gain-of-function mutations in *WAS*. WAS protein participates in the dynamic regulation of actin polymerization. The gain-of-function mutations cause an overactive protein, leading to elevated actin polymerization, defective cytokinesis, increased apoptosis, and neutropenia [13, 15].

Mutations in *G6PC3* (glucose-6-phosphatase catalytic unit 3) were found to be a cause of SCN in 2009 [16]. G6PC3 is involved in the final step of the gluconeogenic and glycogenolytic pathway. Neutrophils of the patients have an increased sensitivity to apoptosis. Associated findings include congenital heart defects, urogenital abnormalities, inner ear hearing loss, and venous angiectasia [16, 17].

Homozygous mutations in protein jagunal homolog 1 (*JAGN1*) has been described as one of the causes of SCN in 2014 by Boztug *et al* [18]. JAGN1 deficient neutrophils show ultrastructural defects in the endoplasmic reticulum, absence of granules, defective N-glycosylation of multiple proteins, increased endoplasmic reticulum stress, and intracellular calcium activation leading to accelerated apoptosis. The phenotypic spectrum of JAGN1 deficiency includes short stature, scoliosis, hip dysplasia, amelogenesis imperfecta, facial dysmorphism, pyloric stenosis, urogenital and cardiac abnormalities. Besides neutropenia, hypogammaglobulinemia, low class-switched memory B cells, and CD4+ T cell lymphopenia are reported in JAGN1-deficient patients. This form of SCN does not respond to Colony Stimulating Factor 3 (CSF3), formerly called granulocyte colony-stimulating factor (GCSF) treatment [18, 19].

Colony stimulating factor 3 (CSF3), the main growth factor that controls both the proliferation and differentiation of myeloid progenitor cells into neutrophils, is the primary ligand for granulocyte colony-stimulating factor receptor

(G-CSFR). G-CSFR is encoded by the colony-stimulating factor 3 receptor gene (*CSF3R*). Somatic *CSF3R* gene mutations occur on a background of inherited mutations affecting genes such as *ELANE*, *HAX1,* and *G6PC*3. Acquired point mutations are localized within the intracellular domain of the receptor, and give rise to the truncated form of the receptor. This type of receptor introduces a premature stop codon and hampers its ability to transduce signals required for neutrophil differentiation. Patients who do not respond to CSF3 should be checked for *CSF3R* mutations [3–5, 7, 20]. Despite acquired *CSF3R* mutations, congenital forms of *CSF3R* mutations are localized within the extracellular or, rarely, the transmembrane domain of the receptor [20, 21].

Recently, an autosomal dominant mutation in *SEC61A1* was reported in a patient with SCN who was born to nonconsanguineous Belgian parents [22]. SEC61A1, encoding the α-subunit of the Sec61 complex controls the endoplasmic reticulum protein transport and passive calcium leakage. The mutation resulted in diminished protein expression, disturbed protein translocation, an increase in calcium leakage from the endoplasmic reticulum, and dysregulation of the unfolded protein response. The index patient presented with recurrent sinopulmonary infections, skin abscess, oral aphthous lesions, and enteritis, and responded well to CSF3 treatment.

Compensatory monocytosis, hypereosinophilia, and polyclonal hypergammaglobulinaemia appeared to be frequently associated with neutropenia and inversely proportional to its severity in SCN patients [13, 23].

Treatment of severe chronic neutropenia should focus on the prevention of infections. It includes antimicrobial prophylaxis, generally with trimethoprim-sulfamethoxazole, and also Colony Stimulating Factor 3 (CSF3). Prior to the era of filgastrim/CSF3 therapy, most patients died of infectious complications within the first 1–2 years of life despite antibiotic prophylaxis. More than 95% of SCN patients respond to CSF3 treatment with an increase in the ANC, a decrease in infections, and a great improvement in life expectancy [24, 25]. The dose and frequency of injection of CSF3 vary widely. For most patients, 5–8 micrograms (mcg) per kilogram (kg) of body weight of CSF3 given as a daily subcutaneous injection is usually sufficient. SCN is a premalignant condition. Studies showed the cumulative incidence of malignant transformation towards AML/MDS as about 22% after 8–15 years of CSF3 treatment [13, 25–27]. Patients who do not respond to filgrastim or who require high doses (>8–10 mcg/kg/day) and patients who develop AML or MDS should be considered for hematopoietic stem cell transplantation (HSCT). The strongly increased AML/MDS risk is a feature shared between *ELANE, HAX1,* and XLN SCN patients. A major risk factor for leukemogenesis in patients with severe congenital neutropenia is the expansion of hematopoietic clones with somatic (acquired) mutations in the gene encoding the G-CSF receptor (*CSF3R*). Due to the risk of developing AML or MDS, regular monitoring with blood counts, and yearly bone marrow aspiration and biopsy, including karyotyping, cytogenetic analysis, and fluorescence *in situ* hybridization should be performed. The most common cytogenetic feature is monosomy 7, which is detectable in approximately two-thirds of malignancies, but other recurrent cytogenetic abnormalities are also observed, such as trisomy 21 or trisomy 18 [23, 27].

1.2 Disorders of molecular processing

Shwachmann-Diamond syndrome and dyskeratosis congenita are in the group of diseases due to defective ribosomal biogenesis and RNA processing.

1.2.1 Shwachmann-Diamond syndrome

Shwachmann-Diamond syndrome is an autosomal recessive bone marrow failure syndrome characterized by neutropenia, exocrine pancreatic insufficiency, hepatic dysfunction, short stature and a wide spectrum of skeletal abnormalities. In addition to neutropenia, some children with SDS have defects in neutrophil chemotaxis or in the number and function of T, B and natural killer cells [28]. Bone marrow examination revealing condensed chromatin and hyposegmented neutrophils are in favor of Shwachman-Diamond syndrome.

1.2.2 Dyskeratosis congenita

Dyskeratosis congenita is a disorder of telomerase activity, usually presenting with neutropenia or pancytopenia due to bone marrow failure, cutaneous findings such as nail dystrophy, leukoplakia, malformed teeth, palmar hyperkeratosis, and hyperpigmentation of the skin [28, 29].

1.3 Disorders of metabolism

1.3.1 Glycogen storage disease type Ib

Glycogen storage disease type Ib is caused by mutations in the *SLC37A4* gene, encoding glucose-6-phosphate translocase (G6PT). It is characterized by hypoglycemia, excessive glycogen accumulation in the liver and kidney, neutropenia, and susceptibility to bacterial infections [4, 30].

1.3.2 Barth syndrome

Barth syndrome is a rare X-linked genetic disease characterized by cardiomyopathy, skeletal myopathy, growth delay, neutropenia, and increased urinary excretion of 3-methylglutaconic acid. Neutropenia can be constant, intermittent, or cyclic. Disabling mutations or deletions of *TAZ* gene, encoding tafazzin (a mitochondrial acyltransferase) cause the disorder by reducing remodeling of cardiolipin, a principal phospholipid of the inner mitochondrial membrane [31]. Survival is poor, largely depending on the severity of heart failure and the availability of a heart transplant.

1.3.3 Pearson syndrome

Pearson syndrome is an extremely rare mitochondrial disorder presenting with early-onset transfusion-dependent macrocytic sideroblastic anemia, neutropenia, and thrombocytopenia [32]. Additional clinical findings are failure to thrive, exocrine pancreatic insufficiency, and liver dysfunction. Bone marrow analyses show characteristic vacuolization of erythroid and myeloid precursor cells and ringed sideroblasts.

1.4 Vesicular trafficking disorders

Autosomal recessive vesicular trafficking disorders are caused by defects in the biogenesis or intracellular trafficking of lysosomes and related endosomal organelles [33]. Neutropenia, low natural killer and cytotoxic T lymphocyte activities and abnormal platelet functions can be observed in the patients.

1.4.1 Chediak-Higashi syndrome

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive lysosomal disorder characterized by frequent infections, oculocutaneous albinism, bleeding diathesis, progressive neurologic deterioration and a high risk of developing hemophagocytic lymphohistiocytosis characterized by pancytopenia, high fever, and lymphohistiocytic infiltration of liver, spleen, and lymph nodes [33, 34]. Treatment of accelerated phase is difficult with poor prognosis. Observation of giant cytoplasmic granulations helps dicrimination of CHS from other PIDs with partial albinism and neutropenia.

1.4.2 Griscelli syndrome type 2

Griscelli syndrome type 2 (GS2) is a rare, autosomal recessive immunodeficiency caused by mutations in *RAB27A*, clinically characterized by pigmentary dilution of the skin and the hair and predisposition to uncontrolled T-lymphocyte and macrophage activation syndrome (known as hemophagocytic syndrome), leading to death in the absence of bone-marrow transplantation. Most patients also develop periods of lymphocyte proliferation and activation, leading to their infiltration in many organs, such as the nervous system, causing secondary neurological damage [34–36].

1.4.3 Hermansky-Pudlac syndrome type 2

Hermansky-Pudlac syndrome type 2 (HPS-2) is caused by mutations in the *AP3B1* gene, have prominent facial features, a tendency toward bleeding, neutropenia, oculocutaneous albinism and high risk for rapidly fibrosing lung disease during early childhood [37].

Examination of the hair shaft of patients with partial albinism can be helpful diagnostically, as irregular large melanin granules can be seen in Griscelli syndrome type 2, poorly distributed regular melanin granules in CHS, and small pigment clumps in Hermansky-Pudlac syndrome type 2 [34].

1.4.4 P14 deficiency

A ubiquitously expressed endosomal protein MAPBPIP or p14, encoded by the *LAMTOR2* (Late Endosomal/Lysosomal Adaptor, MAPK and MTOR Activator 2) gene, is crucial for the function of neutrophils, B cells, cytotoxic T cells and melanocytes. Adaptor molecule p14 defects cause an immunodeficiency syndrome associated with growth delay, short stature, oculocutaneous hypopigmentation, partial albinism, coarse facial features, lymphoid deficiency, neutropenia, and recurrent bronchopulmonary infections [38].

1.4.5 Cohen syndrome

Cohen syndrome, associated with an arrest of myeloid differentiation is caused by an AR mutation of the vacuolar protein sorting 13 homolog B (*VPS13B*, also referred to as *COH1*) gene on chromosome 8q22.2. It has diverse clinical manifestations including failure to thrive, hypotonia, microcephaly, craniofacial and limb anomalies, short stature, obesity, hypermobile joints, mental retardation, and neutropenia [39, 40].

1.4.6 VPS45 deficiency

Vacuolar sorting protein 45 (VPS45) is a peripheral membrane protein that controls membrane fusion through the endosomal/lysosomal trafficking and the release of inflammatory mediators. Autosomal recessive inherited *VPS45* deficiency is a severe primary immune deficiency characterized by neutropenia, myelodysplasia, progressive bone marrow fibrosis, impaired migration, endocytosis, and degranulation of neutrophils, megathrombocytopenia, increased cell apoptosis leading to overwhelming bacterial infections, and early death. Organomegaly, nephromegaly, neuromotor developmental delay, and osteosclerosis are also observed in VPS45 deficient patients [41–43]. Recombinant CSF3 therapy is not sufficient to achieve improvement in ANC counts. An early diagnosis of the condition is important as therapeutic options are currently limited to early hematopoietic stem cell transplantation.

1.5 Well-known primary immunodeficiency diseases associated with neutropenia

Primary immunodeficiency diseases are characterized by recurrent or chronic infections, autoimmunity, inflammation, allergy, or malignancy as a consequence of genetic alterations affecting the immune system. These disorders were initially considered to be rare, but many patients with PIDs have been recognized over the 3 decades with the increase in awareness and availability of better diagnostic facilities. The prevalence and distribution of the ten groups of inborn errors of immunity vary worldwide. Additionally, patients with the same disease may present a different clinical profile and outcome. Due to the limited number of registries, inconsistency in diagnostic criteria, different clinical phenotypes, and lack of molecular diagnosis, the global perspective of these diseases remains unclear. Reports from several PID registries in different countries show a prevalence of 1:8500 to 1:100000 for symptomatic patients [44–46]. Predominantly B-cell deficiencies encompass the main category of PIDs. Although the exact data about the frequency is lacking, a great number of immune deficiencies are known to be associated with mild or severe neutropenia as a result of close interactions both in their ontogeny and during their functional life of myeloid and lymphoid cells. Most of such cases of neutropenia are observed at diagnosis and may recover once appropriate therapy is administered, such as parenteral immunoglobulin replacement in B cell deficiency.

1.5.1 Bruton's disease

X-linked agammaglobulinemia (XLA) is a rare primary immune deficiency characterized by the absence of circulating B cells with a severe reduction in all serum immunoglobulin levels due to mutations in the *BTK* gene. B cells show a developmental arrest in the bone marrow at the pro-B to the pre-B stage in the presence of mutations in *BTK*. Most XLA patients present with recurrent bacterial infections such as otitis, sinusitis, and sinopulmonary infections, developing after 7 to 9 months of age when transplacental maternal immunoglobulin G (IgG) levels decrease below protective levels. *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common responsible encapsulated pathogens. Patients are specifically susceptible to Enterovirus family, and mostly to poliovirus, coxsackie virus (hand, foot, and mouth disease), and Echoviruses. These may cause severe central nervous system conditions as chronic encephalitis, meningitis, and death. Prevalence is approximately 1 per 10,000 [47, 48]. Almost 30% of XLA patients are reported to have profound neutropenia at the time of diagnosis and the resolving

of neutropenia after initiation of regular IVIG replacement therapy [49–51]. The direct involvement of BTK in neutrophil development is not clear.

1.5.2 CD40LG deficiency (Hyper IgM syndrome type I)

The Hyper IgM (HIGM) syndromes are a group of rare genetic disorders leading to loss of T cell-driven immunoglobulin class switch recombination (CSR) and/or defective somatic hypermutation (SHM) with elevated or normal serum IgM and decreased IgG, IgA, and IgE. The most common causes are mutations in the CD40 Ligand (CD154) (*CD40LG*) gene leading to X-linked HIGM (XHIGM) in males. Interaction between CD40L expressed by the T_{helper} subset and its receptor CD40 on B cells induces B cell proliferation, CSR, and SHM. Patients with HIGM are highly susceptible to recurrent sinopulmonary infections, *Pneumocystis jiroveci* pneumonia, and chronic diarrhea due to *Cryptosporidium* infection that may lead to sclerosing cholangitis, hepatitis, and liver cirrhosis [52–55]. About 50% of XHIGM patients have chronic, cyclic or intermittent neutropenia, as a consequence of chronic infection or autoimmunity. Studies also revealed multiple functions of the CD40/CD40L interactions on stromal cells by enhancing the expression of granulopoiesis growth factors [56]. Decreased interaction between T cells and bone marrow stromal cells, resulting in reduced production of G-CSF is one of the mechanisms of neutropenia in XHIGM patients.

1.5.3 Severe combined immunodeficiency

Severe combined immunodeficiency (SCID) syndromes are characterized by a block in T lymphocyte differentiation that is variably associated with abnormal development of other lymphocyte lineages (B and/or natural killer [NK] cells), leading to death early in life unless treated urgently by hematopoietic stem cell transplantation. The overall frequency is estimated to 1 in 75 000–100 000 births [44, 57]. Reticular dysgenesis, caused by a mutation in the *adenylate kinase 2 (AK2)* gene is an autosomal recessive disease with granulocytopenia as well as pancytopenia, lack of innate and adaptive immune responses, and sensorineural deafness [1, 57]. Mitochondrial *adenylate kinase (AK)* regulates levels of adenosine diphosphate. AK2 deficiency results in increased apoptosis of myeloid and lymphoid precursors. This form is one of the rarest and most severe types of SCID. Severe infections occur earlier than in other forms of SCID due to profound neutropenia, in addition to markedly decreased T and NK cells.

1.5.4 Wiskott Aldrich syndrome

Wiskott Aldrich syndrome (WAS) results from a loss of function mutation in Wiskott-Aldrich syndrome protein (*WASP*) and presents with recurrent infections, eczema and microthrombocytopaenia [58]. In its classical form, significant combined immune deficiency, autoimmune complications, and risk of hematological malignancy necessitate early correction with stem cell transplantation or gene therapy. In Wiskott-Aldrich syndrome, neutropenia usually accompanies frequent autoimmune disorders. It is different from the milder form, X-linked thrombocytopenia (XLT) that is caused by the activating *WASP* mutations.

1.5.5 WHIM syndrome

WHIM syndrome (WHIM) is an autosomal dominant congenital immune deficiency with susceptibility to human papillomavirus infection-induced warts, B

cell lymphopenia, hypogammaglobulinema, bone marrow myelokathexis (increase in the granulocyte pool, with hyper mature dystrophic neutrophils), and neutropenia [59]. Gain-of-function mutations in the G protein-coupled chemokine receptor *CXCR4* are causal in this disease. Mutations in this protein lead to increased responsiveness to its chemokine ligand CXCL12 and retention of neutrophils in the bone marrow. Intravenous immunoglobulin (IVIg) and CSF3 have been documented to prevent infections in patients with hypogammaglobulinemia and neutropenia, respectively. Granulocyte colony-stimulating factor can increase neutrophil counts but does not affect cytopenias. CXCR4 antagonist plerixafor has been used to increase absolute lymphocyte, monocyte, and neutrophil counts in the peripheral blood in a dose-dependent manner, correct neutropenia, and other cytopenias in WHIM syndrome [60, 61].

1.5.6 Cartilage-hair hypoplasia

Cartilage-hair hypoplasia is a rare form of skeletal dysplasia, but also a syndromic primary immunodeficiency disorder due to a mutation in the RNase MRP RNA gene (RMRP), a non-coding RNA gene. The main clinical features are chondrodysplasia, short-limbed short stature, sparse and fine hair, Hirschsprung disease, macrocytic anemia, defective T cell-mediated immunity and predisposition to severe infections and cancer [62].

1.5.7 STK4/MST1 deficiency

Biallelic mutations in *STK4*, encoding MST1 have been identified in patients with CD4 lymphopenia accompanying multiple bacterial and viral infections, EBV-related lymphoproliferative disorder and mucocutaneous candidiasis [63–65]. MST1 deficiency has overlapping features with other PIDs involving defects in actin cytoskeletal reorganization, such as DOCK8 deficiency and Wiskott-Aldrich Syndrome. Hypergammaglobulinemia, progressive loss of naive T cells, reduced in vitro T-cell proliferation and defective in LFA-1-mediated adhesion and chemotaxis are the immunological disturbances identified in these patients. Clinically, these disorders and MST1 deficiency may behave very similarly. A thorough diagnostic workup including molecular genetic testing is advised to inform decision-making around stem cell transplantation, which will often be required.

1.5.8 GATA2 deficiency

GATA2 is a transcription factor required for stem cell homeostasis. Clinical presentation of GATA2 deficiency varies from typical Emberger syndrome (deafness and lymphoedema), MonoMac syndrome (susceptibility to mycobacteria, myelodysplasia, cytogenetic abnormalities, myeloid leukemias, pulmonary alveolar proteinosis) [66]. A significant proportion of patients have monocytopenia and macrocytosis in addition to mild neutropenia.

2. Diagnostic work-up in chronic neutropenia

Children with a history of recurrent or unusual infections present a diagnostic challenge. A high index of suspicion could lead to an early diagnosis and treatment of underlying immune deficiency disease. Several points should be taken into consideration in the examination of the patient. These are;

A. Age at the first detection of neutropenia;

B. The indication that required performing a complete blood cell count (CBC) (mild infection/fever, severe infection, fungal infection, aphthous, gingivitis stomatitis, diarrhea, developmental delay);

C. A family history of neutropenia, consanguinity, pregnancy losses, or infectious deaths, and geographic origin;

D. The presence of any severe infections, bacterial or fungal;

E. A physical examination that focuses on the oral cavity (ulceration, gingivitis or stomatitis), skin, lungs, and perirectal area for infection is important. Lymphadenopathy and hepatosplenomegaly must be determined.

F. The presence of any congenital malformation and/or any organ dysfunction;

G. The complete blood count with differential, performed at the time of diagnosis (including the ANC, absolute eosinophil count, absolute monocyte count, absolute lymphocyte count, hemoglobin levels, and platelet levels).

H. Some specific cytological abnormalities observed on the blood, such as large granular lymphocytes, suggestive of Chediak-Higashi syndrome.

The initial workup may also reveal a particular etiology, such as viral infections. After this screening evaluation, bone marrow aspiration, immunological tests (e.g., immunoglobulin G, A, M, E levels, T and B immunophenotype), pancreas markers (serum trypsinogen, fecal elastase), and auto-antibodies against neutrophils may help to determine the diagnosis. The diagnoses according to the system involvement are depicted in **Figure 1**.

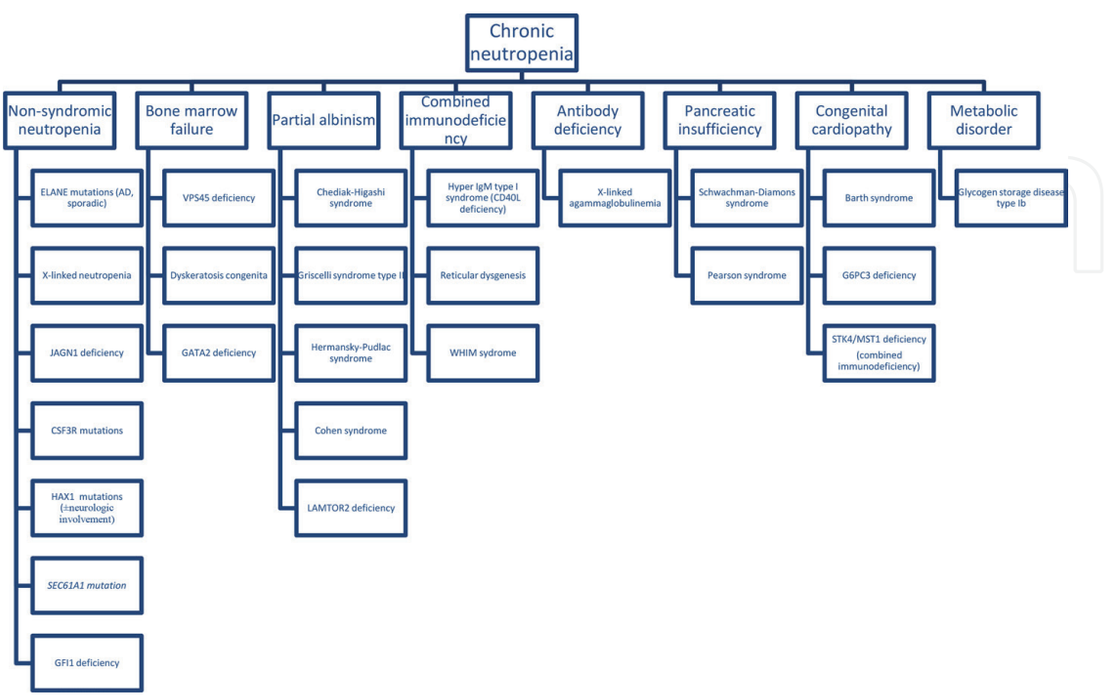

Figure 1.
Differential diagnosis of chronic neutropenia according to system involvements.

Targeted next-generation sequencing panels on the initial genetic investigations, followed-by whole-exome sequencing appears to be the most efficient strategy to identify the molecular etiology. In addition, the search for pathogenic copy-number variants or for regions of homozygosity in the case of consanguineous individuals should be considered. Mutations in some genes such as CSF3R and GATA2 can be either germline or somatic. As hematopoietic cells may acquire somatic mutations, non-hematopoietic tissue may be tested to distinguish germline versus somatic mutations. Buccal swabs or saliva samples may be contaminated by hematopoietic cells. Therefore, the germline status of a mutation should therefore be confirmed by analyzing DNA extracted from non-hematopoietic tissue, such as nails, hair follicles, or fibroblasts.

3. Treatment and follow-up

Treatment of severe chronic neutropenia in PIDs should focus on the prevention of infections, the management of associated organ dysfunction, and the prevention of leukemic transformation. The management of neutropenia will require a flexible, empiric, and patient-centered approach based on the use of cytokines and HSCT with consideration of antibiotic prophylaxis. Although many different genetic mutations may cause neutropenia, the clinical picture is similar. Most SCN patients find great benefit from subcutaneous CSF3 administration, which causes a significant decrease in the frequency of severe bacterial infections and increases the quality of life. The starting dose is 5 mcg/kg with dose modification according to the patient's absolute neutrophil count and the rate of infections. It should be kept in mind that neutropenia in JAGN1 and VPS45 deficiencies do not respond to CSF3. Patients who do not respond to CSF3 or who require high doses (>8–10 mcg/kg/day) and patients who develop AML or MDS should be treated by HSCT.

The treatment of neutropenia should be decided on a patient basis for the other disease groups. For example, patients with Shwachmann-Diamond syndrome require transfusions, pancreatic enzymes, antibiotics, and CSF3. The only definitive therapy for marrow failure is HSCT. Neutropenia, which is frequently detected at the time of diagnosis in XLA (Bruton agammaglobulinemia) patients, improves with regular IVIG replacement. XHIGM (CD40 Ligand deficiency) patients can be cured by HSCT. Future treatment strategies including gene therapy or novel genome editing technologies using CRISPR/Cas9 or TALEN systems will permit the correction of monogenic neutropenia disorders.

The rate of hematological malignancy in many of the inherited neutropenia disorders, regardless of genetic subtype, is far higher than that observed in the general population. The rate of transformation is not precisely documented, but the leukemic transformation has been reported in patients with *WAS, HAX1, G6PC3, SLC37A4* or acquired *CSF3R* gene mutations, whereas no transformation has been observed in patients with *VPS13B or CXCR4* mutations so far [25, 27]. Leukaemogenesis in CN is a multi-step process. In addition to germline mutations, several genetic mutations may occur in myeloid cells. Annual bone marrow examination should be performed to rule out malignant haemopathies, and determine cellularity, assess myeloid maturation, and detect some features that are typical of a precise etiology in the case of chronic neutropenia.

Blood neutrophils and monocytes are the cells both produced in the bone marrow, circulate in the blood, and are recruited to sites of inflammation. Compensatory monocytosis help SCN patients overcome infections. Although both are actively phagocytic, they differ in significant ways. The neutrophil response is more rapid and the lifespan of these cells is short, whereas monocytes become

macrophages in the tissues, can live for long periods, and maintain tissue integrity by eliminating/repairing damaged cells. Over the recent years, an increasing amount of knowledge has been gained in the field of phagocytic cell subpopulations [67, 68]. In addition to their protective role against invading pathogens, the field has highlighted roles for inflammatory conditions including sterile injury, tumor development, atherosclerosis, and autoimmunity. With regard to their high plasticity, neutrophils and macrophages are shown to acquire an anti-tumorigenic N1/M1 or a pro-tumorigenic N2/M2 phenotype, respectively. The impact of M1 macrophages which have overlapping features with N1 subsets of neutrophils need further investigation in PIDs.

4. Conclusion

Neutropenia is a common hematologic manifestation of a wide range of diseases. Paying careful attention to associated features of a patient provides valuable clues leading to a narrow spectrum of differential diagnosis. Genetic investigation may be helpful in making a definitive diagnosis. This is of utmost importance since timely diagnosis helps the patient benefit from available therapeutic modalities such as HSCT and CSF3 administration.

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