Published in final edited form as:
N Engl J Med. 2009 January 1; 360(1): 3–5. doi:10.1056/NEJMp0806821.

The Many Causes of Severe Congenital Neutropenia

David C. Dale, M.D [professor of medicine] and
University of Washington School of Medicine, Seattle.

Daniel C. Link, M.D [associate professor of medicine]
Division of Oncology, Section of Stem Cell Biology, Washington University, St. Louis.

In 1956, RolfKostmann, a Swedish pediatrician, described an autosomal recessive disorder that he called infantile genetic agranulocytosis-which is now called severe congenital neutropenia. The Kostmann form of this disorder is very rare; it is caused by disabling mutations in the *HAXl* gene, which encodes HAX1, a mitochondrial protein that inhibits apoptosis (see table).[1] There are also autosomal dominant and sporadic forms of severe congenital neutropenia that are caused by mutations in the *ELA2* gene, which encodes the serine protease neutrophil elastase.[2] *ELA2* mutations account for approximately 50 to 60% of cases of the disorder. Rare cases of severe congenital neutropenia associated with mutations of the genes encoding the Wiskott-Aldrich syndrome protein *(WAS)*, growth factor independent 1 protein *(GFll)*, and colony-stimulating factor 3 receptor (granulocyte) *(CSF3R)* have also been reported (see table). Neutropenia ofvarying severity occurs in association with complex congenital disorders, such as the Shwachman-Diamond syndrome (a rare, autosomal recessive multisystem disorder primarily featuring digestive enzyme insufficiency, skeletal abnormalities, and often neutropenia), the Barth syndrome (an X:-linked genetic disorder of lipid metabolism causing cellular lipid deficiency, with cardiomyopathy, neutropenia, muscular hypoplasia or weakness, and growth delay), the WHIM syndrome (an autosomal dominant disorder causing warts, hypogammaglobulinemia, recurrent bacterial infection, myelokathexis, severe chronic leukopenia and neutropenia), and the Chédiak-Higashi syndrome (an autosomal recessive multisystem disorder causing hypopigmentation of the skin, eyes, and hair; prolonged bleeding times; easy bruising; peripheral neuropathy; and recurrent infection secondary to neutropenia). Another hallmark of some forms of severe congenital neutropenia is a predisposition to the myelodysplastic syndrome and acute myeloid leukemia; the rate of malignant transformation exceeds 20%.[3]

Clinically, examination of the bone marrow is the most important diagnostic test for evaluating severe congenital neutropenia. In children with this disorder, the marrow typically contains an ample number of early myeloid precursors but has a paucity of mature neutrophils. There is also a reduced number of circulating neutrophils. Treatment with granulocyte colony-stimulating factor (G-CSF) has changed the natural history of this disease; more than 90% of patients have a clinically significant increase in the numbers of

No other potential conflict of interest relevant to this a rticle was reported.

circulating neutrophils and, with long-term G-CSF treatment, a reduction in the severity and frequency of infection.

In this issue of the *Journal*, Boztug et al. (pages 32- 43) report that mutations of the gene for glucose-6-phosphatase, catalytic subunit 3 *(G6PC3)* are associated with a newly discovered form of severe congenital neutropenia. Homozygous mutations of *G6PC3* were identified in five children with the disorder from two con sanguineous pedigrees and an additional seven unrelated patients with severe congenital neutropenia. In contrast to those with other forms of the disorder, children with *G6PC3* mutations frequently have cardiac abnormalities, thrombocytopenia, and urogenital abnormalities. The mutations of *G6PC3* result in a loss of phosphatase activity. G6PC3 catalyzes the hydrolysis of glucose-6-phosphate to glucose and phosphate, the terminal step of the gluconeogenic and glycogenolytic pathways. Another disorder of glucose metabolism, type Ib glycogen storage disease, caused by mutations of the glucose-6-phosphate transporter 1, is also associated with severe chronic neutropenia.

At first glance, the diversity of mutated genes in this disorder argues against a shared mechanism of pathogenesis. However, a common feature of most types of severe congenital neutropenia is increased apoptosis of neutrophils and their precursors. For cases in which there are G-CSF–receptor mutations (of *CSF3R)*, the loss-of-survival signals that are normally transmitted by this cytokine receptor point to a straightforward mechanism of increased apoptosis. Similarly, HAX1 appears to regulate cell survival directly, through the control of certain mitochondrial proteases that regulate the accumulation of Bcl-2–associated X protein (BAX), a proapoptotic protein in the outer mitochondrial membrane. Mutations in *ELA2* result in the mis-folding of neutrophil elastase, leading to endoplasmic reticulum stress and induction of apoptosis through activation of the unfolded-protein response. [4,5] Boztug et al. suggest that stress on the endoplasmic reticulum may also mediate increased apoptosis in neu trophils with *G6PC3* mutations. The investigators present evidence that endoplasmic reticulum stress induced by altered glucose metabolism in G6PC3-deficient neutrophils can lead to apoptosis through the activation of the gene encoding glycogen synthase kinase 3 beta *(GSK3B)* and the subsequent phosphorylation of the myeloid-cell leukemia sequence 1 protein (Mcl-1), an antiapoptotic member of the Bcl-2 family.

The recent advances in our understanding of the genetic basis of severe congenital neutropenia have two important clinical implications. First, they emphasize the need for careful history taking and physical examination in children with severe neutropenia. Nonhematologic features may give important clues as to the correct diagnosis (see table). For example, cardiac abnormalities suggest the presence of *G6PC3* mutations or the Barth syndrome, and neuro-psychological abnormalities suggest mutations of *HAXl*. Other congenital anomalies are not present in patients with severe congenital neutropenia caused by *ELA2* mutations, and their absence probably reflects the myeloid-restricted expression of *ELA2*. Second, selected genetic testing should be performed to establish the diagnosis and inform genetic counseling. Given the high frequency of mutation, *ELA2* genotyping should be performed in all patients with suspected severe congenital neutropenia (or cyclic neutropenia). Sequencing of other genes should be directed by the presence of associated clinical features.

Several challenges remain. First, the genetic basis of severe congenital neutropenia remains unknown in a substantial proportion of children with the disorder. In a study involving North American patients, we observed that nearly 40% of patients had no mutation in *ELA2*, *HAXl*, *WAS*, or *GFJl (G6PC3* was not sequenced). Second, the effect of the genotype on the clinical course of the disorder is unclear. In particular, it will be important to determine whether the genotype influences the risk of leukemic transformation. Finally, better therapies for severe congenital neutropenia are needed. Treatment with G-CSF, though effective in increasing neutrophil counts in almost all forms of the disorder, does not prevent and may even be associated with progression to myelodysplastic syndrome or acute myeloid leukemia. The hope is that, as our understanding of the molecular pathogenesis improves, effective targeted therapies can be developed.

Acknowledgments

Dr. Dale reports receiving consulting fees from Amgen and Maxygen, lecture fees from Amgen, and research support from the Amgen Foundation to develop the Severe Chronic Neutropenia International Registry.

References

1. Klein C, Grudzien M, Appaswamy G, et al. HAX1 deficiency causes autosomal recessive severe congenital neutropenia (Kostmann disease). Nat Genet. 2007; 39:86–92. [PubMed: 17187068]
2. Dale DC, Person RE, Bolyard AA, et al. Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia. Blood. 2000; 96:2317–22. [PubMed: 11001877]
3. Rosenberg PS, Alter BP, Link DC, et al. Neutrophil elastase mutations and risk of leukaemia in severe congenital neutropenia. Br J Haematol. 2008; 140:210–3. [PubMed: 18028488]
4. Köllner I, Sodeik B, Schreek S, et al. Mutations in neutrophil elastase causing congenital neutropenia lead to cytoplasmic protein accumulation and induction of the unfolded protein response. Blood. 2006; 108:493–500. [PubMed: 16551967]
5. Grenda DS, Murakami M, Ghatak J, et al. Mutations of the ELA2 gene found in patients with severe congenital neutropenia induce the unfolded protein response and cellular apoptosis. Blood. 2007; 110:4179–87. [PubMed: 17761833]

Genetic Variants of Severe Congenital Neutropenia.

Gene	Gene Function	Incidence of Variant	Inheritance	Associated Features
ELA2	Serine protease	50–60%	Autosomal dominant, sporadic	Isolated neutropenia
HAX1	Mitochondrial function	Unknown	Autosomal recessive	Neurologic and neuropsychological abnormalities in some cases
GFI1	Transcription factor	Rare	Autosomal dominant	Monocytosis and defects in lymphocyte number and function
WAS	Cytoskeleton function	Rare	X-linked recessive	Monocytopenia and T-lymphocyte activation
CSF3R	G-CSF receptor	Rare	Autosomal dominant	Severe myeloid hypoplasia in the bone marrow; resistant to G-CSF treatment
G6PC3	Glucose metabolism	Unknown	Autosomal recessive	Cardiac defects, thrombocytopenia, and urogenital abnormalities