Epidemiology of Congenital Neutropenia

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KEYWORDS

• Congenital neutropenia • Epidemiology • Birth incidence • Prevalence

KEY POINTS

- Congenital neutropenia is a large family of diseases, and genetic diagnosis is an important criterion for classifying patients and reliably determining the epidemiologic indicators.
- Globally, patient registries were developed in the early 1990s to assess the safety of granulocyte colony-stimulating factor (GCSF) and concentrate expertise on the diseases.
- Approximately 20 years after starting the registries, incidence at birth was determined in 2 countries, roughly between 10 and 15 cases per million births, and the prevalence is probably more than 10 cases per million inhabitants.
- The rate leukemia risk can now be calculated reliably. Risk factors for leukemia seem to depend on both the genetic background and cumulative dose of GCSF.

INTRODUCTION

Congenital neutropenia is characterized by chronic neutropenia caused by a constitutional genetic defect. Epidemiologic investigations of congenital neutropenia aim to define the incidence at birth, prevalence, and several complications that occur in the course of the disease, such as lethal infections or leukemia. The management of congenital neutropenia has changed since granulocyte colony-stimulating factor

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(GCSF) became available for commercial use in 1993. Before this date, the literature was composed exclusively of case reports. The largest survey before 1990 involved 16 cases.[1] However, during this period, several entities have been described, including Kostmann disease, Shwachman disease, cyclic neutropenia, glycogen storage disease type Ib, and WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis syndrome). With its potential risk of leukemia, the availability of GCSF stimulated the development of patient registries. In 1993, such registries were organized in the United States, Canada, France, and Germany, and with the support of Amgen, an International Severe Chronic Neutropenia Registry (ISCNR) encompassing North America and Germany via independent association with public support in France. The establishment of registries allows better definition of diseases and their outcomes. Since the early 1990s, particularly during the last decade, the molecular bases of several entities have been discovered, leading to changes in disease classification. Kostmann syndrome is often considered to be part of the paradigm of congenital neutropenia; it was first described in a Swedish publication in 1950,[2] and subsequently in English in 1956.[3] The syndrome has 3 main characteristics: profound neutropenia (<0.2 G/L) occurring during the first weeks of life, maturation arrest of granulopoiesis at the promyelocyte stage, and death due to bacterial infections. Eleven of the 14 patients in the first report of the disease died in their first year of life from bacterial infections. Nearly 50 years later, a patient's life expectancy routinely exceeds 20 years and the molecular basis of this entity has been identified.[4] Kostmann syndrome is now known to be accompanied by mutation of *HAX1* protein (Kostmann pedigree) and neurologic involvement (mental retardation and epilepsy) if mutation involved 1 of the 2 isoforms of the *HAX1* protein.[5] Thus, the paradigm of congenital neutropenia is early hematologic expression and later neurologic involvement.

Knowledge of the molecular basis of other forms of congenital neutropenia has also modified the disease classification. Until the late 1990s, the literature distinguished between permanent neutropenia (severe congenital neutropenia or Kostmann syndrome) and cyclic neutropenia, which is associated with a regular pattern of change in the neutrophil count, typically every 21 days, with autosomal dominant transmission.[6] This distinction was made based on the International Registry of Chronic Neutropenia,[7,8] in which cyclic neutropenia was not included among the congenital neutropenias. In 1999, Horwitz and colleagues[9] identified mutations in the neutrophil elastase gene (*ELANE*) among 13 pedigrees of patients with cyclic neutropenia. The same team later found that many patients with severe congenital neutropenia also have mutations in *ELANE.*[10] This finding pointed to a continuum between severe congenital neutropenia and cyclic neutropenia, and showed that both can be considered congenital.

The term congenital neutropenia is not used homogeneously in the literature.[11–13] One restrictive definition reserves the term congenital neutropenia for severe forms of the disease that are not associated with immunologic or extrahematopoietic abnormalities, whereas a broader definition includes all diseases that comprise chronic neutropenia, with or without immunologic or extrahematopoietic abnormalities. Thus, only some investigators include glycogen storage disease Ib, Shwachman disease, WHIM syndrome, and Barth disease in the definition of congenital neutropenia.

EPIDEMIOLOGY

Definition of Congenital Neutropenia

Definition of the morbid phenomenon is critical in epidemiology. In this review, the term congenital neutropenia is not restricted to disorders in which neutropenia is the only