CHAPTER 13

CONGENITAL NEUTROPENIA

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KEY POINTS

Congenital Neutropenia

- Congenital neutropenia encompasses a heterogeneous group of inherited diseases.
- The genetic mutations causing congenital neutropenia may have an isolated effect on the bone marrow but can also affect one or more other organ systems.
- The genetic defects underlying the diseases that cause congenital neutropenia have been rapidly identified over the past decade.
- Granulocyte colony-stimulating factor has dramatically improved the prognosis for children with congenital neutropenia.

INTRODUCTION

The congenital neutropenias are inherited hematologic conditions that are usually recognized in infancy or early childhood. Congenital neutropenia is often diagnosed when a young child has a differential white blood cell count performed for symptoms and signs of a severe infection. Congenital neutropenia may also be recognized in evaluating a child with a complex congenital syndrome. The severity of the neutropenia and its clinical consequences vary considerably.

Neutropenia is defined as an absolute blood neutrophil count more than 2 standard deviations below normal. The absolute count is percent neutrophils plus bands counted on a differential multiplied by the total white blood cell count. Using this definition, the blood count to define neutropenia varies by age and race. In children 1 month to 10 years of age, neutropenia is defined by a neutrophil count less than 1500 cells/μL; beyond 10 years of age, neutropenia is defined by a neutrophil count less than 1800 cells/μL in persons of white and Asian descent.[1] In persons of African descent, neutropenia is defined by a count of 800–1000 cells/μL.[1]

The severity and duration of neutropenia are also clinically important. Mild neutropenia is usually defined by neutrophil counts of 1000–1500 cells/μL, moderate neutropenia is 500–1000 cells/μL, and severe neutropenia is less than 500 cells/μL. Acute neutropenia usually is present for only 5–10 days; neutropenia is chronic if its duration is at least several weeks. Almost all congenital neutropenias are chronic neutropenia.

The characteristics and causes of congenital neutropenia are shown in Tables 13–1 and 13–2, and an algorithm for their diagnosis is presented in Figure 13–1.

SEVERE CONGENITAL NEUTROPENIA

Patients with severe congenital neutropenia (SCN) typically present with recurrent bacterial infections and neutrophil counts persistently less than 200 cells/μL. Kostmann described SCN as an autosomal recessive disorder in 1956[2]; subsequently many sporadic cases and families with an autosomal dominant inheritance were reported. The incidence of SCN is estimated at 2 per 1 million births.[3]

Pathophysiology

The genetics of SCN are heterogeneous. Up to 80% of patients have heterozygous mutations in exons 2, 3, 4, or 5 of the gene for neutrophil elastase (NE), also known as elastase-2 (*ELA2;* locus 19p13.3)[4,5] (Fig. 13–2). *ELA2* encodes a potent protease that is synthesized at the promyelocytic stage in neutrophil development and packaged in the neutrophil's primary granules.[4] Genetic and cellular evidence is persuasive that mutations in *ELA2* cause sporadic and autosomal dominant SCN. The

cause for the autosomal recessive cases is still unknown. In autosomal dominant SCN, the same heterozygous mutation is found in all affected family members but not in normal relatives.[6] In a very informative case, the father of a patient with typical SCN showed mosaic expression of the same *ELA2* mutation; half of his somatic cells contained the mutant gene, but the mutant protease was virtually absent in circulating neutrophils. In this natural observation, neutrophils expressing the abnormal gene appeared to be destroyed in the marrow before entering the circulation.[7] Human promyelocytic leukemia cells, such as HL-60 cells, which express the neutrophil esterase mutants, exhibit accelerated apoptosis.[8] Accelerated apoptosis may be mediated through altered expression of Bcl-2 proapoptotic factors, which appear to be normalized with the administration of granulocyte colony-stimulating factor (G-CSF).[9] Several other mutations have been associated with SCN, but their causal role is uncertain. G-CSF receptor mutations, which have been reported in a few cases, were probably acquired mutations during evolution to acute myelogenous leukemia (AML).[8,10] A mutation in *GFI1* has been reported in one child.[11]

Clinical Features and Diagnosis

In addition to severe neutropenia, SCN patients usually have monocytosis, thrombocytosis, and a mild normocytic, normochromic, or hypochromic anemia. The bone marrow characteristically shows "arrest" of neutrophil development at the promyelocyte and myelocyte stage, although some samples show many maturing band and segmented neutrophils, particularly in response to infections. The cellularity of the bone marrow is normal or decreased, with a reduced myeloid-to-erythroid ratio, normal megakaryocytes, and occasional eosinophilia[3] (Fig. 13–3). Anemia and thrombocytosis are probably due to chronic inflammation; monocytosis may also reflect growth factor stimulation of the neutrophil-monocyte lineage. At diagnosis, tests for antineutrophil antibodies and chromosomal abnormalities are negative.[3] Tests for *ELA2* mutations may be helpful but are still largely a research procedure.

Patients with SCN typically have recurrent fevers, oropharyngeal ulcers, and skin, respiratory, and perirectal infections. Deep tissue abscesses in the liver and lungs with bacteremias are not uncommon, and these infections may quickly become life-threatening. Common pathogens include *Staphylococcus aureus, Escherichia coli,* and *Pseudomonas* species. Until recently, SCN was often fatal as a result of infections in early childhood, despite prompt and aggressive antibiotic therapy. Prior to the availability of G-CSF, the mortality by the age of 2 years was estimated at 42%.

Treatment and Prognosis

The availability of G-CSF has markedly changed the outlook for SCN patients. Almost all patients respond to G-CSF with improvement in their quality of life.[12] By contrast, corticosteroids,[13,14] lithium,[15,16] intravenous immunoglobulins,[17,18] or granulocyte-macrophage colony stimulating factor[19] are of little benefit. The role of G-CSF in the treatment of the congenital neutropenias is summarized in Table 13–3. The effectiveness of prophylactic G-CSF was established in a randomized, controlled clinical trial.[20] In this study, the median G-CSF dose for SCN was approximately 5 μg/kg/day; starting at this dose, G-CSF was increased by 5–10 μg/kg/day every 14 days to achieve a neutrophil count greater than 1000 cells/μL. Currently, dosages higher than 50–100 μg/kg/day are generally not recommended because of the low likelihood of benefit and the volume of drug required.[3,21] Adverse effects are generally mild, primarily consisting of transient headache and bone pain.[20] Splenomegaly, osteoporosis, vasculitis, rashes, arthralgia, and hematuria are infrequent adverse events.[22] Allogenic hematopoietic stem cell transplantation is the only established alternative treatment for patients refractory to G-CSF.[23]

SCN patients are at risk of developing myelodysplastic syndrome (MDS) and AML, a risk recognized before the availability of G-CSF. In a population of SCN patient receiving G-CSF, transformation to AML or MDS occurred in about 2% per year.[24] The risk appears to be higher for patients with more severe disease, as reflected by their requirement of higher doses of G-CSF.[6] Monitoring with regular clinical evaluations, blood counts, and an annual bone marrow examination is recommended to assess histologic changes and chromosomal abnormalities, especially the acquisition of monosomy 7. Ras and G-CSF receptor mutations also have been linked to malignant transformation.[22] Survival after hematopoietic stem cell transplantation is more favorable if patients do not have MDS/AML; transplantation should be considered in patients revealing genetic transformation in their bone marrow.

CYCLIC NEUTROPENIA

Cyclic neutropenia (CN) usually presents with recurring episodes of fever, mouth ulcers, pharyngitis, and lymphadenopathy every 3 weeks, which usually resolve spontaneously over about 5–7 days. In 1910, Leale reported the first case in a 19-month-old boy.[25] CN occurs sporadically or by autosomal dominant inheritance; the estimated incidence is 0.5–1 per 1 million births.[26]

Pathophysiology

Mutations of the gene for NE (*ELA2*) were originally implicated in autosomal dominant and sporadic forms of CN prior to the discovery of the same genetic association with SCN.[4,27] *ELA2* mutations predominantly involve exon 4 at its junction with intron 4 (see Fig. 13–2).[27] In both SCN and CN, the neutrophil precursors are subjected to accelerated apoptosis, making marrow production of neutrophils ineffective. The loci of the mutations predicted that they affect function of the active site of the enzyme binding to its substrates or to natural inhibitors.[4]

No abnormality of the gene for the G-CSF receptor or other genes has been documented in well-characterized cases of CN.

Clinical Features and Diagnosis

In most cases, neutrophil nadirs occur every 19–21 days,[28] but some long and shorter cycles are reported, ranging from 11 to 52 days.[29] Neutrophil counts typically fall to zero at their nadir and do not increase above 200 cells/μL for 3–5 days; peaks are generally less that 2000 cells/μL. The monocyte counts also cycle, rising as the neutrophils fall; platelets, eosinophils, lymphocytes, and reticulocytes can oscillate in a pattern of "cyclic hematopoeisis"[29] (Fig. 13–4). The bone marrow histology varies cyclically. During neutropenia, there is "neutrophil maturation arrest" at the promyelocyte or myelocyte stage and the bone marrow may become "hyperplastic" during periods of neutrophil count recovery, showing large numbers of marrow neutrophils (Fig. 13–5). Tests for chromosomal abnormalities and anti-neutrophil antibodies are negative. Mathematical studies suggest that cyclic oscillations in cells of the marrow and blood are a natural feature of hematologic diseases with increased apoptosis of early progenitors.[30,31]

The diagnosis of CN is primarily based on the characteristic fluctuations of blood neutrophils in serial blood counts performed at least two to three times per week for 6–8 weeks.[28] Sequencing of *ELA2* is available and may aid in the diagnosis, but serial blood counts remain important to determine diagnosis and prognosis. Family studies and *ELA2* sequencing indicate that there are mild cases of CN with less severe neutropenia and fewer infections.

Fever, malaise, oral ulcers, and lymphadenopathy are features of almost every cycle in most cases; the mouth ulcers can be extremely deep and painful. Cellulitis, sinusitis, pneumonia, mastoiditis, and recurrent perirectal lesions are also common. Although CN is generally more benign than is SCN, about 10% of patients will die suddenly from peritonitis, necrotizing enterocolitis, and sepsis with *Clostridium perfringens* and *E. coli* bacteremias during a neutropenic period.[32]

Treatment and Prognosis

Historically, the management of CN was supportive care, intermittent antibiotics, and good oral hygiene. Now treatment with prophylactic G-CSF decreases the severity of the neutropenia, shortens the periodicity, and prevents recurrent infections.[33] A typical G-CSF dose is approximately 1–5 μg/kg/day on a once-daily or every-other-day schedule.[34]

Neutropenia may become less severe in adulthood, when the severity and frequency of infections wane; the mechanism underlying this change is not known.[35] Patients with CN have no recognized risk of transformation to MDS or AML, with or without G-CSF treatment.[22]

MYELOKATHEXIS AND WHIM SYNDROME

Myelokathexis (a term for retention of neutrophils in the bone marrow) is a rare congenital disorder characterized by severe neutropenia and lymphocytopenia, first described by Zuezler and by Krill and colleagues in 1964.[36,37] White blood cell counts are usually less than 1000 cells/μL, and neutrophil counts less than 500 cells/μL. The neutrophils in the blood and marrow have very pyknotic nuclei, a distinctive if not entirely diagnostic feature of this disorder. Neutropenia associated with warts, hypogammaglobulinemia, infections, and myelokathexis constitute the WHIM syndrome. Both myelokathexis and WHIM syndrome have autosomal dominant inheritance,[38] although sporadic cases have also been reported. The genetic defect for WHIM syndrome has been isolated to the gene encoding a chemokine receptor (CXCR4) at chromosome 2q21.[39]

Pathophysiology and Clinical Features

Diagnosis of myelokathexis is established by examination of the blood smear and bone marrow. The marrow is hypercellular with many neutrophil precursors, despite the abnormally low peripheral count. In the blood and bone marrow, neutrophils are characterized by hypersegmentation of their nuclear lobules separated by thin filaments of chromatin; they contain cytoplasmic vacuoles and prominent granules[40] (Fig. 13–6). There is accelerated apoptosis of marrow and blood neutrophils, and their marrow precursors, attributable to depressed expression of *bcl*-x.[40] Eosinophils can also appear bizarre, but the lymphocytes, monocytes, and basophils typically appear normal. Killing of bacteria by the neutrophils is normal.[41] Immune function may be primarily affected as a result of abnormal surveillance and trafficking of leukocytes, functions mediated through the CXCR4 receptor and its interactions with CXCL12 (stromal-derived factor-1α).[42]

Treatment and Prognosis

Despite severe neutropenia and lymphocytopenia, serious bacterial infections are very infrequent. Patients with WHIM syndrome have susceptibility to human papillomavirus but not to cytomegalovirus or *Toxoplasma gondii*. Treatment with G-CSF partially corrects the accelerated apoptosis of developing neutrophils[40] and normalizes blood neutrophil levels, increases immunoglobulin levels, and may reduce infections.[43] However, for most patients, this treatment is not necessary.

CARTILAGE-HAIR HYPOPLASIA

Cartilage-hair hypoplasia (CHH) is a rare autosomal recessive disorder characterized by a short-limb dwarfism, hypoplastic hair, and impaired T-cell function with a susceptibility to viral infections, especially varicella-zoster. It was first described by McKusick and

coworkers in 1965 in an isolated Old Order Amish community.[44] In Finland, the incidence of CHH is 1:23,000.[45] Among the Old Order Amish, an isolated religious community, the incidence has been estimated at 1.5:1000.[46] Sporadic cases have been described in many other ethnic populations.

Pathophysiology

The genetic defect of CHH is located at locus 9p13,[47] where mutations to the gene encoding the ribonuclease MRP have been identified.[48] Ribonuclease MRP is an endoribonuclease that cleaves RNA or pre–ribosomal RNA in mitochondrial processing. CHH is associated with increased apoptosis of T lymphocytes with altered expression of Fas and Bax, members of the Bcl-2 protein family.[49] There is remarkable variability of expression among members of affected families, suggesting that other modifying factors play a role in the expression of the CHH phenotype.

Clinical Features

In a study of 88 Finnish patients, 86% had macrocytic anemia, 62% had lymphopenia, and 24% had variable degrees of neutropenia.[50] Rare cases were associated with fatal hypoplastic anemia. Skeletal biopsies have shown cartilage hypoplasia, typically manifested as shortened limbs with increased joint laxity. The hair is characteristically fine, fragile, and sparse, and typically light-colored. Other associated features include Hirschsprung's disease (colonic aganglionosis)[51] and malignancies (lymphoma and basal cell carcinoma).[52] Between 1971 and 1995, a population register center in Finland documented that the most frequent causes of death were pneumonia and sepsis.[53]

Treatment and Prognosis

Hematopoietic stem cell transplantation corrects the immunodeficiency, but not the chondrodyplasia.[54] Treatment of four patients with growth hormone was without benefit.[55]

SHWACHMAN-DIAMOND SYNDROME

Shwachman-Diamond syndrome (SDS) is a rare autosomal recessive disorder characterized by pancreatic insufficiency, neutropenia, and short stature. Shwachman and associates first described the syndrome in 1964.[56] The incidence of this disorder is 1:77,000,[57] with approximately 300 cases reported as of December 2000.[58]

Pathophysiology

The genetic defect is located at 7q11[59] at a site now designated the *SBDS* (Shwachman-Bodian-Diamond syndrome) gene.[60] Although the mutations in *SBDS* are not understood, indirect evidence points to abnormal RNA metabolism that could widely affect cellular function in the pancreas, bone marrow, and bone.[60] The connection between these genetic mutations and the phenotypic expression of the cellular abnormalities has not been established. Cellular manifestations include defects in neutrophil chemotaxis[61] and abnormalities of progenitor cells in the bone marrow, which have a decreased potential to form new colonies and an increased apoptosis rate.[62]

Clinical Features and Diagnosis

Neutropenia is seen in virtually all patients, approximately 66% have neutrophil counts less than 1000 cells/μL, and cyclic fluctuation is common.[58] Cellulitis, otitis media, pneumonia, and osteomyelitis are associated with the neutropenia. Mild normochromic and normocytic anemia occurs in 80% of cases.[58] Thrombocytopenia occurs frequently (24–88% of cases), with recorded fatal hemorrhagic events.[58] Cell-mediated immunity also can be impaired.[63] As many as one third of patients with SDS undergo malignant transformation to MDS and AML, with acquired clonal chromosomal abnormalities.[61]

SDS is a multisystem disorder with variable involvement of other organ systems, including the pancreas, liver, kidneys, and teeth. Malabsorption resulting from pancreatic insufficiency is often severe, particularly in young children. Growth problems occur in the first 2 years; metaphysial chondrodysplasia, metaphyseal dysostosis, rib cage abnormalities, syndactyly, kyphosis, and scoliosis are also common features.

Diagnostic criteria for SDS include evidence of pancreatic insufficiency and the hematologic abnormalities.[58] Pancreatic insufficiency can be established by an elevated 72-hour fecal fat level, a decrease in serum cationic trypsinogen, and an abnormal quantitative pancreatic stimulation test. The hematologic abnormalities are manifested by neutropenia (absolute neutrophil count < 1500 cells/μL), anemia (hemoglobin less than 2 standard deviations below the age-adjusted mean), and thrombocytopenia (platelet count < 150,000 cells/mm^3).[58]

Treatment and Prognosis

Supportive therapy includes pancreatic enzyme replacement and antibiotic therapy for infections. Case studies have shown that G-CSF is effective in increasing the neutrophil count in patients with severe neutropenia[64] and also in decreasing the rate of infections.[65] SDS patients with aplastic anemia may respond to corticosteroids[66] and cyclosporine therapy.[67] The only curative treatment following malignant transformation is a stem cell transplant.[68]

The role of annual bone marrow evaluation in long-term follow-up of patients with SDS is controversial. Frequent marrow examinations monitor for acquired chromosomal abnormalities, which may precede malignant transformation, but some abnormal clones may regress without intervention.[69] If patients with SDS in fact survive the respiratory difficulties and the most serious infections of early life, both the neutropenia and the

pancreatic insufficiency may wane as they age. However, aging also increases the risk for undergoing malignant transformation to MDS and AML. The projected median survival of patients is more than 35 years.[58]

CHÉDIAK-HIGASHI SYNDROME

Chédiak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by hypopigmentation of the hair, eyes, and skin; giant granules in several types of cells; and neutropenia with recurrent bacterial infections. CHS was first reported by Beguez-Cesar in 1943[70] and further defined by Chédiak,[71] Higashi,[72] and Sato.[73] About one half of all cases with CHS are now attributable to mutations of the *CHS1* gene at 1q43 that encodes a lysosomal trafficking regulatory protein (LYST).[74] Mutations of *CHS1* that totally abolish LYST expression cause more severe disease; milder cases are associated with missense mutations.[75]

Clinical Features and Diagnosis

CHS is diagnosed by detection of the giant granules in neutrophils, monocytes, and lymphocytes, which are easily visible by light microscopy and are sometimes more prominent in the bone marrow than in the blood. In neutrophils, the very large granules appear to result from fusion of the primary and specific granules (Fig. 13–7).[76,77] These cells undergo intramedullary destruction resulting in neutropenia. Blood neutrophils have depressed chemotaxis[78] and diminished bactericidal potency.[79] Platelets also have abnormal granules and exhibit defective aggregation leading to easy bruising and bleeding.[80,81] Cytotoxic T-cell and natural killer cell function are also abnormal.[82,83] In the most common and severe form, young children develop recurrent, often life-threatening, bacterial infections and then progress in an "accelerated phase,"[84] characterized by diffuse lymphohistiocytic infiltration of the liver, spleen, lymph nodes, and bone marrow, and progressively worsening pancytopenia.

Treatment and Prognosis

Management is directed primarily to avoiding infections and appropriate institution of aggressive antibiotic treatment. Ascorbic acid improves neutrophil functions in vitro,[85] but its clinical benefits are uncertain.[86,87] G-CSF may increase blood neutrophils but is also an unproven therapy.[88] Systemic corticosteroids have been used to treat an accompanying peripheral neuropathy.[89] Treatment of the accelerated phase with vincristine and corticosteroids can induce temporary remissions, but bone marrow transplantation is the only known cure.[90]

GRISCELLI SYNDROME

In 1978, Griscelli and colleagues described two patients with hypopigmentation of the hair and skin, similar to CHS, but with normal-appearing neutrophils.[91] The three subtypes of this rare autosomal recessive disorder occur predominantly in persons of Turkish and Mediterranean descent.[92] In type 1, attributable to a mutation in the *MYO5a* gene at 15q21 (expressed abundantly in the brain), there is developmental delay and mental retardation without neutropenia or immune deficiency.[93] In type 2, attributable to mutations in *RAB27a* at 15q21, patients have neutropenia and pancytopenia and progress to an accelerated phase similar to that in CHS.[94] *RAB27* is expressed in melanocytes and hematopoietic cells but not in brain.[95] A third form with only hypopigmentation is caused by mutations at 2q37.3 in *MLPH*, a gene encoding melanophilin that is expressed in melanosomes but not brain.[96] Melanophilin is involved in the interactions of the *MYO5a* and *RAB27a* gene products to mediate melanosome transport.[97]

Clinical Features and Diagnosis

Based on the phenotypic similarities between Griscelli syndrome and CHS, a patient with hypopigmentation and immune dysfunction should be evaluated for both conditions. The distinguishing feature of CHS is the presence of large granules in the neutrophils, melanocytes, and keratinocytes. Examination of the hair shafts in patients with CHS shows only small melanin aggregates in comparison to the large clumps seen in patients with Griscelli syndrome. Because of the defect in granule transport, melanosomes accumulate in the melanocytes but are reduced in the keratinocytes in all subtypes of Griscelli syndrome.[98] Confirmation can be provided by mutation analysis.

Patients with Griscelli syndrome have silver hair with hypopigmentation of their skin and eyes. Patients with type 2 are vulnerable to fever and recurrent infections. Hepatosplenomegaly and a combined T-cell and B-cell deficiency are common. Natural killer cell activity, delayed-type hypersensitivity, and the response to an antigenic challenge all are impaired.[99] Immunoglobulin levels may be normal or low; other features are hypofibrinogenemia, hypertriglyceridemia, and hypoproteinemia.[99] The accelerated phase with hemophagocytic lymphohistiocytosis is characterized by fever, pancytopenia, and diffuse lymphocytic infiltration of brain, spleen, liver, and lymph nodes. Neurologic deficits are associated with lymphohistiocytic infiltration in the central nervous system.[95]

Treatment and Prognosis

The accelerated phase is lethal within months without a hematopoietic stem cell transplantation,[95,100] although immune suppression with glucocorticosteroids, antithymocyte globulin, methotrexate, etoposide, and cyclosporin have all been reported to be of benefit, at least transiently.[101–103]

BARTH SYNDROME

Barth syndrome is rare disorder characterized by cardiomyopathy, neutropenia, and skeletal myopathy. In 1983, Barth and associates described a large family with affected males who typically died from sepsis or cardiac failure before the age of 3.[104] Mitochondria appeared normal in cardiac and skeletal muscle. A patient with a similar X-linked condition, reported by Neustein and coworkers in 1979, had abnormal mitochondria on electron microscopy.[105] Barth syndrome has an estimated incidence of 1 per 300,000–400,000 male births, based on the identification of 10 new cases annually in the United States.[106]

Pathophysiology

The locus for the Barth syndrome gene is Xq28,[107] and the disease is due to mutations to the *G4.5* gene (renamed *TAZ*).[108] The gene products of *TAZ*, the tafazzins, may share some homology with acetyltransferases involved in complex lipid metabolism,[109] and defects in cardiolipin synthesis may lead to mitochondrial dysfunction.[110] Molecular abnormalities of several phospholipids, including cardiolipin, were demonstrated in 19 of 25 children with Barth syndrome.[111]

Clinical Features and Diagnosis

Barth syndrome findings include dilated cardiomyopathy, skeletal myopathy, neutropenia, growth retardation, and elevated urinary excretion of 3-methylglutaconic acid.[112] Diagnosis is established by echocardiogram, quantitative urine organic acid analysis including quantification of 3-methylglutaconic acid (can be increased 5- to 20-fold), serial blood counts, and growth monitoring.[106] Neutropenia can be chronic, cyclic, or absent.[112] Cyclic oscillations in Barth syndrome occur at between 21 and 28 days. Peak absolute neutrophil counts are often normal, and nadirs approach zero. During infections, the neutrophil count may rise to normal or high levels.

Treatment and Prognosis

Supportive therapy is critical. Early diagnosis of Barth syndrome has been correlated with improved survival.[106] Cardiac function improves and may be normalized by treatment of congestive heart failure. Infectious complications improve with prompt recognition and aggressive treatment. G-CSF increases neutrophil levels and may be clinically beneficial.[106]

GLYCOGEN STORAGE DISEASE, TYPE 1b

Glycogen storage diseases are genetic disorders that interfere with glycogen synthesis and degradation. Glycogen storage disease (GSD) was first described by Von Gierke in 1929[113] and further defined by Cori and Cori[114] and Senior and Loridan.[115] There are several subtypes of GSD; the subtyping divides patients with primary deficiencies in glucose-6-phosphatase deficiency from those with defects in intracellular glucose transport.[116,117] Neutropenia and neutrophil dysfunction are characteristic features of GSD 1b[118] and have been documented in only a single patient with type 1a.[119] The frequency of GSD type 1 is thought to be less than 1:50,000.[120]

Pathophysiology

GSD 1b is caused by a mutation in the glucose-6-phosphatase transporter gene at 11q23. This gene encodes a protein that delivers glucose 6-phosphate from cytoplasm to the lumen of the endoplasmic reticulum, where it is catalyzed by glucose-6-phosphatase to glucose and phosphate.[121–123]

Clinical Features and Diagnosis

Patients with GSD 1b typically present with hypoglycemia, hepatomegaly, and growth retardation early in the first year of life.[124] Deficiency of the glucose 6-phosphate translocase causes hypoglycemia with irritability, seizures, and coma. Other features include hyperlipidemia, hyperuricemia, organomegaly secondary to glycogen accumulation, inflammatory bowel disease, and osteopenia.

The diagnosis of GSD 1b is established based on clinical features and the absence of an increase in serum glucose levels following the administration of glucagon or oral galactose. Mutation analysis and enzyme studies on samples obtained by open liver biopsy can confirm the diagnosis.[124]

About 90% of patients have neutrophil counts of less than 1000 cells/μL[125] at diagnosis, and usually the neutropenia gradually worsens.[125] Patients may also be anemic and experience frequent epistaxis.[124] The bone marrow may be normal or hypercellular with abundant mature neutrophils, or may show "maturation arrest."[126,127] Marrow neutrophils appear predisposed to early apoptosis.[128] Neutropenia plus neutrophil dysfunction, reduced chemotaxis, and impaired respiratory burst[118,129,130] result in susceptibility to infections of the skin and perioral and perianal areas as well as pneumonia, sepsis, and meningitis. Infections are often caused by *Staphylococcus aureus,* group A streptococci, *Streptococcus pneumoniae, E. coli,* and *Pseudomonas* species.[127] Chronic diarrhea and inflammatory bowel disease are often severe. In these neutropenic patients, it may be difficult to determine whether new gastrointestinal symptoms represent a worsening of chronic inflammatory conditions or a new infection. Late complications of GSD 1b include predisposition to hepatic adenomas with increasing age and progressive renal disease.[124] The relationship between neutropenia and inflammatory bowel disease is unclear.[131] Neutrophil function and counts may improve following portacaval shunt anastomosis[132] and liver transplantation.[133,134]

Treatment and Prognosis

Treatment is directed toward correcting the metabolic abnormalities, as well as prevention of hypoglycemia and seizures. Liver transplantation is indicated in patients with dietary-unresponsive metabolic control and with complications of hepatic adenomas, including hemorrhage, compression, or malignant transformation.[124] G-CSF corrects the neutropenia and reduces infections; splenic enlargement is a universal complication of cytokine administration.[126,135] Low doses should be used, starting at 1–2 μg/kg/day to maintain neutrophils at 1000–2000/mm^3.[136] The inflammatory bowel disease also improves with G-CSF treatment.[135]

WISKOTT-ALDRICH SYNDROME

Wiskott-Aldrich syndrome (WAS) is characterized by microthrombocytopenia, immunodeficiency, and eczema. The first case was first described by Wiskott in 1937,[137] and X-linked inheritance was reported by Aldrich and colleagues in 1954.[138] The clinical manifestations of WAS are variable, and its phenotypic expression may evolve over time. In addition to an increased susceptibility to recurrent infections, patients are at risk to develop autoimmune disorders and malignancies. In its most benign form, X-linked thrombocytopenia, patients have low platelet counts (<70,000/mm^3) and abnormally small platelets, but do not manifest the immunologic abnormalities. Rarely, isolated neutropenia can be the presenting feature of WAS.[139] WAS occurs with a frequency of 4 per 1 million males.[140]

Pathophysiology

The WAS protein (*WASP*) gene is located at Xp11.22–p11.23.[141] More than 150 unique mutations have been reported in over 340 families.[142] The wide range of genotypic manifestations likely correlates with the variability of phenotypic expression. Patients who lacked *WASP* gene expression (those with nonsense mutations, large deletions, small deletions, and small insertions) were found to have an increased risk to develop infections, severe eczema, intestinal bleeding, and malignancies; these null expressions were predictive of mortality and morbidity.[143] The gene product of *WASP* is a cytoplasmic scaffolding protein that stabilizes actin filaments. The protein is believed to be important in the actin cytoskeletal rearrangement that occurs in response to immunoreceptor stimulation.[144]

Clinical Features and Diagnosis

A review of 154 patients revealed that only 27% had the classic triad of microthrombocytopenia, bloody diarrhea, and eczema; hematologic manifestations were present in 20% before the diagnosis of WAS was established. The clinical course was quite variable, even among patients in the same kindred. Autoimmune complications were associated with the risk of future malignancy.[145] Neutropenia, probably on an autoimmune basis, occurs in up to 25% of patients.[146] Other autoimmune processes (arthritis, skin vasculitis, cerebral vasculitis, inflammatory bowel disease, and glomerulonephritis) are also common in early childhood.[146]

Treatment and Prognosis

General measures for management include immunizations, intravenous immunoglobulin therapy, and suppressive antibiotic therapy.[147] Immunizations against *S. pneumoniae, Haemophilus influenzae,* and *Neisseria meningitidis* and treatment with prophylactic antibiotics are recommended.[147] Splenectomy generally increases the platelet counts and reduces the risk for major hemorrhage[147–149] but increases the risk of death from sepsis. Hematopoietic stem cell transplantation is curative from a matched donor; best results are obtained with a sibling donor.[150,151]

CURRENT CONTROVERSIES & FUTURE CONSIDERATIONS

Congenital Neutropenia

- The molecular pathophysiology linking the genetic defects associated with the diseases that cause congenital neutropenia to their phenotypic expression remains under investigation.
- The molecular pathophysiology must account for a wide spectrum of phenotypic expression seen with the diseases that cause congenital neutropenia.
- The risk of leukemic transformation varies substantially in various types of congenital neutropenia. Risk factors for leukemia are not yet fully defined.
- The future treatment of congenital neutropenia may be directed at correcting underlying genetic defects or may include drugs specifically designed to target abnormal molecular pathways

Suggested Readings*

Dale DC, Person RE, Bolyard AA, et al: Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia. Blood 2000;96:2317–2322.

Dale DC, Bonilla MA, Davis MW, et al: A randomized controlled Phase III trial of recombinant human granulocyte colony-stimulating factor (filgrastim) for treatment of severe chronic neutropenia. Blood 1993;81:2496–2502.

Dale DC, Cottle TE, Fier CJ, et al: Severe chronic neutropenia: treatment and follow-up of patients in the Severe Chronic Neutropenia International Registry. Am J Hematol 2003;72:82–93.

**Full references for this chapter can be found on accompanying CD-ROM.*

TABLE 13–1. Characteristics of the Congenital Neutropenias

Disorder	Incidence	Clinical Features
Severe congenital neutropenia	2:1,000,000	Neutrophil counts <200 cells/μL with recurrent bacterial infections.
Cyclic neutropenia	0.5–1:1,000,000	Periodic oscillations of neutrophil counts, with nadirs <200 cells/μL approximately every 21 days and periodic vulnerability to infections, especially oral ulcerations.
Myelokathexis (WHIM syndrome)	~25 case reports	Neutrophil counts <500 cells/μL with lymphopenia despite hypercellular bone marrow. Neutrophils and eosinophils appear "bizarre" in bone marrow and blood. Association of warts, hypogammaglobulinemia, infections, and myelokathexis (retention in the bone marrow) defines WHIM syndrome.
Cartilage-hair hypoplasia	Finland: 1:23,000 Old Order Amish: 1.5:1,000	Short-limb dwarfism with hypoplastic hair, T-cell dysfunction. Neutropenia seen in ~24% of cases.
Shwachman-Diamond syndrome	1:77,000	Exocrine pancreatic dysfunction, short stature, and neutropenia (66% with absolute neutrophil count <1000 cells/μL, often with cyclic fluctuations), mild anemia.
Chédiak-Higashi syndrome	>200 case reports	Hypopigmentation of hair, eyes, and skin with neutropenia and recurrent bacterial infections. Giant peroxidase-positive lysosomal granules in granulocytes from bone marrow and blood. Vulnerability to hemophagocytic lymphohistiocytosis evolution.
Griscelli syndrome, type 2	~60 case reports (all types)	Hypopigmentation of hair and skin, neutropenia typically seen in association with pancytopenia; patients also have impaired T-cell and B-cell function. Vulnerability to hemophagocytic lymphohistiocytosis evolution.
Barth syndrome	1:300,000–400,000 males	Cardiomyopathy, skeletal myopathy, and neutropenia (can be cyclic).
Dyskeratosis congenita	~275 case reports	Abnormal skin pigmentation, nail dystrophy, and mucosal leukoplakia. Bone marrow failure before the first decade of life is common with pancytopenia.
Glycogen storage disease, type 1b	<1:100,000	Hypoglycemia, hepatomegaly, and growth retardation associated with glycogen accumulation in the liver and kidneys. Neutrophil counts typically <1000 cells/μL; neutrophil dysfunction.
Wiskott-Aldrich syndrome	4:1,000,000 males	Microthrombocytopenia, immunodeficiency (25% with neutropenia), and eczema; increased risk of autoimmune disease and malignancy.

TABLE 13–2. Molecular Biology of the Congenital Neutropenias

Disorder	Inheritance	Gene and Locu	Enzyme Defect
Severe congenital neutropenia	AD and S	*ELA2* at 19p13.3	Neutrophil elastase: a prominent enzyme in the primary granules
Cyclic neutropenia	AD and S	*ELA2* at 19p13.3	Neutrophil elastase: a prominent enzyme in the primary granules
Myelokathexis (WHIM syndrome)	AD and S	*CXCR4* at 2q21	CXCR4 gene product: chemokine receptor involved in leukocyte trafficking
Cartilage-hair hypoplasia	AR and S	*RMRP* at 9p13	Ribonuclease MRP: mitochondrial processing of RNA or pre-RNA
Shwachman-Diamond syndrome	AR	*SBDS* at 7q11	SBDS gene product: involved in RNA metabolism
Chédiak-Higashi syndrome	AR	*CHS1* at 1q43	LYST: a lysosomal trafficking regulatory protein
Griscelli syndrome, type 2	AR	*RAB27a* at 15q21	GTPase: expressed in melanocytes and T cells; may have a role in granule release and cytotoxicity
Barth syndrome	X-linked	*TAZ* at Xq28	Tafazzins: involved in cardiolipin synthesis; important in normal mitochondrial function
Dyskeratosis congenita	X-linked	*DKC1* at Xq28	Dyskerin: component of the telomerase complex involved in telomere synthesis
	AD	*hTERC* at 3q21–q28	hTERC gene product: RNA component of the telomerase complex involved in telomere synthesis
	AR	Not identified	
Glycogen storage disease, type 1b	AR	*G6PT* at 11q23	Glucose 6-phosphate translocase: transports glucose 6-phosphate from the cytoplasm to the lumen of the endoplasmic reticulum
Wiskott-Aldrich syndrome	X-linked	*WASP* at Xp11.22–11.23	WASP gene: cytoplasmic scaffolding protein that stabilizes actin filaments

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; S, sporadic.

TABLE 13–3. Treatment of Congenital Neutropenias with G-CSF

Disorder	General Role	Dose	Other Comments
Severe congenital neutropenia	All patients	5–50 μg/kg SQ daily	Maintain ANC > 1000 cells/μL Severe disease that requires higher doses may predict increased risk for transformation to MDS or AML
Cyclic neutropenia	Prophylactic	1–5 μg/kg SQ daily or every other day	G-CSF shortens periodicity of neutropenia Decreases the severity of neutropenia
Myelokathexis (WHIM syndrome)	Generally not necessary Use in patients with recurrent infections	1–5 μg/kg SQ daily	Normalizes ANC G-CSF corrects accelerated apoptosis of neutrophils
Shwachman-Diamond syndrome	Use in patients with severe neutropenia and recurrent infections	1–10 μg/kg SQ daily	Normalizes ANC Possible increased risk of malignant transformation
Chédiak-Higashi syndrome	Neutropenia is generally mild G-CSF may be beneficial with recurrent infections	1–10 μg/kg SQ daily	G-CSF may increase ANC
Barth syndrome	Neutropenia is generally mild G-CSF may be beneficial with recurrent infections	1–10 μg/kg SQ daily	G-CSF increases ANC
Glycogen storage disease, type 1b	90% of patients with ANC < 1000 cells/μL	1–2 μg/kg SQ daily	Maintain ANC > 1000 cells/μL Splenic enlargement is a universal complication of G-CSF use Inflammatory bowel disease improves with G-CSF therapy

Abbreviations: ANC, absolute neutrophil count; SQ, subcutaneously.

Figure 13–1. Algorithm for the diagnosis of congenital neutropenia.

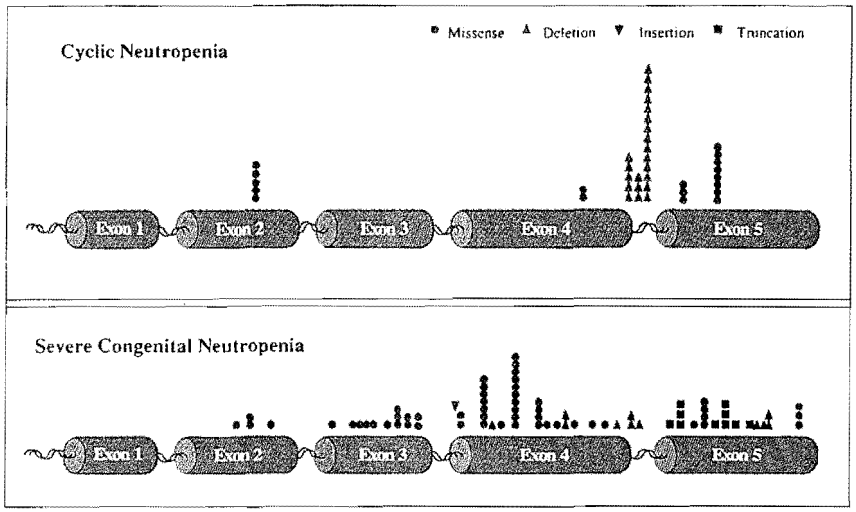

Figure 13–2. The pattern of mutations in the gene for neutrophil elastase in patients with cyclic and autosomal dominant congenital neutropenia.

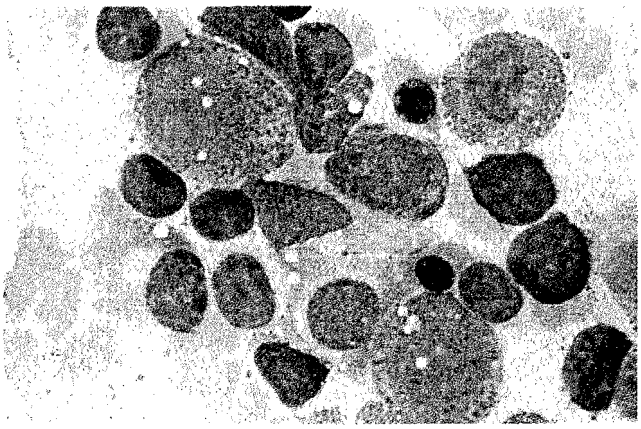

Figure 13–3. Bone marrow aspirates from a patient with severe congenital neutropenia showing neutrophil precursors; mature neutrophils are absent or greatly reduced.

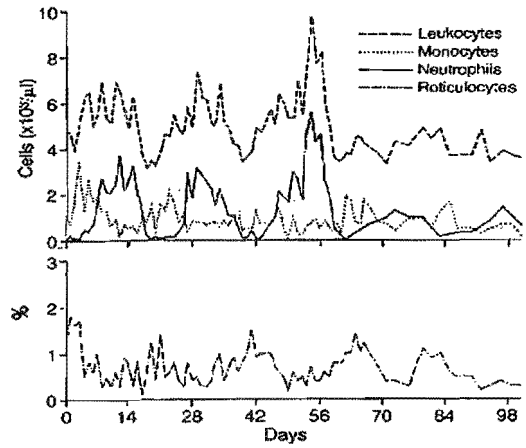

Figure 13–4. Serial blood cell counts for a patient with cyclic neutropenia. Oscillations in absolute leukocyte blood neutrophils, monocytes, and reticulocytes are shown. (From Dale DC, Hammond WP: Cyclic neutropenia: a clinical review. Blood Rev 1988;2:178–185, with permission.).

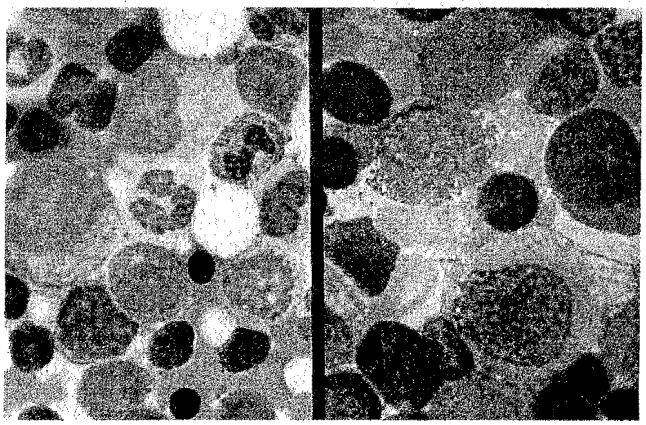

Figure 13–5. Bone marrow aspirate cells from a patient with cyclic neutropenia at the peak and the nadir of the neutrophil cycle.

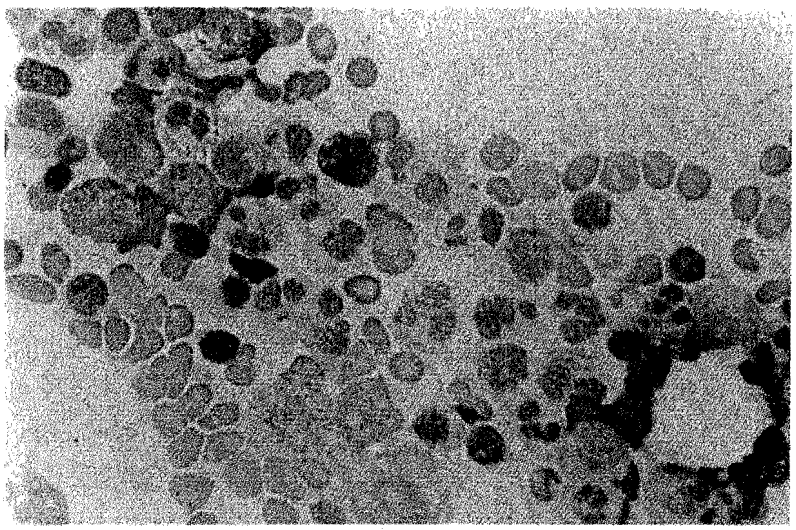

Figure 13–6. Bone marrow aspirate from a patient with myelokathexis. The marrow shows many segmented and hypersegmented neutrophils. By contrast, in the blood, there is severe neutropenia.

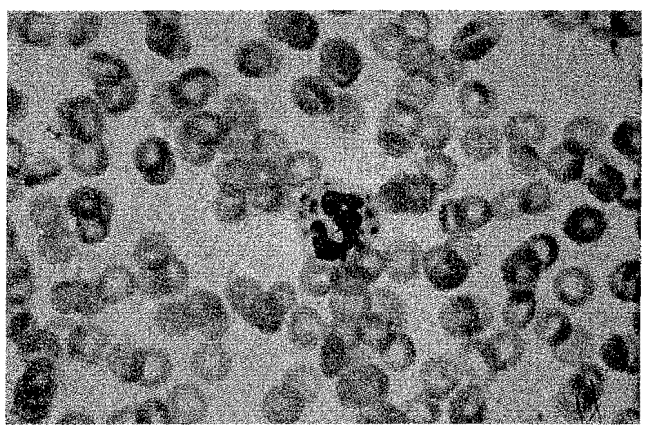

Figure 13–7. Blood smear showing typical appearance of a neutrophil of a patient with Chédiak-Higashi syndrome. The large cytoplasmic granules can be seen easily with standard Wright- or Giemsa-stained blood smears. (From the teaching collection of the American Society of Hematology.)

AUTHOR QUERY FORM

Dear Author,
During the preparation of your manuscript for publication, the questions listed below have arisen. Please attend to these matters and return this form with your proof.
Many thanks for your assistance.

Query References	Query	Remarks
1	This sentence has been moved to the Treatment and Prognosis section under Severe Congenital Neutropenia, where the use of G-CSF is first discussed.	OK
2	Should this read "more than 2 standard deviations," or value is actually between age-adjusted mean and 2 SD below that?	Yes
3	References 64 through 69 have been renumbered to cite in order.	OK
4	Should be hyper- or hypo-?	
5	Tables 1 and 2 have been revised to eliminate overlap; Table 1 now contains incidence and clinical features, and Table 2 contains information on genetics. OK?	Yes