

# Increased frequency of familial Mediterranean fever in Central Anatolia, Turkey

F. Onen<sup>1</sup>, H. Sumer<sup>2</sup>, S. Turkay<sup>3</sup>, O. Akyurek<sup>2</sup>, M. Tunca<sup>4</sup>, H. Ozdogan<sup>5</sup>

<sup>1</sup>Division of Immunology and Rheumatology, <sup>4</sup>Department of Internal Medicine, Dokuz Eylul University School of Medicine, Izmir; <sup>2</sup>Department of Public Health and <sup>3</sup>Department of Pediatric Medicine, Cumhuriyet University School of Medicine; <sup>5</sup>Division of Rheumatology, Department of Internal Medicine, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey.

Fatos Onen, MD, Professor of Medicine; Haldun Sumer, MD, Associate Professor of Medicine; Sadi Turkay, MD, Professor of Medicine; Orhan Akyurek, MD, Specialist in Medicine; Mehmet Tunca, MD, Professor of Medicine; and Huri Ozdogan, MD, Professor of Medicine.

Please address correspondence to: Dr. Fatos Onen, Dokuz Eylul University School of Medicine, Department of Internal Medicine, Division of Immunology and Rheumatology, 35340 Izmir, Turkey. E-mail: [fatos.onen@deu.edu.tr](mailto:fatos.onen@deu.edu.tr)

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## ABSTRACT

**Objective.** It has been observed that familial Mediterranean fever is more prevalent among people coming from central Anatolia in Turkey. To test this observation the frequency of FMF was investigated by a field survey in Sivas, a city located in central of Turkey.

**Methods.** The survey was conducted in a cohort of 4809 persons selected by systematic sampling from 2 districts of Sivas, with a total population of 83,274. Face to face interviewing was done with registered households using a standard questionnaire developed to screen FMF. A second interview was conducted by a rheumatologist and an internist of those individuals who were regarded to have possible FMF.

**Results.** The suspicion of FMF emerged in the cases of 46 individuals during the survey and 36 were interviewed for a second time. FMF was diagnosed in 10 cases. Only one had a previous diagnosis of FMF. The overall frequency of FMF among a cohort of 3,948 inhabitants of Sivas was 1/395 (0.25%).

**Conclusion.** This study indicates that the prevalence of FMF in Sivas may be higher than that in general Turkish population, which has been reported to be 0.1%.

## Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of fever, serositis and arthritis (1,2). The gene responsible for the disease (MEFV) has been recently identified (3, 4). AA type amyloidosis is the most severe complication of the disease, leading to chronic renal failure. FMF affects primarily the populations of the Mediterranean basin, such as Sephardic Jews, Arabs, Turks and Armenians (1,2).

It has been reported previously that FMF in Turkey may be more frequent among people who originate from central Anatolia rather than the Mediterranean

region (5,6). The overall prevalence of the disease in Turkey is estimated as 1/1000 (7,8). To determine the regional difference in the prevalence of FMF in Turkey, a field survey was conducted in Sivas, a city located in central Anatolia with a population of 419,000.

## Materials and methods

The survey was conducted among persons from 2 major districts of Sivas with a population of 83,274. The total sample size was calculated using an assumed prevalence of 0.1%, a precision of 0.01%, and a confidence level of 95%. The sample size was thus determined as 4,483. The study aim was to include 4,809 persons in the survey, taking into account the fact that the number of non-responders might be higher than expected. In this region, the average number of persons per household was 4.1 from data obtained by the health center records. Therefore 1,173 households were selected by systematic sampling.

A questionnaire to record demographic and FMF-related data was prepared, and minor revisions were made after it had been tested on 20 FMF patients. This questionnaire (Table I) was applied to the probands by fifteen senior medical students who received specific training regarding the disease and the questionnaire before going into the field. Direct face-to-face interviewing was done with the registered household. The mother answered the questionnaire for the children in the household.

A tentative diagnosis of FMF was made in subjects who answered "yes" to any one of the filtering questions. These participants were then invited to the hospital for a second interview and a physical examination by a rheumatologist and an internist. These physicians visited the patients at their homes if they did not appear for the hospital

**Table I.** The questionnaire developed for FMF.

I.	Demographic information:
1.	Age
2.	Sex
3.	Birthplace
4.	Paternal and maternal origin
5.	Consanguinity of parents
II.	The filtering question items:
1.	Have you ever had 3 or more abdominal attacks ?
2.	Have you ever had 3 or more attacks of
a.	fever?
b.	chest pain?
c.	joint pain/swelling?
d.	muscle pain?
e.	erythema?
3.	Have you ever had a renal disease?
4.	Is there any member of your family who has had any of above manifestations?
5.	Has any physician ever told you that you were suffering from FMF?
III.	If any of the filtering questions is positive:
1.	How old were you when you first experienced an attack?
2.	Have you ever used colchicine treatment? If yes;
3.	How was the response to colchicine treatment?
4.	Have you had an appendectomy?
5.	Have you ever had an edema?

interview. All were also advised to contact the hospital if they suffered an attack.

Subjects who were not found at home at least 3 times during the survey and those who refused to be interviewed were recorded as non-responders.

## Results

A total of 3948 persons (82.1%) responded to the questionnaire. Among them, 50.1% were female and 49.9% were male; 32.5% were younger than 15 years of age and 67.5% were aged 15 and over. Sivas was the maternal and paternal place of origin of 88% of the subjects.

FMF was suspected in 46 individuals, but only 36 could be interviewed and examined by the specialists. The remainder of the possible FMF patients could not be found for a second interview after at least 3 attempts.

A total of 10 subjects fulfilled the Tel-Hashomer criteria (9), giving a prevalence of 0.25% (95% CI 0.24 – 0.27) in the respondent population (n = 3948). Only one had already been diagnosed as having FMF and was on colchicine treatment. The highest age-specific cumulative prevalence rate of FMF was among subjects aged 10-19 years, as shown in Table II.

The patient population consisted of 8

males and 2 females, the mean age (ranges in parentheses) was 19 years (8 - 42), and the mean age at onset of FMF symptoms was 15.7 years (5-38). Attacks of abdominal pain and fever were present in all of the patients. Six cases complained of arthralgia; one of them had a history of knee arthritis lasting more than one month. Myalgia during attacks was a common complaint and was present in 6 patients. The family history was positive in 7 patients, 5 of whom comprised a mother and her 4 sons among a household of 7 members. Only the father and the smallest son did not have FMF. A physician had also diagnosed FMF in a maternal uncle living in another city 3 years ago. None of the patients were seen during an attack. No genetic analysis was performed in any of the suspected probands.

## Discussion

FMF mainly occurs in 4 ethnic groups: Jews, Armenians, Middle Eastern Arabs and Turks. The prevalence of FMF in Sephardic and Iraqi Jews ranges from 1/250 to 1/1000 (10). The disease is less common among Ashkenazi Jews, with a prevalence of about 1/73,000 (10) although a recent genetic study suggested higher estimates (11).

The prevalence of FMF among a population of 3,948 inhabitants of Sivas was found to be 0.25% in this survey. If the non-responders to the questionnaire were all FMF negative, prevalence of FMF would decrease to 0.21% (95% CI 0.20– 0.22). However we would suggest that the questionnaire response rate of 82.1% was sufficient to consider this a reliable evaluation. On the other hand, if the 10 possible FMF cases who could not be interviewed for a second time were all FMF positive, the prevalence of FMF would increase to 0.51% (95% CI 0.49 – 0.52).

Recently, a national field survey looking for the prevalence of a number of chronic rheumatic disorders of childhood including FMF in Turkey was performed in children aged 16 and under. It was based on cluster centering with 2-level strata. The authors developed a set of diagnostic criteria for the possible or probable diagnosis of FMF.

**Table II.** Age-specific cumulative prevalence rates of FMF in 3,948 subjects.

Age (years)	FMF (-) no. (%)	FMF (+) no. (%)	Total no. (%)	Cumulative FMF (+) no. (%)
0-9	761 (99.9)	1(0.1)	762	1 (0.13)
10-19	1093 (99.4)	7(0.6)	1100	8 (0.43)
20-29	720 (100.0)	-	720	8 (0.31)
30-39	557 (100.0)	-	557	8 (0.25)
40-49	474 (99.6)	2(0.4)	476	10 (0.28)
50-59	187 (100.0)	-	187	10 (0.26)
60+	146 (100.0)	-	146	10 (0.25)
Total	3938 (99.7)	10(0.3)	3948	10 (0.25)

This study showed that 2.8/10,000 children were previously diagnosed as having FMF and, when pooled with the children over 4 years of age with a probable diagnosis of FMF, the prevalence increased to 9.3/10,000 (7).

Another study reported a similar frequency of 1/1000 among young males doing their military service (8). These authors also noted a relatively higher prevalence among probands coming from central Anatolia.

The regional differences with regard to the frequency of FMF in Turkey was initially observed by a group from Istanbul (5), who reported that the majority of their FMF patients originated from the Central, East Anatolia and Black Sea regions rather than the Mediterranean region. This observation was also confirmed by another study from western Turkey (6).

The results of the present survey are concordant with the previous observations. The frequency of FMF was significantly higher among the inhabitants of Sivas (2.5/1000) compared to the results of 2 other surveys (1/1000). Actually, the difference between the results of this and the national survey (7) should be evaluated taking into consideration that this was not a comparative study but rather a local investigation. This difference may be also due to the demographic characteristics of the populations screened in the previous two studies. Both sexes and all age

groups were included in our survey. Furthermore, the differences in the study design, in the criteria used for the diagnosis of FMF, and in the case definitions between the present study and the previous ones may have contributed to these discrepancies.

Sivas has been inhabited since well before the Roman period and has been exposed to internal and external migrations for centuries. The Turkish people of this region lived together with Armenians until the early twentieth century. There has also been a considerable migration of populations from east to west in Turkey from the mid-1900s onwards.

It has been observed that there is often a serious delay in the diagnosis of FMF and hence in the commencement of colchicine therapy which is known to prevent amyloidosis, the most serious complication of the disease. The results of our survey indicate that the high prevalence of FMF in Sivas is important and should be taken into consideration in determining general and regional health policies. Also physicians in general should be informed about this geographic factor in the pathogenesis of the disease because a considerable number of people from this region have moved to western parts of Turkey and to other European countries.

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