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Research Article

Frequency of Anemia and Correlation with Mean Erythrocyte Volume in Children with B12 and Folate Deficiency

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Abstract

Objectives: Vitamin B12 and folic acid deficiency is a disease that may cause neurological and psychiatric findings and anemia. In the literature, only 21.5% of patients with B12 deficiency have anemia. We aimed to investigate the rate of anemia and macrocytosis in these patients.

Methods: A total of 185 children (aged 1-18 years) were enrolled in the study, categorized under 4 groups, i.e. those with a low level of B12 or folic acid, those with low levels of both B12 and folic acid and those with a normal level of both B12 and folic acid. Group 1 consisted of 47 patients with a normal level of B12 and folic acid. Group 2 comprised of 40 patients with low levels of B12 and folic acid and Group 3 had 50 patients with a low level of folic acid but a normal level of B12 and Group 4 consisted of 48 patients with a low level of Vitamin B12 and a normal level of folic acid.

Results: There was no difference among the groups in terms of age (p=0.61) and gender (p=0.924). Anemia rates in groups (HCT<35) are as follows: Group 1 4/47= 9%, Group 2 3/40= 8%, Group 3 7/50= 14% and Group 4 5/48=10%. No statistically significant difference was found between the anemia rates and HCT and MCV values in the groups (p>0.05).

Conclusion: It is important to note that anemia and macrocytosis in children may not occur in most cases in case of folic acid and Vitamin B12 deficiency, and early treatment of these patients may prevent the accumulation of methylmalonic acid and homocysteine, eliminating neurological and psychiatric findings.

Keywords: Anemia, children, folic acid, Vitamin B12

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Vitamin B12 and folic acid deficiency is a disease that develops in the long term mainly due to nutritional deficiency and may cause neurological and psychiatric findings depending on homocysteine (HCY) and methylmalonic acid (MMA) accumulation in the serum with or without anemia. As general information, although it is widely known by health care professionals that megaloblastic anemia occurs in vitamin B12 and folic acid deficiency, neuropsychiatric findings may develop progressively prior to haematological findings. Reflection of B12 deficiency as anemia occurs with serum B12 levels below 100 pg/mL.[1]

While serum homocysteine value increases in both vitamin B12 and folic acid deficiency, methylmalonic acid increases only in vitamin B12 deficiency and these two substances are responsible for neuropsychiatric symptoms.[2] In a study conducted in our country, the limit value of serum B12 level was found to be 257 pg/mL compared to homocysteine and 219 pg/mL compared to MMA excretion in urine. However, the lower limit of serum B12 level in our hospital

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and a large number of laboratories is 180 pg/ml. This may cause clinicians to delay treatment with recommendations such as increasing the rate of foods containing vitamin B12 vitamin in diets when the value does not fall below 180 pg/ml or lack haematological findings due to the absence of anemia and macrocytosis. In one study, only 21.5% of adult patients with B12 deficiency had anemia.[3]

In the paediatric clinic, we retrospectively compared the hematocrit (HCT) and mean corpuscular volumes (MCV) in children with simultaneous complete blood count for determining the levels of B12 and folic acid and we planned this study to investigate to what extent B12 and folic acid deficiency in child patients resulted in HCT decrease and MCV elevation.

Methods

We started our study with the approval of the ethics committee of our hospital. We divided our patients, who applied on 1/6/2017–31/12/2017 to the paediatrics (outpatient clinic) of our (tertiary) hospital and did not have any chronic disease and hematologic disorder, into four groups according to their B12 and folic acid levels.

A total of 185 children (aged 1-18 years) were enrolled in the study, categorized under 4 groups, i.e. those with a low level of B12 or folic acid, those with low levels of both B12 and folic acid and those with a normal level of both B12 and folic acid. Group 1 consisted of 47 patients with a normal level of B12 and folic acid. Group 2 comprised of 40 patients with low levels of B12 and folic acid and Group 3 had 50 patients with a low level of folic acid but a normal level of B12 and Group 4 consisted of 48 patients with a low level of Vitamin B12 and a normal level of folic acid.

The lower limit of vitamin B12 was recognized to be 180 pg/ml and to be 5.9 ng/ml for folic acid, which were the lower limits of the laboratory in our hospital. Patients younger than 1 year, older than 18 years, those with any chronic disease and hematologic disorder and patients who were not examined simultaneously were excluded from the study.

Serum folic acid and vitamin B12 levels were measured using UniCel DxI 600 chemiluminescent method (Beckman Coulter, Inc. USA) that was available in the biochemistry laboratory. Blood count was performed with Sysmex XE-2100 haematology analyzer (TOA Medical Electronics, Kobe, Japan).

Statistical Analysis

Statistical analyses were performed using SPSS 21 software package (IBM, New York, USA). Categorical variables were evaluated by Chi-square test and numerical variables were evaluated by Student's T-test. A p value of <0.05 was (accepted) significant.

Results

The mean age of the patients in the groups was as follows:

Group 1 (n=47)=8.09 years, Group 2 (n=40)=9.08 years; Group 3 (n=50)=8.74 years and Group 4 (n=48)=8.56 years. No statistical difference was found in the mean age (p=0.61). There were 94 male and 91 female patients in all groups. There was no intra-group difference in terms of gender (p=0.924).

Anemia (Hct <35) rates in the groups: Group 1 (4/47)=9%, Group 2 (3/40)=8%, Group 3 (7/50)=14% and Group 4 (5/48)=10%. No statistical difference was found between the anemia rates in the groups (p=0.742).

Although a significant difference was found between vitamin B12 and folic acid levels between the groups (p<0.001), there was no significant difference between HCT and MCVs (p>0.05) (Table 1).

HCT and MCV distributions in the groups are shown in Figures 1 and 2.

Table 1. Mean B12, folate, HCT and MCV values of the groups and statistical evaluation

	Group 1 (n=47)	Group 2 (n=40)	Group 3 (n=50)	Group 4 (n=48)	p
HCT	38.3±2.6	39.1±3.6	37.9±3.3	38.0±2.4	0.275
MCV	78.5±3.7	79.9±4.1	78.3±4.7	77.8±5.7	0.198
Vit B12	460±107	142±19	303±80	145±19	<0.001
Folate	15.2±4.0	4.7±0.7	4.7±0.8	11.4±3.8	<0.001

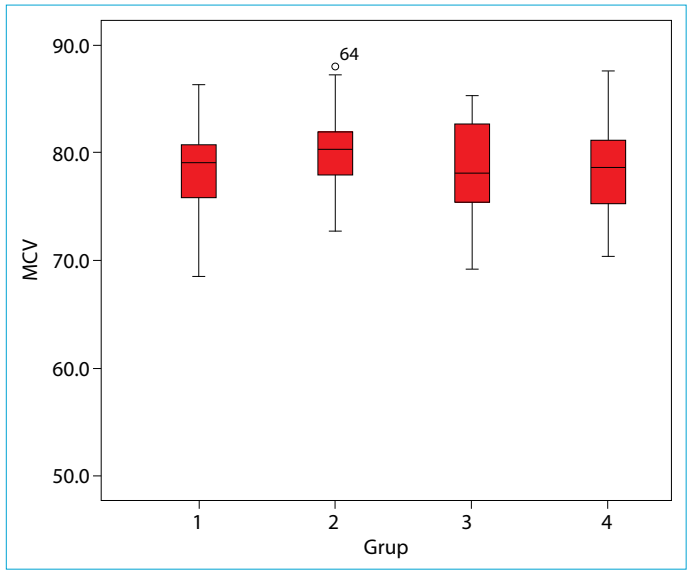

Figure 1. MCV distribution graph of the groups.

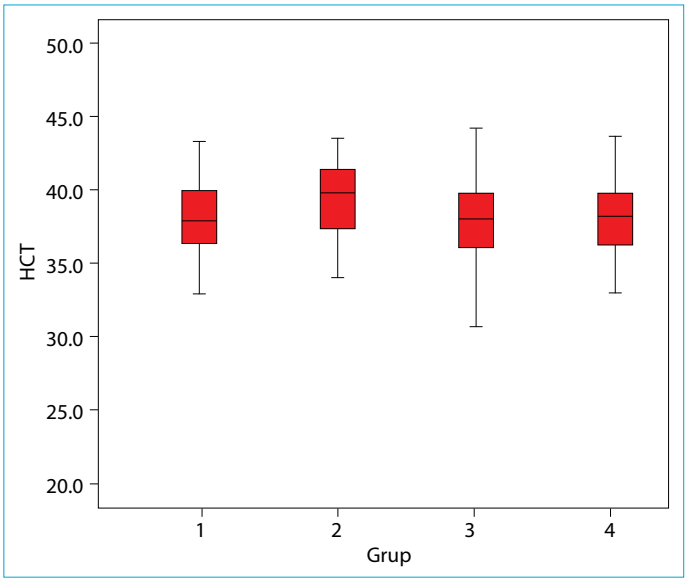

Figure 2. HCT distribution graph of the groups.

Discussion

Neurological and psychiatric findings associated with vitamin B12 deficiency occur prior to anemia. Although the classic finding is subacute combined degeneration, bilateral peripheral sensory neuropathy is the most common.[4] Again, considering the presence of iron deficiency and thalassemia carrier as well as anemia in B12 and folic acid deficiency, MCV is expected to be above the expected value according to age and iron condition. However, in the absence of anemia and the presence of iron deficiency, MCV will not guide us in the early diagnosis of B12 deficiency.

Although we found an intra-group difference between B12 and folic acid values, we did not find a statistically significant difference between the mean HCT and MCV (Table 1). There was no difference between the groups in terms of age and gender ($p>0.05$). In the literature, it has been reported that HCT and MCV are normal in patients with neuropsychiatric findings.[5, 6]

No intra-group difference was found in terms of age and gender ($p>0.05$). In the literature, it is reported that HCT and MCV are normal in patients with neuropsychiatric findings.[5, 6] Although iron condition and neurological symptoms of the patients are not clearly known and patients have not been examined for MMA and HCY, which constitute the limitations of our study.

A statistically significant inverse correlation was found in the literature between the depth of anemia and the severity of neurological involvement. Patients without anemia or macrocytosis tend to show the most severe nervous system involvement.[7] Vitamin B12 acts as a coenzyme for L-methylmalonylcoenzyme A mutase and methionine synthase. Accordingly, vitamin B12 deficiency appears to be directly proportional with the amount of accumulated methylmalonic acid and homocysteine.[8] In contrast, inefficient DNA synthesis and impaired erythropoiesis due to insufficient vitamin B12 cause the majority of haematological disorders.[9]

Vitamin B12 deficiency occurs in Turkey more often than in advanced societies. Önal et al.[10] report in their study on 250 pregnant women and infants that the B12 level was deficient in 81.6% of mothers and 42% of infants. However, B12 deficiency was found to be 2.6% in the adults in Switzerland and 3.4% in the adults in Spain.[11] In a study conducted in Bursa, B12 deficiency was found in 48.8% of the cases. It was also stated in this study that the safe limit for neuropsychiatric findings for vitamin B12 should be 250 pg/ml.[1]

Since the necessary S-adenosyl methionine for myelin synthesis cannot be produced in vitamin B12 deficiency, neuromotor development is impaired. B12 deficiency leads to serious neurological findings in childhood when rapid growth occurs. The most common complaints in infancy are lethargy, hypotonia and convulsions. Rarely, it may lead to coma. With 3-4 months of treatment, symptoms may improve, deteriorate or remain the same. It is reported that brain atrophy or hypoplasia may occur in some patients and the most important factor in preventing neurological findings is diagnosis and treatment.[12]

It is also reported that school children may have lower success in school, difficulty in concentrating, dysmnesia, dizziness and some autonomic symptoms. Functional vitamin B12 deficiency can also be diagnosed by evaluating homocysteine and/or methylmalonic acid levels when the level of B12 is normal. It is stated that this will prevent delay in diagnosis and absence of anemia and/or macrocytosis will not exclude the diagnosis of B12 deficiency.[13]

Conclusion

In conclusion, in case of autonomic symptoms such as hypotonia, lethargy, neurological developmental delay in infancy, numbness in hands, burning, dysmnesia and drop in school success in children and orthostatic hypotension, B12 and folic acid levels should be checked and treatment should be started in the early period.

Disclosures

Ethics Committee Approval: The study was approved by the Haseki Local Ethics Committee (Number 81, Date: 22.03.2018).

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Conflict of Interest: None declared.

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