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CLINICAL STUDY

Association between colchicine resistance and vitamin D in familial Mediterranean fever

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Abstract

Although colchicines are the only effective treatment of familial Mediterranean fever (FMF), resistance to colchicines (CR) which is observed in up to 30% of the patients is still a problem. Clinically, resistance to colchicine is defined as three or more attacks within the last 6 months period while using $\geq$2 mg/day colchicine. Previous studies have shown decreased vitamin D levels in FMF patients compared with healthy controls. The aim of this study is to evaluate whether vitamin D levels differ between CR and non-CR FMF patients. This study included 64 FMF patients who were being followed in Nephrology Clinic of Samsun Research and Education Hospital for at least 1 year. FMF was diagnosed according to the criteria defined by Livneh et al. Serum 25-hydroxy vitamin D (25-OHD) concentration (ng/mL) was detected in all FMF patients who were not in an acute attack period. From 64 patients 29 were accepted as CR. Mean 25-OHD level was 9.39 ± 1.00 ng/mL in CR patients and 18.48 ± 1.09 ng/mL in colchicine responsive patients ($p < 0.001$). Plasma vitamin D levels were significantly lower in colchicine resistant patients. Vitamin D deficiency may be a factor in etiopathogenesis of CR. Studies in larger patient samples that particularly evaluate the response to vitamin D replacement in CR FMF patients are needed.

Keywords

Colchicines, vitamin D, familial Mediterranean fever, resistance to colchicines

History

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by bout of fever and inflammation on serous surfaces (peritoneum, pleura, pericardium, and joint surfaces). FMF is primarily seen in certain ethnic groups originated from Mediterranean region like Sephardic Jews, Armenians, Turks, North Africans, Arabs, Greeks, and Italians although it is not limited to these ethnic groups.[1]

The diagnosis of FMF is based on typical clinical manifestations, positive response to colchicine treatments, and genetic testing. Cloning of FMF gene (MEFV) in 1997 made genetic diagnosis possible.[2] But genetic tests cannot detect all mutations associated with FMF. Some patients carry only one identifiable mutation and in some patients no identifiable mutation can be detected.[3,4]

Untreated inflammatory attacks of FMF may cause progressive secondary amyloidosis.[5] Before introduction of colchicine treatment, amyloidosis was seen in 30–60% of FMF patients.[6] Although incidence of amyloidosis has been decreased with colchicine, it is still a significant problem[7] and up to 30% of the FMF patients are resistant to colchicines. Clinically, resistance to colchicine is defined as three or more attacks within the last 6 months period while using $\geq$2 mg/day colchicines. Many factors including genetic predisposition and environmental conditions might be involved in the etiology of CR although little is known about the absolute etiology of CR in FMF patients. Treatment adherence and potential reasons including demographical factors, socioeconomic status, clinical and laboratory factors, and psychiatric dynamics are thought to be contributing factors.[8]

Vitamin D is the only vitamin synthesized in human body. Vitamin D and its metabolites have important roles on calcium homeostasis and bone metabolism. In addition, vitamin D is known to have roles in regulation of many cellular functions. Studies have suggested associations between vitamin D deficiency and autoimmune diseases, inflammatory bowel disease, rheumatoid arthritis, diabetes, many cancer types, and cardiac diseases.[9,10]

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Several studies showed decreased vitamin D level in FMF patients compared with healthy controls.[11,12] But to the best of our knowledge evaluation of vitamin D level in FMF patients with colchicine resistance has not been reported in literature. The purpose of our study is to evaluate whether there is a difference in vitamin D level between CR and non-CR FMF patients.

Materials and methods

This study included 64 FMF patients who were being followed in Nephrology Clinic of Samsun University Research and Education Hospital for at least 1 year. The diagnosis of FMF was established according to criteria defined by Livneh et al.[13] Patients having other accompanying diseases including infections, malignancies, autoimmune or metabolic diseases were excluded. FMF patients with three or more attacks within the last 6 months period, while using $\geq$2 mg/day colchicine were defined as CR. The study was approved by the local ethics committee and was in accordance with the Helsinki Declaration.

Vitamin D levels reach a peak in autumn and a nadir in spring. There is no evidence for a relationship between season and incidence of FMF acute attack. Blood samples were obtained between January and June 2014, from all FMF patients who were not experiencing an acute attack. Serum 25-hydroxy vitamin D (25-OHD) concentration (25–80 ng/mL) was detected using a commercial RIA kit (Immuno-Biological Laboratories, Minneapolis, MN). Serum levels of calcium (8.7–10.4 mg/dL) and phosphorus (2.4–5.1 mg/dL) were measured with Cobas 8000 auto analyser (Roche Diagnostics, Mannheim, Germany), parathyroid hormone (PTH) level (14–72 pg/mL) was measured with immunoassay method (ADVIA Centaur XP; Siemens Healthcare Diagnostics Inc., Tarrytown, NY).

Peripheral blood samples were collected in tubes containing EDTA and genomic DNA was extracted using salting-out method. All the coding regions, with flanking intronic regions, of the MEFV gene were amplified by polymerase chain reaction (PCR). PCR products were then purified using the ExoSAP-IT (GE Healthcare Bio-Sciences, Piscataway, NJ), following the manufacturers protocol. Sequence reactions were run on an ABI Prism 3130*xl* DNA Sequencer and results were analyzed by a SeqScape sequencing analysis software, version 2.7 (Applied Biosystems, Foster City, CA).

Statistics

To examine the structure of the data Kolmogorov–Smirnov one sample test was performed for normality and Levene test was performed for homoscedasticity assumptions. Results showed that dose of colchicine was not normally distributed ($p<0.05$) and variances were not equal ($p<0.05$), but other variables were normally distributed ($p>0.05$) and variances were equal ($p>0.05$). To analyze the data one way ANOVA was used for the age, illness duration and vitamin D variables using SPSS 20.0 under license of Ondokuz Mayıs University (IBM SPSS Statistics, Armonk, NY). For the colchicine dose variable, permutation test which is known as exact test was executed using with NPMANOVA software. Relations among variables were examined with Pearson correlation analysis. All the numerical variables were expressed as mean ± standard error. Significance threshold was defined as 0.05.

Results

From 64 patients included in this study 41 were females. Mean age was 32.96 ± 2.415 years. Twenty nine patients who had three or more attacks in last 6 months despite using 2 mg or more colchicine were accepted as CR. Twenty of these 29 CR patients were females, their mean age was 31.45 ± 2.72 years and mean duration from diagnosis was 147.83 ± 29.84 months. Their mean colchicine dose was 2.53 ± 0.09 mg/day. Twenty one of 35 non-CR patients were females, their mean age was 34.47 ± 2.11 years, duration from diagnosis was 207.35 ± 22.67 months, and mean colchicine dose was 1.57 ± 0.05 mg/day. Mean values for age and disease duration were not significantly different between two groups (p-values were 0.377 and 0.11, respectively), but colchicine dose was significantly higher in CR group ($p<0.001$).

For M694V mutation 8.6% of the patients were homozygous, 48.5% were heterozygous for M694V mutation, 37.2% had other genetic mutations, and 5.7% were negative for any genetic mutations.

Serum levels of calcium, phosphorus, PTH and 25-OHD were compared between two groups. In CR patients mean 25-OHD level was 9.39 ± 1.00 ng/mL and in non-CR group it was 18.48 ± 1.09 ng/mL. Mean plasma 25-OHD level was significantly lower in CR patients ($p<0.001$) (Table 1).

Mean 25-OHD level was 17.71 ± 1.66 ng/mL in male FMF patients and 12.33 ± 1.02 ng/mL in female FMF patients ($p=0.005$).

Plasma 25-OHD level was similar between FMF patients with different MEFV gene mutations ($p>0.05$) (Table 2).

Discussion

In this study, we observed that mean 25-OHD level in CR FMF patients was significantly lower than non-CR FMF patients.

Role of colchicine in FMF treatment was documented by clinical studies which showed its effectiveness in prevention of recurrent inflammatory episodes and secondary amyloidosis. Imbalance between the disease-associated inflammatory activity and anti-inflammatory capacity of colchicine that could be achieved with tolerable doses may be the cause of CR. Higher inflammatory activity in CR patients may be due to FMF-related MEFV variations such as homozygous M694V genotype.[14] Development of a stronger inflammatory response may also be due to environmental factors (such as infections) or accompanying inflammatory conditions.[15,16] In addition, serum concentration of colchicine may also be affected from variability in colchicine metabolism.[17] To the best of our knowledge there is not any study in the literature which evaluated the association between vitamin D level and colchicine resistance.

Vitamin D is implicated in the initiation and propagation of a range of autoimmune diseases. There are studies which showed lower levels of vitamin D levels in patients with multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus compared with healthy controls.[18] Expression of the 25(OH)D-1α-hydroxylase enzyme in many cells of the

Table 1. Serum Ca, P, PTH and plasma vitamin D levels of the FMF patients and the control group.

	CR patients (mean ± SD)	Non-CR patients (mean ± SD)	*p*
Mean age (years)	31.45 ± 2.72	34.47 ± 2.11	>0.01
Disease duration (months)	147.83 ± 29.84	207.35 ± 22.67	>0.01
Mean colchicine dose (mg/day)	2.53 ± 0.09	1.57 ± 0.05	<0.01
Ca (mg/dL)	9.3 ± 0.4	9.4 ± 0.6	>0.01
P (mg/dL)	3.5 ± 0.3	3.8 ± 0.5	>0.01
PTH (pg/mL)	87 ± 32	45 ± 30	<0.01
Vitamin D (ng/mL)	9.39 ± 1.00	18.48 ± 1.09	<0.01

Table 2. Plasma 25-OHD levels in FMF patients with different MEFV gene mutations.

	Vitamin D levels (ng/mL)
M694V/M694V	10.2 ± 8.09
M694V/other	16.29 ± 8.24
Other/other	12.36 ± 5.44
Negative	14.05 ± 8.7

immune system including activated macrophages and dendritic cells may explain these findings. Produced $1,25(OH)_2D$ acts in an autocrine/paracrine manner and causes down-regulation of antigen-presenting cells, inhibition of T-cell proliferation and decreased production of Th1 cytokines IL-2, IFNγ and TNFα.[19] Therefore, deficiency of vitamin D may cause increased inflammatory response.

A study by Kisacik et al. compared vitamin D levels of 26 FMF patients and 34 healthy controls and found significantly lower vitamin D levels in FMF patients. They concluded that vitamin D deficiency in FMF patients may trigger attacks. In this study, treatment resistant FMF was detected in only two patients.[12] Erten et al. compared vitamin D levels of 99 FMF patients with 51 healthy controls and found significantly lower vitamin D levels in the patients.[11] But the number of CR patients was not reported in this study. In our study, mean vitamin D level was 9.39 ± 1.00 ng/mL in CR FMF patients and 18.48 ± 1.09 ng/mL in non-CR FMF patients. In females, vitamin D level was lower than males (12.33 ± 1.02 and 17.71 ± 1.66 ng/mL, respectively). In all patients, 25 OHD level was below 20 ng/mL (50 nm/ L). Decreased intake or absorption, reduced sun exposure, increased hepatic catabolism, decreased endogenous synthesis (via decreased 25-hydroxylation in the liver or 1-hydroxylation in the kidney) are common causes of vitamin D deficiency. Although we could not assess dietary vitamin D intake of our patient group, dressing habits or inadequate exposure to sunlight in females may be related with low vitamin D levels.

CR was detected in 29 of our 64 patients. Treatment adherence questioned in follow-up visit. All the patients were compliant to the treatment. Therefore, this high rate may be due to small sample size. Another limitation of our study is lack of data about course of CR patients after vitamin D replacement.

In conclusion, vitamin D levels are significantly lower in CR FMF patients than in non-CR FMF patients. This may be a factor which has a role in etiopathogenesis of CR. Studies in larger patient samples that particularly evaluate the response to vitamin D replacement in CR FMF patients are needed.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med*. 1967; 43:227–253.
2. Babior BM, Matzner Y. The familial Mediterranean fever gene-cloned at last. *N Engl J Med*. 1997;337:1548–1549.
3. Samuels J, Aksentijevich I, Torosyan Y, et al. Familial Mediterranean fever at the millennium. Clinical spectrum, ancient mutations, and a survey of 100 American referrals to the National Institutes of Health. *Medicine (Baltimore)*. 1998;77: 268–297.
4. Padeh S, Shinar Y, Pras E, et al. Clinical and diagnostic value of genetic testing in 216 Israeli children with familial Mediterranean fever. *J Rheumatol*. 2003;30:185–190.
5. van der Hilst JC, Simon A, Drenth JP. Hereditary periodic fever and reactive amyloidosis. *Clin Exp Med*. 2005;5:87–98.
6. Ben-Chetrit E, Levy M. Familial Mediterranean fever. *Lancet*. 1998;351:659–664.
7. Tunca M, Akar S, Onen F, et al. Familial Mediterranean fever (FMF) in Turkey: Results of a nationwide multicenter study. *Medicine (Baltimore)*. 2005;84:1–11.
8. Hentgen V, Grateau G, Kone-Paut I, et al. Evidence-based recommendations for the practical management of familial Mediterranean fever. *Semin Arthritis Rheum*. 2013;43(3):387–391.
9. Bouillon R. Vitamin D: From photosynthesis, metabolism and action to clinical applications. In: Jameson JL, De Groot LJ, eds. *Endocrinology*. Vol. 1. Philadelphia, PA: Saunders Elsevier; 2010:1089–1110.
10. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357: 266–281.
11. Erten S, Altunoğlu A, Ceylan GG, et al. Low plasma vitamin D levels in patients with familial Mediterranean fever. *Rheumatol Int*. 2012;32:3845–3849.
12. Kisacik B, Kaya SU, Pehlivan Y, et al. Decreased vitamin D levels in patients with familial Mediterranean fever. *Rheumatology Int*. 2013;33:1355–1357.
13. Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum*. 1997;40(10): 1879–1885.
14. Lidar M, Yonath H, Shechter N, et al. Incomplete response to colchicine in M694V homozygote FMF patients. *Autoimmune Rev*. 2012;12:72–76.
15. Touitou I, Sarkisian T, Medlej-Hashim M, et al. Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. *Arthritis Rheum*. 2007;56:1706–1712.
16. Ben-Zvi I, Brandt B, Berkun Y, et al. The relative contribution of environmental and genetic factors to phenotypic variation in familial Mediterranean fever (FMF). *Gene*. 2012;491:260–263.
17. Lidar M, Scherrmann JM, Shinar Y, et al. Colchicine nonresponsiveness in familial Mediterranean fever: Clinical, genetic,

pharmacokinetic, and socioeconomic characterization. *Semin Arthritis Rheum*. 2004;33:273–282.
18. Cutolo M, Otsa K. Review: Vitamin D, immunity and lupus. *Lupus*. 2008;17:6–10.
19. Tetlow LC, Smith SJ, Mawer EB, et al. Vitamin D receptors in the rheumatoid lesion: Expression by chondrocytes, macrophages and synoviocytes. *Ann Rheum Dis*. 1999;58: 118–121.