Original Article / Özgün Araştırma

Haematological Parameters in Children with Serum Folate Deficiency

Serum Folat Eksikliği Olan Çocuklarda Hematolojik Belirteçler

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Abstract

Objective: Folate deficiency is common globally, especially in low- and middle-income countries. The best-known morbid effects of folate deficiency are haematological in nature. This study aimed to identify the haematological parameters status of folate deficiency in children.

Materials and Methods: Data were gathered from the outpatient clinics electronic database of Gaziantep University Hospital. A total of 200 children were evaluated. The inclusion criteria were paediatric patients with folate deficiency (<4 ng/mL).

Results: Of the 200 children with folate deficiency, 46.5% showed low haemoglobin level (<11 g/dL), reflecting anaemia status. Macrocytic anaemia was detected in 13.5% of the patients. Thrombocytopaenia was detected in 20%, leukopenia in 17%, lymphopaenia in 6%, neutropenia in 5% and pancytopenia in 12% of the patients. Positive correlations were found between folate levels and haemoglobin ($r=0.18$; $p<0.01$), haematocrit ($r=0.17$; $p<0.05$), red blood cell ($r=0.19$; $p<0.01$), lymphocyte count ($r=0.20$; $p<0.01$) and platelet count ($r=0.15$; $p<0.05$). However, inverse correlations were found between folate level and red cell distribution width ($r=-0.18$; $p<0.01$), and no correlations were noted between folate level and mean corpuscular volume ($r=-0.72$; $p>0.05$).

Conclusion: Our data showed that these children not only develop anaemia but also leucopenia, thrombocytopenia and pancytopenia. Monitoring haematological parameters could be useful in children with folate deficiency.

Keywords
Folate, anemia, children

Anahtar Kelimeler
Folat, anemi, çocuklar

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Öz

Amaç: Folat eksikliği düşük ve orta gelirli ülkelerde yaygındır. Folat eksikliğinin en önemli morbid etkisi hematolojiktir. Bu çalışmanın amacı folat eksikliği olan çocuklarda hematolojik parametrelerin değerlendirilmesidir.

Gereç ve Yöntemler: Bu çalışmanın verileri Gaziantep Üniversitesi Hastanesi ayaktan hasta klinikleri elektronik veri sisteminden toplanmıştır. İki yüz çocuk hasta değerlendirilmiştir. Folat eksikliği olan çocuk hastalar çalışmaya dahil edilmiştir (<4 ng/mL).

Bulgular: Folat eksikliği olan 200 çocuk değerlendirilmiş olup, %46,5 hastada anemi mevcuttu. Bunların %13,5'inde makrositik anemi mevcuttu. Hastanın %20'sinde trombositopeni, %17'sinde lökopeni, %6'sında lenfopeni, %5'inde nötropeni, %12 hastada pansitopeni saptandı. Folat seviyesi ve hemoglobin ($r=0,18$), $p<0,01$, hematokrit ($r=0,17$), $p<0,05$, kırmızı küre ($r=0,19$), $p<0,01$, lenfosit sayısı ($r=0,20$), $p<0,01$ ve trombosit sayısı ($r=0,15$), $p<0,05$ arasında pozitif korelasyon mevcuttu, ancak folat seviyesi ve eritrosit dağılım genişliği ($r=0,18$), $p<0,01$ arasında ters ilişki mevcuttu. Ayrıca folat seviyesi ve ortalama eritrosit volümü ($r=-0,72$), $p>0,05$ arasında ilişki bulunamadı.

Sonuç: Bizim çalışmamıza göre folat eksikliği olan çocuklarda yalnızca anemi görülmemekte ayrıca lökopeni, trombositopeni ve pansitopeni de görülmektedir. Ayrıca folat eksikliği olan çocuklarda hematolojik parametrelerin takibi önemlidir.

Introduction

Folate deficiency (FD) is common in many parts of the world, especially in low and middle-income countries. It has become increasingly rare in countries where certain food groups have been supplemented with folate. Folate fortification of food in the developed countries has decreased the prevalence of FD to <1% of the population (1). Also, in countries where the supplementation of foods does not occur, FD is subsequently more frequent. Over the last three decades the prevalence of FD seems to have reduced from 70-75% to 2-10% as reported in various studies in children from different regions. Hovewer, prevalence of FD vary among different communities with different eating habits and socioeconomic levels (2,3).

The best-known morbid effects of FD are hematological. There is a large body of information, derived from studies of various populations, on the prevalence of folate FD as determined by biochemical assays, but it is uncertain how much of this apparent deficiency is translated into morbid hematological change (4). FD is manifest by macrocytic anemia resulting from megaloblastic change in the bone marrow. This form of abnormal hematopoiesis may lead to anemia, neutropenia, and thrombocytopenia (4). Also, changes in hematological parameters, such as hemoglobin (Hb), hematocrit (HTC), red blood cell (RBC), mean corpuscular volume (MCV), red cell distribution width (RDW), and mean platelet volume (MPV) in FD may be useful in diagnosis. Also, there is uncommon data about these parameters (5,6).

The present study evaluates the varying hematological manifestations in 200 children diagnosed as FD. In addition, we compared hematological parameters between FD with anemia (Hb<11 g/dL) and without anemia (Hb≥11 g/dL).

Materials and Methods

The data gathered from our institute Gaziantep University Hospital outpatient clinics electronic database. The period of this cross-sectional retrospective study was from 2019 to 2020. Two hundred children were evaluated: Ninety six females (48%) and 104 (52%) males. Ages of the patients were from 1 to 16 years old. The inclusion criteria were child patients with less than 4 ng/mL folate levels. The hematological parameters were measured using a Sysmex XN1000 analyzer. Serum folate levels were done by Beckman Coulter, UniCel DXI 800 Access immunoassay system on the same day as blood collection. Because it was a retrospective study, patient consent could not be obtained. The study protocol was approved by the Clinical Research Ethics Committee of Gaziantep University (protocol no: 2020/81).

We used serum folate levels cutoff of <4 ng/mL for children to estimate FD since this was a widely used criterion in previous studies (7,8). Macrocytosis was defined as MCV of >85 fL (9). Anemia was defined as Hb levels less than 11 g/dL, thrombocytopenia platelet counts less than 150,000/mm^3 and leucopenia white blood cell (WBC) counts less than 4,000/mm^3 and lymphopenia levels as lymphocyte counts less than 1,500/mm^3 with neutropenia levels as absolute neutrophil counts less than 1,500/mm^3 for children in our study (9). Pancytopenia was defined as Hb levels <11 g/dL, WBC counts <4,000/mm^3, and platelet counts <150,000/mm^3. Their red cell indices [MCV, mean corpuscular Hb (MCH), mean corpuscular Hb concentration (MCHC), and RDW], were noted. This study group was divided into four groups as group 1, cases <3 ng/mL (n=63, 31.5%), and group 2, cases 3-4 ng/mL (n=137, 68.5%) according to folate levels, and group 3, cases <11 g/dL (n=93, 46.5%), and group 4, cases ≥11 g/dL (n=107, 53.5%) according to Hb levels.

Statistical Analysis

Data were analyzed using SPSS 23.0 software (SPSS, Inc., Chicago, IL, USA). Demographic data were shown as means and standard deviation (SD) or percentages. Categorical variables were compared by using chi-square test. Spearman's correlation analysis was performed to examine the correlations between age and folate, and hematological measures. Two-tailed significance values are reported throughout. A probability level of $p<0.05$ was used to indicate statistical significance.

Results

The sample consisted of 200 children with FD (104 males, 96 females) between 1 and 16 (mean ± SD =9.3±4.6) years. The male-female ratio was 1.08. Table 1 shows demographic characteristics of the subjects.

The mean ± SD of laboratory measures, including folate levels, and hematological parameters, are

summarized in Table 2. Anemia was detected in 93 patients (46.5%), anemia without macrocytosis in 66 (33%), anemia with macrocytosis in 27 (13.5%), thrombocytopenia in 40 (20%), leukopenia in 34 (17%), lymphopenia in 12 (6%), neutropenia in 10 (5%), and pancytopenia in 24 patients (12%). Leukopenia coexisted with anemia in 7 (3.5%) patients, leukopenia coexisted with thrombocytopenia in 4 (2%) patients, anemia coexisted with thrombocytopenia in 24 (12%) patients. Folate levels, Hb, HTC, RBC, and lymphocyte levels were significantly lower, and RDW levels was significantly higher in group 1 (folate levels <3 ng/mL). Hb, HTC, RBC, MCV, MCH, MCHC and neutrophil levels were significantly lower, and RDW and lymphocyte levels were significantly higher in group 3 (Hb levels <11 g/dL). There was no statistical significant difference between females and males in all measures.

An examination of the correlation, there were positive correlations between folate levels and, Hb, (r=0.18), p<0.01, HTC, (r=0.17), p<0.05, RBC, (r=0.19), p<0.01, lymphocyte, (r=0.20), p<0.01, and platelet levels (r=0.15), p<0.05, however there were inverse

Table 1. Demographic characteristics

	Total n=200	Group 1, folate levels <3 ng/mL (n=63)	Group 2, folate levels 3-4 ng/mL (n=137)	Group 3, hemoglobin levels <11 g/dL (n=93)	Group 4, hemoglobin levels ≥11 g/dL (n=107)
Age, years Mean ± standard deviation	9.3±4.6	9.2±4.5	9.4±4.8	7.3±4.5	11±4
Gender, n (%)					
Male	104 (52%)	29 (46%)	75 (54.7%)	49 (52.7%)	55 (51.4%)
Female	96 (48%)	34 (54%)	62 (45.3%)	44 (47.3%)	52 (48.6%)

Table 2. Folate, and hematological values

	Total n=200	Group 1, folate levels <3 ng/mL (n=63)	Group 2, folate levels 3-4 ng/mL (n=137)	p	Group 3, hemoglobin levels <11 g/dL (n=93)	Group 4, hemoglobin levels ≥11 g/dL (n=107)	p
Folate (ng/dL)	3.2±0.6	2.4±0.4	3.5±0.2	<0.05	3.1±0.6	3.3±0.5	>0.05
Hb (g/dL)	10.9±2.5	10.3±2.5	11.2±2.5	<0.05	8.6±1.5	12.9±1.2	<0.0001
RBC (/mm^3)	4.3±0.9	4±1	4.4±0.9	<0.05	3.6±1	4.8±0.5	<0.0001
HTC (%)	33.8±7.5	32.3±7.3	34.5±7.6	<0.05	27.5±5.8	39.3±3.4	<0.0001
MCV (fL)	80±10.1	81.2±10.7	79.4±9.9	>0.05	77.8±12.5	81.9±7	<0.05
MCH (pg)	25.8±4.3	26.1±4.5	26.7±4.2	>0.05	24.6±5.4	26.9±2.7	<0.05
MCHC (g/dL)	32.2±3.1	31.9±2.1	33.6±2.4	>0.05	31.6±4.3	32.8±1.2	<0.05
RDW (%)	16±3.6	17±4	15.5±3.4	>0.05	18.1±3.8	14.1±2.2	<0.0001
WBC (mm^3)	8055±4677	7460±4742	8329±4638	>0.05	7712±5306	8354±4053	>0.05
Lymphocyte (mm^3)	3185±2173	2782±2283	3370±2103	<0.05	3207±2692	3167±1604	>0.05
Neutrophile (mm^3)	3670±2588	3684±3029	3663±2370	>0.05	3284±2892	4006±2252	<0.05
Platelet (mm^3)	308.876±196.646	271.000±180.756	32.6291±201787	>0.05	301.547±248.971	315.243±136.783	>0.05
MPV (fL)	9.7±1	9.6±0.8	9.8±1.1	>0.05	9.6±1	9.9±1.1	>0.05

Hb: Hemoglobin, RBC: Red blood cell, HTC: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, WBC: White blood cell, MPV: Mean platelet volume, p<0.05 was accepted to be statistically significant

correlations between folate and RDW levels (r=-0.18), p<0.01. Moreover, there were no correlations between folate levels and, age (r=0.06), p>0.05, MCH (r=-0.48), p>0.05, MCHC (r=0.05), p>0.05, MCV (r=-0.72), p>0.05, MPV (r=0.008), p>0.05, and neutrophil levels (r=0.09), p>0.05.

Discussion

FD is usually due to insufficient dietary intake but can also originate from intestinal malabsorption, defect in folate metabolism. Serum folate concentration is a good indicator of dietary folate intake and the most widely used method for assessing status (10). FD is associated with hematologic abnormalities. Hematologic manifestations of FD include anemia, macrocytosis, leukopenia, thrombocytopenia and pancytopenia (4-6). In this study, we analysed the relationship between hematological status and FD.

Relatively few data on the frequency and diversity of hematologic abnormalities in childhood FD have been reported (4-6,11,12). Hematologic abnormalities of anemia has been frequently associated with FD, but thrombocytopenia, leucopenia, and pancytopenia are less frequently seen (4-6,13). In the present study, anemia was detected in 93 patients (46.5%), thrombocytopenia in 40 (20%), leukopenia in 34 (17%), lymphopenia in 12 (6%), neutropenia in 10 (5%), and pancytopenia in 24 patients (12%) (Table 2).

Folate is a carbon donor for pyrimidine and purine synthesis, which are needed for the rapidly developing erythroid cells. Impaired DNA synthesis, a result of FD, leads to erythroid cell apoptosis and anemia (14,15). In the Azimi et al. (16) study, serum folate had a significant positive correlation with RBC (r=0.271), Hb (r=0.279) and HTC (r=0.316) levels, but not with MCV levels. This shows that MCV levels are not a reliable marker for FD. They found that serum folate was inversely correlated with RDW and MPV, but this was not statistically significant. Another study, De Bruyn et al. (17) reported that for serum folate concentrations ≤5 ng/dL, a significant negative impact was noted on the RBC count, HTC and Hb levels. Ndiaye et al. (10) found that, mean Hb levels was 116.86 (1.18) g/L, and 47.63% of the women involved in the study were anemic. Also, a positive and significant correlation was found between Hb and serum folate levels (r=0.07; p=0.0167). In the study performed by Villalpando et al. (12) 14% of children had low erythrocyte folate levels and anemic children had significantly lower folate levels compared with non-anemic children. Silva et al. (11) analyzed the nutritional status of vitamin B_{12} and folate levels with anemia in 460 children. In their study, Hb levels was positively associated with serum folate levels. In our study there were positive correlations between folate levels and, Hb, (r=0.18, p<0.01), HTC, (r=0.17, p<0.05), RBC levels, (r=0.19, p<0.01), however there were inverse correlations between folate and RDW levels (r=-0.18, p<0.01) but not with MCV (r=-0.72, p>0.05), MCH (r=-0.48, p>0.05), MCHC (r=0.05, p>0.05), and MPV levels (r=0.008, p>0.05). Our finding of a positive association between Hb concentration and folate status is consistent with reports from other studies conducted.

Folate are required in the synthesis of nucleoproteins and deficiency results in defective synthesis of DNA and RNA (18). Thrombocytopenia is believed to be due to impaired DNA synthesis resulting in ineffective thrombopoiesis. Isolated thrombocytopenia is a common indication for hematologic consultation. Testing for folate deficiencies is commonly performed during the evaluation of cytopenias. In the series by Erkurt et al. (19) 5% of the patients admitting with thrombocytopenia had megaloblastic anaemia. Another study, Gupta et al. (13) analyzed the varying clinico-hematological manifestations in 50 children diagnosed as megaloblastic anemia over a four year period. Thrombocytopenia was reported in 30% cases and leucopenia in 14% cases in the study. In the Dhoriya et al. (20) study, found that mean Hb, WBC and platelets in 59 patients of megaloblastic anemia were 6.6 g/dL, 2,800/mm^3 and 57,492/mm^3 respectively. In our study thrombocytopenia was detected in 40 (20%), leukopenia in 34 (17%), lymphopenia in 12 (6%), neutropenia in 10 (5%). Cytopenias is believed to be due to impaired DNA synthesis resulting in ineffective leukopoiesis and thrombopoiesis.

Pancytopenia is simultaneous presence of thrombocytopenia, leukopenia and anemia. Ineffective leukopoiesis, thrombopoiesis and erythropoiesis resulting from programmed cell death in the absence of folate, and reduced survival of precursors in peripheral blood are causes of pancytopenia in FD anemia (21). There is a little study in which micronutrients especially folate and

vitamin B_{12} are associated with pancytopenia (22,23). In our study of children with FD 24 patients (12%), had pancytopenia. Talarmin et al. (24) recognized that vitamin B_{12} and folate deficiencies are common in underdeveloped countries and are responsible of megaloblastic anemia and pancytopenia. In the Sarode et al. (25) study found that out of 139 patients of pancytopenia, 102 cases in whom the biochemical parameters were available, vitamin B_{12} deficiency was detected in 76%, FD in 6.8%, combined B_{12} and folate deficiency in 8.8%; the remaining 7.8% had normal vitamin levels at presentation. A hundred nine pediatric patients with pancytopenia were analyzed by Bhatnagar et al. (23) retrospectively and megaloblastic anemia was found to be the most common etiological factor (28.4%). Gomber et al. (26) in their study reported an incidence of 11% while Mukiibi et al. (27) had 47% cases of megaloblastic anemia presenting as pancytopenia. In the Gupta et al. (13) study, of the 50 children with megaloblastic anemia, 43.8% were presenting as pancytopenia.

Limitations of the retrospective study are the small sample size and the lack of analysis of other variables that reflect the tissue deficiency of folate such as serum homocysteine. Further, this study did not collect any data about the medical history, iron and vitamin B_{12} status of the population. In addition, we did not evaluate the dietary intake of folate to better assess the folate status of participants. Our results reflect an outpatient population, and it is not representative of general population.

Conclusion

Hematologic abnormalities accompanying FD are common. Here, in the present study, our results emphasize that FD should be considered in a children with hematologic abnormalities such as anemia without macrocytosis, anemia with macrocytosis, leukopenia, thrombocytopenia, or pancytopenia, especially in developing geographical areas.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Gaziantep University (protocol no: 2020/81).

Informed Consent: Because it was a retrospective study, patient consent could not be obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.T.A., Design: H.T.A., Supervision: H.T.A., M.Ö., Fundings: H.T.A., M.Ö., Materials: M.Ö., Data Collection or Processing: M.Ö., Analysis or Interpretation: H.T.A., Literature Search: H.T.A., Critical Review: H.T.A., Writing: H.T.A., M.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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