

### A call for screening for benign neutropenia in Arab populations

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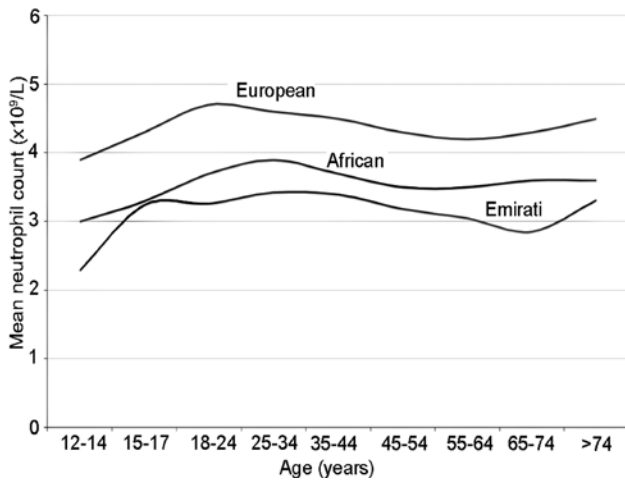
Benign neutropenia (BN), inherited as an autosomal dominant trait, is characterized by an absolute neutrophil count (ANC) of  $<1.5 \times 10^9/L$  (a common cutoff for neutropenia) which, however, does not result in an increased susceptibility to infection. Reports over the last 3 decades have suggested that BN is common among Arabs in Jordan, Kuwait, and Palestine.<sup>1</sup> A recent study in the United Arab Emirates (UAE) found BN in 10.7% of 1,032 adult native Arabs, with 2.3% of the population having a more profound neutropenia (ANC  $0.5-1.0 \times 10^9/L$ ). Since the above results were based on a single complete blood count (performed as a part of obligatory screening for sickle cell and beta-thalassemia) that normally oscillates, the true prevalence of BN among Arabs could be even higher than reported.<sup>1</sup> Indeed, in the UAE, clinicians quickly learn that neutropenia is frequent in clinical practice, is not normally associated with an increased rate of infections, and a detailed hematologic investigation is rarely rewarding. As a consequence, clinicians often adopt an approach of benign neglect toward laboratory reports of neutropenia. Here, we discuss the problems created by the frequent occurrence of BN, and propose population screening as a simple and cost effective solution for Emiratis and Arab populations elsewhere.

The central problem of medical decision-making in patients with BN is that they are difficult to distinguish from patients with secondary neutropenia due to acute viral infections, autoimmune diseases, malignancies, or medications. This is especially so when a patient with BN is acutely ill, and other manifestations of the disease raise the possibility of secondary neutropenia. The following problems have been observed among Emiratis with neutropenia. First, there have been and continue to be a substantial number of outpatient and inpatient consultations for subjects who turn out to have BN. An extensive and costly work-up, and prolonged follow-up of those with moderate and severe BN is frequently required. Second, decision making is often difficult in patients with BN presenting with acute febrile viral infections, the most common of human diseases. Here, an additional complexity is present for patients with bicytopenia (neutropenia and mild anemia), which is common due to the high prevalence of thalassemia trait and iron deficiency (approximately 20%) among

Emiratis. Bicytopenia is a stronger marker of a bone marrow disease than neutropenia alone, and is often an indication for bone marrow biopsy, especially in acutely ill patients. Third, postponement of surgical procedures is frequently required due to neutropenia of uncertain origin. Fourth, the observation of neutropenia can complicate pharmacotherapy for various disorders, especially when the preferred drug has the potential to disturb bone marrow functions. For example, the presence of BN can delay initiation of appropriate drug therapy while investigations are undertaken. Furthermore, BN can readily be misinterpreted as neutropenia secondary to medication, which may lead to inappropriate dose reduction, discontinuation of the drug, or change to a less effective treatment. Among American Blacks in whom the prevalence of BN is higher than in Caucasians, but less than in Arabs (Figure 1), these negative effects on patient management are well documented.<sup>2-5</sup>

The problems enumerated above result inevitably in an increased number of blood tests and clinic visits, unnecessary hospitalizations and extended hospital stays, and inappropriate investigations, including bone marrow biopsy. They all increase considerably and unnecessarily the cost of health care. Beyond financial considerations, the presence of BN in any acutely ill patient raises new diagnostic possibilities, thus adding to the apprehension and anxiety of the patient and family. An additional concern can arise when familiarity of clinicians with BN breeds contempt, such that patients who develop secondary neutropenia are at risk from delayed diagnosis and treatment. In an increasingly litigious environment, clinicians may decide to protect themselves by ordering unnecessary investigations and hospitalizations, and prescribe in a defensive manner.

Much of the difficult decision-making associated with BN in Emirate and probably in Arabs elsewhere could be avoided with prior knowledge of everyone's normal neutrophil count. We suggest that this could easily be achieved by the simple addition of a neutrophil count to the existing premarital screening program for Emiratis. This will not require additional blood tests, since a neutrophil count is part of a CBC that is already required in screening for common hemoglobinopathies. Subjects found to have an ANC  $<1.5 \times 10^9/L$  should be questioned regarding infections, medications, present and past medical diseases, and family history of neutropenia. If secondary neutropenia is excluded, they should be informed of the finding, given educational material, and issued with a 'neutropenia card'. This card would indicate the date and the ANC, and have sufficient space for additional recordings. If the diagnosis of BN is uncertain, further investigation should be performed.



**Figure 1** - Mean neutrophil count in 3 ethnic groups by age.

Where BN is established, family screening for BN should be carried out.

In addition, “as you go” screening should be established in the community, school, and hospital clinics. This should cover a large segment of Emiratis who are unmarried, and those who were married prior to institution of the above screening program. It should also detect BN at a young age, and in some cases before premarital screening. This population approach should avoid screening acutely ill subjects, since their neutrophil count is likely to be altered by intercurrent disease. The health authority should encourage effective screening for BN through existing CME programs, facilitate the development of a unified approach to neutropenic individuals (perhaps through the newly formed Emirates Society of Haematology), and add the ‘neutropenia card’ to their existing screening program. We predict that the cost of screening will be negligible in comparison with the potential savings. If successful, a similar plan might be implemented in other Arab countries, and for Arabs living in predominantly non-Arab countries.

A possible objection to screening for BN is that its costs and benefits are not based on published evidence. The few studies that have been performed in American Blacks indicate that the problems associated with BN are real.<sup>2-5</sup> In the UAE and other Arab countries, studies are urgently needed to determine if those with BN receive less treatment for their intercurrent illness, and if so, have poorer outcomes than those without BN.

It also needs to be determined whether these subjects are indeed being systematically over-investigated as we suspect. In the meantime, within the existing screening program for common hemoglobinopathies, the notification of all subjects with an ANC  $<1.5 \times 10^9/L$  presents a professional and moral obligation on the clinician. Screening for BN among Arab populations appears logical, since its costs will be very small, and the potential benefits considerable. We believe we should embark on systematic screening for BN among Emiratis, adapt similar approach in other Arabs, and simultaneously and methodically collect hard clinical and financial data to confirm that the process is justified.

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