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Original Article

Red cell parameters in infant and children from the Arabian Peninsula

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Abstract: α+-Thalassemia trait and iron deficiency anemia are frequent causes of microcytosis and a common diagnostic challenge in Arabian children. In this study, their prevalences and effects on the red cell parameters were evaluated in 28,457 children aged one day to 6 years. α+-Thalassemia trait was considered to be present when mean cell volume (MCV) was <94 fL at birth and iron deficiency anemia when red cell distribution width (RDW) was >14.5%. The prevalence of α+-thalassemia trait was 15.7% (502/3,191), which was similar to previously reported values for adults (9-14%). Iron deficiency anemia peaked at 7 months (53%) and then declined at a rate of 8% per year. The nadirs of red blood cell count (RBC) and hemoglobin concentration (Hb) occurred at two months of age (physiological anemia). Subsequently, Hb increased at a rate similar to that of MCV, demonstrating the two processes are coupled. The third percentile MCV in children older than 3 months was ≤64 fL, which was significantly lower than that in European children. The third percentile Hb, on the other hand, was similar to that in European children. Thus, α+-thalassemia trait and iron deficiency anemia are exceptionally frequent in Arabian children and their red cell indices are considerably different from European-based norms. Careful interpretation of red cell parameters is required for the evaluation of microcytic anemia in Arabian children.

Keywords: Thalassemia trait, nutritional iron deficiency, geo-ethnicity, decision-making

Introduction

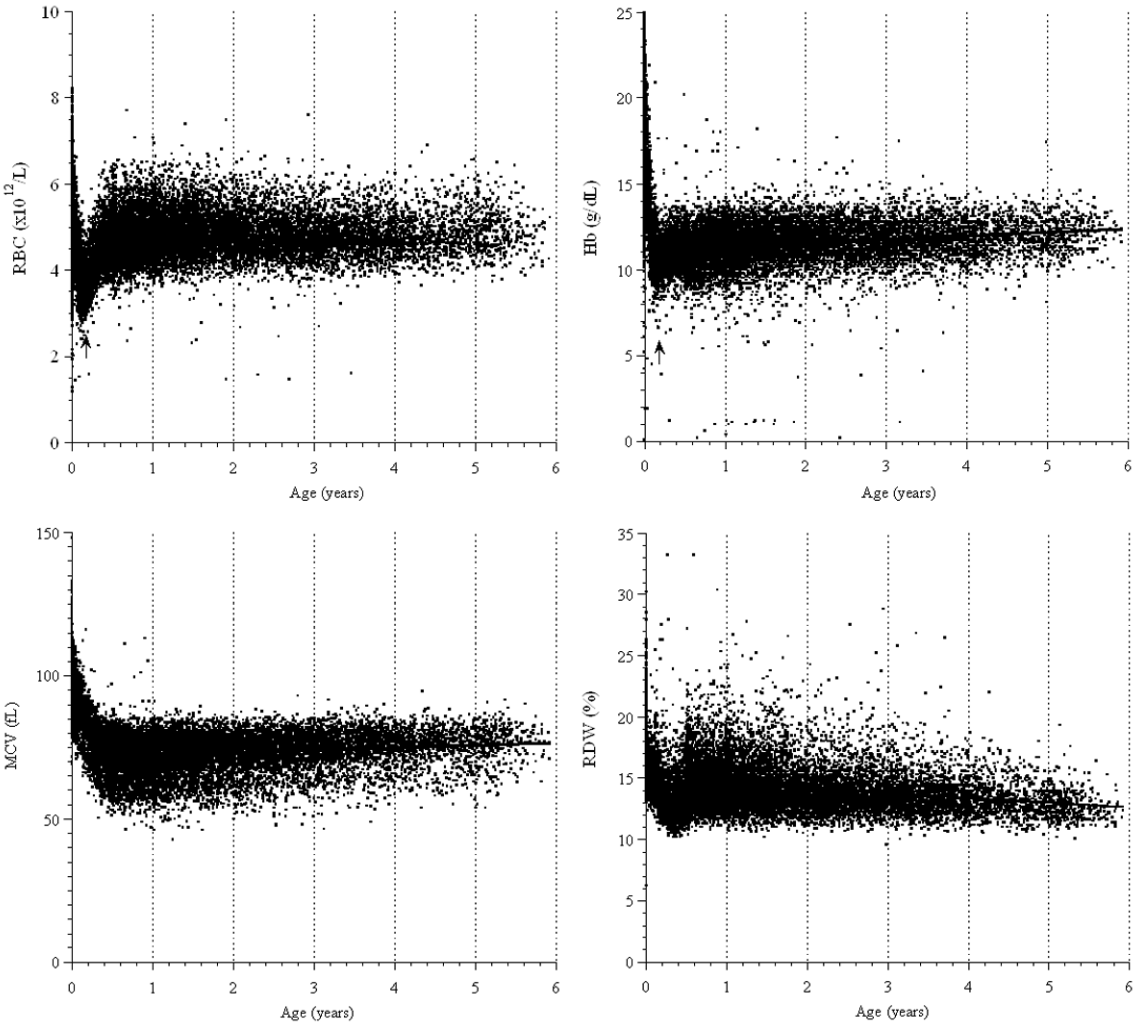
α+-Thalassemia trait (-α/-α) is highly prevalent in the Arabian Peninsula (Yemen, Oman, Bahrain, United Arab Emirates, Kuwait, Qatar, and Saudi Arabia), with an estimated prevalence of 9 to 14% [1]. Iron deficiency anemia is also common in the region, especially among young women [2]. Consequently, half of apparently healthy local population has abnormal findings in the complete blood count (CBC), which is mostly attributed to thalassemia trait and iron deficiency [3-4].

Most Arabian women practice prolonged breastfeeding without iron supplementation and introduce iron-rich food late in infancy, which contribute to the development of iron deficiency. In one regional study, the prevalence of iron deficiency anemia in school-age children was about 10% [5]. Iron deficiency is expected to be even more common in infants and younger children, and its prevention and early treatment are critical for normal development [6].

In clinical practice, red cell reference standards for European young children are commonly used, although they have not been validated in this region [7-8]. Therefore, the purpose of this study is to describe the impact of α+-thalassemia trait and iron deficiency on the red cell indices in a large cohort of Arabian children.

Methods

This study is a retrospective analysis of data from 28,457 children, from one day (<24 hours) to 6 years of age, who were residing in the emirate of Abu Dhabi, United Arab Emirates (UAE). The blood counts were performed between April 2008 and December 2013 at Ambulatory Health Services (SEHA) clinics and hospitals, which are geographically scattered throughout



Rates of RBC, Hb, MCV, and RDW changes

Age (months)	RBC (counts x10^{12}/L/yr)	Hb (g/dL/yr)	MCV (fL/yr)	RDW (%/yr)
0 to 2	-11.01	-48.50	-122.0	-14.10
>2 to 6	+3.04	+2.40	-34.20	-1.43
>6 to 72	+0.01	+0.20	+1.0	-0.39
Relative rates (unitless) of changes for children >6 month of age	+0.002	+0.017	+0.014	0.032

Figure 1. Age-dependent changes (per year) of red cell parameters.

the emirate of Abu Dhabi. Blood was collected in BD Vacutainer® spray-coated K2EDTA tubes and measurements were performed using Cell-Dyne Ruby analyzers (Abbott Laboratories, Illinois, USA). The laboratories performed internal quality controls before running samples and participated in External Quality Assurance program through the College of American Pathologists Proficiency Testing.

α+-Thalassemia genotype and iron studies were not available for these children, and phenotype-derived diagnoses were constructed and used for this analysis. α+-Thalassemia trait (-a/-a) was diagnosed when the MCV was ≤94 fL at birth. This cut-off was previously validated since β-thalassemia trait and nutritional iron deficiency anemia are not phenotypically expressed in the first 24 hours of life [9-14]. In children older than 6 months, phenotype-derived iron deficiency anemia was presumed to be present when the red cell distribution width (RDW) was >14.5%, a commonly used cut-off in our clinical practice [2].

Table 1. Red cell parameters in Arabian infants and children

Days		Weeks			Months				Years
1	2-7	2	3	4	2	3	4-6	7-12	2-6
(3,394)	(995)	(217)	(185)	(203)	(657)	(465)	(1,398)	(4,4140)	(12,661)
RBC ($\times 10^{12}$/L)									
5.1	5.2	4.9	4.6	4.3	3.8	3.9	4.5	4.7	4.8
3.7-6.8	3.7-6.7	3.9-6.3	3.6-5.9	3.1-5.7	2.9-4.9	3.1-4.8	3.6-5.6	3.9-5.9	4.1-5.9
Hb (g/dL)									
17.2	17.3	15.9	14.6	13.4	11.2	10.7	11.2	11.3	11.8
12.8-22.4	13.2-21.8	12.6-20.0	11.1-18.4	9.9-17.4	8.8-14.7	8.9-12.7	9.4-13.1	9.3-13.0	9.6-13.6
MCV (fL)									
102	100	97	94	93	88	83	76	73	75
81-117	84-112	82-109	77-106	73-104	73-99	67-92	60-85	58-82	59-84
RDW (%)									
17.2	16.2	15.4	15.0	15.1	14.7	13.6	12.8	14.4	13.5
13.9-20.4	14.0-20.7	13.3-17.5	13.3-17.3	13.1-18.6	12.7-19.2	11.6-18.1	10.9-17.6	11.8-19.2	11.3-18.5

Values are median and 3rd to 97th percentiles; in brackets are numbers of children.

Standard descriptive and statistical methods were used to analyze the red blood cell count (RBC), hemoglobin concentration (Hb), MCV, and RDW as function of age, divided in three age-bands: 1 day to 2 months, >2 months to 6 months, and >6 months to six years. The rates of changes were set as the slopes (best-fit lines) of the curves of red cell values *vs.* age. The rates of relative changes were set as the slopes (best-fit lines) of the curves of relative red cell values, which were calculated as actual values divided by the mean values at 6 months of age at given age. The level of significance was defined by a 2-tailed *p*-value <0.05 The study was approved by Institutional Review Board of the College of Medicine and Health Sciences, United Arab Emirates University (protocol 14/07).

Results

The children's geo-ethnic origin was UAE (21,775), Yemen (1,173), Oman (1,021), Saudi Arabia (309), Qatar (19), Bahrain (13), and Kuwait (5). RBC, Hb, MCV, and RDW as function of age are shown in **Figure 1** and **Table 1**. From birth, both RBC and Hb rapidly declined and achieved nadirs at about two months (physiologic anemia). Between 6 months and 6 years, the annual increase of RBC was 0.01×10^{12}/L (relative increase = 0.002/year) and that of Hb was 0.2 g/dL (relative increase = 0.017/year). MCV declined gradually in the first 6 months; thereafter, it started to increase by 1.0 fL per year (relative increase = 0.014/year), **Figure 1**.

The prevalence of phenotype-derived iron deficiency anemia (RDW >14.5%) in children older than 6 months is shown in **Figure 2**. It peaked at 7 months (53%); thereafter, its prevalence declined at a rate of 8% per year. The prevalence of phenotype-derived α+-thalassemia trait at birth (MCV≤94 fL) was 15.7% (502/3,191), **Figure 3**. RBC, Hb, and MCV in children older than 6 months, according to a cut-off value of RDW of 14.5%, are shown in **Table 2**. In children with normal RDW, the third percentile MCV was ≤64 fL; this low value is most likely due to the high frequency of α+-thalassemia trait.

In infants with normal RDW, the red cell parameters were compared with those in infants from United Kingdom (UK) (**Table 3**) [7]. Although Hb values in the two groups were nearly identical, RBC was 4% to 11% higher and MCV was 5% to 9% lower in our children. In our two-month-old infants, RBC was 11% higher and MCV was 8% lower than in the same age group infants from UK (**Table 3**). Since β-thalassemia trait and nutritional iron deficiency anemia do not manifest themselves in the first two months, the observed differences are mostly due to α+-thalassemia trait.

Discussion

α+-Thalassemia trait and iron deficiency anemia are common in children from the Arabian Peninsula. The estimated prevalence of phenotype-derived α+-thalassemia trait in our study was 15.7% (**Figure 3**), similar to that found in adults in this same population (9-14%) [1, 2]. As α-Thalassemia trait does not affect survival, its prevalence is expected to be similar in children and adults. In other studies, the prevalence of

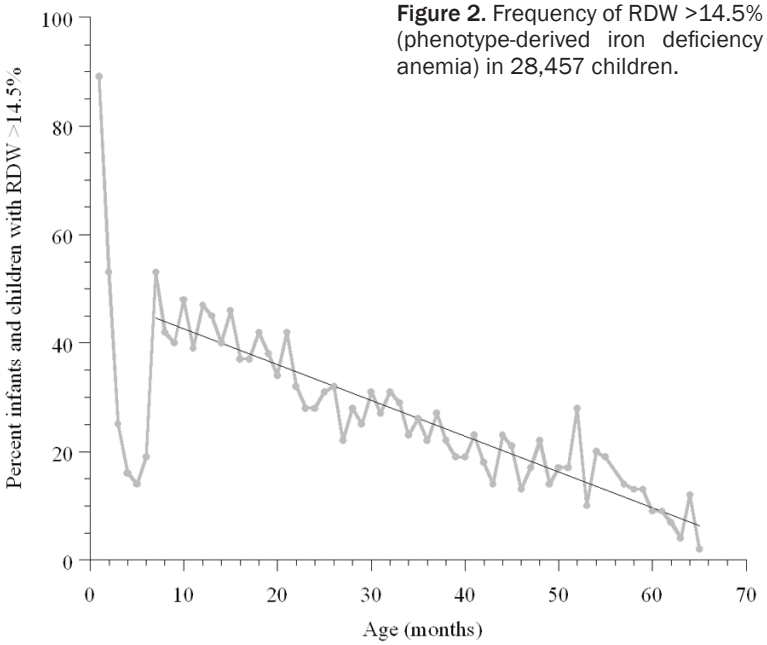


Figure 2. Frequency of RDW >14.5% (phenotype-derived iron deficiency anemia) in 28,457 children.

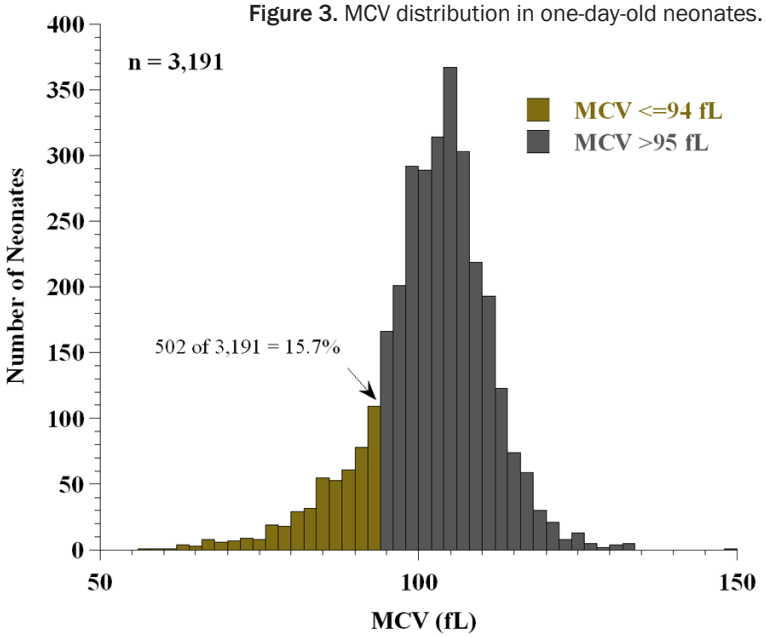


Figure 3. MCV distribution in one-day-old neonates.

α+-thalassemia trait in Peninsular Arabs varied from 7% to 58% [1, 20-23]. Similar prevalence is found in other geo-ethnic groups residing in our region, e.g., 13% in African Arabs (Egyptian, Sudanese, Ethiopian, and Somali) and South Asians (Indian, Pakistanis, and Bangladeshis) and 11% in Eastern Mediterranean populations (Jordanians, Lebanese, Palestinians, and Syrians) [unpublished data]. Emirati population is ethnically diverse and includes ancestors from Arabian Peninsula, Persia, Baluchistan, and East Africa [15]. This population history explains the heterogeneity of α+-thalassemia mutations in Emiratis [1]. The cultural practice of intra-tribal and close-kin marriages results in an increased prevalence of rare recessive autosomal disorders [16-17]. α+-Thalassemia trait (-α/-α) is a common homozygous autosomal recessive condition and consanguineous marriages have been implicated in explaining its uneven distribution, accelerated selection, and overall high frequency in Arabian populations [2, 24].

The uneven distribution of α+-thalassemia trait in local tribes (7% to 58%) could produce a sampling bias in our study [2]. This potential error is minimized here by the large sample taken from sites scattered throughout Abu Dhabi region. Other possible causes of microcytosis like α^{o}-thalassemia trait (--/αα) and some hemoglobinopathies are relatively rare in Peninsular Arabs [1, 18].

The prevalence of phenotype-derived iron deficiency anemia rapidly increased between 6 and 8 months of age, demonstrating an accelerated development of iron deficiency in infants (**Figure 2**). It then progressively declined until 6 years of age. In the region, iron supplementation is inconsistent and prolonged breast-feeding without timely introduction of iron-rich food contributes to the development of iron deficiency. The sensitivity and specificity of RDW in the diagnosis of iron deficiency anemia are relatively low and its use could have affected our results [19]. Nonetheless, the observed age-dependent frequency of iron deficiency phenotype (**Figure 2**) is similar to that in

Table 2. Red cell parameters in Arabian children with normal and high RDW

Age (months)	RDW ≤14.5%				RDW >14.5%			
	n	RBC ($\times10^{12}$/L)	Hb (g/dL)	MCV (fL)	n	RBC ($\times10^{12}$/L)	Hb (g/dL)	MCV (fL)
>6 to 12	2,560	4.6 3.9-5.6	11.5 9.7-13.2	75 62-83	2,202	4.8 4.0-6.0	10.9 8.9-12.8	70 56-79
>12 to 24	3,338	4.7 4.0-5.7	11.9 10.2-13.6	75 62-83	2,060	5.0 4.1-6.1	11.0 8.2-12.9	69 55-80
>24 to 36	2,085	4.7 4.0-5.7	12.0 10.2-13.7	75 63-83	3,332	4.8 4.0-5.8	11.9 9.9-13.8	76 61-84
>36 to 48	1,540	4.7 4.0-5.6	12.0 10.2-13.4	76 64-84	390	5.0 4.0-6.0	11.2 9.0-13.6	70 55-83
>48 to 60	820	4.7 4.0-5.8	12.0 10.3-13.8	77 64-85	169	5.0 4.1-6.2	11.4 9.5-13.4	70 58-82
>60 to 72	387	4.8 4.1-5.9	12.2 10.4-13.9	77 64-85	26	5.4 4.4-6.5	11.8 9.6-13.5	69 54-80

Values are median and 3rd to 97th percentiles; n = number of children.

Table 3. Red cell parameters in Arabian vs. United Kingdom infants

Age (months)	Arabian[1]				United Kingdom[2]			
	n	RBC ($\times10^{12}$/L)	Hb (g/dL)	MCV (fL)	n	RBC ($\times10^{12}$/L)	Hb (g/dL)	MCV (fL)
2	458	3.9 (3.2-4.5)	10.8 (9.3-12.4)	83 (73-90)	119	3.5 (3.1-4.1)	10.8 (9.1-12.5)	91 (85-98)
5	517	4.6 (3.9-5.4)	11.4 (10.0-12.9)	74 (64-82)	93	4.3 (3.8-4.9)	11.5 (10.1-12.9)	79 (73-84)
13	333	4.7 (4.1-5.5)	11.7 (10.0-13.1)	74 (64-81)	42	4.5 (3.9-5.1)	11.9 (10.5-13.3)	78 (73-84)

Values are mean (95% reference intervals); n = number of children. [1]Only infants with RDW ≤14.5%. [2]Reference #7.

other studies [5, 8]. In addition, our results are consistent with reported high frequency of iron deficiency in school-age children and young adults in UAE [3, 5].

The examination of age-dependent erythroid changes shows a rapid decline of RBC and Hb with nadirs at about two months, a finding that is consistent with the development of physiologic anemia (**Figure 1**). After 6 months, the relative rates of Hb and MCV increments are similar, 0.017 per year and 0.014 per year, respectively (**Figure 1**). This finding indicates hemoglobin synthesis is coupled to red cell volume, with microcytosis resulting from decreased production of hemoglobin. In contrast, relative rate of RBC increment is considerably smaller, 0.002 per year (**Figure 1**).

In Arabian children, the third percentile of MCV distribution is markedly low (≤64 fL), even after excluding children with high RDW (**Table 2**). Therefore, we compared our results with the published reference intervals for healthy European infants from Sheffield, UK [7]. At two months of age (before the expected appearance of β-thalassemia trait and the development of nutritional iron deficiency), MCV was lower and RBC was higher in Arabian children compared to UK children (**Table 3**). In the two groups, however, Hb levels were nearly identical. These findings confirm the considerable effect of α+-thalassemia trait on the MCV in our population. It should be noted that α+-thalassemia heterozygote state (-α/αα) also mildly affects the distribution of red cell parameters; this effect, however, has not been quantified in this study. α+-Thalassemia heterozygote is clinically silent, but its frequency in native UAE population is higher than that of α+-thalassemia trait [2]. α+-Thalassemia heterozygote produces a slightly lower Hb and MCV and a slightly higher RBC than the normal genotype and contributes to the observed distribution of red cell indices in our population [25].

In infants of European descent, iron studies are less frequently used in practice since microcytosis with elevated RDW is a good predictor of iron deficiency anemia (as thalassemia trait is relatively rare). The findings of our study indicate that the interpretation of microcytosis is more difficult in Arabian infants since α+-thalassemia trait and iron deficiency anemia are both frequent, and many children have the two conditions at the same time [19]. Therefore,

a judicial use of iron studies and therapy is needed in children from the Arabian Peninsula [19].

In summary, α+-thalassemia trait and iron deficiency anemia are very common in Arabian Peninsula. As a result, red cell values in Arabian children are considerably different from those in European children. In Arabian children, evaluation of microcytic anemia requires careful interpretation of the red cell indices.

Disclosure of conflict of interest

None.

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