

# CO-EXISTENCE OF HELICOBACTER PYLORI INFECTION IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER (FMF) AND THE EFFECT OF *Helicobacter Pylori* IN THE FREQUENCY AND SEVERITY OF FMF ATTACKS

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## INTRODUCTION

- Familial Mediterranean Fever (FMF) is an ethnically restricted disease of unknown aetiology with autosomal recessive inheritance, restricted mainly to certain ethnic groups of Mediterranean and Middle East origin. It is characterised by recurrent episodes of fever and inflammation of the peritoneal, pleural and synovial membranes, which cause abdominal and pleuritic pain and arthralgia, respectively.
- The FMF gene has been localised to the short arm of chromosome 16. The expression of Mediterranean Fever (MEFV) gene is under the control of several cytokines like most of the other inflammatory genes.
- Monocytes stimulated by IFN- $\gamma$ , TNF and LPS enhance MEFV expression in vitro, while IL-4, IL-10 and TGF- $\beta$  stimulation of monocytes suppresses its expression.
- There are conflicting reports on TNF- $\alpha$ . Increased levels of IL-8 and IL-6 are also associated with FMF attacks and IL-6 appears to play an important role in the evolution of FMF attacks. Whether TNF- $\alpha$  or IL-1 $\beta$  has a function in initiating the attacks remains to be established.
- The inflammatory reactions both in FMF and in H. Pylori infection have similarities. H. Pylori infection results in the release of bacterial and host dependent substances that resemble the active inflammatory substances that take places in the inflammatory processes in FMF. The question whether the inflammatory mechanisms that are active in H. pylori infection can trigger or increase the severity and frequency of attacks in patients with FMF is worth evaluating.

## AIM

The aim of this study was to evaluate if there is a significant relation between H. pylori infection and FMF; if H. Pylori infection has an effect on the frequency and severity of FMF attacks; and if the eradication of H. pylori decreases the frequency and severity of FMF attacks.

## RESULTS

- 32 patients were included. Three H.pylori-positive patients who failed to eradicate infection were excluded and 29 patients completed the study.
- All patients were males with a mean age of 21.2 years of age (21.2 $\pm$ 1.0 years in H. pylori-positive group and 21.20.8 years in H.pylori-negative group, with no significant difference).
- Comparison of H. pylori-positive and-negative groups for the clinical and laboratory findings of FMF episodes is shown in Table-1.
- The attack frequency and number of days with attack, were significantly higher in H. Pylori-positive group than both H.pylori-negative patient group and those who became H. Pylori negative after the eradication treatment. There was no statistically significant difference between the frequency of attacks, number of days with attack and laboratory results between initially H.pylori-negative patient group and those who became H. pylori-negative after the eradication treatment.
- When H. pylori-positive and -negative patient groups were compared for the laboratory parameters before and during the FMF attacks, there was no significant difference between the groups. However, when these parameters were compared in each group before and during the attacks, CRP, erythrocyte sedimentation rate (ESR), WBC, fibrinogen ( $p < 0.01$ ) and ferritin ( $p < 0.05$ ) levels were significantly higher during the attacks in H. pylori-positive patients (Table 1).
- In H.pylori-negative patient group, CRP, ESR, WBC, fibrinogen and ceruloplasmin levels were significantly higher during the attacks; and although, ferritin levels were slightly higher during the attacks, the difference was not significant. Serum iron and iron binding capacity were not significantly different in this group either.
- H.pylori-positive patients and patients who became H.pylori-negative after the eradication treatment were also compared for the laboratory parameters before and during the attacks and no statistically significant difference was found ( $p > 0.05$ ).

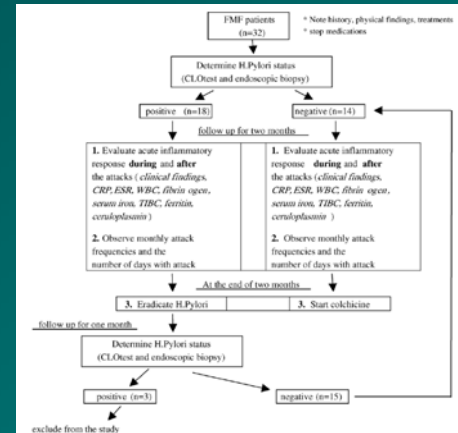
Table 1  
Comparisons of the frequency and duration of attacks and the mean inflammatory parameters during an attack between the three study groups

Group	Frequency	Duration	CRP	ESR	WBC	Fibrinogen
H. pylori-positive (n = 15)	2.53 $\pm$ 0.52	6.47 $\pm$ 1.51	71.73 $\pm$ 59.56	49.8 $\pm$ 24.79	8853 $\pm$ 2963	540 $\pm$ 131
H. pylori-negative (n = 14)	2.00 $\pm$ 0.68	4.00 $\pm$ 1.30	94.89 $\pm$ 59.35	46.29 $\pm$ 19.81	9885 $\pm$ 3381	564 $\pm$ 107
P-value	<0.05	<0.01	>0.05	>0.05	>0.05	>0.05
H. pylori-negative after eradication (n = 14)	1.40 $\pm$ 0.91	3.13 $\pm$ 2.13	52.61 $\pm$ 39.75	40.27 $\pm$ 23.67	8946 $\pm$ 3256	530 $\pm$ 190
P-value	<0.05	<0.01	>0.05	>0.05	>0.05	>0.05

## MATERIALS AND METHODS

- 32 FMF patients (age range 20-25) were included.
- Diagnostic criteria of Livneh et al. were used and laboratory parameters were also followed up along with the clinical parameters.
- All patients underwent upper GI endoscopy. Antrum and corpus biopsies were used for rapid urease test (CLOtest<sup>®</sup>, Delta West Ltd.) and for histopathological examination. Patients were classified into (+) and (-) groups according to H. pylori status.
- They were followed for 2 months to observe the monthly attack frequencies and the number of days with attack. At the end of the second month, colchicin treatment was started.
- H. Pylori positive patients were given eradication treatment consisting of clarithromycin 500 mg (bid) plus amoxicycliline 1 g (bid) along with lansaprazole 30 mg (bid) for 10 days.
- Same diagnostic procedures for H. pylori were repeated 1month after the completion of the treatment.
- The study was continued with patients with successful eradication at the end of this evaluation. They were followed up for 2 months to determine the frequency of FMF attacks.
- Thus, three groups of patients were followed up: (a) H.pylori-positive patients, (b) H. pylori-negative patients and (c) patients who became negative after the treatment.

**Statistical methods :** Student's t-test, Mann-Whitney U-test and Wilcoxon two-pair tests were used to compare quantitative data. For the comparison of qualitative data, chi-square test was used. ( $p < 0.05$  as significant).



## CONCLUSION

- Our results makes us think that H. pylori infection, which causes a chronic inflammatory response, can increase the frequency and severity of attacks in patients with FMF and that if the impact of inflammatory response can be diminished by the eradication therapy, attack frequency and severity of FMF can be decreased.
- The decrease of the inflammatory effects of cytokines after the eradication therapy can be speculated as the reason for the significant difference of frequency and duration of attacks between H. pylori-positive patients and patients who become H. pylori-negative after the eradication therapy. However, it is difficult to explain the lack of significant differences in the levels of acute phase reactants between the groups. The role of cytokines, levels of which cannot be measured, or the effects of cytokines directly on the expression of MEFV gene, can be responsible for the significant differences in the attack frequency and duration.
- The evaluation of the levels of cytokines and bacterial products that play roles in the inflammatory mechanisms, before and during the attacks, and their relationships with acute phase reactants, is very important. The evaluation of the interaction of H. pylori infection and the expression of MEFV gene is also important. The roles of yet unknown cytokines, which can play a role in the pathogenesis of both diseases should also be kept in mind. As for today, the correlation between H. pylori infection and FMF diseases seems unlikely; however, studies evaluating these interactions, relations and roles will be needed to reach better conclusions.