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Etiology of anemia in children aged between 6 months and 18 years

6ay-18 yaş arasındaki çocuklarda anemi etiyolojisi

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Abstract

Aim: Anemia is an important public health problem that concerns human and community health. In this study, we aimed to determine the etiology of anemia in different age groups and create social awareness.

Methods: The study (retrospective cohort study) included anemia patients between 6 months and 18 years old who applied to the Pediatric Hematology and Oncology Outpatient Clinic of KSU Medical Faculty between January 2015 and January 2018.

Results: 1120 patients were included in the study. There were 873 with iron deficiency anemia, 184 with thalassemia minor, 25 with vitamin B12 deficiency anemia, 13 with autoimmune hemolytic anemia, 10 with hereditary spherocytosis and the other etiology of anemia. While 16.4% of all patients and 33.8% of patients aged 6-12 years had thalassemia minor. On the other side, 81.3% of patients aged 6 months-2 years, 74.3% of patients aged 2-6 years, 60.4% of patients aged 6-12 years and 85.0% of patients aged 12-18 years had iron-deficiency anemia. Iron deficiency anemia was common in males (60.2%) in the 2-6 years age group (P=0.002), but it was common in females (80.6%) in the 12-18 years age group (P<0.001).

Conclusion: As a result of this study, it has been concluded that screening and iron supplementation should be done in societies at risk.

Keywords: Anemia etiology, Iron-deficiency anemia, Thalassemia minor, Screening, Vitamin B12 deficiency

Öz

Amaç: Anemi, insan ve toplum sağlığını ilgilendiren önemli bir halk sağlığı sorunudur. Bu çalışmada farklı yaş gruplarında anemi etiyolojisini belirlemeyi ve sosyal farkındalık yaratmayı amaçladık.

Yöntemler: Çalışmaya (retrospektif kohort çalışması), Ocak 2015-Ocak 2018 tarihleri arasında, KSU Tıp Fakültesi Çocuk Hematoloji ve Onkoloji Polikliniğine başvuran 6 ay - 18 yaş arasındaki anemi hastaları dahil edilmiştir.

Bulgular: Çalışmaya 1120 hasta dahil edildi. 873 hastada Demir eksikliği anemisi, 184 hastada talasemi minör, 25 hastada vitamin B12 eksikliği anemisi, 13 hastada otoimmün hemolitik anemi, 10 hastada ise kalıtsal sferotositoz ve diğer anemi etiyolojileri vardı. Tüm hastaların %16,4'ünde, 6-12 yaş arası hastaların %33,8'inde talasemi minor vardı. Tüm hastaların %77,9'unda demir eksikliği anemisi vardı. 6 ay ile 2 yaş arası hastaların %81,3'ünde, 2-6 yaş arası hastaların %74,3'ünde, 6-12 yaş arası hastaların %60,4'ünde ve 12-18 yaş arası hastaların %85,0'inde demir eksikliği anemisi vardı. Demir eksikliği anemisi 2-6 yaş grubunda erkeklerde (%60,2) sık görülürken (P=0,002), 12-18 yaş grubunda kadınlarda (%80,6) yaygındı (P<0,001).

Sonuç: Bu çalışmanın sonucunda risk altındaki toplumlarda tarama ve demir takviyesinin yapılması gerektiği sonucuna varılmıştır.

Anahtar kelimeler: Anemi etiyolojisi, Demir eksikliği anemisi, Talasemi minor, Tarama, B12 vitamini eksikliği

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Introduction

Anemia is an important global public health problem that shows the socio-economic development of every nation and individual. The incidence of anemia worldwide is between 22.9-26.7%.The prevalence is over 40% in Turkey [1]. anemia is evaluated according to the mean erythrocyte volume (MCV) in three main headings: microcytic, macrocytic and normocytic anemia [2]. The most common anemia is iron-deficiency anemia [3].

Hemoglobin is generally high in new-born babies and mostly consists of hemoglobin F. The lifespan of hemoglobin F is shorter than that of adult hemoglobin and begins to collapse earlier. Exposed iron is stored. Iron stores are sufficient until the baby is 6 months old. After this time, iron supplementation with food is important to prevent anemia [2]. The iron demand is increasing in infancy and in puberty due to the higher growth rate at that period. The iron demand also increases due to menstrual bleeding in adolescent girls. Iron deficiency has an important effect on neurological development as well as anemia. Even if iron deficiency is treated, these developmental retardations can be irreversible [4].

As in all over the world, the prevalence of anemia and iron-deficiency anemia is high in our country and in our region. There are not enough studies showing the etiology of anemia in our region. In this study, it was aimed to raise awareness about the etiology of anemia and anemia itself for our region and to draw attention to this social problem by showing that anemia is common in our society. By that, it was aimed to attract patients, their relatives, and health professionals to take preventive measures before anemia occurs.

Materials and methods

This was a retrospective single-center cohort study. We started this study after we received the approval from the Kahramanmaras Sutcu Imam University (KSU) Faculty of Medicine Clinical Studies Ethics Committee (08.11.2017-2017/18). Patients with anemia between 6 months and 18 years of age who were admitted to the Department of Pediatric Hematology and Oncology between January 2015 and January 2018 were selected for this study. Patients with chronic diseases and migrants were excluded from the study.

The patients were divided into four age groups: 6 months-2 years (infantile), 2-6 years (pre-school), 6-12 years (school age), 12 -18 years (adolescence). Gender was divided into two groups: male and female. Demographic data and information about erythrocyte transfusions as well as hemoglobin electrophoresis, complete blood counts, biochemical profiles, LDH, folic acid, vitamin B12, ferritin levels and anemia etiologies of the patients included in our study were obtained from the medical records.

In our study, for the parameters evaluated, we worked with the complete blood count and reticulocyte fluorescent impotence method by using Sysmex XN-3000 brand fully automatic blood counting device.

Ferritin, folic acid, and vitamin B12 were studied by the chemiluminescence method on the Siemens Adevia Centaur XP fully automatic hormone analyzer. Iron, iron binding capacity, LDH, total bilirubin, and direct bilirubin were studied photometrically on Siemens Adevia 1800 Chemistry System.

Statistical analysis

Statistical analyses were performed using the SPSS (v. 22). Normality distribution was assessed by the Kolmogorov-Smirnov Test. The Independent Sample T-Test was used for two independent samples that fit the normal distribution. The Mann-Whitney U Test was used for samples that did not show normal distribution. The Two-Sample Chi-Square Test was used to analyze data with two variable frequencies, while the Single Sample Chi-Square Test was applied to data with single sampling frequency. Mean, standard deviation, minimum and maximum values of the data were calculated. $P<0.05$ was accepted as statistically significant.

Results

1120 patients between 6 months-18 years old with anemia and without chronic disease and foreign origin were included in the study. 30.6% of the patients (343) who participated in the study were 6 months-2 years, (304) 27.1% were 2-6 years, (139) 12.4% were 6-12 years and (334) 29.8% were 12-18 years old. There were more patients aged between 6 months - 2 years and 12 - 18 years ($P<0.001$). Of the patients who participated in the study, (566) 50.5% were female and (554) 55.5% were male. 120 (35%) of the patients between the ages of 6 months and 2 years were female and 223 (65%) were male ($P<0.001$). Of the patients aged 12-18 years, 255 (76.3%) were female and 79 (23.7%) were male ($P<0.001$). This difference was statistically significant. 58.2% of the patients aged 2 to 6 years were male which was statistically significant, too ($P=0.004$).

54.0% of the patients aged 6-12 years were male ($P=0.351$) (Table 1). Of all the patients, 81.3% aged between 6 months and 2 years, 74.3% aged between 2-6 years, 60.4% aged between 6-12 years and 85.0% aged 12-18 years had iron deficiency anemia.

Table 1: Distribution of patients by age and gender

Age groups	Female		Male		Total	
	n	%	n	%	n	%
6 months-2 years	120	35	223	65	343	30.6
2-6 years	127	41.8	177	58.2	304	27.1
6-12 years	64	46	75	54	139	12.4
12-18 years	255	76.3	79	23.7	334	29.8
Total	566	50.5	554	49.5	1120	100

It was noticed that the frequency of iron deficiency anemia increased in infants and adolescents.

77.9% of the patients were diagnosed with iron-deficiency anemia, 2.2% had vitamin B12 deficiency anemia, 0.2% had anemia due to folic acid deficiency, 0.3% had thalassemia major, 0.4% had thalassemia intermedia, 16.4% had thalassemia minor, 0.3% had congenital dyserythropoietic anemia, 0.2% had sickle cell anemia, 0.1% had G6PDH deficiency anemia, 1.2% had autoimmune hemolytic anemia and 0.9% had hereditary spherocytosis.

Iron-deficiency anemia was seen the most which was followed by thalassemia minor, vitamin B12 deficiency anemia, autoimmune hemolytic anemia, and hereditary spherocytosis, respectively. Of the 873 patients with iron-deficiency anemia, (452) 51.8% were female and (421) 42.2% were male. On the other side, of the 25 patients with vitamin B12 deficiency

anemia, (17) 68% were female and (8) 8% were male. The gender distribution of the patients with anemia due to folic acid deficiency (1) was equal ((1) 50% female and (1) 50% male). Of the 3 patients with thalassemia major (1) 33.3% were female and (2) 66.7% were male. In addition, (83) 25% of the patients with thalassemia intermedia were female and (101) 75% were male. Of the 3 patients with CDA, (2) 66.7% were female and (1) (33.3%) were male. The gender distribution of the patients with sickle cell anemia was equal, too ((1) 50% were female and (1) 50% were male). One patient with G6PDH deficiency anemia was male. Of the 13 patients with autoimmune hemolytic anemia (4) 30.8% were female and 9 were male (69.2%). Eventually, of the 10 patients with hereditary spherocytosis, (4) 40% were female and (6) 60% were male. The difference between them was not statistically significant (P=0.360).

The mean age of patients with iron deficiency anemia was 6.6 (6.1) years. The WBC, RBC, PLT, ferritin, folic acid and LDH levels of males were statistically higher than females (P<0.001). MCV, MCH, total bilirubin and direct bilirubin levels of the male patients were found to be statistically lower than that of the females (P<0.001). The mean age of males was younger than that of the girls (Table 2).

Table 2: Average laboratory characteristics according to gender of patients with iron deficiency anemia

Parameters	Minimum-Maximum		Mean (SD)		Mean (SD)	*P*-value
	Female (n:452)	Male (n:421)	Female (n:452)	Male (n:421)	(n: 873)	
Years (Age)	1-17	1-17	9.0 (6.3)	4.1 (4.7)	6.6 (6.1)	<0.001
WBC(mm^3)	2220-22580	1870-28330	8022 (3274)	8877(3394)	8443 (3362)	<0.001
RBC($10^6/mm^3$)	2.5-6.8	2.8-6.4	4.62 (0.64)	4.91 (0.58)	4.76 (0.63)	<0.001
HGB(g/dL)	3.1-11.9	4.0-12.1	8.88 (1.81)	8.88 (1.57)	8.88 (0.63)	0.634
HCT(%)	12-40.1	15.4-36.6	28.72 (5.00)	28.69 (4.17)	28.71 (4.62)	0.386
MCV(fL)	38.8-92.1	38.6-88.7	62.22 (9.27)	58.68 (8.29)	60.50 (8.98)	<0.001
MCH(pg)	2.7-29.5	10.6-28.9	19.17 (3.79)	18.18 (3.38)	18.68 (3.63)	<0.001
MCHC(g/dL)	22.4-37.9	9.0-39.7	30.79 (2.82)	30.9 (3.30)	30.84 (3.06)	0.234
RDW(%)	12.3-60.8	13.5-50.5	20.99 (7.63)	21.28 (6.80)	21.13 (7.24)	0.167
PLT($10^3/mm^3$)	108-1070	55-1420	375 (144)	417 (173)	397 (161)	<0.001
Iron(ug/dL)	3.0-73.0	4.0-55.0	17.4 (13.7)	17.6 (12.6)	17.5 (13.2)	0.876
Iron binding (ug/dL)	147-725	271-567	404.9 (88.9)	406.0 (62.0)	405.0 (78.0)	0.455
T.saturation(%)	1-17	1-13	4 (3)	3 (3)	4 (3)	0.852
Ferritin(ug/L)	0.00-72.90	0.10-90.00	6.80 (8.65)	10.39 (13.30)	8.68 (12.09)	<0.001
Vit. B12(ng/L)	63-1507	141-1624	392 (182)	435 (243)	404 (208)	0.165
Folic acid(ug/L)	1.8-64.1	2.6-78.9	10.96 (8.39)	13.41 (8.99)	12.13 (8.69)	<0.001
T. bil. (mg/dL)	0.06-1.90	0.06-3.40	0.44 (0.26)	0.37 (0.25)	0.40 (0.26)	<0.001
D. bil. (mg/dL)	0.00-1.10	0.00-0.56	0.16 (0.11)	0.14 (0.08)	0.15 (0.10)	<0.001
LDH(U/L)	99-713	122-771	240 (91)	283 (86)	260 (90)	<0.001
Reticulocytes	0.80-5.10	0.86-4.70	2.28 (1.12)	2.07 (1.12)	2.20 (1.11)	0.389

SD: Standard deviation, WBC: Number of leukocytes, RBC: Number of erythrocytes, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW: Erythrocyte distribution width, PLT: Platelet count, T. saturation: Transferrin saturation, Vit. B12: Vitamin B12, T. Bil: Total bilirubin, D. Bil: Direct bilirubin, LDH: Lactate dehydrogenase

The mean age of patients with thalassemia minor was 6.3 (4.9) years. The levels of MCV, RDW and iron binding capacity of patients with iron deficiency anemia were significantly higher than those with thalassemia minor (P<0.001). RBC, HGB, HCT, MCHC, iron, transferrin saturation, ferritin, total bilirubin, direct bilirubin (all P<0.001) and MCH (P=0.031) levels were statistically significantly lower There was no statistically significant difference in age (P=0.406), WBC (P=0.100), PLT (P=0.484), vitamin B12 (P=0.382), folic acid (P=0.571), LDH (P=0.386) and reticulocyte values (P=0.734) (Table 3).

Table 3: Laboratory features of patients with iron deficiency anemia and thalassemia minor diagnosis

Parameters	Minimum-Maximum		Mean (SD)		*P*-value
	Patients with iron deficiency anemia (n: 873)	Patients with T. minor (n: 184)	Patients with iron deficiency anemia (n: 873)	Patients with T. minor (n: 184)	
Years (Age)	1-17	1-17	6.6 (6.1)	6.3 (4.9)	0.406
WBC (mm^3)	1870-28390	4040-19270	8443 (3362)	8752 (2856)	0.100
RBC ($10^6/mm^3$)	2.5-6.8	3.23-6.89	4.76 (0.63)	5.51 (0.64)	<0.001
HGB (g/dL)	3.1-12.1	6.3-13.0	8.88 (0.63)	10.46 (1.00)	<0.001
HCT (%)	12.0-40.1	20.1-39.2	28.71 (4.62)	32.23 (3.28)	<0.001
MCV (fL)	38.6-92.1	41.4-90.2	60.50 (8.98)	58.8 (7.0)	0.006
MCH (pg)	2.7-29.5	12.8-29.4	18.68 (3.63)	19.08 (2.45)	0.031
MCHC (g/dL)	9.0-39.7	15.5-35.9	30.84 (3.06)	32.37 (2.10)	<0.001
RDW (%)	12.3-60.8	13.1-78.3	21.13 (7.24)	19.86 (7.17)	<0.001
PLT ($10^3/mm^3$)	55-1420	124-960	397 (161)	378 (122)	0.484
Iron (ug/dL)	3.0-73.0	21.0-146	17.5 (13.2)	59.47 (31.06)	<0.001
Iron binding (ug/dL)	147-725	290-592	405.0 (78.0)	343 (71)	<0.001
T. saturation(%)	1-17	6-56	4 (3)	8 (12)	<0.001
Ferritin (ug/L)	0.0-90.0	1.5-203	8.68 (12.09)	41.3 (40.3)	<0.001
Vit. B12 (ng/L)	63-1624	150-1068	404 (208)	387 (183)	0.382
Folic acid (ug/L)	1.8-78.9	1.5-41.3	12.13 (8.69)	12.42 (8.24)	0.571
T. bil. (mg/dL)	0.06-3.40	0.10-3.20	0.40 (0.26)	0.56 (0.44)	<0.001
D. bil. (mg/dL)	0.00-1.10	0.06-1.00	0.15 (0.10)	0.20 (0.15)	<0.001
LDH (U/L)	99-771	114-896	260 (90)	255 (90)	0.386
Reticulocytes(%)	0.80-5.10	0.96-2.30	2.20 (1.11)	1.78 (0.72)	0.734

SD: Standard deviation, WBC: Number of leukocytes, RBC: Number of erythrocytes, HGB: Hemoglobin HCT: Hematocrit, MCV: Mean erythrocyte volume, MCH: Mean erythrocyte hemoglobin, MCHC: Mean erythrocyte hemoglobin concentration, RDW: Erythrocyte distribution width, PLT: Platelet count, T. saturation: Transferrin saturation, Vit. B12: Vitamin B12, T. Bil: Total bilirubin, D. Bil: Direct bilirubin, LDH: Lactate dehydrogenase, IDA: Iron deficiency anemia, T. minor: Thalassemia minor

Discussion

Anemia is a serious public health problem as for the individual, family, and society. The development of countries and the frequency of anemia are related to each other. Anemia affects about half of society in developing countries. Children under the age of five are particularly at risk because of the rapid growth and development [5]. The prevalence of anemia worldwide is between 22.9-26.7% [1]. In our study; after migrants and those with chronic diseases were excluded, of the 5089 patients who applied to our outpatient clinic 22% had anemia. Between aged 6 months-2 years (30.6%) and between aged 12-18 years (29.8%) anemia is more common.

In 2011, Stevens et al. [6] found out in their worldwide study that 38% of pregnant women and 43% of children under five years of age were anemic. It is thought that 32 million pregnant women and 273 million children under the age of 5 are anemic around the world. In addition to that, Akkermans et al. [7] determined in their study (which included patients from the Netherlands, Germany, and England) that 18.9% of 1-3-year-old children were anemic. An estimated 20 percent of children in America are thought to have anemia [8]. Furthermore, the rate of anemia was detected as 22% in our study. Anemia is most common in the infant (6 months-2 years) and adolescents (12-18 years) period. In these periods, rapid growth and development, as well as the onset of menstruation in girls during adolescence, may increase the frequency of anemia.

Zuffo et al. [9] found out in Brazil that anemia was more common in boys in daycare centers and nurseries. The reason for the more frequent occurrence of anemia in men is due to their higher growth rates. Balcı et al. [10] observed in their study in Denizli that girls are more anemic in the adolescent period. It is thought that the increase in iron loss with menstruation may cause this [11]. In our study, no significant difference was found between girls (50.5%) and men (49.5%) in terms of the incidence of anemia. According to age groups, we detected that 65% of the patients aged between 6 months and 2 years, 58.2% of the patients between 2-6 years of age and 54% of the patients between 6-12 years old were male while 76.3% of the patients between 12-18 years of age were female. Muriuki et al. [12] found out in their study that 23.6% of children aged 0-7 years in Kenya and 17.6% of the same age group in Uganda had

iron deficiency anemia. Andre et al. [13] discovered in their review of iron deficiency anemia and nutrition in Brazilian children under 5 years of age that the frequency of iron deficiency anemia in children and boys younger than 24 months increased.

Schneider et al. [14] determined in a study in California that 12-36-month-old children of low-income families have evaluated risk factors for anemia; iron deficiency was found to be significantly higher in males than in females.

In our study, iron deficiency anemia is common in all age groups. 66.7% of patients aged 6 months to 2 years. Iron deficiency anemia was common in males (60.2%) in the 2-6 years age group, but it was common in females (80.6%) in the 12-18 years age group.

Koç et al. [15] found out in their study in Sanlıurfa that 58.9% of the children between 6-16 years with had iron-deficiency anemia, 19% had chronic disease anemia, 10% had the intestinal parasitic infection and 6.3% had thalassemia minor. They pointed out that iron deficiency and parasitic diseases are serious problems in school-age children.

The most common anemia in our study was with 873 (77.9%) patients iron deficiency anemia. Among the rest of the patients, the following data were obtained: 184 (16.4%) thalassemia minor, 25 (2.2%) anemia due to vitamin B12 deficiency, 13 (1.2%) OIDA, 10 (0.9%) hereditary spherocytosis, 4 (0.4%) thalassemia intermedia, 3 (0.3%) thalassemia major, 3 (0.3%) CDA and 2 (0.2%) anemia due to folic acid deficiency and 1 (0.1%) anemia due to G6PDH deficiency. On the other side, 81.3% of patients aged 6 months-2 years, 74.3% of patients aged 2-6 years, 60.4% of patients aged 6-12 years and 85.0% of patients aged 12-18 years had iron-deficiency anemia.

The first thing that stands out in our study is that iron deficiency anemia is seen above 80% in adolescence and infantile period. Hereditary spherocytosis is the fifth most common cause of anemia. Hereditary spherocytosis is common in Kahramanmaras province and has an important place in the differential diagnosis of anemia [16].

Thalassemia is a disease which is seen 1-4% all around the world [17]. Thalassemia is more common in the Mediterranean, Sub-Saharan Africa, the Middle East and India [18]. Kahramanmaras province as a Mediterranean region is located in the region where thalassemia is common and this is a reason why it should be considered for differential diagnosis of thalassemia in the microcytic anemia. While 16.4% of all patients and 33.8% of patients aged 6-12 years had thalassemia minor. One reason for the increase could be that children start school and come into contact with a wider environment and the rising attention of people in the social environment. All patients with thalassemia major are between 6 months and 2 years old and all patients with the diagnosis of thalassemia intermedia are between the ages of 2-6 years. Sickle cell anemia is not common in our region. Two patients diagnosed were siblings and migrated from Sırnak.

However, this study has some limitations. Firstly, the study was designed retrospectively. Secondly, patients who came to the hematology and oncology outpatient clinic were evaluated in this study and do not reflect the population.

As a result; in our study, we have shown that iron deficiency is common in Kahramanmaras province of Turkey. It is more common especially between 6 months-2 years of age and 12-18 years of age.

In terms of anemia, it is appropriate to educate the children, to perform screening in appropriate age groups and to run iron supplement for children at risk. In addition, the thalassemia minor prevalence is high in our region and it has an important role in the differential diagnosis of iron deficiency anemia. It is important to perform screening before marriage and to conduct family screening and genetic counselling when thalassemia trait is detected.

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