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Benign ethnic neutropenia: importance of it as India is now center for medical tourism and educational hub

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Abstract:

Benign ethnic neutropenia is a condition characterized by a lower than normal absolute neutrophil count in individuals of certain ethnic backgrounds but is not at an increased risk of infection. It is a common cause of chronic neutropenia in people of African , Middle Eastern and West India descent. It is seen in less than 1% in the white population living in the US . Despite its prevalence, many physicians are not familiar with this benign condition, resulting in unnecessary evaluation and testing for neutropenia in otherwise healthy individuals. This article provides an overview of benign ethnic neutropenia including its clinical significance, underlying mechanisms and implications for medical practice. The discussion includes a review of relevant literature, highlighting the importance of recognising BEN to avoid unnecessary medical intervention and to ensure appropriate clinical management.

Introduction

Neutropenia is defined as an absolute neutrophil count of less than 1500/ microlitre. ANC is also useful for classification of the severity of neutropenia with mild defined as ANC between 1000/microlitre and 1500/ microlitre, moderate neutropenia as an ANC between 500/microlitre and 1000/ microlitre and severe neutropenia as ANC of less than 500/ microlitre. Clinical significance of neutropenia is an increased risk of infection which depends both on its severity and duration.[1, 2]

Neutropenia can be either congenital or acquired. Congenital neutropenia is mostly from autosomal dominant mutations in the ELANE gene. Acquired neutropenia can be due to a variety of causes - viral , infections , medications and therapeutic radiations. Then there is benign neutropenia with low absolute neutrophil count, asymptomatic and not increased risk of infection. [1, 2]

BEN is caused by a genetic variation in the ACKR1/DARC gene. This variation is also associated with the Duff- null trait which protects against Malaria.
Several studies have shown that individuals with BEN have normal bone marrow cellularity and normal myeloid maturation implying the neutropenia is due to defect in the release of mature granulocytes from the bone marrow.[1- 3]

This review encompasses all aspects of benign ethnic neutropenia providing information about this condition and helping to guide clinical decision making as to when an aggressive work up and referral are indicated and when it is appropriate to monitor.

Materials and methods

In this study we have received routine blood samples of RIMT students for their medical examination at the time of admission.

5 part Haematology Coulter.

Observations

Out of 100 students, 42 students are black belonging to African countries.

We studied the haemogram of these students and found that 15 % of the students out of 42 students are having low absolute neutrophil count i.e mild between 1000microlitre - 1500 microlitre.

As other causes of neutropenia are excluded with thorough medical examination and repetition of haemogram done after 2 weeks these students are grouped under benign ethnic neutropenia. So this is asymptomatic and is discovered incidentally during routine medical examination.

Review of literature

BEN is a common condition predominantly observed in individuals of African, Caribbean, Middle Eastern, and West Indian descent. It is characterized by persistently low absolute neutrophil counts (ANC) without increased susceptibility to infections. The phenomenon is attributed to genetic and physiological variations rather than pathological processes.

1. **Prevalence and Ethnic Distribution****
   a. BEN is most prevalent in individuals of African ancestry, with rates reaching 25-50% in certain populations, 10-15% in Middle Eastern and Jewish communities, and less than 1% in White populations.
   b. Children with BEN tend to exhibit lower ANCs than adults, consistent with normal variations in age-specific neutrophil ranges.

2. **Genetics and Mechanisms**
   a. The condition is strongly linked to the *Duffy-null polymorphism (rs2814778)* in the promoter region of the *DARC gene*, which inhibits the expression of the Duffy antigen receptor. This genetic trait is particularly common in malaria-endemic regions and may have evolved as a protective adaptation.
   b. Proposed mechanisms include:
   c. Impaired release of neutrophils from bone marrow.
   d. Enhanced migration of neutrophils into tissues, leading to lower circulating counts.

3. Clinical Implications
   a. BEN poses significant challenges in contexts such as chemotherapy and clozapine therapy, where neutropenia-related complications are critical considerations.
   b. Misinterpretation of BEN as pathological neutropenia often results in unnecessary medical investigations or treatment alterations, contributing to healthcare disparities.

4. Critiques of Existing Research: Misuse of Race in Diagnoses and Studies
   a. The first PDF critiques how historical research conflated race with genetic predispositions, leading to race-based rather than ancestry-informed diagnostic frameworks.
   b. It calls for replacing race-based language like "ethnic" with terms such as "familial" or "constitutional neutropenia" to reduce bias and enhance scientific clarity.

5. **Structural and Historical Factors**
   a. Many studies on BEN neglect structural determinants of health, such as socioeconomic status, environmental exposures, and systemic racism, which significantly influence health outcomes.

6. Clinical and Diagnostic Recommendations
For Physicians:

a. Recognize BEN as a benign condition requiring minimal intervention in the absence of infection, cytopenias, or organomegaly.
b. Differentiate BEN from pathological neutropenia through detailed patient history and, where necessary, genetic testing.

7. **For Treatment Protocols:**
   a. Adjust ANC thresholds for chemotherapy and clozapine management in patients with BEN to avoid unwarranted dose reductions or treatment discontinuation.

8. **For Research:**
   a. Expand reference ranges for neutrophil counts to be inclusive of diverse populations.
   b. Conduct genome-wide studies to uncover other genetic loci associated with BEN and its mechanisms across various ethnicities.

Several studies have investigated the clinical implications of BEN. A study by Hsieh et al. (2007) found that individuals with BEN had a similar risk of infection as those with normal neutrophil counts, supporting the benign nature of the condition. Another study by Reich et al. (2009) highlighted the importance of recognizing BEN in the context of chemotherapy dosing, as individuals with BEN may be misclassified as having chemotherapy-induced neutropenia, leading to inappropriate dose reductions.[3- 5]

The recognition of BEN has significant implications for clinical practice. It is essential for healthcare providers to be aware of this condition to avoid unnecessary investigations and treatments. For instance, individuals with BEN may be erroneously diagnosed with chronic idiopathic neutropenia or autoimmune neutropenia, leading to inappropriate use of granulocyte colony-stimulating factor (G-CSF) or other interventions. Additionally, the presence of BEN should be considered when interpreting complete blood counts (CBC) in individuals from high-prevalence ethnic groups, to ensure accurate diagnosis and management[4, 5]

This article provides a comprehensive overview of Benign Ethnic Neutropenia, emphasizing the importance of recognizing this condition in clinical practice to avoid misdiagnosis and unnecessary treatments.

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