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Antistreptococcal Response is Exaggerated in Children with Familial Mediterranean Fever

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Abstract: Familial Mediterranean fever (FMF) is an autosomal recessive disorder. Although the pathogenesis of the disease is not yet completely understood, enhanced acute-phase responsiveness is considered to be one of the most important mechanisms. The presence of high levels of antistreptolysin O (ASO) antibodies and streptococcus-associated diseases, such as acute poststreptococcal glomerulonephritis (AGN) and acute rheumatic fever (ARF), has been reported in patients with FMF. In order to better understand the effect of FMF on antistreptococcal antibody response, we measured ASO and antideoxyribonuclease B (anti-DNAse B) levels in patients with FMF and compared them with those in healthy controls. The study consisted of two parts. In the first step, antistreptococcal antibody levels were analysed in 44 patients with FMF and 165 healthy children who had no history or clinical evidence of upper respiratory tract infection (URTI) for the last 4 months. In the second step, antistreptococcal antibody levels were measured in 15 patients with FMF and 22 healthy controls in response to documented group A β-haemolytic streptococcal pharyngitis. In the first part of the study, ASO and anti-DNAse B levels in patients with FMF were found to be significantly higher than those in healthy controls ($P < 0.001$). In the second part, ASO and anti-DNAse B titres were found to be significantly higher in patients with FMF than in controls ($P < 0.001$ and < 0.05, respectively) 4 weeks after a positive throat culture. We concluded that patients with FMF have an exaggerated response to streptococcal antigens and might be prone to poststreptococcal non-suppurative complications, such as ARF.

Keywords: Antistreptolysin O; Antideoxyribonuclease B; Familial Mediterranean fever; Streptococcal pharyngitis

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Introduction

Familial Mediterranean fever (FMF) (MIM 249100) is an autosomal recessive disease characterised by recurrent episodes of fever and polyserositis. It is seen predominantly in Turks, Jews, Armenians and Arabs. Mutations in a newly discovered gene, MEFV, which encodes for a protein called pyrin, are responsible for the disorder. Pyrin is proposed to be a direct or indirect downregulator of inflammation, specifically in neutrophils [1]. Although details are still unknown, enhanced acute-phase responsiveness appears to be an important mechanism in the pathogenesis of FMF.

A relationship between group A β-haemolytic streptococcal (GABS) infections and acute rheumatic fever (ARF) as well as acute poststreptococcal glomerulonephritis (AGN) has been known for many years. Clinicians have long appreciated that the development of these non-suppurative complications of streptococcus, is associated with an enhanced anti-streptococcal antibody response [2].

High levels of antistreptolysin O (ASO) titres were reported in 50%–60% of FMF patients in different cross-sectional studies [3,4]. In addition, AGN has been characterised as a type of renal involvement [5,6], and rheumatic heart disease has been reported to be more

frequent in patients with FMF than in the normal population [7,8]. Previously published data suggest that patients with FMF may be prone to poststreptococcal complications and that the predilection might be the result of an exaggerated antistreptococcal antibody response [8].

In this study, we aimed to understand better the effect of FMF on antistreptococcal antibody titres in order to assess potential risks for poststreptococcal complications.

Materials and Methods

This study was approved by the Ethics Committee of the Ankara University School of Medicine and written informed consents were obtained from all participants. The study consisted of two surveys. Forty-four Turkish individuals with FMF who had been followed at the clinics of Ankara University School of Medicine were included in the first part of the study. Their ages ranged from 4 to 18 years, with a mean of 10 years. The diagnosis of FMF was made according to the established clinical criteria [9] and/or molecular analysis where appropriate [10]. None of the patients had a history or clinical evidence of a streptococcal throat or skin infection within the previous 4 months. A control group, consisting of 165 sex-matched healthy children (age range from 4.5 to 16 years, mean 9 years) with no history or clinical evidence of a streptococcal throat or skin infection for the last 4 months, was also enrolled in the study. All patients and controls were questioned and examined by one of the authors, who also obtained a throat culture from each child following the examination. Once a throat culture was found to be negative, a serum sample for the determination of ASO and antideoxyribonuclease B (anti-DNAse B) levels was obtained from each patient or control subject. This part of the study was completed in approximately 1 year.

Fifteen patients with FMF (age ranged from 5.5 to 11 years; mean 7.4 years) and 22 children without FMF (age range from 1.5 to 12 years; mean 8 years), who presented with signs and symptoms of acute-onset pharyngitis, were enrolled in the second part of the study. All of these 37 children had positive throat cultures for GABS at the initial visit. All patients and individuals in the control group with a positive throat culture received oral penicillin for 10 days, and throat cultures became negative in all subjects following penicillin therapy. Because maximal antistreptococcal antibody levels are usually reached 3–5 weeks after streptococcal throat infection, sera for ASO and anti-DNAse B levels were obtained 4 weeks after the initial acute visit [10].

As the diagnostic serological reaction to streptococcus might be missed unless multiple antigens are tested, we chose to determine the ASO and anti-DNAse B levels in patients with FMF with and without a GABS infection [11]. The sera were kept frozen at –20°C before testing. ASO titres were determined using nephelometric techniques according to the manufacturer's recommendations (Array Systems, Beckman Coulter Inc., USA). Anti-DNAse B levels were determined using a method based on the inhibition of enzymatic cleavage of DNA (Dade Behring, Marburg, Germany). Control sera with established ASO and anti-DNAse B titres were included in each test run. 'Upper limits of normal' (ULN) for ASO and anti-DNAse B levels were determined for the first part of the study by separating the upper 15% from the lower 85% of the control group, as described previously [12].

In the first part of the study, differences for proportions above ULN of ASO and anti-DNAse B levels between the patients with FMF and healthy controls were determined by the hypothesis test for sample proportions versus the hypothesised value (z test). For the second part, comparisons between the patients with FMF and healthy controls for logarithmic transformed ASO and anti-DNAse B levels 4 weeks after a positive throat culture were evaluated by Student's t-test. Differences were considered significant if $P < 0.05$.

Results

In the first part of the study, ULN for ASO and anti-DNAse B for healthy controls were calculated as 181 Todd units and 200 units, respectively. Sixteen (36%) of the 44 individuals with FMF had elevated ASO titres

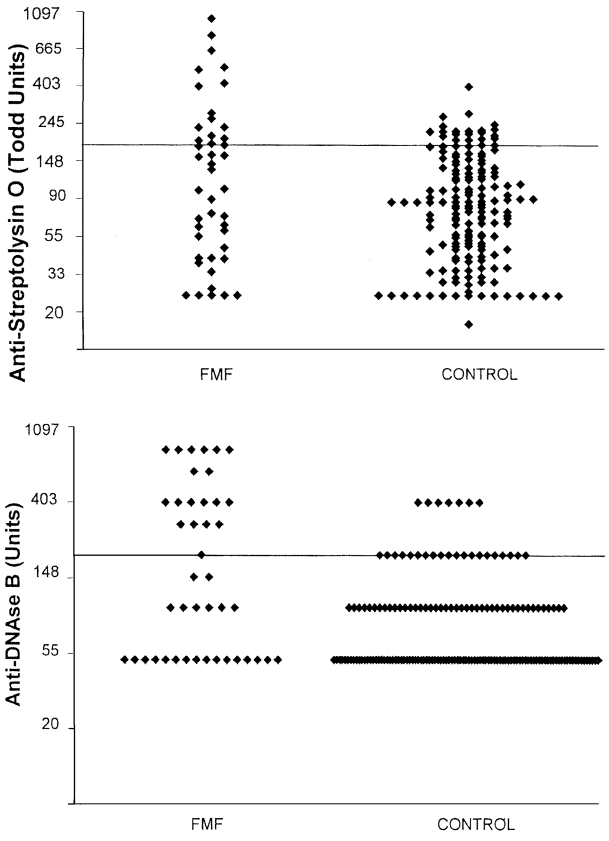

Fig. 1. Logarithmic distribution of antistreptolysin O (ASO) and anti-DNAse B titres in FMF patients ($n = 44$) and healthy controls ($n = 165$).

Table 1. ASO and anti-DNAse B values 4 weeks after a positive throat culture among FMF patients and healthy controls

	FMF $n = 15$	Healthy controls $n = 22$	P**
ASO (Todd units)	470 ± 275*	240 ± 183	<0.001
Anti-DNAse B (units)	608 ± 429	464 ± 572	<0.05

* Mean ± SD.
**After logarithmic transformation.

(above ULN), and 18 (41%) had high anti-DNAse B levels (Fig. 1). These rates were found to be significantly higher than those in healthy controls ($P<0.001$).

The results of the second part of the study are shown in Table 1. Antistreptolysin O and anti-DNAse B titres 4 weeks after a positive throat culture were found to be significantly higher in FMF patients (470 Todd units and 608 units, respectively) than in control subjects (240 Todd units and 464 units, respectively), ($P<0.01$ and $P<0.05$, respectively).

Discussion

High ASO titres in patients with FMF have been reported in a few previous studies [3,4], although the significance and specificity of those results remain uncertain. Our study reveals that individuals with FMF frequently have high ASO and anti-DNAse B levels, even in the absence of recent streptococcal pharyngitis. There are two possible explanations for this result:

1. There might have been patients with unrecognised streptococcal throat infection in the last 4 months in the FMF group. Previous epidemiological studies have suggested that about half of the true streptococcal infections, which result in an antibody response and carry a risk for non-suppurative complications, never come to the physician's attention [13].
2. Elevated anti-streptococcal antibody levels may persist longer and may not even be returned to normal in patients with FMF.

It may not be uncommon to misdiagnose a patient with FMF as having ARF when a high antistreptococcal antibody level is detected, as the two disorders share similar clinical manifestations. Based on our results, it is not surprising to note that ARF is one of the most common incorrect diagnoses among FMF patients with arthritis [14].

Our study also demonstrates that there is an enhanced antistreptococcal antibody response 4 weeks after documented streptococcal throat infection in patients with FMF as compared to control subjects.

Although ARF can follow any GABS pharyngitis, it was demonstrated that children who developed ARF had an exaggerated antibody response to streptococcal antigens when they were compared with healthy children who had recovered from a streptococcal upper respiratory tract infection [11]. On the basis of evidence in previous reports, there is a strong consensus that ARF represents an abnormal host immune response in genetically predisposed individuals to some GABS antigens, cross-reacting with heart, brain and joint tissues [15,16,17]. Interestingly, the basic defect of FMF, which is proposed to be the impaired control of the immune response, could lead directly or indirectly to immune hyperreactivity against streptococcal antigens.

Our results emphasise that, whatever the reason, children with FMF have high antistreptococcal antibody levels at any time and give augmented responses to streptococcal antigens following throat infections. Therefore, it is reasonable to speculate that FMF could be a predisposing condition to the development of poststreptococcal non-suppurative complications, including ARF.

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