

Lymphocyte subset reference ranges in healthy Saudi Arabian children

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In an attempt to establish the reference ranges for lymphocyte subsets in children, the distribution of lymphocyte population-bearing surface markers such as CD3 (T cells), CD19 (B cells), CD4 (T helper/inducer cells), CD8 (T suppressor/cytotoxic cells), and CD16 and/or CD56 on CD3⁺ cells (NK cells) has been studied among healthy Saudi Arabian infants and children. Normal adult blood donors were used for comparison. Anticoagulated peripheral blood was stained with monoclonal antibodies and the lymphocytes were analyzed by flow cytometry for the expression of the above markers. Absolute and percentage values for most lymphocyte populations differed substantially not only between children and adults but also among children from different age groups. Absolute numbers of all the lymphocyte subsets decreased with age from 1 month to 13 years; the median value declined from 4.1 to 1.9 (T cells), 1.6 to 0.6 (B cells), 0.5 to 0.3 (NK cells), 2.7 to 1.0 (CD4⁺ T cells) and 1.5 to 0.8 × 10³ cells/mm³ (CD8⁺ T cells). HLA-DR⁺ T cell counts changed significantly from 0.3 to 0.2 × 10³ cells/mm³ during the same age period. In contrast, the lymphocyte percentage increased in all the subsets except B cells and CD4⁺ T cells with time. The percentage values increased from 66 to 74 (T cells), 8 to 11 (NK cells), 23 to 39 (CD8⁺ T cells) and 4 to 9 (HLA-DR⁺ T cells). The values changed from 24 to 12 and 46 to 39 for B cells and CD4⁺ T cells, respectively, with age from 1 month to 13 years. The variations in CD4⁺ and CD8⁺ T cells resulted in a decrease in CD4⁺/CD8⁺ ratio from 2.0 to 1.1 with age. These data should be useful as reference values for lymphocyte subsets in various diseases of infants and children.

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Lymphocyte subset analysis or immunophenotyping has been a useful test for the diagnosis and monitoring of immunodeficiency syndromes, malignant hematological disorders, autoimmune diseases and post-transplant complications (1–6).

In order to make a precise evaluation of the affected individuals, reference values for lymphocyte populations must be established.

Several studies have reported on the variation in lymphocyte subsets in healthy humans (7–16). Differences have been associated with race, (12–16) age (7–10, 12) and sex (7, 10, 12). Therefore, in order to apply lymphocyte immunophenotyping to identify disease states and evaluate immune status, it is necessary to determine a reference range for the local human population of different age groups. Age-related changes in blood lymphocyte subpopulations among healthy infants and children have been reported (8, 9, 17–25) but their values are not

yet well established for different age groups. The present study was carried out to establish the reference values for lymphocyte immunophenotyping of Saudi infants and children by flow cytometry using peripheral blood of healthy children aged from 1 month through 13 years. Healthy Saudi adult blood donors were studied for comparison.

Materials and methods

Subjects

One hundred and two healthy Saudi children from 1 month to 13 years and 30 normal blood donors with an age range of 18 to 44 years were studied. The children were seen in the Pediatric Clinic of King Khalid University Hospital, Riyadh, for routine examination or vaccination. All children and adults were considered healthy if they had no past history

of any disease; had normal blood pressure, pulse rate, and hemoglobin; had no fever, cough or infection; were not on any medication; and the donors had not donated blood in the past 3 months. In addition, all children and adult blood donors were screened for syphilis, HIV, hepatitis B, and hepatitis C infection by routine serologic test and were found negative.

Blood samples were collected in EDTA tubes and used within 6 hours of storage at room temperature. Subjects were grouped into five age categories: Group A, ages 1 month through 11 months; Group B, ages 1 year through 2 years; Group C, ages 3 years through 5 years; Group D, ages 6 through 13 years and Group E, ages 18 through 44 years.

Flow cytometry and immunophenotyping

Two-color immunophenotyping of lymphocytes was performed by a lysed whole-blood method using combinations of mouse monoclonal antibodies directly conjugated to fluorescein isothiocyanate (FITC) or phycoerythrin (PE) (Becton Dickinson Immunocytometry Systems, San Jose, CA, USA) as described earlier (16) (Table 1). All samples were analyzed by a FACScan flow cytometer (Becton Dickinson) calibrated with CaliBRITE beads and AutoCOMP software; immunophenotyping results were obtained with SimulSET software (Becton Dickinson) as instructed by the manufacturer.

Briefly, 100 µl of blood was mixed with 20 µl each of Simultest reagent in separate tubes and incubated for 15–20 min. Lysing solution (2 ml; Becton Dickinson) was added to each tube. Following 10 min of incubation, the tubes were centrifuged to remove lysed red cells and washed twice with the cell wash (Becton Dickinson). Washed cells were resuspended in 0.5 ml of the cell wash and analyzed immediately by the flow cytometer.

Statistical methods

The data for each cell type were tested by nonparametric Kruskal-Wallis test to analyze the two parameters with respect to different age groups. Differences in values of each parameter between age groups were assessed using the Mann-Whitney U test (non-paired) and the two-tailed Student's t-test using StatPac Gold-statistical analysis package version 3.2 (Waloniak Associates, Inc., Minneapolis, MN, USA). A p-value <0.05 was considered statistically significant.

Results

Lymphocyte subset analysis of 102 healthy Saudi infants and children of different age groups and 30 healthy Saudi adults was carried out. The results are

Table 1. Monoclonal antibody combinations used in the immunophenotyping of lymphocyte subpopulations

Reagent (FITC/PE)	CD number (FITC/PE)	Functional identity of relevant subsets
LeucoGATE	CD45/CD14	Immunophenotype three cell differential (lymphocytes, monocytes and neutrophils)
Isotype control	IgG ₁ /IgG ₂	Direct conjugate control for nonspecific staining
Leu-4/Leu-3	CD3/CD4	CD4 ⁺ T cells
Leu-4/Leu-2	CD3/CD8	CD8 ⁺ T cells
Leu-4/HLA-DR	CD3/HLA-DR	Activated (MHC class II expression) T cells
Leu-4/Leu-11 + 19	CD3/CD16 + 56	NK cells (CD3 ⁺ , CD16 ⁺ , CD56 ⁺)
Leu-4/Leu-12	CD3/CD19	T (CD3 ⁺ , CD19 ⁺) and B (CD3 ⁺ , CD19 ⁺) cells

FITC – fluorescein isothiocyanate, PE – phycoerythrin, MHC – major histocompatibility complex.

presented in Tables 2 and 3 as medians with percentiles P25 and P75.

The lymphocyte count fell gradually with increasing age from 6.6×10^3 cells/mm³ in Group A to 2.0×10^3 cells/mm³ in Group D to 2.0×10^3 cells/mm³ in Group E.

The percentage of lymphocytes in the total WBC population declined from 67% in the infants (Group A) to 39% in older children (Group D) and to 28% in adults. The values differed significantly between Group A and Groups B, C, D and E, between Group C and Groups D and E, and between Group D and Group E ($p < 0.05$).

The T cell counts dropped from 4.1×10^3 cells/mm³ in Group A to 1.9×10^3 cells/mm³ in Group D and to 1.6×10^3 cells/mm³ in Group E. The values differed significantly between Group A and Groups B, C, D and E, and between Group B and Groups C, D and E ($p < 0.05$). The T cell population, when expressed as a percentage of total lymphocytes, increased progressively from infancy to adulthood. The percentage T cell value remained approximately 66% in Groups A, B, and C and increased to 74% in Group D and 76% in Group E, differing significantly from those of Groups A, B and C ($p < 0.05$). The absolute B cell counts declined from 1.6×10^3 cells/mm³ in Group A to 0.6×10^3 cells/mm³ in Group D. The values differed significantly between Group A and Groups B, C, D and E ($p < 0.05$). Similarly, the value of Group B was significantly different from that of Groups C, D and E ($p < 0.05$). The percentage B cell values were 24% in Groups A and B, 20% in Group C, and 12% in Groups D and E. Like absolute values, percentage B cell values differed significantly between Groups A, B and Groups C, D and E and Group C and Groups D and E ($p < 0.05$). The percentage value of NK cells varied insignificantly between 7% and 11% in children from the ages of 1 month through 13 years, and was 14% in adults. However, the absolute NK cell counts differed significantly between Group A and

Table 2. Absolute and percentage values of lymphocyte subsets for healthy children

Phenotype	Medians (P25–P75)				
	Group A (1–11 months) (n=40)	Group B (1–2 years) (n=28)	Group C (3–5 years) (n=24)	Group D (6–13 years) (n=10)	Group E (18–44 years) (n=30)
WBC					
Absolute count*	9.7 (8.0–12.0)	9.4 (8.4–11.0)	6.3 (5.0–8.0) ^{ab}	6.5 (5.7–8.1) ^{ab}	8.7 (5.5–9.7) ^{ab}
Lymphocytes					
Percentage	67 (61–74)	57 (39–69) ^a	50 (38–56) ^a	39 (29–40) ^{abc}	28 (24–35) ^{abcd}
Absolute count*	6.6 (5.0–7.8)	5.4 (3.3–6.2) ^a	2.6 (2.3–3.9) ^{ab}	2.5 (2.1–2.6) ^{ab}	2.0 (1.6–2.3) ^{abc}
T cells					
Percentage*	66 (61–70)	65 (61–70)	66 (62–69)	74 (71–76) ^{abc}	76 (70–79) ^{abc}
Absolute count*	4.1 (3.1–4.8)	3.3 (2.2–4.1) ^a	2.2 (1.6–2.7) ^{ab}	1.9 (1.7–1.9) ^{ab}	1.6 (1.4–1.9) ^{abc}
B cells					
Percentage*	24 (20–27)	24 (20–27)	20 (15–24) ^{ab}	12 (11–13) ^{abc}	12 (11–13) ^{abc}
Absolute count*	1.6 (1.1–1.9)	1.1 (0.7–1.6) ^a	0.6 (0.4–0.8) ^{ab}	0.6 (0.4–0.8) ^{ab}	0.3 (0.2–0.3) ^{abc}
NK cells					
Percentage*	8 (5–11)	7 (5–10)	9 (6–11)	11 (7–11)	14 (8–19) ^{abc}
Absolute count*	0.5 (0.3–0.7)	0.3 (0.2–0.6)	0.3 (0.2–0.4) ^a	0.3 (0.2–0.4) ^a	0.3 (0.2–0.5) ^a

*Expressed in 10^3 cells/mm³ as medians with percentiles P25 and P75 in parenthesis.

†Expressed as a percentage of total lymphocytes.

a, b, c, d, e: differed significantly from groups A, B, C, D and E ($p < 0.05$).

Table 3. Absolute and percentage values of T lymphocyte subsets for healthy children

Phenotype	Medians (P25–P75)				
	Group A (1–11 months) (n=40)	Group B (1–2 years) (n=28)	Group C (3–5 years) (n=24)	Group D (6–13 years) (n=10)	Group E (18–44 years) (n=30)
HLA-DR ⁺ CD3 ⁺					
T cells					
Percentage [†]	4 (2–6)	6 (5–7) ^a	5 (4–7) ^a	9 (7–15) ^{abc}	10 (7–12) ^{abc}
Absolute count*	0.3 (0.2–0.4)	0.3 (0.2–0.4)	0.2 (0.1–0.2) ^{ab}	0.3 (0.2–0.3) ^c	0.2 (0.1–0.3) ^b
CD4 ⁺					
Percentage [†]	46 (38–51)	41 (36–44)	43 (38–45) ^a	39 (36–42) ^a	42 (38–48) ^a
Absolute count*	2.7 (2.2–3.3)	1.9 (1.4–2.8) ^a	1.2 (1.0–1.7) ^{ab}	1.0 (0.8–1.1) ^{ab}	0.9 (0.8–1.0) ^{abc}
CD8 ⁺					
Percentage [†]	23 (18–27)	25 (20–30)	29 (20–31) ^a	39 (27–39) ^{abc}	38 (34–44) ^{abc}
Absolute count*	1.5 (1.1–1.7)	1.1 (0.8–1.8)	0.8 (0.6–1.0) ^{ab}	0.8 (0.7–1.0) ^{ab}	0.8 (0.9–1.1) ^{ab}
CD4 ⁺ : CD8 ⁺ ratio	2 (1.5–2.6)	1.6 (1.3–2.1) ^a	1.5 (1.3–2.0) ^a	1.1 (0.9–1.4) ^{abc}	1.1 (0.9–1.4) ^{abc}

*Expressed in 10^3 cells/mm³ as medians with percentiles P25 and P75 in parenthesis.

†Expressed as a percentage of total lymphocytes.

a, b, c, d, e: differed significantly from groups A, B, C, D and E ($p < 0.05$).

Groups C, D and E ($p < 0.05$). Among the T cell subsets, CD4⁺ and CD8⁺ T cells showed variations in both absolute and percentage values of infants and children. The absolute CD4⁺ T cell values declined from 2.7×10^3 cells/mm³ in Group A to 1.0×10^3 cells/mm³ in Group D and to 0.9×10^3 cells/mm³ in Group E. Similarly, the percentage value fell significantly from 46% in Group A to 39% in Group D

($p < 0.05$). Absolute CD8⁺ T cells declined with age but unlike CD4⁺ T cells, percentage CD8⁺ T cells increased. The absolute CD8⁺ T values dropped from 1.5×10^3 cells/mm³ in Group A to 0.8×10^3 cells/mm³ in Groups C and D. The variations were significantly different between Groups A and B and Groups C and D ($p < 0.05$). The percentage CD8⁺ T cells increased from 23% in Group A to 39% in

Group D. The values differ significantly between Group C and Group A, and between Groups D and E and Groups A, B, and C. The CD4⁺/CD8⁺ ratio was 2.0 in Group A, 1.5 in Group C and 1.1 in Groups D and E. The differences in ratios were significant between Group D and Groups A, B and C and between Group A and Groups B and C ($p < 0.05$).

The percentages of T cells expressing the activation marker HLA-DR varied from 4% in Group A to approximately 6% in Groups B and C, to 9% in Group D, and to 10% in Group E. These variations were significant between Group A and Groups B, C, D and E, and between Groups B and C and Groups D and E ($p < 0.05$). The absolute counts for activated T cells varied between 0.2 and 0.3×10^3 cells/mm³ in different age groups and the values differed significantly between Group C and Groups A, B and D and Group B and Group E ($p < 0.05$).

Discussion

Our findings show that the absolute and percentage values for most lymphocyte subsets differ not only between children and adults but also between children from different age groups. Therefore, the reference values for all lymphocyte subsets of either adults or children of mixed age groups cannot be used for infants and children. In this study, we have evaluated the immunophenotype of lymphocyte subpopulations in healthy infants and children divided in smaller age groups in order to provide reference values for lymphocyte subsets at every stage of childhood. Our study included children aged between 1 month and 13 years and healthy adult blood donors.

Absolute counts of WBC, total lymphocytes, T cells, B cells and NK cells decreased from infants to older children. Similar declines were seen in absolute counts of CD4⁺ and CD8⁺ T cell populations. The relative percentage of all except T cells, CD8⁺ T cells and HLA-DR⁺ T cells declined significantly with age. T cells, CD8⁺ T cells and HLA-DR⁺ T cells, on the contrary, showed an increase with time. The variations in the values of CD4⁺ and CD8⁺ T cells resulted in the CD4⁺/CD8⁺ ratio, which also decreased with age. These observations confirm and extend the findings of other studies (17–25).

It was reported over 60 years ago (26) that total leukocyte and absolute lymphocyte counts were highest at birth and decreased with age. Variations in the percentage of lymphocyte subsets have been reported, although the absolute counts decline. Total T cells and CD8⁺ T cell percentages were found to increase with age (27). However, more recent reports show that the percentage of T cells, including

both CD4⁺ and CD8⁺ subsets, increase with age and that the CD4⁺/CD8⁺ ratio is unchanged across age groups (20, 24). These observations contradict our findings and the results of two other studies, done on Japanese children, which showed a decrease in CD4⁺/CD8⁺ ratio as a result of an increased percentage of CD8⁺ and a decreased percentage of CD4⁺ T cells subsets with time (14, 24). It is suggested that this discrepancy between immunophenotype patterns seen in Japanese, Saudi Arabian and Caucasian populations may be due to the influence of racial and environmental factors. We have reported that the healthy Saudi Arabian blood donors have a significantly high percentage and number of CD8⁺ T cells, and a low CD4⁺/CD8⁺ ratio compared to healthy Caucasians (16). The varying influence of racial and environmental factors on human lymphocyte immunophenotype has been demonstrated by several investigators (11–15).

B cells were found to decline with age in our study; however, no age-related changes were reported by Osugi et al. (25). The percentage of NK cells was shown by the same workers to increase significantly with age, whereas it remained unchanged in our study. In another report, NK cell percentage was reported to decline with time (9, 21). Such contradictions in different findings can also be attributed to the influence of racial and environmental factors.

The percentage of HLA-DR⁺ T cells has been shown to increase significantly with age in this investigation whereas there was little change in their number over time. Most of the earlier studies support our findings (21–24). The functional role of the HLA-DR⁺ T cells in both normal subjects and patients is unclear, though there is some evidence that it features a T cell primed for cytolytic activity (28).

In conclusion, immunophenotyping childhood diseases has highlighted the need for reliable lymphocyte reference ranges in normal infants and children. This is especially important for children infected with HIV and for those with congenital heart disease in whom T cell enumeration plays a vital role in diagnosis and disease management. The higher number in infants, particularly of CD4⁺ cells, is of relevance to pediatric HIV disease. Because the normal range of such values is between two and three times higher in infants than in adults, extrapolation from adult normal values when making management decisions on HIV-infected infants is definitely inappropriate and potentially harmful. The finding of a higher CD4⁺/CD8⁺ ratio in infants compared to older children or adults and the significant variations in the normal range of this parameter should also be taken into account when designing a therapeutic regimen based on CD4⁺ and CD8⁺ T cell number and CD4⁺/CD8⁺ ratio.

The data presented in this report confirm and extend the earlier findings on immunophenotyping in infants and children. We have systemically established the absolute and percentage values for the major lymphocyte subsets in infants and children of ages between 1 month and 13 years. The reference values provided by this study will prove to be valuable for interpreting changes in various diseases, including infections that occur in children of different age groups.

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