Benign Neutropenia in Orthopedics: A Developing World Perspective

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Abstract

Infection complications in orthopedic surgery can impose significant costs and reduce quality of life. Neutropenia is a known risk factor for infection and delayed wound healing. Recent studies have revealed a high prevalence (10% - 20%) of neutropenia in several populations, most notably of the Middle East and African countries. This is due to a condition called Benign Ethnic Neutropenia (BEN) which is genetically determined (also known as familial benign neutropenia) and does not increase the risk of infection or impact overall survival. This creates novel and confusing clinical situations that could negatively affect the cost and quality of patient care like delay of surgical interventions, unnecessary investigations and use of antibiotics. Hence, there is a need for timely recognition of BEN and its differentiation from neutropenia that increase risk of infections. In this paper, we review characteristics of the BEN, use of complete blood count and management steps in the diagnosis of BEN. By increasing physician awareness, addressing diagnostic challenges, and implementing administrative policies, the impact of benign neutropenia on cost and quality of care can be mitigated.

Introduction

Neutropenia is a widely recognized risk factor for infection, and in the fields of orthopedics and surgery, it can significantly impact wound healing (1-7). Neutropenia is defined as absolute neutrophil count (ANC) < 1.5×10^9/L, and its prevalence in the general population is less than one precent. Over the past decade, research has revealed that in many populations of the Middle East and Africa, the prevalence of neutropenia is significantly higher, at least ten times more common than in populations of European descent (8-14). This is due to a high prevalence of Benign Ethnic Neutropenia (BEN), a genetic condition that does not increase the risk of infection (8, 12, 13). Yet, this benign condition presents a challenge in clinical practice as it can be difficult to differentiate from neutropenia that does increase the risk of infection. In this article, we will provide a brief overview of BEN, discuss its implications for practice, and outline the steps that physicians can take to differentiate between benign and non-benign neutropenia.

Various Types and Terminologies of Neutropenia

In addition to the numeric definition of neutropenia, it is commonly classified into two major groups: primary and secondary neutropenias. Traditionally, primary neutropenias are characterized by rare inherited gene mutations and are predominantly observed in pediatric populations. On the other hand, secondary neutropenias typically develop later in life as a result of underlying disease processes (such as malignancy, systemic lupus erythematosus, splenomegaly, vitamin B12 and folate deficiency, and infection) or the use of certain medications. Both primary and secondary neutropenia increase the risk of infection. In contrast, BEN is an inherited condition that does not elevate the risk of infection, making it distinct from other forms of primary neutropenia. Thus, BEN is sometimes referred to as primary or benign familial neutropenia.

Implications of Secondary Neutropenia in Orthopedic Surgery

Infection Risk: Neutrophils play a critical role in the body's immune response to infection, as they are responsible for combating bacterial and fungal pathogens (5). Orthopedic surgeries involving the implantation of prosthetic devices or invasive procedures carry an inherent risk of infection (2). In patients with neutropenia, the decreased neutrophil count may compromise their ability to effectively combat infections, thereby potentially increasing the risk of postoperative complications.(7). Generally, as severity and duration of neutropenia increase, the risk of infection progressively rises.

Wound Healing: Neutrophils also contribute to the early stages of wound healing by assisting in debris removal and promoting tissue repair. With reduced neutrophil levels, patients with neutropenia may experience delayed wound healing, which can prolong recovery and heighten the risk of wound complications in orthopedic surgical procedures (5, 6).

Origins of Benign Ethnic Neutropenia

Benign Ethnic Neutropenia has emerged in West Africa and represents a human adaptation to Plasmodium vivax, a widely distributed type of malaria and a significant cause of global mortality. BEN individuals lack receptors on their red blood cells, encoded by two alleles (Fy+/Fy+), which are responsible for binding to P. vivax. Inheriting a mutated gene from both parents (genotype Fy-/Fy-) results in the absence of these receptors, rendering individuals resistant to P. vivax. Additionally, such individuals test negative for the common Duffy antigen on red blood cells (15). Consequently, in West Africa, the population has

widespread resistance to P. vivax, resulting in the near eradication of the parasite from the region.

The reason for the low neutrophil count in BEN individuals remains uncertain. One speculation is that reduced neutrophil levels may be an unintended byproduct of this genetic mutation. Another possibility is that the lower neutrophil count might be a selection of reduces initial inflammatory response, which can be detrimental during P. vivax infection (16).

Prevalence of Neutropenia in General and Patient Populations

Benign neutropenia is estimated to affect approximately 300 million individuals worldwide (14). The prevalence of this condition decreases in an eastward direction from West Africa due to the diffusion and migration of individuals with the benign neutropenia genotype. In certain African countries, the recorded prevalence is approximately 40%, while in North African populations it is around 20%, and in Middle Eastern populations it is roughly 10% (9, 12, 14).

Understanding the prevalence of neutropenia in patient populations holds practical importance. In a study conducted in the United Arab Emirates, the frequency of neutropenia in outpatient is similar to that in general population and among inpatients is significantly lower yet remains high. In orthopedic outpatient department it was 7.9%, while in the general population was 10.9% (17). In contrast, among inpatients, the prevalence of neutropenia did not show an increase. This disparity in prevalence between outpatients and inpatients carries practical significance and can be attributed to the unique clinical characteristics associated with BEN.

Complete Blood Count and Diagnosis of BEN

The complete blood cell count (CBC) report - produced by automated haematological analysers and the most common blood test worldwide - provides absolute counts of the five types of white blood cells: neutrophils, lymphocytes, monocytes, eosinophils and basophils. Neutropenia is defined by neutrophil count of less than 1.5×10^9/L. However, the same report also provides total leucocyte count (sum of individual counts) and their five percentages of total leucocyte count. These additional six numerical results, provide no useful additional information about leucocytes and, therefore, are unnecessary. They are considered obsolete remnants of past hematology technology and have been debated for removal from the CBC report (18). They introduce information noise that could divert clinicians' attention from abnormal

result of absolute cell count - the sole relevant counts in decision-making processes (19). Moreover, the presence of these unnecessary counts (total and percent leucocytes) has the potential to confuse busy clinicians. For instance, a neutropenic patient may exhibit a normal total leukocyte count, adding unnecessary complexity to the interpretation. In short, clinicians should focus their attention to absolute counts of leucocytes.

Clinical Characteristics of Benign Ethnic Neutropenia

Healthy individuals with BEN typically do not have a history of recurrent infections, most are unaware of the condition, may or may not have a family history of neutropenia, and exhibit normal physical examination findings. However, physician should be aware that, due to the fact that this condition is common in general population, patients with any disease (especially with common ones) could have BEN as well; moreover, among such patients could be those with the diseases and clinical situations known to be associated with secondary neutropenia, an additional diagnostic challenge to physicians.

The overall survival of individuals with BEN remains unaffected. This is supported by evidence showing that the prevalence of BEN in children is equivalent to that in adults (13, 14). In other words, if BEN were causing higher death rates among children, they would be eliminated from the population, leading to a lower frequency of BEN among adults in the same population.

The lower limit of normal range of neutrophil count in apparently healthy children and adults with BEN is around 0.9 - 1.0 x10^9/L (13, 14). A small fraction of these individuals present with severe neutropenia (<0.5 x10^9/L), and rare healthy children have been observed with neutrophil counts as low as 0.05x10^9/L. Nonetheless, neutrophil counts naturally fluctuate, both in individuals without and with BEN. Consequently, individuals with BEN may have normal and low neutrophil counts (13). The exact proportion of those with BEN whose first (or only) neutrophil count is normal at the time they are first time seen by physician, is not well established; in one population with prevalence of BEN of around 11% it is estimated that additional two precent of general population has BEN (14).

Furthermore, during times of increased stress such as that due to acute trauma, surgery, infection, and pregnancy, individuals with BEN may experience an increase (i.e., normal or elevated) of neutrophil count. Indeed, women with BEN do not experience neutropenia during pregnancy. This unique clinical characteristic helps explain the lower prevalence of neutropenia observed in hospitalised patients, who tend

to experience higher levels of stress, compared to outpatients. These unique dynamics of neutrophil count could be used in the diagnosis of BEN (17).

Importance of Benign Ethnic Neutropenia

The recognition of the high prevalence and geographic distribution of BEN is a recent development and there is still limited awareness of it among health workers. In populations with high prevalence of neutropenia, the discovery of neutropenia in a patient presenting with a new problem should trigger three possible etiological explanations: i) benign neutropenia unrelated to the new problem, ii) secondary neutropenia related to (part of) the new problem, iii) secondary neutropenia unrelated to the new medical problem.

Investigating neutropenia necessitates additional time, tests, potential consultations, and adjustments to patient management. These adjustments may involve actions such as the administration of antibiotics, discontinuation or modification of medications, or changes to surgical plans or hospital discharge schedules. The cumulative effect of these steps may increase healthcare cost and have implications for the quality of patient care.

The higher prevalence of neutropenia in the Middle East and African countries, estimated to be approximately ten times more frequent, can influence the perspective of physicians regularly encountering patients with unexplained neutropenia. They may develop a tendency to generalise and assume that all cases are benign in nature. This assumption carries the risk of misdiagnosing secondary neutropenia and implementing inappropriate management strategies, ultimately leading to unfavourable outcomes.

Approach to a Neutropenic Patient (in a Population with Endemic Neutropenia)

In clinical practice, an ideal patient with BEN would exhibit the following characteristics: multiple CBC reports showing an ANC of less than 1.5x10^9/L, a close family member with a known history of neutropenia, no prior significant medical illnesses, and specifically, no history of frequent fevers or other signs and symptoms of infection. Additionally, this patient should not be taking any medications. Table 1 provides an overview of the main steps involved in assessing a neutropenic patient using a combination of history, physical examination, and laboratory results when presenting to a physician.

Management Step	Result / Finding	Likely cause is context dependent*
History	BEN	BEN
	Recurrent infections	Secondary neutropenia
	Other diseases	Secondary neutropenia is part of many
	Medications	Secondary (see Table 2)
	Neutropenia in family	BEN
Physical examination	Abnormal	Secondary neutropenia
	Normal	BEN
Laboratory	ANC < 1.5x10^9/L, single result	Neutropenia
	ANC < 1.5x10^9/L in previous tests	BEN
	ANC > 1.5x10^9/L in previous tests	BEN and Secondary neutropenia
Abbreviations: BEN, Benign Ethnic Neutropenia; ANC, absolute neutrophil count * Beware of Occam's razor (see text)		

Table 1. How to differentiate benign from secondary neutropenia

History: While only a small fraction of patients may acknowledge previous occurrences of neutropenia without associated infections, some individuals may disclose a history of neutropenia in their close family members. This line of questioning becomes more valuable as awareness of benign neutropenia grows among patients and healthcare providers in populations with endemic neutropenia. Although recurrent infections are not commonly reported in individuals with benign neutropenia, it is important to consider common viral infections of the upper respiratory tract when evaluating this information. When assessing the significance of past infections, information regarding hospitalizations and the use of antibiotics can offer insights into

their relevance in the context of neutropenia. Furthermore, a patient's history of medical conditions can help identify those associated with neutropenia, such as hematological diseases, viral and bacterial infections, radiation therapy, chemotherapy, systemic lupus erythematosus, and malignancies. Evaluating the causative role of current medication use in neutropenia is challenging because drug compendiums often list all possible adverse effects which often includes neutropenia. Nevertheless, Table 2 provides a list of well-established drug groups known to cause secondary neutropenia.

Drug Group	Drug Example
Antipsychotic	Cozapine, risperidone
Anticonvulsant	Carbamazepine, valporic acid, phenytoin
Hyperthyroidism	Methimazole, propylthiouracil
Inflammatory bowel diseases	Sulfasalazine
Antibiotics	Penicillin, beta-lactams, trimethoprim-sulfamethoxazole
Antiarrhythmic	Procainamide
Chemotherpay and immunosupression	Methotrexate, azathioprine, and others

Table 2. Medication groups and drugs with strong association of neutropenia

Physical examination: A thorough physical examination can provide valuable clues suggestive of infection or medical conditions associated with secondary neutropenia.

Laboratory Investigations: When evaluating a patient suspected of having BEN, it may be necessary to perform several repeated CBCs over a span of a few days. The computerization of laboratory results nowadays provides a significant advantage in examining past results and can save time in the differential diagnosis of neutropenia. However, it is crucial to interpret these results in the context of the patient's condition (diagnosis) at the time of testing. For instance, if the absolute neutrophil count is within the normal range during an acute illness (e.g., bacterial infection, physical trauma), it would support the diagnosis of BEN. Finally, future genotyping for BEN of selected patients may become available and screening of general population for neutropenia (as it is now performed for beta thalassemia and sickle cell) could remove many diagnostic uncertainties from current clinical practice.

Beware of Occam's Razor

In any population with a high frequency of multiple conditions, physicians should exercise caution in the differential diagnosis and avoid the misuse of Occam's razor. Occam's razor refers to the principle of reasoning that encourages physicians to avoid making multiple diagnoses in a patient, relying on the wisdom of experienced medical professionals who assert that the simplest diagnosis is usually the correct one. However, in populations where multiple medical conditions are common, it is possible for an individual to have two or more conditions simultaneously. For instance, in populations where BEN is prevalent, there is also a high frequency of other blood conditions such as alpha and beta thalassemia traits, iron deficiency anemia, and G6PD deficiency (20). The presence of neutropenia in conjunction with such conditions may strongly suggest the presence of a hematological disease. Therefore, in such populations, it becomes necessary to exercise caution when applying Occam's razor, as multiple diagnoses in a single patient may be required. Similarly, physicians should interpret neutropenia in specific patient subgroups where the likelihood of secondary neutropenia is heightened, such as patients taking certain medications (refer to Table 2) or patients with conditions known to be associated with secondary neutropenia.

Conclusion

The high prevalence of BEN in certain populations, such as the Middle East and Africa, highlights the importance of physician awareness. Differentiating BEN, a genetic condition without increased infection risk, from other forms of neutropenia that do pose infection risks is challenging. It involves obtaining a detailed history of present illness and family history, assessing previous infections, medication use, and associated conditions, conducting a thorough physical examination, and performing laboratory investigations. Physicians should prioritize absolute leukocyte counts over unnecessary total and percentage counts to avoid confusion. Repeated CBCs and contextual interpretation are crucial. Caution should be exercised when applying Occam's razor in populations with a high frequency of multiple conditions, as coexisting conditions are possible. Specific patient subgroups, such as those on medications or with conditions associated with secondary neutropenia, require careful consideration. Understanding BEN's epidemiology, recognizing its clinical importance, emphasizing the use of absolute neutrophil count, and following basic clinical steps enable optimal care, preventing misdiagnosis and ensuring appropriate management. Continued research and education are essential for improved patient outcomes and efficient healthcare.

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