Do Vitamin B12 Levels Need to be Evaluated in FMF Cases Having Long Term Colchicine Treatment?

Sare G Ozlu¹, Muferet Erguven², Oznur Yılmaz Hamzah²

Abstract

Background: Colchicine used in the treatment of FMF inhibits absorption of Vitamin B12.

Objective: To evaluate serum vitamin B12 levels in cases with Familial Mediterranean Fever (FMF) receiving long term colchicine therapy.

Method: Serum vitamin B12 and folic acid levels, and full blood count of 70 patients with FMF that received more than 5 years of colchicine therapy were evaluated. The results were compared with 80 patients that received less than 5 years of colchicine therapy and 70 healthy children.

Results: Mean age of the patient group was 15.5±2.45 years; and the mean age of the patients that received less than 5 years of colchicine therapy was 10.24±4.02 years. Mean vitamin B12 level of the patients that received more than 5 years of colchicine therapy (208.37±40.57 pg/ml) was significantly lower than the patients that received less than 5 years of colchicine therapy (390.77±124.19 pg/ml) and the control group (478.31±135.76 pg/ml) (p=0.0001, p<0.005). MCV was significantly lower in patients who received more than 5 years of colchicine therapy (p=0.38, p<0.005). However, MCV was in normal limits in all three groups. There was no significant difference between the groups in terms of folic acid, hemoglobin and hematocrit values. Conclusion: Long term colchicine therapy may decrease serum vitamin B12 levels, but does not lead to megaloblastic anemia. Even if serum vitamin B12 levels are sufficient for 3-5 years in cases where there is no other illness, we must consider that neurological findings can appear before anemia and have to evaluate serum vitamin B12 levels at certain intervals in patients under long term colchicine therapy.

Key words: Colchicine, vitamin B12, anemia

Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessively inherited disease, characterized by attacks of recurrent fever and polyserositis, and seen especially in Mediterranean countries (in Sephardic Jews, Armenians, Arabs, Turks) [1-4]. Since the disease can present in many different ways, diagnosis is difficult in absence of pathognomonic clinical and biological findings [1]. Diagnosis is based on Tell-Hashomer criteria. Colchicine is used in treatment of the disease since 1972, and it decreases number and frequency of attacks and prevents the development of amyloidosis. It has few side effects and most commonly gastrointestinal side effects like diarrhea are encountered. Other side effects are pancytopenia, myopathy and less commonly rash.
Colchicine decreases receptor levels of vitamin B12-intrinsic factor (IF) complex in mucosal cells and by this way inhibits absorption of vitamin B12 \([6,7]\). This effect is dose dependent and reversible \([8,9]\). In studies on adults, myopathy is a commonly seen side effect in patients receiving moderate amounts of colchicine and is frequently together with axonal polyneuropathy \([10]\). It is demonstrated that this neuropathy occurs as a result of axonal degeneration due to vitamin B12 deficiency, and not as a direct effect of colchicine. In several studies, evaluation of vitamin B12 levels at certain intervals was recommended for patients receiving long term colchicine therapy \([11]\).

In our study, we aimed to evaluate serum vitamin B12 levels in patients with Familial Mediterranean Fever receiving long term (>5 years) colchicine therapy.

**Material And Methods**

The study was carried out in the pediatric rheumatology outpatient clinic of Goztepe Research Hospital, Istanbul, Turkey, between January 1999 and October 2005. Serum vitamin B12 and folic acid levels and full blood count of 70 patients with FMF who have received colchicine treatment for more than five years were evaluated. They had no other chronic, systemic and endocrinological disease and they were not vegetarians. The results were compared to those of 80 patients with FMF who received colchicine treatment for less than 5 years and also to those of 70 healthy children. The patients were diagnosed according to Tell-Hashomer criteria (Table 1). GraphPad Prisma V3 programme was used in statistical analysis.

**Results**

The mean age of the patients receiving >5 years of colchicine therapy \((15.5±2.45\) years\) was significantly higher than the mean age of the group that received less than 5 years of colchicine therapy \((10.24±4.02\) years\) and the mean age of the control group \((10.36±3.06\) years\) \((p=0.0001, p<0.05)\). Serum vitamin B12 levels of the patients that received colchicine for more than 5 years \((208.37±40.57\) pg/ml\) was significantly lower than the patients that received colchicine for less than 5 years \((390.77±124.19\) pg/ml\) and the control group \((478.3±135.76\) pg/ml\) \((p=0.0001, p<0.005)\). However, vitamin B12 levels were within normal limits in all of the cases (Table 2). Mean corpuscular volume (MCV) was significantly higher in the group that received >5 years of colchicine \((p=0.038, p<0.05)\). However,

### Table-1: Tell Hashomer criteria

<table>
<thead>
<tr>
<th>Major Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Relapsing fever attacks accompanied with peritonitis, sinovitis or pleuritis.</td>
</tr>
<tr>
<td>2. AAA type amyloidosis without predisposing disease.</td>
</tr>
<tr>
<td>3. Response to long term colchicine therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Relapsing attacks of fever</td>
</tr>
<tr>
<td>2. Erysipela like erythema</td>
</tr>
<tr>
<td>3. AAA diagnosis in a first degree relative.</td>
</tr>
</tbody>
</table>

**Diagnosis:** 2 major and 1 major 2 minor criteria

**Probable diagnosis:** 1 major and 1 minor criteria

### Table 2. Vitamin B12, folic acid, hemoglobin, and hematocrite values of cases who have been receiving colchicine therapy for less than 5 years and for more than 5 years

<table>
<thead>
<tr>
<th>Duration of Colchicine Treatment</th>
<th>&lt;5 years</th>
<th>&gt;5 years</th>
<th>Control</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>10.24±2.02</td>
<td>15.5±2.45</td>
<td>10.36±3.06</td>
<td>30.28</td>
<td>0.0001</td>
</tr>
<tr>
<td>B12 (Pigcr/ml)</td>
<td>390.77±124.19</td>
<td>208.37±40.57</td>
<td>478.3±135.76</td>
<td>53.34</td>
<td>0.0001</td>
</tr>
<tr>
<td>Folic acid (ng/ml)</td>
<td>7.07±1.64</td>
<td>6.44±1.24</td>
<td>6.92±1.58</td>
<td>1.79</td>
<td>0.169</td>
</tr>
<tr>
<td>Hgb (gr/dl)</td>
<td>11.51±1.93</td>
<td>11.81±1.4</td>
<td>11.64±1.51</td>
<td>0.42</td>
<td>0.659</td>
</tr>
<tr>
<td>Htc (%)</td>
<td>34.85±4.06</td>
<td>36.06±3.72</td>
<td>35.93±4</td>
<td>2.36</td>
<td>0.096</td>
</tr>
<tr>
<td>MCV (µ³)</td>
<td>77.54±4.27</td>
<td>78.58±3.84</td>
<td>76.17±5.93</td>
<td>3.33</td>
<td>0.038</td>
</tr>
</tbody>
</table>
MCV levels were also within normal limits in all three groups.

There was no statistically significant difference in terms of folic acid, hemoglobin and hematocrit levels among three groups. (Table 2)

**Discussion**

Goldfinger et. al. reported that colchicine treatment decreases the frequency of attacks in patients with FMF [13]. Later, it was demonstrated that it also prevents febrile attacks and development of amyloidosis [14-19]. Although in pediatric doses, colchicine is safely used, it can rarely cause gastrointestinal side effects like nausea, vomiting, diarrhea; temporary alopecia, azospermia, reversible bone marrow suppression, myopathy, neuropathy and chromosomal abnormalities [20,21,22].

Previously, it was claimed that the neuromuscular phenomena (neuropathy, myopathy) caused by colchicine treatment was more likely due to intoxication and was more common in elderly and patients with renal insufficiency [10]. In 1998, Harel et. al. reported myoneuropathy in two children without intoxication and renal insufficiency. Palopoli et. al. proposed that neuropathy in patients receiving colchicine was due to vitamin B12 deficiency [11]. In this study, it was reported that colchicine decreased B12-IF receptors in intestinal mucosa and decreased vitamin B12 absorption in a dose-dependent manner. Yesilova et all reported that plasma total homocysteine levels were significantly higher while vitamin B12 and folate levels were significantly lower in Behçet’s disease and they concluded that these findings may be related to increased use or accelerated catabolism of folate and vitamin B12 due to chronic inflammation [23]. Vitamin B12 deficiency can present with neurological symptoms before appearance of clinical and laboratory findings of anemia. In our study, we also demonstrated that vitamin B12 levels in patients who have been receiving colchicine treatment for more than 5 years were significantly lower than the other groups; however the values were within normal limits in all of the cases.

There are few studies on effects of colchicine treatment on vitamin B12 levels in children. As a result of our study, we suggest that even though vitamin B12 levels in patients with no other known risk factors can be sufficient for the organism for 3-5 years, we must consider that neurological symptoms can appear before anemia and must check vitamin B12 levels at certain intervals in patients who have been receiving colchicine therapy for more than 5 years.

In conclusion, colchicine is a very effective treatment in preventing attacks and amyloidosis in FMF. It has few side effects within therapeutic doses and most of the side effects are reversible. Therefore, we can say that colchicine is a quite safe and effective drug in FMF. However, since it can decrease vitamin B12 levels in long term use, it will be useful to check serum vitamin B12 levels in patients receiving long-term colchicine therapy.

**Competing interests:** We have no competing interest.

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**References**


17. The International FMF Consortium: Ancient missense mutations in a new member of the RoRet gene family are likely to cause FMF. Cell 1997; 90:797-807.


