Original Article

Prevalence of neutropenia discovered in routine complete blood cell counts among healthy adults from Saudi Arabia at different altitudes

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Abstract

Background: People of African, Middle Eastern, and West Indian descent are disproportionately affected by benign ethnic neutropenia (BEN), one of the most common causes of chronic neutropenia. The prevalence of chronic benign neutropenia among the general population is endemic in Middle Eastern countries.

Objective: The current study aimed to investigate the prevalence of BEN in three different regions of Saudi Arabia and explore the effect of altitudes on it.

Methods: In this retrospective cross-sectional study, the lab reports were collected and screened over two years (September 2020 to August 2022) from the different labs and clinics serving chronic patients located in Jeddah (Sea level), Najran (1293 m above sea level) and Asir (2200 m above the sea level) region. Complete blood count (CBC) reports were analyzed for patients above 12 years from both genders. Exclusion criteria include significant abnormalities in the biochemical and CBC reports. The mean ANC and the prevalence of neutropenia were compared and statistically analyzed by age group and gender amongst three different cities.

Results: A total of 11762, 8534, and 10225 laboratory investigations from the Jeddah, Najran, and Asir regions, respectively, were investigated in this study. The mean ANC for the population from the Jeddah region was 3.37±2.45 x 109/L, while in Najran and Asir regions, it was found to be 3.01±1.54 x 109/L and 2.86±1.44 x 109/L respectively. Laboratory findings of isolated neutropenia were frequent, with a prevalence ranging from 19.64% to 35.2%.

Conclusion: People living in various regions of Saudi Arabia frequently have mild to moderate neutropenia. Furthermore, isolated neutropenia is more prevalent among people living at high altitudes. Environmental and altitude factors and underlying ethnic neutropenia are likely to be key contributors to this high frequency.

Keywords: Isolated Neutropenia, Absolute Neutrophil count, Benign Ethnic Neutropenia, High altitudes, Kingdom of Saudi Arabia.

INTRODUCTION

Neutrophils make up most blood leukocytes and are essential in host defense systems against infection [1]. The number of neutrophils in the blood is called absolute neutrophil count (ANC) [1]. The ANC ranges typically from 2.5 to 7 x 109//L [2].

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The chance of getting an infection rises with decreasing ANC. Having ANC < 0.5x 109//L significantly increases the susceptibility to infection and can put a person at risk for infections and potentially fatal complications [3]. Neutropenia refers to a state in which there is an abnormally low count (<1.5 x 109//L) of circulating neutrophils in the peripheral blood. A significant decline in the peripheral neutrophil count is a critical clinical issue that must be addressed. Prevalence and incidence of neutropenia-associated infection are proportional to the ANC and duration of neutropenia [1]. The severity of neutropenia is categorized according to the relative risk of infection and can be as mild (ANC 1 to 1.5 × 109/L)), moderate (ANC 0.5 to 1 × 109/L), or severe (ANC < 0.5 × 109/L) [4]. Some potential causes of neutropenia include the inability of the bone marrow to produce an adequate number of neutrophils or an unusually rapid breakdown of neutrophils. It may be due to genetic abnormalities, microbial infection, cancer, nutritional deficiency, autoimmune deficiencies, or drug-induced [5].

At routine checks, it has been noted that some healthy patients present with low ANC (< 1.5 x 109/L), which is not associated with any visible disease burden [6-8]. This disorder is known as benign neutropenia or, in some circumstances, chronic benign neutropenia (CBN). A particular population group, such as Africans, Caribbean, Middle Eastern, and West Indian descent, frequently experiences benign neutropenia without any discernible phenotype or genotype [9,10]. This condition is known as benign ethnic neutropenia (BEN) [9,10]. The prevalence of chronic BEN in the general population is estimated to be 10-15% in Middle Eastern nations [6]. Saudi Arabia is a country on the Arabian Peninsula between the Red Sea and the Persian Gulf, having an area of about 2.15 million km², making it the second-largest country in the Arab world. The current population of Saudi Arabia in 2022 is 36.40 million. [11,12]. According to the findings of a study conducted in Saudi Arabia, the prevalence of isolated neutropenia was 20% [6]. The effect of altitudes on the hematological parameters is well established. In this study, we investigated the prevalence of BEN in three different regions of Saudi Arabia at different altitudes

Methods

This study was planned and carried out in conformity with the guidelines of the Helsinki principles. Ethical approval and subject consent waiver were obtained from the research ethics committee at King Khalid University (HAPO-06-B-001) (approval number ECM#2021-4405). In this retrospective cross-sectional study, the lab reports were collected and screened over two years (September 2020 to August 2022) from the public, government hospital labs, and the medical clinics serving chronic patients located in the Jeddah (Sea level), Najran (1293 m above the sea level) and Asir (2200 m above the sea level) region. Lab reports for patients above 12 years were reviewed for complete blood count (CBC), thyroid profiles, lipid profiles, renal function test, liver function test, fasting blood glucose, and HbA1c%. No bias was associated with the random selection of laboratory investigation from those who came to the lab for regular checkups. Exclusion criteria include significant abnormalities in the biochemical parameters of the liver, kidney or lipid profile, thyroid profile, prediabetes, or diabetes patients were excluded. Inclusion criteria consist of laboratory investigation with normal CBC, normal value of liver, kidney or lipid and thyroid profile, and non-diabetic patients.

Statistical analysis

Statistical analysis was performed by IBM® SPSS, version 24 (SPSS Inc. Chicago, USA. Standard descriptive such as Chi-square ($\chi 2$) was used for analyzing categorical variables, and results were expressed as frequency, percentage, and mean. The Kolmogorov-Smirnov test or Shapiro-Wilk test was used the assess the normality of data. Independent-samples T-test and Mann-Whitney test were used to analyze the difference between groups based on normally or non-normally distributed data. The linear association between neutropenia and gender, age, and altitude was assessed using Spearman and Pearson correlation tests. The level of statistical significance was set at $p < 0.05$.

Results:

A total of 11762, 8534, and 10225 laboratory investigations from the Jeddah, Najran, and Asir regions, respectively, were investigated in this study. The descriptive characteristics of the study population from three different regions are presented in table 1. There was no significant difference (p=0.385) in the age of the study population in different regions stratified by gender. Statistically significant differences (p<0.05) were observed in terms of the mean value of total leucocytes count (TLC) and differential leucocytes counts (DLC), i.e., neutrophil, basophil, eosinophil, lymphocytes, and monocytes count.

Table 1: Statistical descriptive characteristics and differential leucocyte count at different altitudes.

	Jeddah		Najran		Asir		
	Female	Male	Female	Male	Female	Male	*P* value*
Age (Median±IQR)	39±19	43±21	37±17	41±19	37±18	41±20	0.385†
Leucocytes (Mean±SD)	6.57±2.48	6.58±2.75	6.15±1.93	6.16±2.02	6.01±1.92	6.05±1.89	0.000†
Neutrophil (Mean±SD)	3.39±1.11	3.35±1.98	3.01±1.58	3.01±1.48	2.85±1.46	2.88±1.41	0.000†
Basophil (Mean±SD)	0.06±0.02	0.05±0.02	0.04±0.02	0.04±0.03	0.02±0.01	0.21±0.02	0.000†

Eosinophil (Mean±SD)	0.23±0.30	0.22±0.20	0.20±0.16	0.20±0.15	0.20±0.15	0.21±0.22	0.000†
Lymphocytes (Mean±SD)	2.42±1.38	2.42±0.86	2.40±0.71	2.40±0.68	2.44±0.75	2.44±0.75	0.000†
Monocytes (Mean±SD	0.53±0.20	0.55±0.18	0.48±0.16	0.49±0.17	0.47±0.18	0.48±0.15	0.000†

* The level of statistical significance was set at p<0.05; †Analyzed by Kruskal-Wallis test

The mean ANC for the population from the Jeddah region was 3.37±2.45 x 109/L, while in Najran and Asir regions, it was found to be 3.01±1.54 x 109/L and 2.86±1.44 x 109/L respectively. A statistically significant difference (p<0.05) was observed between the mean value of ANC among three different regions. The mean ANC for the Jeddah, Najran, and Asir regions in other gender stratified by age group is presented in table 2. The difference remains statistically significant (p<0.05) when comparing the mean ANC value between the different regions per age group and per gender, respectively (Table 2). Similarly, a statically significant difference was observed for basophil, eosinophil, and monocytes (p<0.05). However, for lymphocytes and TLC, a statistically significant difference (p<0.05) was observed when comparing three regions per age group, but it was statistically not significant when comparing three regions per gender (Table 2).

Table 2: Statistical Description of Mean DLC and TLC of the study population in different regions stratified by gender and age group.

		Jeddah		Najran		Asir		P value
		Female	Male	Female	Male	Female	Male	
Leucocytes	12-20	6.68±2.25	6.65±2.11	6.23±1.94	6.03±1.84	5.97±2.05	6.13±1.86	†0.000
	21-40	6.56±2.21	6.56±2.11	6.18±2.21	6.18±1.95	5.98±2.05	6.05±1.90	‡0.125
	40-60	6.50±2.23	6.58±3.53	6.05±1.92	6.15±1.96	6.01±1.90	6.02±1.87	
	Above 60	6.77±3.77	6.59±2.13	6.24±1.96	6.23±1.84	6.10±1.93	6.09±1.88	
Neutrophil	12-20	3.40±1.60	3.36±1.62	3.09±1.52	2.94±1.46	2.76±1.51	2.39±1.38	†0.000
	21-40	3.36±1.67	3.34±1.61	3.03±1.52	3.02±1.52	2.84±1.47	2.88±1.41	‡0.016
	40-60	3.36±±4.01	3.32±2.45	2.94±1.44	2.97±1.44	2.88±1.45	2.85±1.41	
	Above 60	3.57±4.72	3.42±1.62	3.06±1.46	3.08±1.46	2.92±1.46	2.92±1.47	
Basophil	12-20	0.03±0.02	0.03±0.03	0.02±0.02	0.02±0.02	0.02±0.02	0.02±0.02	†0.000
	21-40	0.03±0.02	0.03±0.02	0.02±0.02	0.02±0.02	0.01±0.02	0.02±0.02	‡0.000
	40-60	0.03±0.05	0.03±0.04	0.02±0.02	0.02±0.02	0.02±0.2	0.02±0.02	
	Above 60	0.03±0.02	0.03±0.02	0.02±0.02	0.02±0.02	0.02±0.02	0.02±0.02	
Eosinophil	12-20	0.21±0.17	0.22±0.17	0.20±0.16	0.19±0.14	0.20±0.14	0.22±0.20	‡0.000
	21-40	0.21±0.19	0.21±0.19	0.20±0.20	0.19±0.14	0.20±0.15	0.20±0.22	‡0.000
	40-60	0.20±0.31	0.22±0.55	0.19±0.14	0.20±0.16	0.20±0.15	0.20±0.15	
	Above 60	0.22±0.55	0.23±0.18	0.21±.16	0.20±0.14	0.22±0.16	0.22±0.26	
Lymphocytes	12-20	2.47±0.84	2.48±0.76	2.40±0.67	2.37±0.68	2.50±0.79	2.47±0.72	†0.000
	21-40	2.42±0.80	2.43±0.95	2.40±0.70	2.40±0.68	2.44±0.74	2.44±0.72	‡0.632
	40-60	2.41±0.91	2.44±0.78	2.38±0.70	2.40±0.68	2.43±0.76	2.45±0.79	
	Above 60	2.44±3.11	2.33±0.87	2.42±0.79	2.38±0.67	2.45±0.72	2.42±0.72	
Monocytes	12-20	0.55±0.22	0.54±0.18	0.49±0.19	0.47±0.14	0.47±0.15	0.48±0.14	†0.000
	21-40	0.53±0.18	0.54±0.18	0.48±0.16	0.49±0.16	0.47±0.15	0.47±0.15	‡0.000
	40-60	0.52±0.22	0.55±0.18	0.48±0.15	0.50±0.17	0.47±0.24	0.47±0.15	
	Above 60	0.54±0.19	0.56±0.19	0.49±0.17	0.51±0.18	0.47±0.16	0.49±0.17	

* The level of statistical significance was set at p<0.05. †Kruskal Wallis test for age group, ‡Mann-Whitney U test for gender

Table 3: Prevalence of different types of isolated neutropenia in Jeddah, Najran, and Asir regions stratified by gender.

		Jeddah	Najran	Asir	*P* value†
Mild Neutropenia	Female	1074	1135	1498	0.000
	Male	952	929	1268	
	Overall	2026 (17.22%)	2064 (24.18%)	2766 (27.05%)	
Moderate Neutropenia	Female	139	254	442	0.408
	Male	73	106	206	
	Overall	212 (1.8%)	360 (4.21%)	648 (6.33%)	

Severe Neutropenia	Female	43	59	118	0.746
	Male	30	37	69	
	Overall	73 (0.62%)	96 (1.12%)	87 (1.82%)	

The level of statistical significance was set at $p<0.05$. †Chi-square test

The Overall BEN in Jeddah region was 19.64%, mainly 17.22% mild neutropenia, 1.8% moderate neutropenia, and 0.62% severe neutropenia. In the Najran region, the prevalence of overall BEN in the study population was 29.51%, mainly 24.18% mild neutropenia, 4.21% moderate neutropenia, and 1.12% severe neutropenia. In the Asir region, the overall prevalence of BEN was 35.2%, with individuals having mild neutropenia 27.05%, moderate neutropenia 6.33%, and severe neutropenia 1.82%. The prevalence of different classes of BEN in three different regions stratified by gender is presented in table 3. Furthermore, the prevalence of mild neutropenia in three different regions per gender was statistically significant ($p<0.000$). However, the prevalence of moderate and severe neutropenia in three different regions per gender was statistically insignificant ($p>0.05$). Partial correlation was used to determine the correlation between altitudes and neutropenia by controlling age and gender. A significant positive correlation was observed between the height (altitudes) from the sea level ($r=0.105$) and neutropenia. It means that the height of the altitudes tends to increase neutropenia. Furthermore, the Spearman correlation between ANC and height of altitudes was significant ($p=0.000$) and negative ($r= -0.120$).

Discussion

There are some endemic regions around the world where BEN is more common. The primary reason behind the prevalence of BEN is yet to be figured out. The prevalence of BEN is known to be higher in some ethnic groups, including Arabs [11]. The prevalence of this disease is also rising among people in the Middle East due to a number of factors, including consanguinity in marriages [7]. This is a retrospective cross-sectional study, using the dataset of CBC available in different public, and government hospital labs and medical clinics in three different cities of Saudi Arabia at different altitudes, at sea level (Jeddah), 1293 m from sea level (Najran) and 2200 m from sea level (Asir). The mean ANC for the population from the Jeddah region was 3.37±2.45 x 109/L, while in Najran and Asir regions, it was found to be 3.01±1.54 x 109/L and 2.86±1.44 x 109/L respectively with significant difference between the gender ($p=0.000$). Our results are in agreement with the previous studies [6,11,12]. The prevalence of BEN in the Jeddah region was 19.64%, mainly 17.22% mild neutropenia, 1.8% moderate neutropenia, and 0.62% severe neutropenia. In the Najran region, the prevalence of overall BEN in the study population was 29.51%, mainly 24.18% mild neutropenia, 4.21% moderate neutropenia, and 1.12% severe neutropenia. In the Asir region, the overall prevalence of BEN was 35.2%, with individuals having mild neutropenia 27.05%, moderate neutropenia 6.33%, and severe neutropenia 1.82%. Our reports agree with the previous studies. The prevalence of benign neutropenia among healthy Arabs and its mode of inheritance was studied by Denice et al. (2009). They reported the prevalence of 10.7% BEN with 2.3% moderate neutropenia among healthy individuals in Saudi Arabia [7]. In another study, Gari et al. reported that BEN among the Saudi Arabian general population was up to 20%, with an average neutrophil count of 1.48 x 109/ L [6]. Recently, Awan et al. demonstrated that the prevalence of isolated neutropenia ranges from 11% to 23% in Southern and Western Saudi Arabia [11]. In another study, the same group reported that Saudi residents who live at a high altitude frequently experience isolated neutropenia [12]. BEN is believed to be the primary cause of this high prevalence [12]. In their study, the overall prevalence of isolated neutropenia at high altitudes was 18.5% (mild 12.4%; moderate neutropenia 6%) [12]. The prevalence of isolated neutropenia was statistically significant between high altitudes and sea level. It our investigation, a significant positive correlation between height from the sea level and neutropenia indicates that height of the altitudes will tends to increase the neutropenia. Furthermore, a significant negative correlation between ANC and height from the sea level suggests that neutrophil count decrease with altitudes. Our results are in agreement with recent reports [11,12]. Also, According to older studies, the number of neutrophils drops with increasing altitude [13]. However, some literature reported that newborn infants born at sea level have lower ANC than those born at higher altitudes [14-16]. But there was no evidence that adults experienced this effect. In another study, after eight months of constant exposure to an altitude of 3,500 meters, the researchers noted a slight but statistically significant decrease in neutrophil counts [17]. Our studies agree with the previous studies regarding the substantial decrease in ANC with altitudes [11-16]. Our investigation demonstrated that the prevalence of neutropenia is as high as 35.2%, at high altitudes and 19.64%, at sea level, without any significant difference between the gender. According to various reports, altitudes affect the ANC. Hence our studies revealed considerable variations of neutropenia between the sea level and altitudes.

African-descended people in the United States and the United Kingdom have been observed to experience BEN, which has been linked to a regulatory variation in the Duffy Antigen receptor for the chemokines gene [18]. Other populations around the world, such as Africans, African Americans, and Afro-Caribbeans, have also been reported to have BEN, which has not been linked to a higher risk of infection [6,19]. According to earlier research, BEN is

inherited as an autosomal dominant feature in an Arab tribe and is diagnosed as neutropenia when the ANC is less than 2 x 109/L [7]. The outcome of this study will provide a better understanding of the prevalence of BEN at different altitudes and sea levels.

Conclusion

The ANC at higher altitudes is lower than individuals residing at sea level. Furthermore, the prevalence of isolated neutropenia is statistically more significant in people living at high altitudes. This may be due to the widespread occurrence of BEN, a genetic disorder that appears to be passed down in an autosomal dominant fashion. An increase in the prevalence of neutropenia in Saudi Arabia may be linked to the country's proximity to North African countries and the migration of their citizens to the peninsula.

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