

THE PREVALENCE OF CELIAC DISEASE AMONG PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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ABSTRACT – *Context* – Familial Mediterranean Fever and celiac disease are both related to auto-inflammation and/or auto-immunity and they share some common clinical features such as abdominal pain, diarrhea, bloating and flatulence. *Objective* – We aimed to determine the association of these two diseases, if present. *Methods* – Totally 112 patients diagnosed with Familial Mediterranean Fever and 32 cases as healthy control were included in the study. All participants were examined for the evidence of celiac disease, with serum tissue transglutaminase IgA levels (tTG IgA). *Results* – Totally 144 cases, 112 with Familial Mediterranean Fever and 32 healthy control cases were included in the study. tTG IgA positivity was determined in three cases with Familial Mediterranean Fever and in one case in control group. In that aspect there was no significant difference regarding the tTG IgA positivity between groups ($P=0.81$). Duodenum biopsy was performed to the tTG IgA positive cases and revealed Marsh Type 3b in two Familial Mediterranean Fever cases and Marsh Type 3c in the other one while the biopsy results were of the only tTG IgA positive case in control group was Marsh Type 3b. In HLA evaluation of the celiac cases; HLA DQ2 was present in two celiac cases of the Familial Mediterranean Fever group and in the only celiac case of the control group while HLA DQ8 was present in one celiac case of the Familial Mediterranean Fever group. *Conclusion* – We did not determine an association of Familial Mediterranean Fever with celiac disease. Larger studies with subgroup analysis are warranted to determine the relationship of these two diseases.

HEADINGS – Familial Mediterranean Fever. Celiac disease. Child.

INTRODUCTION

Familial Mediterranean Fever (FMF) is a hereditary disease of chronic autoimmune inflammation characterized by frequently relapsing fever, polyserositis, and/or arthritis⁽²¹⁾. The gene responsible for FMF (MEFV gene) is located on the short arm of chromosome 16 and encodes an immuno-regulatory protein called pyrin⁽¹⁾. Pyrin has been determined to have an important role in the activation of interleukin 1 beta (IL-1 β) and the overproduction of IL-1 β is reported to be responsible for FMF⁽²⁵⁾. In that aspect, FMF is an auto-inflammatory disease, meaning that it is a disorder of inappropriate inflammation⁽¹¹⁾. It is clearly known that auto-inflammatory diseases may overlap with, or mimic, autoimmune diseases⁽¹²⁾.

On the other hand, celiac disease (CD) is an autoimmune disorder, caused by a gluten intolerance⁽¹⁸⁾. Patients with CD may present with gastrointestinal symptoms such as diarrhea, steatorrhea, weight loss, bloating, flatulence, and abdominal pain in addition

to non-gastrointestinal abnormalities including liver disease, iron deficiency anemia, bone disease, and skin disorders^(7, 24). In CD, infiltration of both CD4+ and CD8+ T cells in the small intestine are induced by dietary gluten⁽¹⁰⁾. In pathogenesis of CD, the inflammatory cytokine IL-15 was determined to be up-regulated within celiac intestinal mucosa, and suspected to promote inflammation⁽⁴⁾. In diagnosis of CD, assays for anti-tissue transglutaminase IgA (tTG IgA) and anti-endomysial IgA (EMA) are regarded as serological screening tools with their high specificities and sensitivities⁽²³⁾. As CD is an immune-mediated enteropathy, it has been associated with some autoimmune and inflammatory diseases with common pathogenic mechanisms^(9, 17).

Since FMF and CD are both related to auto-inflammation and/or auto-immunity and they share some common clinical features especially regarding the gastrointestinal system; we aimed to determine the association of these two diseases. Since the symptoms of these two diseases may mimic each other, clinicians should be aware of this relationship, if present.

Declared conflict of interest of all authors: none

Disclosure of funding: no funding received

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METHODS

This is a prospective, cross-sectional study. Totally 112 patients diagnosed with FMF in the Pediatric Gastroenterology Department of Gaziantep Children Hospital between 2012 and 2014, and 32 Children as healthy controls were included in the study. Informed consent was obtained from the parents of all participants. The study protocol was approved by the Ethics Committee of Gaziantep University.

Age and gender were recorded in all cases. Among FMF cases, the disease age, colchicine usage period, the type of FMF gene mutations were also recorded. Healthy controls were selected among the patients admitted to the hospital for a routine healthy child control without any signs or symptoms and without the history of any auto-inflammatory diseases. Parents of healthy children were informed about the study and asked for participation; and children whose parents accepted the contribution were included in the study. After 8 hours of fasting, blood was obtained from all participants and complete blood sample, serum iron, iron binding capacity, ferritin, vitamin B12 and folic acid levels were studied.

All participants were examined for the evidence of CD, with serum tTG IgA levels. In cases with positive results for tTG IgA, duodenum biopsy was obtained with flexible endoscopy to confirm the CD diagnosis and HLA DQ 2 and 8 were studied.

Statistical analysis

Statistical Package for Social Sciences software (SPSS 17, Chicago, IL, USA) was used for analysis. Descriptive parameters were shown as mean \pm standard deviation or in numbers. Variables were compared using the Student's *t* test or Mann-Whitney U test. Pearson's chi square test was used to analyze the differences in means and proportions between patients and controls. A *P* value of <0.05 was considered as significant.

RESULTS

Totally 144 cases, 112 with FMF and 32 healthy control cases were included in the study. The demographic features and laboratory data of study participants are summarized in Table 1.

TABLE 1. The demographic features and laboratory data of study participants

	FMF (n=112)	Control (n=32)	P
Age (months)	122.6 \pm 41.4	123.2 \pm 41.6	0.91
Male / Female	52/60	16/16	0.71
Hemoglobin (mg/dL)	12.5 \pm 1.1	12.6 \pm 1.5	0.74
MCV	78.6 \pm 6.6	80.2 \pm 5.6	0.38
Iron	69.0 \pm 31.8	66.8 \pm 36.3	0.84
Iron binding capacity	312.7 \pm 67.4	304.0 \pm 55.7	0.63
Ferritin	28.5 \pm 25.1	47.3 \pm 38.3	0.13
Vitamin B12	478.7 \pm 319.3	499.0 \pm 255.7	0.80
Folic acid	9.6 \pm 3.2	9.9 \pm 3.3	0.77
Cases with celiac disease	3 (2.7%)	1 (3.1%)	0.81

FMF: Familial Mediterranean Fever; MCV: Mean corpuscular volume

In FMF group, the mean age at the diagnosis of FMF was 29.5 \pm 20.7 months and the FMF cases were on colchicine treatment for 849.6 \pm 534.3 days at the time of this study. Among FMF cases, 28 were homozygote, 59 were heterozygote, 9 were compound heterozygote and 8 cases had 2 different mutations. On the other hand no FMF gene mutations were determined in eight cases. Among those mutations the most common one was the M694 V (n=40) mutations followed by E148 (n= 28) (Table 2). In evaluation of FMF cases, arthralgia was present in three cases and arthritis was reported in 57 cases. The most commonly effected joint was the ankle (n= 41) followed by the knee (n= 12) joint (Table 3).

tTG IgA positivity was determined in three cases with FMF and in one case in control group. In that aspect there was no significant difference regarding the tTG IgA positivity between groups (*P*=0.81) (Table 1, Figure 1). Duodenum biopsy performed to the tTG IgA positive cases and revealed Marsh Type 3b in two FMF cases and Marsh Type 3c in the other one while the biopsy result of the only tTG IgA positive case in control group was Marsh Type 3b (Table 4). In HLA

TABLE 2. Genetic Profile of Familial Mediterranean Fever cases

	Number of cases	Percentage
Homozygous	28	25.0
Heterozygous	59	52.7
Compound heterozygous	9	8.0
Two different mutations	8	7.1
Without mutations	8	7.1

TABLE 3. Symptoms of Familial Mediterranean Fever cases at admission

	Number of cases with this symptom	Percentage
Abdominal pain	104	92.9
Arthritis	60	53.6
Thoracic pain	28	25.0
Skin eruptions	2	1.8

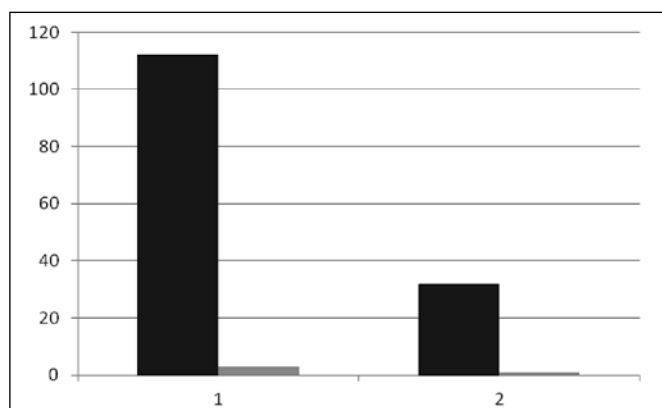


FIGURE 1. Study participants with and without celiac disease. Black lines are the study participants; 1: Familial Mediterranean fever group and 2: Control group; black lines show the cases with celiac disease in these groups

TABLE 4. Characteristics of cases diagnosed with celiac disease

	Age (months)	Gender	Biopsy	HLA DQ2	HLA DQ8
1st case of FMF group	156	F	Marsh 3c	Negative	Positive
2nd case of FMF group	144	F	Marsh 3b	Positive	Negative
3rd case of FMF group	29	M	Marsh 3b	Positive	Negative
1st case of control group	72	F	Marsh 3b	Positive	Negative

FMF: Familial Mediterranean Fever

evaluation of the celiac cases; HLA DQ2 was present in two celiac cases of the FMF group and in the only celiac case of the control group while HLA DQ8 was present in one celiac case of the FMF group.

Since the number of patients with the diagnosis of CD was very low, correlation analysis could not be performed.

When those four cases diagnosed with celiac disease were evaluated; three of them were female while one of them was male. The mean age of them was 100.2 months and the mean age of the disease was 68 months in CD cases with concomitant FMF. Interestingly, iron, vitamin B12 or folate deficiency was not determined in any of the cases.

DISCUSSION

In this study we aimed to determine the association of FMF with CD, if present. However, we did not determine any relationship between these two immune mediated diseases. The prevalence of CD among FMF cases was 3/112 (2.7%) and the prevalence of CD among control cases was 1/32 (3.1%) and the difference did not make any sense statistically. In that aspect although these diseases are both immune mediated and sharing common clinical features, different genetic predispositions together with different immunological pathways and responses may be the cause of this result.

There are some case reports in literature about the association of FMF with CD. Krums et al.⁽¹³⁾ reported a 33-year-old man who suffered from FMF and CD. A 3 year old girl with both FMF and CD was also reported⁽²⁰⁾. Similarly, a 14 year old girl with recurrent arthritis was also reported to have CD in association with FMF⁽¹⁴⁾. Baş et al.⁽²⁾ presented a patient with type 1 diabetes mellitus associated with FMF who also had autoimmune thyroid disease and celiac disease. Interestingly Yilmaz et al.⁽²⁷⁾ described the case of a female patient with FMF under long-term colchicine treatment who presented with severe diarrhea due to gluten-related enteropathy and they hypothesized that long-term colchicine treatment may have intensified the severity of malabsorption in FMF patients with underlying CD.

On the other hand, similar with our study, in a study of Kuloglu et al.⁽¹⁵⁾, 50 children with FMF were examined for the evidence of CD, with antigliadin antibodies IgA, anti-gliadin antibodies IgG, and anti-endomysial antibodies IgA and 17 children with CD were evaluated for the presence of clinical and laboratory features of FMF and six predominant mutation analysis for MEFV gene. In that study none of the patients in FMF group were diagnosed with CD and

none of the patients in CD group had complaints consistent with FMF. Although four patients with CD were carrying heterozygous MEFV mutations, MEFV had heterozygous frequency in patients with CD was defined as similar to the normal population in Turkey. In conclusion this study did not reveal any association between CD and FMF⁽¹⁵⁾.

FMF and CD are both genetically determined immune mediated diseases. T cells, both CD4+ and CD8+ gluten specific T cell clones within the small intestinal mucosa, are key players in the pathogenesis of CD⁽⁸⁾. An up-regulation of the pro-inflammatory cytokine interferon (IFN)-gamma and the down-regulatory cytokine interleukin (IL)-10, which is caused by T cells, contribute to the CD disease activation⁽⁵⁾. On the other hand, in FMF patients increased transcription of the pro-inflammatory cytokines (TNF- α , IL-6 and IL-8) has been reported⁽¹⁹⁾.

Familial Mediterranean Fever is an auto-inflammatory disease and it has also been reported to occur together with some other autoimmune disorders, such as systemic Lupus erythematosus, rheumatoid arthritis and Hashimoto's thyroiditis^(3, 6, 22). It is also clear that, CD is an autoimmune disease and related to many autoimmune conditions including thyroid autoimmunity, dermatitis herpetiformis, and Type 1 diabetes mellitus^(16, 26).

Although some case reports are present, any association of these two common entities, FMF and CD, has not been reported yet and we also did not determine any relationship.

There are some limitations of this study that should be mentioned. The study population was not large enough to make a generalization. On the other hand, since the number of patients with CD was very low, we could not make any correlation analysis. With a larger study population, correlation analysis may reveal an association of CD with the disease age, colchicine usage time, or genetic mutations, if present.

In conclusion, we did not determine an association of FMF with CD. Larger studies with any subgroup analysis are warranted to determine the relationship of these two diseases.

Author contribution

Işıkay S participated in the concept, design, supervision, data collection and/or processing, analysis and/or interpretation, literature search, writing and critical review. Işıkay N participated in the design, supervision, analysis and/or interpretation, writing and critical review. Kocamaz H participated in the resource and data collection and/or processing.

Işıkay S, Işıkay N, Kocamaz H. Prevalência da doença celíaca entre pacientes com Febre Familiar do Mediterrâneo. *Arq Gastroenterol.* 2015;52(1):55-8.

RESUMO – Contexto – A Febre Familiar do Mediterrâneo e a doença celíaca são ambas relacionadas com auto-inflamação e/ou auto-imunidade e partilham algumas características clínicas comuns tais como dor abdominal, diarreia, distensão abdominal e flatulência. **Objetivo** – Determinar a associação destas duas doenças, se presente. **Métodos** – Um total de 112 pacientes diagnosticados com Febre Familiar do Mediterrâneo e 32 casos como controle saudável foram incluídos no estudo. Todos os participantes foram examinados para a evidência da doença celíaca, com níveis de IgA séricos transglutaminase (tTG IgA). **Resultados** – Um total de 144 casos, 112 com Febre Familiar do Mediterrâneo e 32 casos controle saudável foram incluídos no estudo. A positividade tTG IgA foi determinada em três casos com Febre Familiar do Mediterrâneo e em um caso no grupo controle. Neste aspecto não há nenhuma diferença significativa em relação a positividade tTG IgA entre os grupos ($P=0,81$). Biópsia de duodeno realizado para os casos positivos de tTG IgA e revelou Marsh tipo 3b em dois casos de Febre Familiar e Marsh tipo 3C no outro, enquanto o resultado da biópsia do único caso positivo tTG IgA no grupo controle foi Marsh tipo 3b. Na avaliação de HLA dos casos de doença celíaca, HLA DQ2 esteve presente em dois casos de doença celíacas do grupo Febre Familiar do Mediterrâneo e no caso celíaco do grupo controle, enquanto HLA-DQ8 estava presente em um caso de doença celíaca do grupo Febre Familiar do Mediterrâneo. **Conclusão** – Não se determinou uma associação de Febre Familiar do Mediterrâneo com doença celíaca. Maiores estudos com análise de subgrupo são necessários para determinar a relação entre estas duas doenças.

DESCRITORES – Febre Familiar do Mediterrâneo. Doença celíaca. Criança.

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Received 7/9/2014
Accepted 1/10/2014