

The prevalence of familial Mediterranean fever in the Turkish province of Denizli: A field study with a zero patient design

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ABSTRACT

Objective. This study had two aims: (1) to investigate the prevalence of familial Mediterranean fever (FMF) and Behçet's disease (BD) in school students in Denizli, a province in western Turkey; and (2) to determine whether the previously suggested "zero patient design" was reliable for use in a prevalence survey.

Methods. The field survey was performed in two stages. In the first stage 7,389 students (3,847 females and 3,542 males) were asked to fill out a questionnaire in the classroom. In the questionnaire, filtering questions for FMF (the presence of recurrent attacks of fever accompanying abdominal pain, joint pain/swelling, and/or chest pain) and BD (presence of aphthous stomatitis) were asked.

The second stage consisted of two parts. In the first, 3225 questionnaires were completed by 1778 female and 1447 male students calculated according to the zero patient design, who were selected randomly from among 7389 students for evaluation. Students with any suspicion of FMF and Behçet's disease were called to the hospital for detailed investigation. In the second step the remaining students were evaluated.

Results. Out of 3225 children questioned in the first step, 156 claimed recurrent abdominal pain and/or chest pain, and/or joint pain/swelling with accompanying fever, which might suggest the presence of FMF. However, this diagnosis was excluded after further clinical evaluation. In the second step 152 students were called for detailed investigation: 2 patients, one 10 years and the other 12 years old, were diagnosed as having FMF. None were diagnosed to have Behçet's disease.

Conclusion. The prevalence of FMF in Turkey in general is about 0.093%. The prevalence rate found in this survey was lower (0.027%) which may be due

to the historic background of the region. This is the first study that has shown that the "zero patient design" can be used in an epidemiological survey.

Introduction

Epidemiological data are very important not only for defining the geographical and ethnic distribution of diseases, but also to gather background information for genetic studies (1). It may be useful for decisions regarding the rational use of health resources, both manpower and economic resources. The prevalence of some rheumatic diseases may vary both between countries and between different regions of the same country. These regional differences are probably due to ethnic and geographical factors, and may be the result of a confounder effect (2-4). Ascertaining the prevalence of a rare disease is difficult and costly. In a recent paper it was suggested that comparative estimates of the frequency of rheumatic diseases could be made relatively easily even if the true prevalence is unknown (5). If we take a sample size (3/prevalence of frequent region) in a region with unknown frequency and do not find any case in this region we can say with 95% confidence that the prevalence of rheumatic disease is rarer in the second region than in the known region. The authors have called this statistical term the 'zero patient' design.

FMF is an autosomal recessive disorder characterized by attacks of fever and serositis. It is common in Jews, Arabs, Armenians and Turks (1, 6, 7). In a field study, Özen *et al.* (1) have reported the prevalence of familial Mediterranean fever (FMF) in the childhood age as being 0.095% (1/1075) in Turkey. In the same study they did not find any patients with Behçet's disease (BD) (1).

The history of mainland Turkey is characterized by many eastern and western

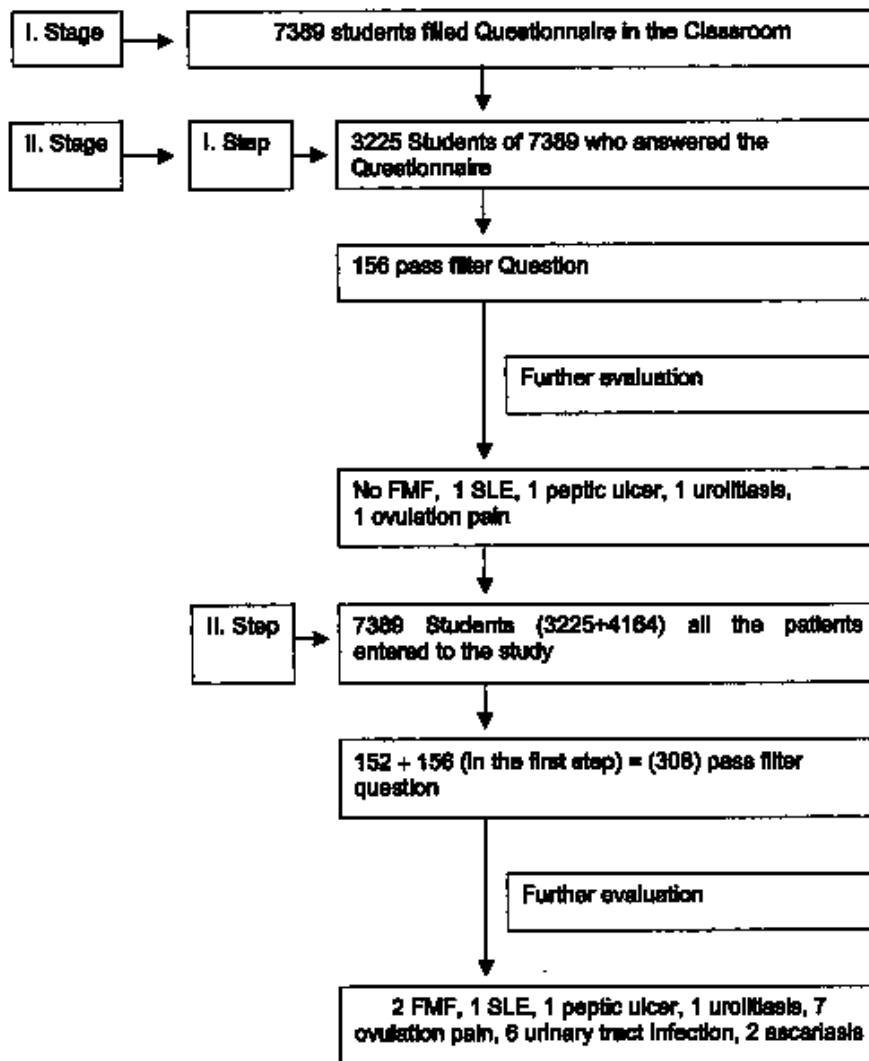


Fig. 1. Study design.

migrations, mixing with and sometimes dominating the local Anatolian people. Denizli is a province in the western region of Turkey. Settlement in this area started in 1000 BC, somewhat later than that of eastern Anatolia. Subsequently the ancient Hittite Kingdom (where today Turkish FMF patients are known to be very common), the Persians and later the Romans ruled the region. Turkish colonies moved in and assimilated the local people in the 13th century.

It has been our personal observation that FMF is rare in the Denizli region. Our aim in this study was to discover the prevalence of FMF and Behçet's disease in childhood in Denizli and to test the "zero patient design" hypothesis suggested by Yazici *et al.* (5).

Materials and methods

The study was conducted in Denizli, a region in the western part of Turkey. The population is about 750,000. The school age population is about 150,000. In the present study we included only students more than 9 years and younger than 17 years of age. We did not include students less than 9 years of age since we thought that they would not be able to understand the questionnaire fully. The population of students between 9 and 17 years old was about 80,000 in Denizli. The data were obtained from regional representatives of the Minister of National Education in Denizli.

The sample size was calculated using the computer program Epi-Info (version 6.0) to estimate the lowest assum-

ed prevalence of 0.093% with a 0.05 error rate and a 95% confidence interval. The calculated effective sample size was about 6,800. The number of the students entered into the study was 7,389.

Five regions – north, south, west, east and central – were designated according to geography of Denizli. The selected schools and classes were determined randomly in each region. The sample size in each region was calculated according to the population size of students in that region. We also calculated the number of students who entered the trial in each age group.

The survey was done in two stages (Fig. 1). The first stage was conducted by 10 physicians; 3 physicians were residents in internal medicine; 3 were interns rotating in internal medicine; 3 were general practitioners; and the last one was a rheumatologist. All physicians participating in the survey had undergone special training in the theoretical background and practical features of FMF and Behçet's disease.

A two-part questionnaire was specifically developed for this study. In the first part demographic data on the participants was recorded. In the second part we asked the subjects filtering questions for FMF and Behçet's disease. The filtering question for FMF was whether they had ever suffered attacks of abdominal, chest and joint pain/swelling accompanied by fever (1). In the second part of this question we asked whether the attacks resolved spontaneously and whether an infectious cause was discarded by a physician. The filtering question for Behçet's disease was whether they had recurrent aphthous lesions. Lastly we asked whether other family members had been diagnosed with FMF or Behçet's disease.

The questionnaire was filled in by the students themselves. Every item was explained to them by the researchers. Any question asked by the students who attended the study was answered carefully. The older groups needed less time to fill the questionnaire than the younger groups.

The second stage was performed in two steps. In the first step, we randomly selected 3,225 questionnaires filled by

students according to the 'zero patient' design. The number 3225 was obtained by dividing 3 by 0.0093 (the prevalence of FMF in Turkey). The students were selected from each region proportionally in the first step.

In the second stage, students who answered in the affirmative to any of the filtering questions were invited to the Department of Rheumatology in Pamukkale University Hospital for detailed clinical examination and if required, laboratory evaluation. A pathergy test to evaluate skin hyperactivity was performed in all patients who had more than 3 recurrent aphthous stomatitis in a year. Then the remaining students, a total of 7389, were evaluated to see if they fulfilled the Tel-Hashomer diagnostic criteria (8) for a definite diagnosis of FMF.

Results

The questionnaires were evaluated in the first stage of the study. In the first step of the second stage of the survey 3225 (1778 girls and 1447 boys) students were selected randomly for the evaluation. The mean age of this first group was 13.056 ± 2.39 years. One-hundred and fifty-six students claimed in the questionnaire that they have had recurrent attacks of abdominal and/or chest pain and/or joint pain and swelling. Detailed evaluation of these students revealed that 156 students did not have any recurrent attacks compatible with FMF. One of the remaining 4 patients had recurrent attacks of joint swelling. Further evaluation of this 14-year-old female patient revealed that she had been previously diagnosed with systemic lupus erythematosus (SLE). The remaining 3 students were diagnosed as having urolithiasis, peptic ulcer and ovulation pain (mittel schmerz), respectively (Fig. 1).

Thirty-nine students were called to the Department of Rheumatology due to complaints of aphthous stomatitis. Only 10 of them had more than 3 recurrent aphthous stomatitis attacks in a year. The pathergy test was negative in all of these patients. They did not have any additional complaints compatible with Behçet's disease. No patient was diagnosed with Behçet's disease.

In the second step of the second stage of the survey 7389 [3847 (52.1%) female, 3542 (47.9%) male] students entered the study. The mean age was 12.9 ± 2.1 year. The age and sex distribution of the first group was compatible with the second group. In this second step an additional 152 students claimed in the questionnaire that they had recurrent attacks of abdominal and/or chest pain and/or joint pain and swelling. These students were separated from the previously mentioned 156 students of the first step. Detailed evaluation of these students revealed that 136 of 152 students did not have complaints compatible with FMF. The remaining 16 students had recurrent attacks of abdominal pain. Two male students, one 10 year old and the other 12 year old, had recurrent abdominal pain attacks with accompanying fever that was compatible with FMF. Both of them had been diagnosed with FMF earlier and had been treated with 1 mg colchicine daily. The treatment prevented all of the attacks completely. Neither of these 2 patients had a diagnosis of FMF in a family member. Re-evaluation of 14 of the 16 students revealed that 6 female patients had ovulation pain, 6 female patients had urinary tract infection, and 2 male patients had ascariasis (Fig. 1). In this second step an additional 47 patients from the first step were also evaluated for complaints of recurrent aphthous stomatitis. A pathergy test was done only in 9 patients who had recurrent aphthous stomatitis with more than three attacks in a year. None of them tested positive for skin hyperactivity. None of the students screened had or has been diagnosed with Behçet's disease.

None reported any family history of either FMF or Behçet's disease.

Discussion

FMF is an autosomal recessively inherited disease which is almost completely restricted to non-Ashkenazi Jews, Armenian, Arabs, and Turks (1,6,7). It has become a fairly universal disease due to the extensive population movements of the twentieth century (9). These ethnic groups are thought to have acquired the disease at least 2000

years ago (1,6,7) in the eastern Mediterranean basin. The most common mutation, M694V, spread from the eastern Mediterranean to Spain, Turkey, Armenia, Iraq and subsequently to north Africa with the Sephardic expulsion of 1492 (6,7,10).

Few prevalence studies on FMF have been performed in Turkey. The largest of them found a prevalence rate of 0.093% (1/1075) (1). Another survey reported a prevalence rate of 0.11% (11). These studies focused on the general population of Turkey and did not mention regional differences. It is known that FMF in Turkey is most common in central Anatolia (12). In unpublished data from the Turkish FMF study group, 52% of 2314 FMF patients originated from the central Anatolia region. Only 8% of these patients originated from the Aegean region in which Denizli is also located. The ratio of the population of the Aegean region to the general population of Turkey is 15%; this suggests that FMF is less frequent in the Aegean region. In our study we found a prevalence rate for FMF of 2.7/10000 in Denizli, a part of the Aegean region (western Anatolia); this is in agreement with the findings of the Turkish FMF study group.

The peoples of many civilizations have lived in Turkey. Central Anatolia was inhabited in much earlier times compared to the western regions. We had previously suggested that FMF may be a disease pertaining to the first human settlers around Mesopotamia (13). However, Denizli is not a part of that region, which may be one of the explanations for the low FMF prevalence in Denizli. A second explanation could be that the Semitic Assyrian trade colonies arrived in eastern Anatolia in 2000 BC, and mutations for the FMF gene are very frequent in Semitic groups. However, it may be speculated that Denizli, being located in the Aegean region of Turkey, could have been affected less by these Semitic migrations.

This is the first epidemiological survey performed according to the "zero patient" design (5). It confirms the hypothesis suggested by Yazici *et al.* that finding null patients in a survey has a significant meaning. If we had not car-

ried out the second step in the survey we could still have said that the prevalence of FMF is less than the general prevalence of FMF all over Turkey. Conducting the second step of the study however has confirmed this.

Behçet's disease is a chronic multi-system disorder of unknown cause. Although it occurs worldwide, it is generally regarded as being most common in the Mediterranean basin, the Middle East, and the Far East (4, 14). Behçet's disease is relatively rare in childhood and only recently have series of pediatric patients been reported (15-17). In the survey conducted by Ozen *et al.*, no child was found to have Behçet's disease. Although the children who attended our survey were older, we also failed to find any with Behçet's disease.

There is a certain delay in the diagnosis of FMF since the findings may be non-specific. This might have partially afflicted or positively screened patients number. Another cause for false negative answers may be that patients do sometimes ignore their symptoms. However, Ozen *et al.* (1), and Dinc *et al.* (11) used the same filter questions and reported prevalences of 0.093%

and 0.11%, respectively.

In conclusion we can say that although FMF is frequent in Turkey, it is less frequent in the region of Denizli. The zero patient design is an inexpensive, convenient, and reliable epidemiological method that can be used successfully in field surveys.

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