Neutropenia and eosinophilia among Ethiopian immigrants to Israel: Familial or environmental?

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KEY MESSAGES
- Ethiopian immigrants have a higher prevalence of eosinophilia (marked environmental influence) and neutropenia (familial-genetic nature) than the general Israeli population.
- Lack of knowledge about these laboratory findings may lead to unnecessarily categorizing immigrant patients due to erroneous interpretations of their laboratory results.

ABSTRACT

**Background:** Due to trends of population movements, Israeli family physicians are treating increasing numbers of African immigrants from Ethiopia. These immigrants were found to have complete blood counts (CBC) that are different from other ethnic groups, with a higher prevalence of eosinophilia and neutropenia.

**Objectives:** To evaluate haematological findings in an attempt to define whether they behave as familial (genetic) or environmental.

**Methods:** Retrospective chart review of 300 patients from a primary care clinic: 100 individuals of Ethiopian heritage born in Ethiopia (EE); 100 individuals of Ethiopian heritage born in Israel, whose parents were born in Ethiopia (EI), and a control group of 100 patients who were not of Ethiopian heritage (C).

**Results:** Absolute eosinophilia (greater than 500/dl) was found in 13% of the EE study group significantly higher than the two other groups ($P < 0.05$), with no difference between EI and C. neutropenia (defined as less than 1500/dl) was found in 32% of EE group, 20% of EI, and 1% of C ($P < 0.01$).

**Conclusion:** On the one hand, findings point to a marked environmental influence on the eosinophilic response (most probably due to intestinal parasites present in immigrants from Ethiopia). On the other hand, a familial-genetic nature is probably the reason for the higher prevalence of neutropenia in this population, although some environmental influence may play a role. The knowledge of these findings may be useful for physicians treating people migrating from Africa.

Introduction

Since 1984, several waves of Ethiopian immigrants have settled in Israel (15 000 in 1991 and 55 000 from 1991 until 2005).\textsuperscript{[1]} Two characteristic haematological findings have been described among this group of immigrants: neutropenia,\textsuperscript{[2–5]} and eosinophilia.\textsuperscript{[6–8]}

Neutrophil counts have been long reported to vary greatly amongst ethnic groups. This phenomenon of low absolute neutrophil counts does not appear to be associated with a clinical disadvantage as compared with matched population controls and it is known as benign familial neutropenia (BFN).\textsuperscript{[3]} It is of common occurrence in people of African descent (25–50%),\textsuperscript{[9]} including African American and the African Caribbean as well as in Jews of Ethiopian and Yemenite background.\textsuperscript{[2–5,10–13]}

Eosinophilia was found in 14% of the Ethiopian immigrants to the US,\textsuperscript{[14]} 27% of African adult immigrants to Las Palmas de Gran Canaria,\textsuperscript{[15]} and 44% of Ethiopian Jews in Israel.\textsuperscript{[7]} The finding of eosinophilia was presumed to be the result of atopic
diseases and parasitic infections occurring before the immigration.

The purpose of this study was to compare two subgroups of Israelis of Ethiopian ethnicity: those born in Ethiopia (EE) and those born in Israel (EI) with a control (C) of the general population to define whether the haematological findings exhibit patterns of a familial (ethnic-genetic) or environmental (environmental factors that existed in Ethiopia and were no longer relevant with migration).

**Methods**

**Study design**

A retrospective review of the medical charts of 300 patients from a large community clinic of Clalit Health Services (the largest HMO in Israel treating more than 65% of the Israeli population) in the city of Beer-Sheva, Southern Israel was conducted. The clinic was chosen due to the large population of Ethiopian ethnicity it serves. The study included: 100 individuals of Ethiopian heritage born in Ethiopia (EE); 100 individuals of Ethiopian heritage born in Israel, whose parents were born in Ethiopia (EI), and a control group of 100 patients who were not of Ethiopian heritage (C), from the same clinic. Patients between 10 and 30 years of age with at least one blood count in their file were included. CBS are periodically performed in the clinic population. The study started in 2007.

The research department of the HMO selected randomly individuals for the EE study group from the total clinic population born in Ethiopia. These selected participants were then matched by age and gender with the other two randomly assigned populations, EI and C.

Exclusion criteria: women who in the year preceding the blood count had a positive documentation of pregnancy; individuals who had taken medications known to influence blood count in the year prior to the blood count (e.g. anti-mitotic, anti-epileptic, anti-psychotic medications, SSRIs, long-term use of system glucocorticoid steroids); and individuals who were HIV+ or had any other known immune disorders.

**Sample size**

To create an accurate sample, we assumed that the average white blood count (WBC) in the general adult population would be 7800 cells per cc (± 1500), and 4500 (± 1100) in the study sample of immigrants of Ethiopian origin. Therefore, a sample size of 26 individuals per group was sufficient (based on power of 80% with a confidence interval of 95%). The sample size for each group was calculated at 100 participants to ensure an error range inclusive of the hypothetical premise at a higher significance level.

**Statistical analysis**

The data was entered into EpiData 2.1 programme, converted to, and then analysed by the SPSS 17 programme. The comparison of the groups was analysed by a chi-square test for non-continuous variables, and a t-test or ANOVA for continuous variables. The correlation was analysed by Pearson’s test for linear values. Eosinophilia was defined as eosinophils >500 cells/μl. Neutropenia rates in the three groups were studied and defined in two distinct ways: <2000 cells/μl or >2000 cells/μl and <1500 cells/μl, 1500–2500 cells/μl and >2500 cells/μl.

The statistical difference between eosinophilia rates and neutropenia rates were tested by a chi-square test for each group pair separately, also, neutrophils were subjected to a t-test analysing the total white blood count. The correlation between neutropenia and eosinophilia in individuals was analysed using a chi-square test and a Pearson correlation coefficient.

An internal review board (The Helsinki Committee of the Meir Medical Centre—Approval #25/2008 k) approved this study. The ethics committee waived the need for informed consent, as the study did not involve patient contact (chart review using existing data and information blinded from identifiable data of the subjects).

**Results**

Table 1 provides sample population characteristics. In the control group, 34% of the participants were not

| Table 1. Study population characteristics. | Group C (n = 100) | Group EI (n = 100) | Group EE (n = 100) | P value |
|-------------------------------------------|------------------|-------------------|-------------------|--------|
| Born in Israel %                          | 66%              | 100%              | 0%                |        |
| Age, mean ± SD (years)                   | 23.55 ± 5.6      | 21.92 ± 4.5       | 23.76 ± 5.4       | 0.027  |
| Gender, male (%)                         | 41%              | 40%               | 42%               | 0.960  |
| Years in Israel, mean ± SD               | 13.6 ± 5.6       | 21.9 ± 7.2        |                   | 0      |
| Indication for blood counts (%)          |                  |                   |                   |        |
| Infection                                | 8%               | 8%                | 12%               |        |
| Follow-up                                | 57%              | 53%               | 41%               | 0.219  |
| Other                                    | 35%              | 39%               | 47%               |        |
| History of atopy (%)                     | 6%               | 19%               | 11%               | 0.017  |
| History of parasite infection (%)        | 3%               | 2%                | 2%                | 0.864  |

EE = born in Ethiopia, Ethiopian parents; EI = born in Israel, Ethiopian parents; C = control.
Israeli born, most of which came from the former USSR and only isolated cases from Argentina, Cuba, Romania and Hungary (all Caucasian), who lived in Israel for about 10 years, with no history of parasitic disease alike immigrants from Africa. The average age at time of the blood count was 23.5 ± 5.6 years. There was a statistically significant difference \((P < 0.05)\) between the average age of group EI (being somewhat younger at 21.9) as compared to the other two groups, but no known clinical significance was noted. Forty-one per cent of the participants were male. There was no significant difference for reason provided for blood count or history of parasitical diseases. A significant difference between group EI and the other two groups regarding history of atopic diseases was noticed. EI ad a higher incidence of atopic diseases (19%), while EE (11%) and C groups (6%) were significantly lower. Table 2 displays comparisons of the average blood count among the three groups. There were no significant differences regarding the red blood cell and platelets counts. However, there were significant differences in the white blood cells count. The average of the white blood cell sum (WBC) was significantly lower \((P < 0.01)\) in the EE group (6000 cells/mm³) as compared to the EI group (6520 cells/mm³) and the control group (7440 cells/mm³). The average absolute neutrophil count was significantly lower \((P < 0.001)\) in the EE and EI groups (3080 and 3470 cells/mm³, respectively) as compared to the control group (4210 cells/mm³). There was no statistical difference, between the EE and EI groups as to the absolute number of neutrophils and their percentage of the WBC.

Using the accepted definition of neutropenia \(<1500\) neutrophils cells/mm³, a statistical significance was noted between the three groups \((P < 0.001)\) (Figure 1).

The average lymphocyte count was significantly lower \((P < 0.05)\) for EE (2150 cells/mm³) and EI (2210 cells/mm³) as compared to the control group (2420 cells/mm³). Again, the values were not significantly different between EE and EI.

The average eosinophil count was significantly higher \((P < 0.001)\) for EE as compared to the other two groups with no difference between EI and C (190 and 180 cells/mm³, respectively).

No correlation was found between the indication to perform a CBC (follow-up, illness or other) and the existence of neutropenia and/or eosinophilia.

### Discussion

#### Main findings

Patients born in Ethiopia (EE) have a higher prevalence of eosinophilia than those of Ethiopian heritage who were born in Israel (EI) and those in the control group (C). The EI and the C group showed no differences as for the prevalence of eosinophilia.

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**Table 2. Comparison of blood counts between groups.**

|                       | EE        | EI        | C         | Sig EE to C | Sig EE to EI | Sig EI to C | Between the three groups |
|-----------------------|-----------|-----------|-----------|-------------|--------------|-------------|--------------------------|
| RBC cells × 10⁶/μl mean ± SD | 4.76 ± 0.46 | 4.72 ± 0.49 | 4.77 ± 0.45 | 0.923       | 0.514        | 0.450       | 0.71                     |
| Haemoglobin gr/dl mean ± SD | 13.67 ± 1.53 | 13.43 ± 1.88 | 13.62 ± 1.53 | 0.813       | 0.317        | 0.425       | 0.54                     |
| HCT % mean ± SD        | 40.41 ± 4.41 | 40.08 ± 5.16 | 40.76 ± 4.24 | 0.575       | 0.628        | 0.314       | 0.588                    |
| MCV (fl) mean ± SD     | 85.16 ± 4.68 | 84.94 ± 6.81 | 85.29 ± 4.77 | 0.845       | 0.786        | 0.669       | 0.9                      |
| MCH (pg) mean ± SD     | 28.69 ± 1.93 | 28.45 ± 2.75 | 28.58 ± 1.94 | 0.683       | 0.478        | 0.707       | 0.75                     |
| MCHC % mean ± SD       | 33.41 ± 1.91 | 33.47 ± 1.24 | 33.48 ± 1.06 | 0.722       | 0.790        | 0.918       | 0.92                     |
| RDW, mean ± SD         | 13.37 ± 1.25 | 13.88 ± 1.65 | 13.27 ± 0.91 | 0.525       | 0.019        | 0.002       | 0.003                    |
| WBC cells/mm³ mean ± SD | 6000 ± 1920 | 6520 ± 1970 | 7440 ± 1600 | 0           | 0.063        | 0           | 0                       |
| Lymphocytes cells/mm³ mean ± SD | 2150 ± 650 | 2210 ± 6800 | 2420 ± 700 | 0.006       | 0.495        | 0.038       | 0.015                    |
| Neutrophils cells/mm³ mean ± SD | 3080 ± 1570 | 3470 ± 1710 | 4210 ± 1280 | 0           | 0.098        | 0.001       | 0                       |
| Eosinophils cells/mm³ mean ± SD | 270 ± 230 | 190 ± 170 | 180 ± 130 | 0.003       | 0.012        | 0.661       | 0.003                    |
| Thrombocytes cells × 10⁹/μl mean ± SD | 260 ± 69 | 273 ± 59 | 263 ± 62 | 0.732 | 0.149        | 0.247       | 0.31                     |

RBC: red blood cells; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; RDW: red cell distribution width; WBC: white blood cells.
Neutropenia was found to be more prevalent in both groups of patients of Ethiopian origin (32% of EE, and 20% of EI), than in the local control population (1%).

**Interpretation of the study**

Our findings point to a marked environmental influence on the eosinophilic response of EE (most probably due to the higher prevalence of intestinal parasites in these immigrants) and to a familial-genetic explanation for the higher prevalence of neutropenia in this population. Because neutropenia is more prevalent in the EE group than the EI group, we believe this may indicate some environmental influence as well.

The total leukocyte count of sub-Saharan Africans has been documented to be lower than the one presented in most medical textbooks, and there is also a considerable difference in their mean neutrophil and eosinophil counts. It is estimated that approximately 25% to 50% of persons of African descent and some ethnic groups in the Middle East have BFN. In several studies in the United States Caucasians had significantly higher mean concentrations of leukocytes and neutrophils than African Americans. The use of separate haematological reference values for these two distinct groups has been suggested.

**Implications**

In the last decade, many people of African origin have emigrated, mainly to Europe. Some medical aspects of these immigrants deserve special attention. The immigrant group may have health and cultural characteristics that, if not acknowledged by medical providers, may adversely affect health outcomes. Many health systems worldwide are struggling on the national level to develop structured systems and guidelines to optimize the health delivery to the new arrivals, but currently, there is no consensus about the best approach. Physicians should use isolated reports in the literature to guide and learn more about the health status of their immigrant patients until guidelines are generated.

In this study, we analyzed two haematological characteristics of Ethiopian immigrants to Israel, eosinophilia and neutropenia. As there is a constant flow of immigrants from Ethiopia and other African countries, this information may be useful for physicians treating similar populations.

Recognizing BFN in the immigrant populations can help health providers to avoid unnecessarily categorizing and useless testing of patients due to erroneous interpretations of their laboratory results. Also, therapeutic approaches could and should be optimized for the different populations. This improvement is clearly illustrated in the article by Hershman et al. that discusses the disparities in breast cancer survival between African American and Caucasian women. When WBC counts fall below conventionally defined treatment thresholds for patients undergoing adjuvant chemotherapy, reduced doses or treatment delays may occur. This can lead to race-based differences in treatment duration and outcomes (based on incorrectly interpreting BFN as pathological) This phenomenon was also seen in women receiving adjuvant therapy for breast and colon cancer, and could affect cancer survival. Kourtis and colleagues suggested that the relevant division of AIDS table does not take into account the available evidence of low absolute neutrophil counts in African infants and that a systematic collection of data from many African settings may help establish a different absolute neutrophil count cut-off point to be used for re-defining severe and life-threatening neutropenia in people of African descent.

If a health provider is not aware of the benign condition mentioned, unneeded tests for the diagnosis of neutropenia may be requested, or certain pharmacological therapies may be discontinued. Alternatively, leucocytosis may not be recognized in these patients during severe and life-threatening infections as they might fall below the radar detection level for this condition.

The presence of eosinophilia among the EE population was found to be affected by environmental factors. On arrival in Israel, these patients were found to be highly infested with intestinal parasites such as Ancylostoma duodenal infections and were found to have increased levels of serum immunoglobulin E (IgE) levels with eosinophilia. Relative eosinophilia was also associated with helminthic infection in a recent study about immigrants to Spain. High levels of IgE were found in Ethiopian children on arrival to Israel, which gradually declined to those of Israeli-born children, several years of living in the new environment, suggesting that environment was the main contributing factor affecting IgE levels in this population. This correlation was also seen among African adult immigrants to Las Palmas de Gran Canaria, with eosinophilia being found in up to 27.0% of these immigrants. This was explained by the presence of filariasis, schistosomiasis, and other hookworm infections.

**Strengths and limitations**

The main strength of this study is that we were able to study two generations of a same ethnic group to
understand the bases of the haematological findings. The major limitation is a potential selection bias since patients from only one community clinic were studied.

Conclusion

Our findings support the premise that different haematological findings in African immigrants may have different causes. The neutropenia found in our study group seemed to be of a genetic nature while the eosinophilia has a marked environmental influence, seeming to decrease in the younger generation who had grown up in the new environment. For physicians who serve immigrant populations from Africa, this information may help to re-define haematological norms, thus avoiding possible diagnostic and therapeutic errors.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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