Article

Isolated Neutropenia/Benign Ethnic Neutropenia: A Common Clinical and Laboratory Finding in Southern and Southwestern Saudi Arabia

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Abstract: Objectives: Isolated mild neutropenia is a common clinical problem. The current study aims to validate our previous findings regarding the high prevalence of isolated neutropenia in Southern and Southwestern Saudi Arabia and explore the effect of altitude or regional differences. **Methods**: In this retrospective cross-sectional study, laboratory results of a commercial laboratory were screened over a period of 5 years (2016–2020) in seven different cities in South and southwestern Saudi Arabia. Participants' laboratory investigations were reviewed and excluded for any abnormal complete blood count, renal profile, liver profile, lipid profile, thyroid function test, fasting blood glucose, or HbA1c findings. Descriptive analysis and 95th percentile range were calculated using standard statistical methods. **Results**: A total of 91,880 complete blood count results were included in the final analysis. isolated neutropenia is common laboratory finding, with a prevalence ranging from 11-23%. The 2.5th percentile of the neutrophil count was lower than 1.5×10^9/L in all seven cities. **Conclusions**: Mild to moderate neutropenia is common in Southern and Southwestern Saudi Arabia. Benign ethnic neutropenia (BEN) may explain this high prevalence. Since BEN has no clinical significance, the reference range for normal neutrophil counts needs to be adjusted to reflect the effect of BEN.

Keywords: Isolated neutropenia; benign ethnic neutropenia; reference intervals; Saudi Arabia

1. Introduction

Neutrophils are the most abundant leukocytes in the peripheral blood. They play a pivotal role in the innate immune system and are a key regulator of the adaptive immune system [1,2]. The absolute neutrophil count (ANC) normally ranges from 1.8 to 7.5×10^9/L [3]. Marked reduction in the peripheral neutrophil count is regarded as a serious clinical problem that needs to be addressed. Peripheral neutrophils constitute only a minute fraction of the total body neutrophils that are mainly in the bone marrow. The number of neutrophils in the peripheral circulation may be affected by multiple factors, including stress, smoking, pregnancy, and drugs, that affect the measured fraction of the neutrophil count. Altitude may also be associated with lower neutrophil counts [4]. Reduced ANC is defined as a count less than 1.5×10^9/L and is known as neutropenia. In severe cases,

neutropenia predisposes an individual to infections or even life-threatening consequences. Neutropenia is categorized into three subtypes based on the ANC: mild (1.0–1.5 × 10^9/L), moderate (0.5–1.0 × 10^9/L), and severe (<0.5 × 10^9/L).

Decreased production or increased destruction of neutrophils may cause neutropenia [3]. Moreover, as first reported in 1941 by Forbes et al., low neutrophil count (<1.5 × 10^9/L) in certain ethnicities with no predisposition to infections indicates no clinical disadvantage in the affected individuals. This condition is known as benign ethnic neutropenia (BEN) [5,6].

In ethnicities with reduced circulating neutrophil counts, the bone marrow cellularity, morphology, number of granulocyte colony-forming units, and maturation of myeloid cells remain normal. However, slight reduction in the number of progenitors has been observed in some cases of BEN [5]. Additionally, a slight increase in ANC has been reported in individuals with BEN after exercise [7]. Subjects with BEN show a circadian variation of the neutrophil count similar to that observed in subjects without BEN [8].

BEN is most common in Africans, Afro-Americans, Ethiopian Jews, and Yemenite Jews [6,9–11]. We previously showed that a higher prevalence of isolated neutropenia was observed in two cities (Jeddah and Abha) in Saudi Arabia [12]. We aimed to confirm our previous findings through a large sample size from seven different cities (Jeddah, Taif, Al Baha, Abha, Khamis Mushait, Najran, and Gizan) in Southern and Southwestern Saudi Arabia. We also aimed to explore any potential association of neutropenia prevalence with altitude or any regional differences.

2. Methods

The study protocol was approved by the ethical and research committee of King Khalid University, Abha, Saudi Arabia (ECM#2019–68)–(HPO–06–B–001) and was conducted in accordance with the Helsinki Declaration. In this retrospective study, results of a commercial laboratory (Al-Borg Laboratories) were screened over a period of 5 years (2016–2020) in seven different cities in Saudi Arabia. Laboratory investigations included complete blood count (CBC), renal profile, liver profile, lipid profile, thyroid function test, fasting blood glucose measurement, and HbA1c measurement. Screened participants were either customers who do lab tests for health check-ups or follow up of chronic health conditions. Data were collected from the laboratories located in Jeddah (sea level), Taif (1,898 m above sea level), Al Baha (2000 m), Abha (2,270 m), Khamis Mushait (1,700 m), Najran (1,293 m), and Gizan (sea level). Exclusion lab criteria were applied to exclude any pre-existing health conditions. Subjects selected were all having normal CBC, biochemical, kidney, liver, sugar, lipid and thyroid profiles and thus were assumed healthy and proper to estimate the neutrophil count normal range.

Inclusion and Exclusion Criteria

Male and female patients aged 13–60 years were included. To estimate the white blood cell count (WBC) reference, the following exclusion criteria were applied: any abnormalities, unless mild, in the renal profile (serum blood urea nitrogen, creatinine), liver profile (ALT, AST, total bilirubin, and direct bilirubin), lipid profile (cholesterol, HDL, LDL, and triglyceride), thyroid function test (TSH, T4), and diabetic profile (fasting blood sugar and HbA1c).

For CBC, individuals with hemoglobin (Hb) concentration of 12–19 g/dl, platelet count of 140–450 × 10^9/L, and WBC count of less than 11.5×10^9/L were included. For low WBC count, the exclusion was applied only if other blood cell types were abnormal, e.g., concurrent anemia or thrombocytopenia. Analyses were performed with both inclusion and exclusion of neutrophil counts less than 0.5 × 10^9/L.

Blood Collection and Laboratory Analysis

To ensure no inter laboratory variations in the obtained results, the different branches follow organizational standard operating protocols of blood sample collection for CBC. blood samples were collected into liquid K3 EDTA tubes and processed within 2 hours of

collection. Sysmex automated analyzers (Sysmex Corporation, Kobe, Japan) were utilized for WBC enumeration and differential count.

Statistical Analysis

The participants' data were de-identified for any personal information before importing to an Excel datasheet. After extraction, data were revised, coded, and transferred into the statistical software IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA). Normal distribution assessment was applied for all scale parameters. Data for both sex and age were stratified into two groups: young adults (13–40 years old) and middle-aged adults (41–60 years old). Descriptive analyses using the mean and 95% confidence interval, median, range, standard deviation (SD), and percentiles (2.5th, 25th, 75th, and 97.5th) were utilized to assess the normal population range. Student's t-tests were used to compare continuous variables between different sex and age groups. A p-value <0.05 was considered statistically significant. Since plasma volume is known to be reduced with altitude, we explored any association between neutrophil count and hematocrit considering that lower hematocrit is associated with higher plasma volume and vice versa.

3. Results

For the present study, 91,880 CBC results were included in the final analysis. Table 1 summarizes the frequency of neutropenia in the studied population, while Table 2 depicts the statistical analysis of the mean, SEM, median, SD, range, and percentiles (2.5th, 25th, 75th, and 97.5th). Comparison between groups based on sex and age group is depicted in Table 3.

Mild neutropenia was the most common type of neutropenia among the study participants of all cities. The city of Al Baha showed slightly lower frequency in comparison with others, while the highest prevalence was observed in Najran and Gizan (17%). A high prevalence of moderate neutropenia was observed in Abha (5%), Najran (5%), and Gizan (6%). Severe neutropenia was rare among all types, with only 88 cases out of 91,880 (Table 1). Pearson correlation between hematocrit and neutrophil count was not significant.

The lowest value of ANC for the 2.5th percentile was found in Najran (0.83×10^9/L), while the highest was found in Jeddah (1.05×10^9/L). Additionally, the 2.5th percentile ANC value of the study participants in the remaining cities was between the ANC values found in Jeddah and Najran (0.83–1.05×10^9/L). The highest prevalence of isolated neutropenia was found in Najran (23% with mild and moderate forms). Gizan had a prevalence of 22%, making it the second most prevalent city for neutropenia, while in Taif, Jeddah, Khamis Mushait, Abha, and Al Baha, the frequency of neutropenia (combined mild and moderate) was found to be 11%, 15%, 16%, 17%, and 18%, respectively. Severe neutropenia was the rarest, with only 88 cases out of 91,880 (0.096%).

Table 1. Frequency of neutropenia in the studied populations.

		Jeddah	Taif	Al Baha	Abha	Khamis Mushait	Najran	Gizan
Number	Female	29738	3486	1867	4689	6554	2188	2885
	Male	24001	2765	1359	3315	4807	1840	2386
	Overall	53739	6251	3226	8004	11361	4028	5271
Mild neutropenia (1.0–1.5×10⁹/L)	Female	3544	287	249	631	748	365	464
	Male	2744	200	190	310	564	302	412
	Overall	6288 (12%)	487 (8%)	439 (14%)	941 (12%)	1312 (12%)	667 (17%)	876 (17%)

Moderate neutropenia (0.5–1×10⁹/L)	Female	961	93	81	235	252	135	139
	Male	712	69	55	156	198	119	106
	Overall	1673 (3%)	162 (3%)	136 (4%)	391 (5%)	450 (4%)	254 (6%)	245 (5%)
Severe neutropenia (<0.5×10⁹/L)	Female	15	7	7	8	5	3	3
	Male	13	2	8	7	3	5	2
	Overall	28 (0.05%)	9 (0.14%)	15 (0.46%)	15 (0.19%)	8 (0.07%)	8 (0.20%)	5 (0.10%)

Table 2. Descriptive analysis of distribution of neutrophils count ($\times10^9$/L) in the studied populations.

City	Number	Mean	SEM	Median	SD	Min	Max	2.5th per	25th per	75th per	97.5th per
Jeddah	53741	3.18	0.01	3.05	1.35	0.50	8.98	1.05	2.14	4.03	6.19
Taif	6251	3.15	0.02	3.02	1.35	0.50	8.55	1.00	2.11	4.01	6.15
Al Baha	3226	2.74	0.02	2.55	1.29	0.50	8.65	0.90	1.73	3.55	5.61
Abha	8004	2.76	0.01	2.55	1.32	0.50	8.77	0.87	1.73	3.58	5.87
Khamis Mushait	11361	2.90	0.01	2.74	1.34	0.51	8.83	0.91	1.84	3.74	5.93
Najran	4030	2.56	0.02	2.40	1.22	0.52	7.99	0.83	1.57	3.34	5.39
Gizan	5271	2.43	0.02	2.16	1.16	0.50	8.47	0.89	1.59	3.05	5.42

[1] Total numbers indicate all subjects analyzed after applying the exclusion criteria. Neutrophils <0.5 were excluded from this analysis with no change in distribution. **SEM**: standard error of the mean and **SD**: standard deviation of the mean.

Table 3. Mean (±standard deviation) of the neutrophil count with respect to gender and age group distribution.

Age group (years)	13-40		41-60	
Gender	M	F	M	F
Jeddah	3.18 ±1.36	3.22 ±1.36	3.12 ±1.32	3.17± 1.34
P values		0.34*	0.09**	
Taif	3.10±1.37	3.20±1.35	3.19±1.33	3.05±1.36
P values		0.73*	0.41**	
Albaha	2.741±.29	2.77±1.27	2.76±1.30	2.69±1.32
P values		0.1*	0.13**	
Abha	2.76±1.26	2.74±1.34	2.75±1.31	2.81±1.35
P values		0.8*	0.91**	
Khamis	2.90 ±1.35	2.94±1.36	2.85±1.29	2.87±1.33
P values		0.001*	0.01**	
Najran	2.52±1.19	2.62±1.26	2.48±1.14	2.61±1.28
P values		0.71*	0.34**	
Gizan	2.39±1.17	2.49±1.20	2.36±1.11	2.44±1.15
P values		0.001*	0.01**	

5% trimmed mean reported. Independent Student's t-test was used

* Comparison for gender.

** Comparison for age group.

While some comparison is statistically significant, the difference between the mean neutrophil counts is not clinically significant.

4. Discussion

The present study was conducted to authenticate our previous findings of a high prevalence of isolated neutropenia and explore any geographical association by including other cities and a large dataset of participants. After excluding abnormal tests results, 91,880 CBCs were included for determining the frequency of neutropenia in the study population. The current study validates our previous findings in which the prevalence of neutropenia was found to be 18%. The findings of this study are consistent with those of Gari et al. [10] who also reported a high prevalence (20%) of neutropenia in Jeddah. Several other studies have shown a variable frequency of neutropenia among different populations [9,13–15]. Moreover, the findings of this study indicated that the 2.5^{th} percentile of neutrophil count was lower than what is accepted now as lower end of the reference range;1.5×10^9/L, in all seven cities. This finding is most likely explained by racial effect. We postulate, as explained below, that this prevalence is most likely explained by Benign ethnic neutropenia.

BEN has a positive association with Duffy-null phenotype [16]. Atypical chemokine receptor-1 (*ACKR1*) gene, also known as the Duffy antigen receptor for chemokines (DARC), encodes the Duffy antigens (Fy^a and Fy^b). A single nucleotide polymorphism (SNP) at codon 42 (G125A, rs12075) results in two types of encoded proteins, Fy^a and Fy^b. Fy^a antigen includes glycine, while Fy^b contains aspartic acid [17]. The Duffy-null phenotype (Fy^{a-b-}), also symbolized as erythroid silent (ES), occurs due to another SNP, rs2814778 at position 46 (-46 T > C). The Duffy antigen expression is inhibited in individuals with homozygous C/C polymorphisms [18]. Individuals with rs2814778 suffer from an abnormal phenotype of neutrophils with enhanced egression into the tissues from the blood [19]. *Plasmodium vivax* enters the red cells through DARC. Duffy-null phenotypes therefore may provide a natural resistance to *P. vivax*. Consequently, this protective role of Duffy-null phenotypes in malaria endemic regions has undergone positive selection leading to its high prevalence in some ethnicities [20]. Although molecular analysis for rs2814778 of Duffy-null phenotypes was not conducted in this study to corelate the high frequency of this phenotype with BEN, the prevalence of Duffy-null phenotypes in Saudi Arabia reported in various studies could be linked with BEN. Duffy-null phenotype (Fy^{a-b-}) at a frequency of 62 to 78% have been reported in Saudi Arabia populations [21,22]. Therefore, the isolated neutropenia reported in this current study may be Duffy-null phenotype-induced BEN.

We previously noticed a higher prevalence of isolated neutropenia at a high altitude in comparison with sea level [12]. In this study, the prevalence of isolated neutropenia in Taif city (1,898 m above sea level) was not different from that in the coastal Jeddah city in the current study. Furthermore, in this study, we did not find any association between altitude levels and plasma volumes. Nonetheless, owing to many confounding factors, including different prevalence of BEN, the effect of altitude on the neutrophil count should not be dismissed without further research.

The ANC, usually above 1.5×10^9/L, is used as an inclusion criterion for clinical trials [23]. This can potentially lead to exclusion of otherwise healthy individuals with physiologically lower neutrophil counts [24]. The same criterion is also used to grade chemotherapy-associated toxicity, which helps in dose adjustment of crucial treatments. Dose intensity of chemotherapy is important, and dose reduction or delay is associated with increased mortality [25,26]. In high-prevalence BEN populations, low ANC should not be considered a factor for altering the treatment strategies in certain clinical conditions. For instance, use of clozapine and deferiprone also induces neutropenia. Administration of

these drugs can commence if the ANC is above 0.5×10^9/L, in the absence of any other comorbid condition. In patients with malignancies, if the ANC ranges between 0.5×10^9/L and 1.0×10^9/L, chemotherapy may be administered safely [27].

In clinical practice, individuals with ANC <1.5×10^9/L usually undergo unwarranted laboratory and clinical investigations without any significant findings. Although the differential diagnoses of neutropenia are wide, BEN can be determined based on the appropriate clinical scenario. BEN is usually an incidental finding of isolated mild neutropenia with no other hematological abnormalities. It is not associated with increased risks of infections [28]. Previous studies have indicated the chronicity of the condition, and when absent, follow-up usually indicates the stability and benign nature of the condition [29]. Clinical history can also suggest the presence of other causes of neutropenia. For instance, in cyclic neutropenia, recurrent infections, especially oral lesions and low neutrophil counts, at 21-day intervals are common. Meanwhile, in BEN, recurrent infections are infrequent, while ANC remains low. Moreover, since molecular analysis for rs2814778 of Duffy-null phenotypes is not available in clinical laboratories, the Duffy phenotype could be utilized as a marker for identifying individuals with BEN. In current clinical practice, the diagnosis of BEN depends on the exclusion of other causes of neutropenia.

This study has the advantage of large sample size and the availability of extended lab tests to exclude many health conditions. Nonetheless, it has some limitations. It was a retrospective analysis with few demographics and health-related data. Some micronutrient deficiencies that may affect neutrophil counts such as B12 and folate deficiencies were not assessed.

5. Conclusions

Isolated neutropenia is common in the southern and southwestern Saudi Arabia. BEN, extensively reported in Middle Eastern countries, is likely to explain many cases of mild isolated neutropenia. However, the effects of other factors, including geography, altitude, and autoimmune diseases, should be explored. In light of the above results, we suggest that the 2.5th percentile of ANC for Saudi Arabians could be set at 1.0×10^9/L. Additionally, ANC of > 0.8×10^9/L, when isolated, chronic and stable with benign medical history, should not be considered alarming in the absence of fever, pyogenic infection, or inflammation.

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Data Availability Statement: Data is available to readers upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

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