
Vitamin B12 levels in familial Mediterranean fever patients treated with colchicine

A.I. Gemici^{1*}, Ö.G. Sevindik², S. Akar³, M. Tunca¹

¹Department of General Internal Medicine,

²Department of Haematology and

³Rheumatology, Dokuz Eylul University School of Medicine, Izmir Turkey.

*Present address: Department of Haematology, Celal Bayar University School of Medicine, Manisa, Turkey.

Ali Ihsan Gemici, MD

Ömür Gökmen Sevindik, MD

Servet Akar, MD

Mehmet Tunca, MD

Please address correspondence to:

Dr Mehmet Tunca,

Dept. of General Internal Medicine,

Dokuz Eylul University School

of Medicine, Balçova,

35350 Izmir, Turkey.

E-mail: mehmet.tunca@deu.edu.tr

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ABSTRACT

Objectives. *Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease characterised by paroxysmal attacks of serosal inflammation. Colchicine is highly effective in preventing these attacks but it may also disrupt the intestinal absorption of vitamin B12. We hypothesised that patients treated with colchicine for a prolonged period could develop deficiency of the vitamin.*

Methods. *Ninety-five adult FMF patients on regular colchicine treatment for at least 2 years and age and sex-matched 90 healthy controls were enrolled and complete blood count with platelets, vitamin B12 and folic acid were measured in each person. We also investigated 15 adult FMF patients who were not yet on colchicine.*

Results. *The mean vitamin B12 values were not significantly different between the groups (352.12 (SD=171.62) pg/mL vs. 360.96 (SD=146.53) pg/mL, p=0.71), but there were significantly more vitamin B12 deficient cases among FMF patients (12 vs. 3; p=0.021) and 3 out of these 12 had megaloblastic anaemia. None of the vitamin B12 deficient controls had anaemia. We could not identify any disorder which might have causative effect for the deficiency among this subgroup. The mean vitamin B12 value of 15 colchicine-naïve cases was not significantly different from patients on colchicine (p=0.356).*

Conclusion. *We did not observe significant vitamin B12 deficiency among colchicine-treated FMF patients but some cases may be more prone to developing this potentially serious disorder.*

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease characterised by paroxysmal attacks of fever and serosal inflammation. The disease is primarily

endemic among Sephardic Jews, Armenians, Turks and North African Arabs with a prevalence of 1:300-1:2000 (1). The most serious complication of FMF is development of AA type ("secondary") amyloidosis. Both the clinical features of FMF and amyloidosis can be effectively prevented by regular administration of colchicine at a dosage of 1.5–2.0 mg daily (2). Although colchicine is essentially a safe drug with few side-effects such as diarrhea and abdominal distention, there are a number of studies done on animals and humans showing that it may disrupt the intestinal absorption of vitamin B12 and it is regarded as an agent which may cause the deficiency of the vitamin (3-5). This aspect of colchicine treatment has been approached only once in a small number of FMF patients with normal results (6). We hypothesised that patients treated with colchicine for a prolonged period could develop deficiency of the vitamin.

Patients and methods

Ninety-five adult FMF patients on regular colchicine treatment for at least 2 years and age- and sex-matched 90 healthy controls were enrolled in the study. Current colchicine dose and the number of years of treatment were recorded for each patient. All patients and controls gave written informed consent and the study was approved by the medical ethics committee of Dokuz Eylul University.

Exclusion criteria were known vitamin B12 deficiency or being on vitamin B12 treatment, pregnancy, being on a vegetarian diet, existence of certain co-morbidities (malnutrition, phenylketonuria, hypothyroidism, atrophic gastritis, any kind of malabsorption, gastrectomy, ileal resection, Zollinger Ellison syndrome, pernicious anaemia, chronic alcoholism) and usage of drugs which could cause vitamin B12 deficiency (H₂ receptor antagonists, any

Competing interests: none declared.

kind of antacids, proton pump inhibitors and metformin).

The following parameters were measured in each person: complete blood count with platelets, vitamin B12 and folic acid. Blood samples were obtained in the morning after at least 8 hours fasting. Complete blood count analysis was performed with the flow cytometric method by using Beckman Coulter 750 autoanalyzer. Folic acid and vitamin B12 were measured using solid phase chemiluminescent immunometric assay by Siemens Immulite 2500 LA USA autoanalyzer kits.

Normal reference values of the laboratory were as follows: Folic acid 3-15 ng/mL (sensitivity %4,21) and vitamin B12 193-982 pg/mL (sensitivity %9,76). Vitamin B12 deficiency was defined as less than lowest reference value. Anaemia was defined as haemoglobin value less than 13 g/dL for men and 12 g/dL for women.

Statistics

Data were analysed by using SPSS 11.0 for Windows (SPSS, Inc., Chicago, IL). Variable distributions were assessed by the Kolmogorov-Smirnov normality test. According to the variable distribution, Student *t*-test or Mann-Whitney U-test was used for comparison of groups. Categorical variables were compared by using the chi-square test. Normally distributed variables were expressed as mean ± standard deviation. Non-parametric variables were expressed as median and range. A *p*-value less than 0.05 was accepted as statistically significant.

Results

Demographic characteristics and laboratory findings of patients and controls are summarised in Table I. Among the FMF patients, mean age at the time of diagnosis was 28 and they were on colchicine treatment for a median of 10 years (range: 2-46 years). The average dose (S.D.) of colchicine was 1.56 (0.37) mg. Among patients with low and normal vitamin B12 levels, the mean (SD) colchicine dose (1,37 mg (0.43) vs. 1.59 mg (0.36), *p*=0.076) and the median duration of treatment (11 years vs. 10 years, *p*=0.835) were comparable.

Table I. Demographic characteristics and laboratory findings of patients and controls.

	Patients (n=95)	Controls (n=90)	<i>p</i> -value
Age, mean (SD), years	40.05 (11.44)	36.97 (11.39)	0.068
Female, n (%)	52 (54.7)	54 (60)	0.469
Haemoglobin, mean (S.D.), g/dL	13.32 (1.91)	14.00 (1.39)	0.006
Haematocrit, mean (S.D.), %	39.36 (5.19)	41.26 (3.82)	0.005
Folic acid, mean (S.D.), pg/mL	8.49 (4.41)	8.63 (3.28)	0.319
Vitamin B12, mean (S.D.), pg/mL	352.12 (171.62)	360.96 (146.53)	0.71

Table II. The number of vitamin B12 deficient cases among patients and controls.

Vitamin B12 level	Patients (n=95)	Controls (n=90)	<i>p</i> -value
≤193 pg/mL (%)	12 (12.6)	3 (3.3)	0.021
>193 pg/mL (%)	83 (87.4)	87 (96.7)	

Although the mean vitamin B12 values were not significantly different between the groups there was significantly more vitamin B12 deficient cases among FMF patients (12 vs. 3; *p*=0.021) and 3 out of these 12 patients had megaloblastic anaemia. None of the vitamin B12 deficient controls had anaemia (Table II).

Actual B12 serum concentrations of B12 deficient patients on colchicine therapy were as follows: 147, 150, 151, 153, 161, 162, 165, 175, 177, 181, 186 and 191 pg/mL. Actual B12 serum concentrations of B12 deficient controls who were not on colchicine therapy were 150, 152 and 174 pg/mL. To verify the possibility of the disease itself as a risk factor for vitamin B12 deficiency, we investigated 15 adult patients who were not yet on colchicine. Their mean level of the vitamin was 334.93 pg/mL (range: 189-518 pg/mL), there was thus a single patient with lower than normal vitamin B12. This finding was not significantly different from FMF patients on colchicine (*p*=0.356).

Discussion

Colchicine is an ancient drug essentially used for gouty arthritis and FMF. Almost half a century ago it was reported that the drug could cause reversible reduction in the quantity of intrinsic factor-vitamin B12 (IF-B12) receptors, the population of villus cells and alter the function of ileal mucosa. The issue was not revisited but colchicine has remained in the list of drugs causing vitamin B12 deficiency (3-5).

Megaloblastic anaemia is one of the major presentations of vitamin B12 deficiency. The mean haemoglobin and haematocrit values of FMF patients were lower than controls (Table I). Anaemia may be a clue for an ongoing chronic and subclinical inflammation despite “satisfactory” treatment with colchicine. Three FMF patients with vitamin B12 deficiency had also megaloblastic anaemia, with obvious findings in peripheral smears. None of healthy controls with vitamin B12 deficiency had anaemia. Among the 15 patients who were not yet on colchicine, 4 of them had anaemia without any megaloblastic features.

Our patients were on regular colchicine therapy for a median of 10 years. There was no significant difference between mean folic acid and vitamin B12 levels but 12 patients and 3 controls were vitamin B12 deficient (which was not statistically significantly different either). We could not identify any comorbidity (particularly disorders such as thyroid disease, gastritis or type II diabetes mellitus), clinical presentations or difference in the levels of acute phase reactants (CRP and ESR) which could potentially highlight the subgroup of “deficiency-prone” patients. In order to rule out the debatable possibility of the disease itself causing the deficiency, the findings of our colchicine-naïve patients were limited by the small size of the group.

Vitamin B12 deficiency develops insidiously and many of the patients may not have either neurologic symptoms no anaemia (7). The disorder has seri-

ous consequences, however, such as cognitive decline and dementia (8). More-over, it may be more appropriate to have 50% higher cut-off values in order to better detect the so-called "subclinical cobalamin deficiency" (9). Since vitamin B12 measurement is readily available in many of the health facilities at a reasonable price and even oral supplements are effective (10), early detection and prompt treatment of its deficiency should be desirable.

In conclusion, although colchicine therapy seems to have no significant effect on vitamin B12 absorption some patients with FMF may be at higher risk of developing vitamin B12 deficiency and megaloblastic anaemia. We recommend regular vitamin B12 meas-

urements every 2-3 years. Oral supplements to each patient should also be considered where laboratory facilities are scarce.

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