Hematological Parameters in Native Highlanders of Ladakh Aged 4–19 Years

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Abstract Hematological adaptations to high altitude (HA) are long studied but are focused either on lowlanders visiting HA or native highlanders from Andes and Tibet. The literature on native highlanders from the Indian sub-continent or paediatric highlanders is scarce. We aimed at assessing hematological parameters in native highlanders of Ladakh, India, aged 4–19 years and derive nomograms in an age stratified manner specific to these native highlanders. A total of 335 self-reported healthy native high-

landers of Ladakh, without any known comorbidities and not on hematinic nor any drugs in the age group of 4–19 years were included in the study. Complete hemogram including red cell indices was measured. R ver 3.4.0 was used to compare the hematological parameters based on gender/age stratification, pubertal and nutritional status. The hematological reference ranges were created for various parameters in the paediatric population. The mean (SD) haemoglobin (Hb) concentration was 14.74 (2.07) gm/dL. The mean hematocrit (Hct) was 40.43 (5.57%) %, mean corpuscular volume (MCV) was 81.87 (7.22) fL, white blood cell (WBC) count was 7596 (2172) cells/ μ L and platelets was 378.4 (152.8) $\times 10^3/\mu$ L. Hct and MCV

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increased with age. Hb concentration, Hct, and MCV in girls was significantly lower than boys. Severely underweight subjects (body mass index < 16) showed significantly higher platelet counts compared to their nourished counterparts. The hematological nomograms for the native paediatric highlanders from Ladakh, India have been reported in this study.

Keywords Hemogram · Paediatric · Highlanders · Ladakh · India

Introduction

High altitude (HA) has always intrigued physiologists because of the remarkable ability of man to adapt to the hostile environment. Hematological changes associated with HA exposure is believed to be driven by hypobaric hypoxia of HA. Paul Bert back in 1878 in his book *Pression Barometrique* suggested that adaptation to HA might include the increase in red blood cell (RBC) count and hemoglobin (Hb) concentration [1]. Viault in 1890 further quantified this in his studies by measuring RBC count at Lima (sea level) and Morocochoa, a mining township at 4372 m in the Andes. Since then almost all studies conducted in HA natives or the lowland visitors of HA have consistently documented an increase in RBC count and Hb with the ascent to HA [2]. There are three major shortcomings with the available literature on hematological parameters in HA. Firstly, the majority of the studies on HA physiology and hematological adaptation have focused on the hematological adaptation in lowlanders visiting HA or have compared the hematological profile of native highlanders from Andes and Tibet with those of the neighboring lowlanders [3–6]. Secondly, these studies have mostly been directed towards an adult population with no or little reference to pediatric age group. Lastly, these studies have been done mostly on the Highlanders of Andes and Tibet with no data on Indian highlanders. Moreover, hematological reference ranges in the pediatric age groups are scarce. We attempted at answering a few of these questions through this study.

Ladakh (“land of high passes”) is a region in the Indian state of Jammu and Kashmir between the Kunlun range and the Great Himalayas. It is populated by people of Indo-Aryan descent who are putatively different from the Tibetans. We aimed at assessing hematological parameters in native highlanders of the age group of 4–19 years. The objectives of the study were to assess the hemogram of these individuals and derive reference ranges for the hematological parameters in an age-stratified manner specific to native highlanders.

Materials and Methods

This is a cross-sectional observational study conducted on the native highlanders of Ladakh region of 4–19 years’ age group. A total of 1328 children were screened for various inclusion and exclusion criteria. Being ‘native highlander’ was the mandatory inclusion criteria defined as individuals who were born and brought up at an altitude greater than 3500 m. Native highlander children of either gender fulfilling were included. Exclusion criteria comprised of (a) children who have ever visited low altitude or sea level in their lifetime (b) any known co-morbidities (c) children on any hematinic or drugs for prophylactic or therapeutic purposes (d) children from extremely high altitude (defined as above 4500 m). A total of 335 children (163 girls and 172 boys) were included in the study. Informed consent was taken from their guardians as per the revised ethical guidelines for human experimentation of Helsinki Declaration of 2000 [7].

The blood samples were drawn through school visits. After adequate antiseptic precautions, blood samples were drawn from the ante-cubital vein and collected in 3 mL EDTA vacutainers. The blood sample was then processed within 3–5 h of collection using an XP-100 impedance-based hematology analyzer (Sysmex, Kobe, Japan).

Rv3.4.0 was used for statistical analysis [8]. All continuous variables were described as mean (SD), median (range; minimum to maximum). Student *t* test and ANOVA was used to compare the differences in the measured variables based on gender, age stratification, pre/post pubertal and BMI status. *p* < 0.05 was considered as statistically significant and confidence intervals were reported as 95%.

Results

The mean (SD) age of the subjects was 126 (43) months. The median age was 133 months with subjects ranging from 35 to 254 months. The number of subjects in various age groups included less than 5 years of age (*n* = 19), 5–8 years (*n* = 65), 8–10 years (*n* = 51), 10–12 years (*n* = 74), 12–15 years (*n* = 109) and children more than 15 years (*n* = 17) respectively. The mean values of various hematological parameters obtained in our study are tabulated in Table 1. Table 2 compare the various hematological parameters in the different age-stratified groups in our study. Table 3 compare the hematological parameters between girls and boys. Supplementary Figs. 1–7 illustrate the comparison of various hematological parameters stratified by age groups, gender, BMI (between < 16 and ≥ 16) and pubertal status among both genders.

Table 1 Mean values of hematological parameters

Variable	Mean (SD)	Min–max
RBC ($10^6/\mu\text{L}$)	4.93 (0.57)	1.97–7.98
Hb (gm/dL)	14.74 (2.07)	6.1–22
Hct (%)	40.43 (5.57)	18.02–70.70
MCV (fL)	81.87 (7.22)	50.49–101
RDW-SD (fL)	43.81 (3.53)	36–60
WBC (cells/ μL)	7596 (2172)	1740–15,740
Platelets ($10^3/\mu\text{L}$)	378.4 (152.8)	70–952

RBC red blood cell, Hb hemoglobin, Hct hematocrit, MCV mean corpuscular volume, RDW red cell distribution width, WBC white blood cell

Discussion

Studies have found that the Tibetan highlanders have a lower hemoglobin and hematocrit as compared to those of Andean highlanders with no compromise in the oxygen-carrying capacity [4, 9]. No such studies have been carried out from India. A study was conducted by Shrivastava et al. on Indian population, in which he compared the hemogram of lowlanders with those of the mid-altitude residents (1676–2115 m) in the age group of 21–25 years. They found that there was an increase in the RBC count, Hb concentration and packed cell volume (PCV) in comparison to lowlanders (altitude of 696 m) [10]. The mean corpuscular volume (MCV) was found to be lower in the mid-altitude residents as compared to the lowlanders. These data and interpretations cannot be extended to native highlanders (> 3500 m) or to those of children and adolescents.

In our study, we assessed the hematological profile of native highlanders of Ladakh plateau (3500 m) in the age group of 4–19 years. These individuals were born and brought up in Ladakh with no history of travel to lowland thus avoiding physiological variations secondary to altitude shifts. In the literature search, we did not find any similar studies assessing the hemogram of children and adolescents in native highlanders. Moreover, hematological nomograms stratified as per age among Indian pediatric population are not available. In the absence of such data, the reference range for pediatric populations has been adapted from Mayo Clinic data [11]. Table 4 compares the various RBC indices (RBC count, Hb, Hct, MCV) found in our study with that of the reference range prescribed by Mayo Clinic for the same age stratification [11, 12].

RBC Count

The mean RBC count in boys was found to be significantly higher than the girls ($p < 0.0001$). The RBC count doesn't change significantly with age, suggesting an adaptation to high altitude hypoxia beginning early in childhood.

Hemoglobin

In our study, the hemoglobin concentration for boys was found to be 15.37 (1.93) gm/dL and girls 14.08 (1.8) gm/dL. The hemoglobin values in our study are closer to the Tibetan highlanders, most probably owing to similar environmental and evolutionary pressures of the Great Himalayas [13]. In the Indian subcontinent, a study conducted on the adults residing in mid-altitude 2118 m, the mean hemoglobin concentration of 15.3 gm/dL [10] is in tune with our findings. Moreover, the mean hemoglobin concentration of boys is significantly higher (Table 3) than those of the girls which is in accordance with the gender difference in hemoglobin seen in Indian Pediatric population [14]. We also assessed the variation in the hemoglobin concentration in the various age groups in our study population and found that the mean hemoglobin concentration doesn't vary significantly with age.

Hematocrit

In our study, the mean hematocrit is 40.43 (5.57)% as compared to the reference range of 35–49 in Indian Pediatric population [14]. We further compared the change in hematocrit with age and found that hematocrit increases with age from 38.68 (3.39)% at less than 5 years to 44.23 (3.75)% above 15 years. The increase was found to be statistically significant ($p = 0.003$). On comparison of mean hematocrit between boys and girls in our study, we found that the boys have significantly higher hematocrit (41.32 (5.78)) than girls (39.48 (5.02)) ($p = 0.002$). This is in agreement with the difference in hemoglobin concentration between boys and girls, thus hinting towards a physiological variation between the genders. We further analyzed the difference in Hct between pre-pubertal and pubertal subjects in our study (Suppl Fig. 3). We found that the Hct increased significantly in pubertal boys as compared to pre-pubertal boys. This might be attributed to the testosterone surge in pubertal boys and the erythropoiesis stimulating effects of testosterone. The same was not found between pre-pubertal and pubertal girls. This lack of difference was probably secondary to the menstrual cycles post-menarche, associated fall in ferritin and in turn the hematocrit.

Table 2 Comparison of hematological parameters in various age groups

Age	Hematological parameters (Mean $\pm$ 2SD)									
	RBC ($10^6/\mu\text{L}$)		Hb (gm/dL)		Hct (%)		MCV (fL)		RDW - SD (fL)	
	Mean (SD)	Min-max	Mean (SD)	Min-max	Mean (SD)	Min-max	Mean (SD)	Min-max	Mean (SD)	Min-max
< 5 (n = 19)	4.90 (0.44)	4.34–5.77	14.27 (1.52)	11.2–17.2	38.68 (3.39)	31.8–45.36	79.07 (3.36)	73.31–84.7	43.26 (3.02)	37–47
5–8 (n = 65)	4.89 (0.43)	3.68–5.77	14.54 (1.89)	7.2–21.5	38.88 (4.55)	18.57–46.01	79.47 (7.26)	50.49–99.7	43.71 (4.12)	36–60
8–10 (n = 51)	4.93 (0.59)	3.72–7.21	15.04 (1.58)	10.7–20.2	40.36 (5.98)	23.37–61.44	81.16(6.29)	55.41–92.2	43.77 (2.73)	38–56
10–12 (n = 74)	4.91 (0.73)	1.97–7.98	14.85 (2.01)	8.8–22	40.20 (6.53)	18.02–70.7	82.16 (7.88)	52.21–101	44.08 (3.51)	36–58
12–15 (n = 109)	4.94 (0.47)	3.8–6.54	14.69 (2.28)	6.1–18.5	41.24 (5.18)	22.7–53.27	83.57 (7.28)	54.77–100	43.70 (3.55)	36–60
> 15 (n = 17)	5.24 (0.43)	4.49–6.08	15.06 (1.57)	12.1–17.5	44.23 (3.75)	38.17–51.5	84.49 (5.44)	69.8–92.3	44.53 (4.40)	36–55
<i>p</i> value	0.304		0.592		0.003*		0.002*		0.884	
									0.077	
										< 0.001*

RBC red blood cell, Hb hemoglobin, Hct hematocrit, MCV mean corpuscular volume, RDW red cell distribution width, WBC white blood cell

*Significant *p* values

Table 3 Comparison of hematological parameters between girls and boys

Hematological parameters	Girls (n = 163)		Boys (n = 172)		<i>p</i> value
	Mean (SD)	Min–max	Mean (SD)	Min–max	
RBC ($10^6/\mu\text{L}$)	4.80 (0.45)	3.68–7.21	5.06 (0.61)	1.97–7.98	< 0.001*
Hb (gm/dL)	14.08 (1.8)	6.3–17.9	15.37 (1.93)	6.1–22.0	< 0.001*
Hct (%)	39.48 (5.02)	18.57–57.06	41.32 (5.78)	18.02–70.70	0.002*
MCV (fL)	82.19 (8.49)	50.49–101.0	81.56 (5.7)	57.92–99.7	0.422
RDW- SD (fL)	43.83 (4.2)	36–60	43.79 (2.81)	36–55	0.911
WBC ($/\mu\text{L}$)	7720 (1976)	1740–15,740	7477 (2024)	3430–15,040	0.268
Platelets ($10^3/\mu\text{L}$)	350.74 (126.57)	70–632	404.66 (137.33)	94–952	< 0.001*

RBC red blood cell, Hb hemoglobin, Hct hematocrit, MCV mean corpuscular volume, RDW red cell distribution width, WBC white blood cell

*Significant *p* values

MCV

The mean MCV in our study is 81.87 (7.22) fL as compared to 89.83 fL in the study by Shrivastava et al. at 2118 m. On comparing the MCV amongst the stratified age groups it was found that the MCV steadily rose with age (Table 2). The increase in MCV with age was found to be statistically significant. We further analyzed the difference in MCV between girls and boys and found them to be statistically insignificant (Table 3). The MCV of pubertal boys was found to be significantly higher than pre-pubertal boys which is in tune with the Hct findings (Suppl Fig. 4). A similar difference was not found between pre-pubertal and pubertal girls.

Platelets

Observations made in residents and visitors of high altitude (> 3000 m) have suggested that there is an increased incidence of thrombotic events in such individuals as compared to the low land dwellers [15]. The mean platelet count in our study was found to be $378.4 (152.8) \times 10^3/\text{mL}$ with a highest mean platelet count of $429.3 (112.4) \times 10^3/\text{mL}$ in 5–8 years age group and gradually decreasing to $292.1 (88.9) \times 10^3/\text{mL}$ in the > 15 years age group. The decrease in platelet count with age was found to be statistically significant. In a study conducted by Hudson JG et al. the mean platelet counts in residents of El Alto, Andes (4200 m) was $471 \times 10^3/\text{mL}$ [16]. In another study conducted on soldiers of Indian Army deployed at 3500 m for durations of 3–8 months the mean platelet count was found to be $342 \times 10^3/\text{mL}$ at the end of 8 months as compared to $254 \times 10^3/\text{mL}$ at induction [17]. The decreased platelet count in the children of Ladakh as compared to the residents of El Alto and that of the Indian soldiers deployed to HA might be due their better adaptation to HA owing to a long history of evolution in the cold hypobaric hypoxic weather of Ladakh. This hypothesis

needs to be validated by further genetic studies in the future. On comparison of platelet counts between boys and girls in our study we found that the mean platelet count in boys is significantly higher ($p < 0.001$) than girls.

Total Leukocyte Count

The mean WBC count in our study sample is 7596 (2172)/ μL , which is within the reference range of 4000–11,000/ μL for Indian pediatric population [14]. In a study conducted by Siques et al. on military recruits (16–19 years) inducted from sea level (SL) to an altitude of 3550 m for a period of 8 months they found that WBC counts showed no changes (6037/ μL in HA vs. 6002/ μL at SL) [12]. We also found that the variations in mean WBC count amongst the age group (Table 2) and between boys and girls (Table 3) are not significant.

Nutritional Status and Hematological Parameters

In an attempt to evaluate if nutritional status, measured by body mass index (BMI), affects the hematological adaptation of native highlanders we compared the various hematological parameters between severely undernourished ($\text{BMI} < 16$) and adequately nourished ($\text{BMI} \geq 16$) subjects (Table 5). The platelet count was found to be significantly higher in the undernourished subjects as compared to the adequately nourished counterparts. This difference could be probably secondary to malnourishment being a pro-inflammatory state leading to increased platelet, an acute phase reactant. This hypothesis needs to be evaluated in a separate study designed to answer this question. No other hematological parameters studied by us were found to be significantly different between the two groups.

Table 4 Age stratified hematological parameters prescribed by Mayo Clinic versus our study population

Age (in years)	RBC indices		Hb (gm/dL)		Hct (%)		MCV (fL)	
	RBC ($10^6/\mu\text{L}$)		Hb (gm/dL)		Hct (%)		MCV (fL)	
	Mayo	Study	Mayo	Study	Mayo	Study	Mayo	Study
		Mean (SD)	Min-max	Mean (SD)	Min-max	Mean (SD)	Min-max	Mean (SD)
< 5	3.80–5.20	4.90 (0.44)	4.34–5.77	14.27 (1.52)	11.2–17.2	38.68 (3.39)	31.8–45.36	79.07 (3.36)
5–8	3.80–5.20	4.89 (0.43)	3.68–5.77	14.54 (1.89)	7.2–21.5	38.88 (4.55)	18.57–46.01	79.47 (7.26)
8–10	3.80–5.20	4.93 (0.59)	3.72–7.21	15.04 (1.58)	10.7–20.2	40.36 (5.98)	23.37–61.44	81.16 (6.29)
10–12	3.80–5.20	4.91 (0.73)	1.97–7.98	14.85 (2.01)	8.8–22	40.20 (6.53)	18.02–70.7	82.16 (7.88)
12–15	3.80–5.20	4.94 (0.47)	3.8–6.54	14.69 (2.28)	6.1–18.5	41.24 (5.18)	22.7–53.27	83.57 (7.28)
>15	–	5.24 (0.43)	4.49–6.08	15.06 (1.57)	12.1–17.5	44.23 (3.75)	38.17–51.5	84.49 (5.44)

RBC red blood cell, Hb hemoglobin, Hct hematocrit, MCV mean corpuscular volume

Table 5 Comparison of Hematological parameters between BMI < 16 and BMI ≥ 16

Hematological parameters	BMI < 16 (n = 44)		BMI ≥ 16 (n = 291)		p value
	Mean (SD)	Min–max	Mean (SD)	Min–max	
RBC (10 ⁶ /μL)	4.81 (0.43)	3.71–5.77	4.95 (0.56)	1.97–7.98	0.104
Hb (gm/dL)	14.58 (1.37)	12.2–17.3	14.77 (2.05)	6.1–22.0	0.550
Hct (%)	39.37 (3.34)	30.22–46.01	40.58 (5.74)	18.02–70.70	0.171
MCV (fL)	81.67 (4.50)	73.31–96.9	81.90 (7.51)	50.49–101.0	0.843
RDW- SD (fL)	43.27 (3.18)	36–53	43.89 (3.60)	36–60	0.280
WBC (cells/μL)	7425 (2171)	1740–12,690	7621 (1977)	3430–15,740	0.545
Platelets (10 ³ /μL)	428.39 (98.3)	208–624	370.87 (137.99)	70–952	0.008*

RBC red blood cell, Hb hemoglobin, Hct hematocrit, MCV mean corpuscular volume, RDW red cell distribution width, WBC white blood cell

*Significant p values

Strengths and Limitations

Our study is strengthened by a large cohort with equally distributed boys and girls. There are no studies on hematological adaptation in the children and adolescents of Ladakhi origin. This study will act as a stepping stone for further studies on native highlanders of Ladakh as well as a source of comparison with other native highlanders. Our study is limited by the absence of stratification of subjects between 3500 and 4500 m.

Conclusion

The hematological nomograms for the native highlanders from Ladakh, India have been reported in this study. We found some differences in the hematological parameters with growing age and between girls and boys. Further studies to unravel the molecular and evolutionary basis of such differences should be undertaken.

Authors' Contributions UY: Study design, data collection and analysis, manuscript preparation. SK: Data analysis, manuscript preparation. SAB: Study design. SKD: Data analysis, manuscript preparation. SY: Data collection and analysis. VKLK: Data collection. AA: Data collection. PM: Study design. SV: Study design, manuscript preparation. NV: Study design. VN: Study design, manuscript preparation.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Standards This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the 14 Corps

Institutional Ethics Clearance Committee. Written informed consent was obtained from parents/guardians of all subjects.

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