

Appendectomy in familial Mediterranean fever: clinical, genetic and pathological findings

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Abstract

Background

Abdominal attacks of familial Mediterranean fever (FMF) may simulate acute appendicitis and bring about considerable uncertainty. The similar presentation of the two clinical entities often leads to an unnecessary appendectomy.

Methods

182 consecutive FMF patients were retrospectively reviewed for this study. Clinical and genetic data was compared between those who had undergone an appendectomy (n=71) and those who had not (n=111).

Results

The frequency of appendectomy found in FMF was far above the reported rate in the general population (40% vs. 12-25%).

The rate of non-inflamed appendectomies was extremely high (80% vs. 20%) and remained constant over time. Tertiary hospitals and improved therapeutic and diagnostic measures that have evolved over the years did not reduce misdiagnosis of acute appendicitis in FMF. Severe phenotype and homozygosity for M694V were identified as risk factors for appendectomy in FMF. A change from the regular diffuse involvement to right lower quadrant abdominal pain was found to be the best predictor of inflamed appendix in FMF patients undergoing appendectomy for suspected acute appendicitis.

Conclusion

Reliance on clinical parameters should improve diagnostic accuracy of acute appendicitis in the FMF patient population.

Key words

FMF, appendectomy, pathology.

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Introduction

Appendicitis is the most common reason for emergency abdominal surgery, with an overall lifetime occurrence of approximately 12% in men and 25% in women (1). The diagnosis of appendicitis has been traditionally based on the patient's history and physical examination. Typically, the clinical findings with the highest predictive value for acute appendicitis are: right lower quadrant abdominal pain, abdominal rigidity and migration of pain from the periumbilical region to the right lower quadrant (2). However, these classic findings are present in only 50% of patients (3), which makes the diagnosis of appendicitis a frequent medical challenge, as evident from the lack of acute inflammatory changes in an estimated 15% of the removed appendixes (4). Several imaging techniques, such as ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) were increasingly utilized over the past 15 years, and helped to improve diagnostic accuracy and patient outcomes. However, the ability of these tools to predict appendicitis is still incomplete (5).

Familial Mediterranean fever (FMF) is an autosomal recessive disease with febrile attacks, mostly accompanied by serositis (6, 7). As an accurate diagnostic laboratory marker is still lacking and genetic analysis is of low sensitivity and specificity, the diagnosis of the disease relies mainly on clinical criteria (8).

Acute abdominal pain is the most common attack manifestation in FMF patients, often mimicking acute appendicitis (8, 9). In the past, patients were offered preventive elective appendectomies, so that a future episode of appendicitis would not be attributed to FMF and a perforated appendix would not go untreated (10). However, this approach was abandoned, mainly because it was thought to potentially increase the risk of abdominal adhesions in individuals, already susceptible to this complication by recurrent peritoneal inflammation (11, 12). Indeed, a recent paper by Berkun *et al.* has shown increased spontaneous bowel obstruction in FMF patients undergoing an appendectomy (13), further underscoring the long term harmful results of an unnecessary operation.

The aim of the present study was to determine the frequency of appendectomy in FMF patients, characterize the diagnostic accuracy of acute appendicitis and examine the factors associated with our findings in these concerns.

Methods

One hundred and eighty-two patients were included in this retrospective study, which was aimed at determining the frequency and the results of appendectomy in FMF.

Patients were consecutively recruited for the study during their routine follow-up visit to the FMF clinic of the National Center for FMF at our medical center. Inclusion in the study was based solely on agreement of patient manifestations and disease course with criteria for the diagnosis of FMF (13). The study was conducted in accord with the requirements of the Human Experimentation Review Board of the Sheba Medical Center.

All the 182 FMF patients underwent a clinical interview and examination. Additional clinical and genetic data were abstracted from the charts. FMF severity was assessed using a newly published severity score (14). In this system, a patient is assigned to a severe, intermediate or mild disease group based on the frequency and duration of attacks and number of sites involved in the attacks and over the disease course.

Study and control groups

All recruited patients who reported an appendectomy were assigned to the study (operation) group. The others were included in the control group. The appendectomies were performed in various hospitals, all over the country, and by different surgeons in each hospital. The decision to perform an appendectomy was based on the discretion of the surgeon, based on physical findings and imaging data available to him, to which we had no access, given the retrospective nature of the study.

The outcome of the operation was retrieved from pathological reports and patients' charts. Risk factors for appendectomy were analyzed by comparing patients of the study and control groups

Competing interests: none declared.

with regard to variables such as current age, age at FMF onset and diagnosis, gender, ethnic origin, FMF disease severity, pattern of abdominal pain during a typical FMF attack and FMF gene (Mediterranean FeVer gene or MEFV) mutation carriage. Finally, various factors that may predispose for an inflamed appendix were explored in patients of the study group, by comparing patients with inflamed and non-inflamed appendectomies, in respect to gender, type of medical facility at which the operation was performed (tertiary or peripheral hospital), MEFV mutation carriage in general and homozygosity for M694V, in particular, time period of operation (divided into pre-colchicine, colchicine, CT and genetic eras), relationship of operation to FMF diagnosis (before or after), disease severity, pain pattern during typical FMF abdominal attacks and during the specific attack leading to the appendectomy.

Statistical analysis

The sample size was computed as 180 patients to reflect our entire population of 8,000 FMF patients, with a power of 90%. This calculation was based on the assumptions that the rate of appendectomy in FMF is at least twice that of the normal population (namely at least 40%) and that the risk factors for appendectomy and for a non-inflamed appendix are not known.

Patients who had undergone or had not undergone an appendectomy were compared for differences in clinical and genetic parameters, using the chi-square test for categorical variables, and the two-tailed Student *t*-test for comparison of continuous variables; *p*-values of <0.05 were considered statistically significant.

Results

Of the 182 consecutive FMF patients included in the study, 104 were females (57.1%). Seventy-one of 182 patients (39%) had undergone an appendectomy. The results of the appendectomies are listed in Table I. Only 13 of histologic specimens of appendectomies (18.3%) showed evidence of acute inflammation in the appendix, peri-appendicitis was evident in 6 (8.4%)

Table I. Results of appendectomies in FMF.

Number of patients studied	182
Number of patients (%) with appendectomy	71/182 (39)
Number of patients (%) with inflamed appendix	13/71 (18)
Number of patients (% of appendectomies) with non-inflamed appendix	All 58 (82) Normal appendix 29 (41) Unknown 19 (27) Peri-appendicitis 6 (8) Elective 4 (6)

Table II. Risk factors for appendectomy in patients with FMF.

Variable	Patient group*	
	Appendectomy (71 patients)	No appendectomy (111 patients)
Current age (years)	38.4 ± 14.3	35.6 ± 13.7
Age of FMF onset (years)	10 ± 11.3	12.3 ± 13
Age of diagnosis (years)	18.3 ± 13.8	19.9 ± 13.7
Diagnostic delay (years)	5.8 ± 12.1	6.1 ± 8.4
Male gender (%)	39	45
Non-Ashkenazi origin (%)	83	88
Severe disease (%)**	51	34
Diffuse abdominal pain at typical attack (%)	84	83
MEFV gene Any 2 mutations	60	57
analysis (%) M694V/ M694V***	27	13

*Differences between patient groups are not significant unless indicated. ***p*=0.03, ****p*=0.02

while no evidence of inflammation was noted in 29 (40.8%) of the cases. Four (5.6%) of the appendixes were electively removed. No pathological data was available for 19 (26%) of the patients, mainly in procedures performed before 1990.

Risk factors for appendectomy in patients with FMF were determined by comparing study and control groups (Table II). There were no gender or age differences. MEFV mutations were comparably distributed among the groups: 60% of the patients who had undergone an appendectomy carried double MEFV mutations and 27% carried a single mutation vs. 57.1% and 25.7%, respectively, among the non-operated patients. With respect to the type of mutations, only the frequency of M694V/M694V differed between the groups, as it was more abundant in appendectomized patients. Diffuse abdominal pain characterized the typical FMF attack in the 2 patient groups (Table II). However, only 57.6% of the operated patients described a similar distribution of pain during the attack that led to the appendectomy (not

shown). Overall, only severe phenotype and homozygosity for M694V are statistically significant risk factors for appendectomy in FMF.

Risk factors for inflamed appendix, in FMF patients undergoing appendectomy, were studied by comparing 2 subpopulations of the study group; patients with acute appendicitis to patients in whom appendiceal inflammation could not be proven (Table III). Gender, higher experience and volume of operations (characterizing tertiary hospitals), effect of medical progress, including institution of colchicine prevention, improved imaging abilities and emergence of genetic diagnosis, failed to differentiate between the patient groups. Only localized right lower quadrant abdominal pain, contrary to the usual diffuse abdominal pain, proved to be a significant predictor of an inflamed appendix.

Interestingly, peri-appendicitis was evident in 6/58 (8%) of the non-inflamed appendixes (Fig. 1), a rate four-fold higher than expected, compared to the general population.

Table III. Factors that predict appendectomies with inflamed appendices.*

Variables		Inflamed appendix (13)	All other appendices (58)
Male gender (%)	31	41	
Appendectomy in tertiary hospital (%)		46	57
MEFV gene analysis	Any 2 mutations (%)	88	83
	M694V/M694V (%)	23	27
Effect of medical progress (%)***	1972 or before (pre-colchicine era)	15	14
	1973-1984 (colchicine entered)	23	30
	1985-1997 (CT entered)	31	32
	1998 onwards (The genetic era)	31	24
Appendectomy performed after FMF diagnosis (%)		38	27
Severe disease (%)	31	58	
Diffuse abdominal pain in typical attack (%)		92	85
Localized attack on operation (%)**	54	23	

*No differences were observed between the 2 patients groups except: ** $p=0.037$

***Figures are the proportion (%) of the appendectomies from the total of the same group, performed in the indicated time period. In each time period the rate of non-

Discussion

This study shows that FMF patients are subjected to a high rate of appendectomy, with a consequently exceedingly low incidence of acute appendicitis. We found that a severe disease and M694V homozygosity, which usually underlies a more severe phenotype, increase the risk for this operation (Table II). Additional analysis, now focusing on patients who underwent an appendectomy, suggests that accounting for a change in the pattern of the FMF attack may increase diagnostic accuracy in this patient population (Table III). Finally, periappendicitis emerged, in this study, as a FMF specific entity.

A high rate of appendectomy among FMF patients may well be anticipated in a patient population, which suffers frequent abdominal attacks that lead to numerous emergency room visits. Indeed, increased number of attacks (defining a severe disease) was found to put our FMF patients under increased risk for appendectomy. Yet, the two-fold rate of appendectomy compared to the general population and the extremely low incidence of acute appendicitis are disturbing, since the index of suspicion for acute appendicitis in this scenario is intuitively lower than in the general population, as the attack may be automatically attributed to FMF. Taken together, the rate of appendectomy might

be expected to be at most mildly higher in FMF patients than in the general population. Thus, it implies that contrary to general belief, not all abdominal pain in FMF patients is automatically attributed to FMF. Rather, a typical attack is often misdiagnosed as acute appendicitis, subjecting the patient to a needless surgical procedure.

Another interesting finding encountered was that only peri-appendiceal inflammation is evident in 8% of the non-inflamed appendices (Fig. 1), a rate four-fold higher than expected, compared to the general population. Peri-appendicitis is defined as serosal inflammation of the appendix without muscular and mucosal involvement, a microscopic diagnosis evident in 1.9% of appendectomies (15-17). In the majority of cases of peri-appendicitis, the intra-peritoneal causes for inflammation, most commonly acute salpingitis, are recognized during surgery (17) while no obvious explanation can be found in 7/43 patients (17). The peritoneal inflammation associated with an acute abdominal attack of FMF may involve the appendiceal serosa and manifest histologically as peri-appendicitis, strengthening our conclusion that acute FMF attacks are commonly misdiagnosed as acute appendicitis.

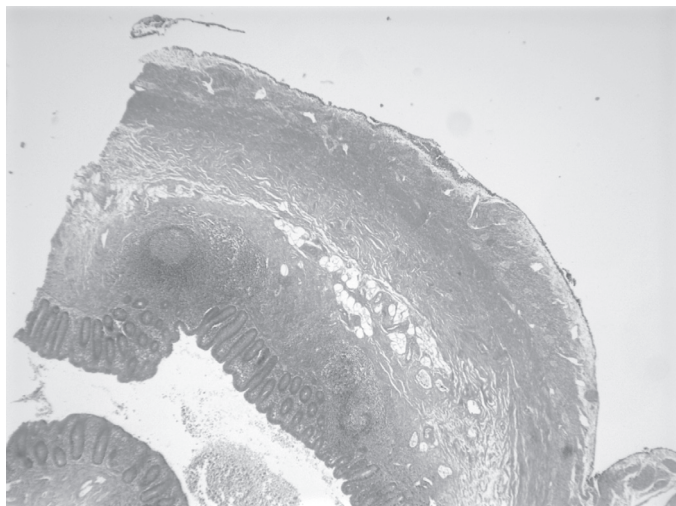
We found a similar frequency of appendectomy among male and female FMF

patients, contrasting with the normal or unaffected population, in which a two-fold rate is described in females, presumably due to confounding gynecological causes for lower abdominal pain. This may be interpreted similarly to the higher overall frequency of appendectomy detailed above. Namely, an increased exposure to the hazard of the emergency room, ultimately subjects men, comparably to their women counterparts, to more surgical procedures.

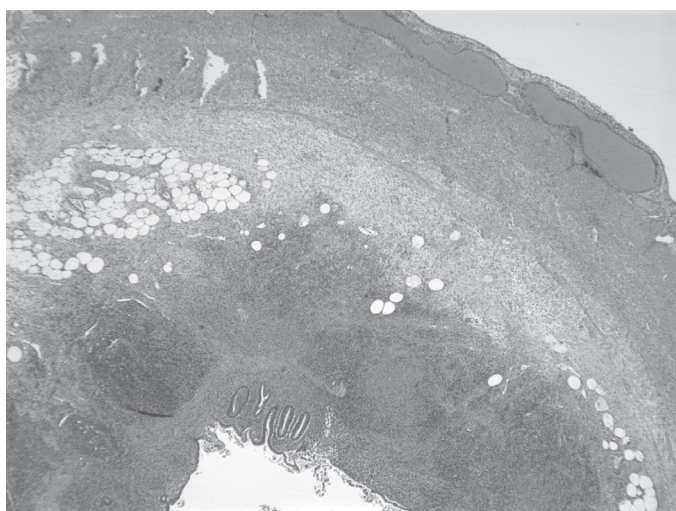
It is noteworthy that our results indicate that 60-70% of appendectomies in this FMF patient population were performed 5 to 6 years before the diagnosis of FMF was determined (Table III). As the diagnostic delay in FMF is typically around a mean of 10 years (18), it may be deduced that a large number of the operated patients, with ultimately non-inflamed appendix, had experienced FMF attacks prior to the operation. Therefore, routine pre-operative screening for a personal or family history of symptoms compatible with FMF, should undoubtedly reduce the frequency of unwarranted surgical interventions.

Our data show that homozygosity for M694V is a risk factor for appendectomy (Table II), conforming with numerous studies of genotype-phenotype correlations in FMF patients, which had demonstrated a more severe disease course for those such afflicted (19-21). Also, the overall low rate of MEFV mutations, found in the present study, is in accordance with previous findings in FMF patient populations (8). It confirms the low sensitivity and specificity of genetic analysis in the FMF population.

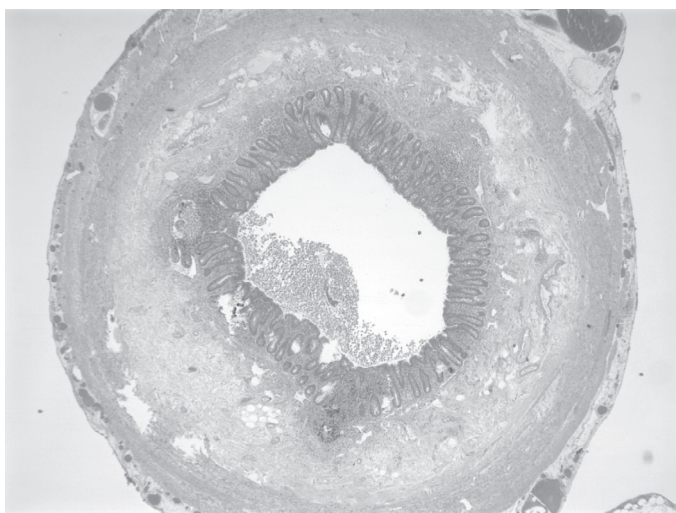
Laboratory parameters, including leukocyte count and C-reactive protein (CRP), typically rise both during FMF related peritonitis (9) as well as in acute appendicitis, and thus do not aid in distinguishing between the two pathologies. Similarly, we have shown that urinary leukotriene B4 (LTB4), although variably elevated in FMF patients, suffering from an acute abdominal attack, is not sufficiently increased to validly differentiate between acute FMF and acute appendicitis (22). Procalcitonin, a propeptide of calcitonin,

**Fig. 1.**

A. Appendix wall showing an inflammatory infiltrate limited to the serosal surface without evidence of neutrophilic infiltration within the muscularis propria, fulfilling the histologic criterion for the diagnosis of peri-appendicitis. H&E X 20.



B. Appendix wall showing dense neutrophilic infiltration within the muscularis propria compatible with the histologic criterion for the diagnosis of acute appendicitis. Since drainage of an exudate into the appendix from an alimentary tract infection may also induce a mucosal neutrophilic infiltrate, evidence of muscular wall infiltration is required in order to establish the diagnosis. H&E X 20.



C. Appendix wall without inflammation. H&E X 20.

is considered an early marker of the systemic inflammatory response. In a recent study, procalcitonin values above 0.12 ng/ml delineated patients with pathologically proven acute appendicitis from patients with FMF attacks (23). A larger scale study, eval-

uating procalcitonin levels in FMF patients during attacks as well as in attack-free intervals, is needed in order to establish its role in the on-time diagnosis of the cause of abdominal pain in an acute abdomen of a patient already known to suffer from FMF.

In the past fifteen years, imaging modalities have been used increasingly for diagnosing or ruling out acute appendicitis; specifically abdominal CT was expected to replace exploratory emergency surgery (24). However, as detailed in Table III, our results indicate that neither widespread use of CT scans nor advent of genetic testing for FMF, improved diagnostic accuracy in an acute situation. Part of the explanation for this finding is that the pathology revealed on CT scans of FMF patients studied during acute attacks, including engorged mesenteric vessels, thickened mesenteric folds and mesenteric lymphadenopathy (25), is not specific. A case control study that involves a search for CT features of FMF attacks is still awaited.

The bottom line is that a change from the regular diffuse involvement to right lower quadrant abdominal pain is the best predictor of inflamed appendix in FMF patients, undergoing appendectomy for suspected acute appendicitis. The inclusion of this basic clinical concept, with other measures, helping to detect acute appendicitis, should improve diagnostic accuracy of this common clinical entity in FMF patients. In addition, in countries where FMF is prevalent, routine pre-operative screening for a personal or family history of symptoms compatible with FMF is advised, as it would prompt an ad hoc diagnosis of FMF and circumvent an unwarranted surgical intervention.

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