THE EVOLUTION OF THE DIAGNOSIS OF CONGENITAL NEUTROPENIAS IN THE ERA OF MOLECULAR TECHNOLOGIES

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Introduction

Congenital neutropenias (CN) constitute a group of rare genetic disorders characterized by: severe recurrent infections secondary to neutropenia, various organic dysfunctions and a high risk of leukemic transformation. Their incidence is estimated to be 1-4 cases per 1 million inhabitants. .

Objective of the study

This review aims to provide a comprehensive overview of the latest literature sources on the clinical and diagnostic features of congenital neutropenias.

Material and Methods

Were studied the articles published in the last 10 years, searched through databases such as: PubMed, MEDLINE, Google scholar.

Review

CN are rare genetic diseases characterized by an absolute number of neutrophils less than 1.5x109 /l that are associated with specific clinical phenotypes (pyogenic infections, gingivo-stomatitis, chronic periodontitis, etc.)

In 1956 the Swedish physician Rolf Kostmann described an autosomal recessive hematologic disorder with severe neutropenia with an absolute neutrophil count (ANC) less than 0.2x109/L and early onset of severe bacterial infections. And from that point the history of CN has starts

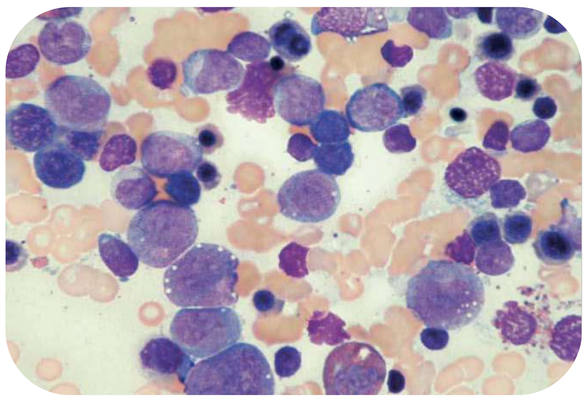

***Figure 1**. Tipical aspect of the bone marrow in a CN patient:The bone marrow usually shows a maturation arrest of neutrophil precursors at an early stage (promyelocyte/myelocyte level) with few cells of the neutrophilic series beyond the promyelocyte stage (x100)*

Clinical Features

Patients with CN develop severe bacterial infections in the first year of life. The risk of infection correlates with the degree(tab.1) and duration of neutropenia. The most frequently affected sites of infections are skin and mucosal linings in the oropharynx with bronchial and lung infections also common. Patients with CN are at risk for fatal sepsis, a feature that must be remembered.

Common clinical features associated with CN:

- Periodontitis
- Gingivitis
- Dental decay
- Oral aphthae
- GI inflammation mimicking inflammatory bowel
- Lack or diminished inflammatory infiltrates and pus in response to bacterial infections.
- A predisposition to bone fractures secondary to osteopenia
- inner ear hearing loss(in G6PC3 deficiency or GFI1 deficiency)
- epilepsy and delayed neurocognitive development (in HAX1 deficiency or CLPB-deficiency

***Table 1.** Classification of CN according to clinico-hematological aspects of neutropenia*

Classification of CN according to the severity of neutropenia	
Types of neutropenia	**ANC variance**
Mild neutropenia	ANC 1000e1500/mL
Moderate neutropenia	ANC 500e1000/mL
Severe neutropenia	ANC <500/mL
Persistent neutropenia	ANC continuously <1500/mL
Intermitent neutropenia	ANC occasionally <1500/mL
Cyclic neutropenia	ANC with periodic oscillations and nadir <1000

Two turning points revolutionized the scientific community studying CN:

1. Approval for the use of granulocyte colony-stimulating factor(G-CSF) – filgrastim - 1993
2. 2. Large-scale implementation of molecular-genetic techniques for CN diagnosis as RT-PCR; FISH; NGS sequencing etc (2000s)

Currently, mutations in more than 20 genes have been implicated as the cause of SCN.∗1 These mutations affect
the function of a variety of proteins that exert widely diverse intracellular functions, among which protein trafficking, actin cytoskeleton organization, mitochondrial integrity, transcriptional control and signal transduction.(tab. 2)

***Table 2.** Moleccular Clasification of Congenital Neutropenias*

Disorder	Genetic Defect	Recessive CN	Dominant CN	Clinical Presentation: Neutropenia plus
Congenital neutropenia with ELA 2 mutations	**ELA2**	-	+	Preleukemic syndrome / MDS
Congenital neutropenia with GFI-1 mutation	**GFI-1**	-	+	B-/T-cell deficiency
WHIM syndrome	**CXCR4**	-	+	Myelokathexis, IgG deficiency, warts
Shwachman-Diamond syndrome	**SBDS**	+	-	Exocrine pancreas insufficiency
Glycogen storage disease, type Ib	**Glucose-6-phosphate-Translocase**	+	-	Hypoglycemia, lactic acidosis
Hyper IgM	**CD40-L**	**X-linked**	-	IgG, IgA, IgE deficiency
Barth syndrome (3-methylglutaconic aciduria)	**Taz 1**	**X-linked**	-	Dilatative cardiomyopathy, skeletal myopathy, short stature
Congenital neutropenia with WASP mutation	**WASP**	**X-linked**	-	Monocytopenia, platelets normal
Hermansky-Pudlak syndrome	**AP3B1**	+	-	Partial albinism, short stature, IgG deficiency, platelet dysfunction
Congenital neutropenia with p14 (MAPBPIP) mutation	**P14/MAPBPIP**	+	-	Partial albinism, short stature, IgG deficiency
Griscelli syndrome	**Rab27a**	+	-	Partial albinism, hemophagocytosis
Chediak-Higashi syndrome	**LYST (CHS1)**	+	-	Partial albinism, T-/natural killer
Congenital neutropenia (unclassified)	**Not known**	+	**?**	Elevated IgG levels

Diagnosis

The diagnosis of CN relies on clinical and hematological features. Before the diagnosis of congenital neutropenia can be established, it is important to document the duration of neutropenia and whether it is persistent versus intermittent by serial complete blood counts. A single documentation of a low neutrophil count is not sufficient. To monitor the oscillatory pattern of neutrophil counts in patients with cyclic neutropenia, 2-3 blood counts per week for six weeks are needed. Patients with CN often have increased absolute numbers of monocytes and B cells, accompanied by hypergammaglobulinemia.

Morphological assessment of stained peripheral blood neutrophils and bone marrow progenitor cells are helpful to clarify the etiology of CN(fig.1)

The genetic confirmation of the diagnosis is mandatory.

Conclusion

Knowledge of the genetic defects of CN has valuable implications not only in the classification of these nosological entities, but can also serve as a target for potential molecular therapies in the near future.

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