

REVIEW

A Molecular Classification of Congenital Neutropenia Syndromes

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Current knowledge on the molecular pathogenesis of severe congenital neutropenia indicates that the clinical diagnosis includes a heterogeneous group of disorders following different patterns of inheritance. Similarly, multifaceted syndromes associated with neutropenia can be classified molecularly, which in turn allows for a better understanding of the basis of the neutropenia. Many of the neutropenia disorders can be treated with G-CSF (filgrastim) to

increase the neutrophil count, thereby reducing infection morbidity and mortality. In some instances hematopoietic stem cell transplantation remains the only curative treatment currently available. This review describes and classifies, on a molecular basis, both primary congenital neutropenia and multifaceted syndromes associated with neutropenia. *Pediatr Blood Cancer* 2007;49:609–614. © 2007 Wiley-Liss, Inc.

Key words: agranulocytosis; congenital neutropenia; leukopenia; primary immunodeficiency

INTRODUCTION

Severe congenital neutropenia includes a variety of hematological disorders characterized by severe neutropenia with absolute neutrophil counts (ANCs) below 500/ μ l and associated with severe systemic bacterial infections from early infancy. The genetic basis of many of the inherited forms of congenital neutropenia have been documented. Genetic alterations have also been identified in multifaceted syndromes accompanied by neutropenia, which have allowed a further sub-classification of the multifaceted syndromes with neutropenia as detailed below.

CLASSIFICATION OF PRIMARY NEUTROPENIA

Inherited defects in bone marrow production of leukocytes are characterized by selective loss of neutrophil production without accompanying congenital anomalies. The diagnosis is generally based on clinical and laboratory features, which may now be supplemented by genetic testing (Table I).

Disorders of Granulocytopoiesis

Reticular dysgenesis. Complete failure of myeloid and lymphoid development leads to reticular dysgenesis, a very rare and severe form of combined immunodeficiency [1]. It is characterized by severe leukopenia, defective cellular and humoral immunity, and absent lymphoid tissue. Erythroid and megakaryocyte development is normal. Treatment is with hematopoietic stem cell transplantation (HSCT) [2].

Cyclic neutropenia. Cyclic neutropenia is an autosomal dominant disorder characterized by regular oscillations in the number of peripheral blood neutrophils, with nadirs often below 200/ μ l and approximately 21-day periodicity [3,4]. During nadirs, patients may suffer from malaise, fever, oral ulcers, and lymphadenopathy. Severity ranges from asymptomatic to life-threatening, including colitis with Clostridial or gram negative sepsis [3,5], but myelodysplastic syndrome and leukemia have not been reported [6].

Both sporadic and autosomal dominant cyclic neutropenia derive from mutations in the *ELA2* gene encoding neutrophil elastase [4,7]. The diagnosis of cyclic neutropenia is generally established by monitoring neutrophil counts three times weekly for 6–8 weeks, and is confirmed by sequencing of the *ELA2* gene. Management includes symptomatic therapy for periodic fever and

mucositis, antibiotics for infection (including anaerobic coverage for abdominal pain), and G-CSF for symptomatic patients with ANCs frequently below 500/ μ l [6,8].

Severe congenital neutropenia and Kostmann disease. Severe congenital neutropenia (SCN) was first described by Kostmann [9] as an autosomal recessive disorder in an isolated population in Sweden. Other forms of SCN have since been identified with sporadic occurrence or with autosomal recessive or dominant inheritance [6,10–12]. Although the nomenclature is still in flux, we suggest that the term SCN refer to the entire disorder and that *Kostmann disease* refer to the autosomal recessive subtype (discussed below) [13].

SCN is characterized by ANCs consistently below 200/ μ l, with recurrent, severe infections developing in the first months of life. Bone marrow examination characteristically shows a myeloid “maturation arrest” at the myelocyte stage of development [14]. Prior to the era of G-CSF therapy, most patients died in the first 2 years of life [6].

Mutations in the *ELA2* gene are responsible for 60% of SCN cases (98/164; Severe Chronic Neutropenia International Registry, unpublished work), whether sporadic or autosomal dominant [7,11,15,16]. The bone marrow of SCN patients shows accelerated apoptosis of neutrophil precursors [17]. Expression of mutant neutrophil elastase may induce apoptosis through aberrant sub-cellular targeting of the protein or induction of a strong unfolded protein response [4,18,19].

Additional, rare cases of autosomal dominant SCN arise from mutations in genes—*GF11*, *PRDM5*, and *PFAAP5*—mediating transcriptional repression of myeloid genes, including *ELA2* [20–22]. A inherited mutation in the G-CSF receptor gene has also been reported in SCN [4,23], although acquired mutations are more

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common [17]. A shared molecular mechanism for neutropenia caused by these mutations may be the down-regulation of the transcription factor lymphoid enhancer-binding factor 1 (LEF-1) [11,24].

Mutations in most autosomal recessive SCN kindreds, including several originally studied by Kostmann, have been identified in the *HAX1* gene [13], which encodes a mitochondrial protein. Therefore, the eponym “Kostmann disease” best fits this specific mutation and mode of inheritance.

More than 90% of SCN patients respond to G-CSF with increased neutrophil numbers and reduced infections, thus improving both survival and quality of life [6,8,25]. However, during long-term therapy with G-CSF, increasing proportions of SCN patients acquire mutations in the G-CSF receptor gene, then myelodysplasia often characterized by monosomy 7, progressing to myeloid leukemia [17,26–29]. Also, G-CSF responders retain a risk of death from sepsis despite seemingly adequate ANC's [29], perhaps due to functional defects in the neutrophils [30].

MULTIFACETED SYNDROMES ACCOMPANIED BY NEUTROPENIA

Neutropenia occurring within complex phenotypes has recently been clarified by the identification of underlying genetic defects

and the resultant classification of the syndromes into disorders of ribosomal dysfunction, metabolism, vesicular transport, and immune function. These advances afford better understanding of the spectrum of disorders and provide new tools for genetic diagnosis.

Disorders of Ribosomal Dysfunction

Shwachman–Diamond syndrome (SDS) is a rare multi-organ disorder with autosomal recessive inheritance [31]. The clinical findings of neutropenia, pancreatic exocrine insufficiency, short stature, metaphyseal dysplasia suggest the diagnosis. Patients are at risk for development of progressive bone marrow failure and eventual conversion to myelodysplasia and acute myelogenous leukemia. Growth failure and short stature are usually noted during the first or second year of life and puberty is often delayed (Table I).

Pancreatic insufficiency is often present in early infancy manifested by steatorrhea, weight loss, and failure to thrive. Later in childhood pancreatic function often improves rendering the clinical diagnosis more challenging. Skeletal anomalies include metaphyseal dysostosis in about 50% of affected children, as well as rib-cage defects, clinodactyly, syndactyly, kyphosis, and osteopenia.

TABLE I. Classification of Congenital Neutropenia Syndromes

Disorder (inheritance)	Blood findings	Genes (chromosome)
Disorders of granulocytopoiesis		
Reticular dysgenesis (possible AR)	Neutropenia	Unknown
Cyclic neutropenia (AD)	Lymphopenia Periodic neutropenia Periodic monocytosis Periodic changes in platelet and reticulocyte counts (within normal range)	ELA2 (19p13.3)
Severe congenital neutropenia (AD, AR)	Neutropenia MDS/AML	ELA2 (19p13.3) GFI1 (1p21) GCSFR (1p35-p34.3) PFAAP5 (13q12-q13) PRDM5 (4q25-q26) HAX1 (1q21.3)
Variant SCN3: Kostmann disease (AR)		
Disorders of ribosomal dysfunction		
Shwachman-diamond (AR)	Neutropenia Aplastic Anemia MDS/AML	SBDS (7q11)
Dyskeratosis congenital (XLR, AD, AR)	Pancytopenia	DKC (xq28) TERC (3q21-q28) TERT(5p15.33) Others
Disorders of metabolism		
Barth syndrome (XLR)	Neutropenia	TAZ1 (Xq28)
Glycogen storage disease, Type 1b (AR) ⁺	Neutropenia	G6PT1 (11q23)
Pearson's syndrome (MT)	Neutropenia Pancytopenia	Mitochondrial DNA deletions
Disorders of vesicular transport		
Chédiak–Higashi syndrome (AR)	Neutropenia	LYST (CHS1) (1q42.1-q42.2)
Cohen syndrome (AR)	Neutropenia	COH1 (8q22-q23)
Griscelli syndrome, Type II (AR)	Pancytopenia	Rab27a (15q21)
Hermansky–Pudlak syndrome, Type II (AR)	Neutropenia	AP3P1 (5q14.1)
p14 deficiency (probable AR)	Neutropenia Decreased B and T cells	MAPBIP (1q21)

Neutropenia is the most common hematological manifestation of SDS but anemia and thrombocytopenia may occur. ANC's fall below 1,000/ μ l in approximately two-thirds of patients, and the neutropenia may be intermittent. Associated chemotactic defects may contribute to gingivitis or more serious pyogenic infections. Bone marrow studies may show myeloid hypoplasia but are nondiagnostic.

Around 90% of patients who meet the clinical criteria for SDS harbor mutations in the *SBDS* gene [32,33]. Studies in yeast indicate that protein may serve a function in rRNA maturation, suggesting that SDS may share with other bone marrow failure syndromes some common pathogenesis in ribosomal dysfunction.

Treatment includes pancreatic enzyme replacement. Administration of G-CSF increases the ANC to the normal range but should only be employed in patients with persistently severe neutropenia accompanied by recurrent infections. Marrow cytogenetics abnormalities, particularly i(7q), may precede transition to myelodysplasia and leukemia. Currently there are insufficient studies to document a beneficial role for HSCT.

Dyskeratosis congenita (DC) consists of a triad of abnormal skin pigmentation, nail dystrophy, and oral leukoplakia [34,35]. Other common abnormalities include epiphora, developmental delay, pulmonary disease, short stature, esophageal webs, dental carries, tooth loss, and hair loss. Skin findings include macular or reticular hyperpigmentation and macular hypopigmentation.

Pancytopenia is the hematological hallmark of DC, with a mean age of onset at 10 years; but more than 90% of patients develop at least a single cytopenia by age three. Approximately 50% of patients develop aplastic anemia. Often aplastic anemia precedes the onset of abnormal skin, dystrophic nails, or leukoplakia.

Genetic defects have been identified in about 60% of DC patients, of whom the large majority have the X-linked form, caused by mutations in the *DKC1* gene encoding the nucleolar protein dyskerin, resulting in a defect in ribosomal function. X-linked recessive disease is usually more severe, with an earlier clinical onset. About 10% of patients have autosomal dominant disease, which is associated with mutations in the telomerase components *TERC* [35,36] or *TERT* [37]. Ribosomal function might affect clinical severity in the context of telomerase dysfunction [38].

About two-thirds of patients with DC die as a result of bone marrow failure. Almost 9% of patients develop cancer including Hodgkin's disease and carcinomas [34,39]. The role of HSCT has not been defined by prospective clinical studies.

Disorders of Metabolism

Barth syndrome is an X-linked recessive disease caused by mutations in the *tafazzin* gene [40]. It is characterized by cardiomyopathy, skeletal muscle weakness, neutropenia, and growth retardation. The ANC in Barth syndrome ranges from 500/ μ l to 1,500/ μ l. There is wide variation in clinical presentation ranging from severe debilitating disease to nearly asymptomatic cases. The characteristic symptoms are not consistently present in every patient and the clinical situation may change with age. The most serious finding is cardiomyopathy presenting as biventricular dilatation or left ventricular dysfunction (Table I).

Patients have reduced concentrations and altered composition of cardiolipin, a mitochondrial phospholipid; tafazzin defects affect acyl remodeling of cardiolipin, leading to changes in mitochondrial

architecture and function [41]. At present the mechanism of the neutropenia is not known [42].

Glycogen storage disease type 1b (GSD1b) is an inborn disorder of metabolism caused by inherited defects of the glucose-6-phosphatase complex [43], which has roles in both glycogenolysis and gluconeogenesis. Clinical features include hypoglycemia, hyperlactacidemia, hyperlipidemia, and hyperurecemia, with hepatomegaly, growth retardation, osteopenia, and kidney enlargement.

Neutropenia and neutrophil dysfunction are hallmarks of GSD1b. Patients are susceptible to recurrent bacterial infections, aphthous ulcers, and inflammatory bowel disease. Often the ANC falls below 500/ μ l; both myeloid hyper- and hypocellularity have been reported in bone marrows [44]. Neutropenia arises from a striking tendency of the cells to undergo apoptosis in the circulation. Treatment with G-CSF reduces the incidence of infection.

Pearson's syndrome. Large deletions in mitochondrial DNA, whose integrity depends on a specific DNA polymerase, are the hallmark of Pearson's syndrome, a rare and fatal congenital disorder involving the hematopoietic system, exocrine pancreas, liver, and kidneys [45]. Onset occurs in infancy with macrocytic anemia often accompanied by neutropenia and/or thrombocytopenia. The bone marrow shows normal cellularity but striking abnormalities include vacuolization of erythroid and myeloid precursors, hemosiderosis, and ringed sideroblasts. The mitochondrial defect likely leads to impaired hematopoiesis through activation of caspases and accelerated apoptosis [46].

Disorders of Vesicular Transport

This constellation of autosomal recessive disorders combine neutropenia with partial albinism and other features, all derived from defects in formation or trafficking of lysosome-related organelles [47] (Table I).

Chédiak-Higashi syndrome (CHS) is an autosomal recessive disorder characterized by increased susceptibility to infections arising from defective intracellular granule movement. The syndrome also includes partial oculocutaneous albinism and mild bleeding diathesis, progressive peripheral neuropathy, and predisposition to life-threatening hemophagocytic syndrome following viral infections, especially with Epstein-Barr virus [46]. CHS was initially characterized by the presence of giant cytoplasmic granules in neutrophils, monocytes and lymphocytes but it is now recognized as a disorder of subcellular vesicular dysfunction with increased fusion of cytoplasmic granules in all granule-bearing cells. Pigmentary dilution involving the hair, skin, and ocular fundi results from pathologic aggregation of melanosomes and is associated with failure of decussation of the optic and auditory nerves. Giant granules in the neutrophils interfere with trans-endothelial migration through narrow passages into tissue. Patients also have moderate neutropenia associated with ineffective myelopoiesis.

CHS derives from mutations in the lysosomal trafficking regulator gene *LYST* [48], which encodes a protein analogous to the yeast vacuolar sorting protein VPS15 and postulated to mediate protein-protein interaction and protein-membrane associations in vesicle transport [49].

HSCT is the only curative treatment for the hemophagocytic syndrome, but does not correct or prevent the peripheral neuropathy [50].

Cohen syndrome is an autosomal recessive condition that includes developmental delay, facial dysmorphism, pigmentary retinopathy, and neutropenia [51]. The gene responsible for Cohen syndrome, *COH1*, shares homology to a yeast protein which functions in vesicular sorting and intracellular protein trafficking.

Griselli syndrome (GS) is a rare autosomal recessive disorder characterized by pigmentary dilution of the skin, a silver-gray sheen of the hair, the presence of large clumps of pigment in the hair shafts, and abnormal accumulation of end-stage melanosomes in melanocytes [52]. In addition to albinism, type II GS has a high risk of hemophagocytic syndrome [52,53]. Unlike CHS, peripheral blood granulocytes do not show giant granules. Patients often have mild neutropenia. GS II is caused by a mutation in *RAB27a*, which encodes a small GTPase protein involved in the function of the intracellular-regulated secretory pathway [47,54]. HSCT is the only curative treatment for the hemophagocytic syndrome.

Hermansky–Pudlak syndrome type II (HPSII) is an autosomal recessive disease that is caused by disruption of the adaptor protein-3 complex [55,56]. The adaptor protein (AP) complex plays a fundamental role in vesicle formation and in cargo selection in the vesicular trafficking system of the cell. Patients with HPSII present with mutations in the gene encoding for the beta sub-unit of the AP-3 complex [56]. Clinically the syndrome is characterized by oculocutaneous albinism and platelet defects due to absence of platelet dense bodies. Disruption of the AP-3 complex differentially affects vesicular trafficking in melanocytes, platelets, cytotoxic T lymphocytes, and natural killer cells [55]. Neutropenia, often severe, is associated with diminished amounts of neutrophil elastase.

p14 Deficiency is an autosomal recessive disorder leading to congenital neutropenia, with ANC below 500/ μ l, partial albinism, short stature, and B-cell and cytotoxic T-cell deficiency [57]. Protein p14 is required for the proper biogenesis of endosomes and the subcellular relocation of mitogen-activated protein kinase signaling to late endosomes [47].

Disorders of Immune Function

Cartilage-hair hypoplasia (CHH) is an autosomal recessive disorder characterized clinically by short-limbed dwarfism secondary to metaphyseal dysplasia, fine hair, immunodeficiency, and an increased incidence of cancer. It arises from mutations in the *RMRPG* gene, which encodes the RNA component of a ribonuclear protein ribonuclease [58]. Abnormalities of both T-cell function and the humoral immune system have been reported. The disorder is associated with moderate to severe neutropenia with ANC of 100–2,000/ μ l. Case reports have documented benefits of G-CSF treatment (Table II).

Hyper-IgM syndrome is an immunodeficiency syndrome with elevated IgM, caused by at least three different genetic defects [59]. The disease results from mutations in the gene for CD40 ligand in the more common X-linked recessive form, or mutations in CD40 itself in the autosomal recessive form [60,61]. CD40 ligand on the T cell membrane interacts with CD40 on B lymphocytes to induce class switching from IgM production to IgG and IgA; defects in either result in deficiencies of IgG and IgA accompanied by elevated IgM. Patients are predisposed to infections by pyogenic bacteria, as well as autoimmune disease and hepatic malignancies.

Neutropenia, which may be cyclic or episodic, is commonly seen in the X-linked recessive disorder and has been reported in the autosomal recessive form. The basis for the neutropenia remains unknown, but in some cases may be autoimmune [59,62]. Treatment for the immune deficiency by IgG replacement may not correct the neutropenia. In at least some cases, the neutropenia responds to G-CSF.

Neutropenia may also accompany common variable immune deficiency, isolated IgA deficiency, and X-linked agammaglobulinemia [59,63].

Schimke immuno-osseous dysplasia is a rare autosomal recessive disorder characterized by variable multisystem clinical problems including spondyloepiphyseal dysplasia; in utero and

TABLE II. Classification of Neutropenia Found in Disorders of Immune Function

Disorder (inheritance)	Blood	Gene
Cartilage-hair hypoplasia (AR)	Neutropenia Lymphopenia Macrocytic anemia	RMRP (9p21-p12)
Hyper-IgM syndrome (XLR)	Neutropenia Pancytopenia	CD40L (Xq26)
Common variable immunodeficiency (probable AR)	Neutropenia Decreased IgG Decreased IgM	TNFRSF13B (17p11.2)
IgA deficiency (unknown)	Neutropenia Decreased IgA	Unknown or TNFRSF13B (17p11.2)
X-linked agammaglobulinemia (XLR)	Neutropenia Absent B cells	BTK (Xq22)
Schimke immuno-osseous dysplasia (probable AR)	Neutropenia Pancytopenia Lymphopenia	SMARCAL1 (2q34-q36)
Myelokathexis and WHIM syndrome (AD)	Neutropenia Lymphopenia Decreased IgG	CXCR4 (2q21)
Wiskott–Aldrich syndrome (XLR)	Neutropenia Lymphopenia	WAS (Xp11.23–p22)

XLR, X-linked recessive; AD, autosomal dominant; AR, autosomal recessive; MDS/AML; myelodysplasia/acute myelogenous leukemia; MT, mitochondrial.

postnatal growth retardation; proteinuria progressing to nephrosis and renal failure; lymphopenia, often associated with neutropenia and other cytopenias; and defective cellular immunity [64]. The disorder is caused by mutations in the *swi/snf*-related matrix-associated actin-dependent regulator of chromatin, subfamily a-like 1 gene (*SMARCAL1*) [65]. The immunodeficiencies can be treated with HSCT [66]; neutropenia, seen in 40% of patients, responds to G-CSF therapy.

Myelokathexis and WHIM syndrome. Myelokathexis is a rare autosomal dominant disorder characterized by moderate to severe neutropenia accompanied by neutrophil hyperplasia in the bone marrow and striking degenerative changes in the neutrophils, including cytoplasmic vacuoles, prominent granules, and nuclear hypersegmentation with very thin filaments connecting pyknotic-appearing nuclear lobes [67]. Recurrent warts and hypergammaglobulinemia often accompany myelokathexis, hence the acronym warts, hypergammaglobulinemia, infections, and myelokathexis (WHIM). WHIM syndrome arises from a truncating mutation in the cytoplasmic tail domain of the gene encoding the chemokine receptor-4 (*CXCR4*), a G-protein-coupled-receptor with the unique ligand stromal-derived factor I (*SDF-1*) [68]. Myeloid cells fail to be mobilized from the bone marrow, where they undergo eventual apoptosis [69]. Marrow retention and neutropenia are partially corrected by G-CSF or GM-CSF therapy.

Wiskott–Aldrich syndrome. Very rare cases of neutropenia are associated with activating mutations in the gene encoding the Wiskott–Aldrich syndrome protein, resulting in an X-linked form of SCN. The patients also have defects of immunologic function, including reduction of lymphoid and natural killer cell numbers, reduced lymphocyte proliferation, and disturbed phagocytic function; but they have normal platelet counts [70]. The bone marrow shows trilineage dysplasia with markedly reduced granulocytopenia. The neutropenia responds to G-CSF therapy.

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