Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome – Is It Related to Ethnicity? An Israeli Multicenter Cohort Study

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Objectives To evaluate the ethnic distribution of Israeli patients with the syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA).

Study design The medical records of patients with PFAPA attending 2 pediatric tertiary medical centers in Israel from March 2014 to March 2019 were retrospectively reviewed. Patients with concomitant familial Mediterranean fever were excluded. Ethnicity was categorized as Mediterranean, non-Mediterranean, and multiethnic. Findings were compared with patients with asthma under treatment at the same medical centers during the same period.

Results The cohort included 303 patients with PFAPA and 475 with asthma. Among the patients with PFAPA, 178 (58.7%) were of Mediterranean descent (Sephardic Jews or Israeli Arabs), 96 (33.0%) were multiethnic, and 17 (5.8%) were of non-Mediterranean descent (all Ashkenazi Jews). Patients with PFAPA had a significantly higher likelihood of being of Mediterranean descent than the patients with asthma (58.7% vs 35.8%; $P < .0001$). The Mediterranean PFAPA subgroup had a significantly earlier disease onset than the non-Mediterranean subgroup (2.75 ± 1.7 vs 3.78 ± 1.9 years, $P < .04$) and were younger at disease diagnosis (4.77 ± 2.3 vs 6.27 ± 2.9 years, $P < .04$).

Conclusions PFAPA was significantly more common in patients of Mediterranean than non-Mediterranean descent. Further studies are needed to determine the genetic background of these findings. *(J Pediatr 2020;227:268-73)*.

The syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is an autoinflammatory disease that affects mostly toddlers. Symptoms include recurrent flares of fever accompanied by 1 or more of the following: pharyngitis, tonsillitis, oral aphthae, cervical adenitis, and occasionally, abdominal pain and arthralgia.[1-4] We and others have shown that PFAPA may present simultaneously with familial Mediterranean fever (FMF), another autoinflammatory disease that is common in patients of Mediterranean ancestry.[5,6] In addition, the experience of our tertiary pediatric rheumatology clinics suggests a higher prevalence of PFAPA alone, with no other autoinflammatory manifestations, among children of Mediterranean ancestry. Therefore, the aim of this study was to determine the ethnic distribution of Israeli patients with PFAPA and to analyze differences in demographic characteristics, clinical features, and response to therapy by ethnic group.

Methods

We reviewed the medical records of all children with PFAPA attending the pediatric rheumatology division of 2 large Israeli tertiary-level medical centers (Schneider Children's Medical Center of Israel and Ruth Rappaport Children's Hospital) between March 2014 and March 2019. Inclusion criteria for the study were clinical diagnosis of PFAPA by a pediatric rheumatologist and absence of other autoinflammatory manifestations.

As FMF is common in children of Mediterranean ancestry, to avoid referral bias, we excluded children whose differential diagnosis included FMF based on a finding of 2 mutations (among the 9 most common clinically relevant *MEFV* mutations tested), regardless of clinical presentation. In children with no or one mutation, besides typical characteristics, we distinguished FMF attacks from PFAPA attacks by the absence of aphthous stomatitis, pharyngitis, and adenitis as well as a lack of abortive response to corticosteroids. In addition, all children with FMF attacks were assessed according to the pediatric

FMF	Familial Mediterranean fever
PFAPA	Periodic fever, aphthous stomatitis, pharyngitis, and adenitis

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Yalcinkaya-Ozen criteria for FMF.[7] All tracked cases of PFAPA were validated according to previously established clinical criteria.[8] The study was approved by each hospital's local Helsinki Committee.

Patient ethnicity was categorized as Mediterranean (family history on both sides traceable to the Mediterranean region, ie, Sephardic Jews and Israeli Arabs), non-Mediterranean (ie, Ashkenazi Jews and Ethiopian Jews), and multiethnic (1 parent of Mediterranean origin and 1 of non-Mediterranean origin). Patients with asthma attending the pulmonology clinics of the same medical centers during the same period served as controls. We chose asthma for comparison because it has no predilection for a particular ancestry among Caucasians.[9]

In addition to ethnic background, data were collected on demographics (both patients with PFAPA and controls), clinical manifestations, laboratory measures, family history of disease (first- and second-degree relatives), and results of Sanger sequencing, performed in some patients from both medical centers, for the 9 most common *MEFV* mutations (M694V, M694I, M680I, K695R, R761H, A744S, P369S, V726A, and E148Q). The genetic tests were ordered as part of the workup of periodic fever, either by the primary care physician or the pediatric rheumatologist. We also recorded the number and frequency of PFAPA flares, treatment administered, and response to treatment, documented at each clinic visit, and outcome. Response to corticosteroids was defined as defervescence within 12 hours after intake of 1 oral dose. Response to colchicine was defined as a reduction or complete resolution of flares.

Data analysis was carried out using IBM-SPSS v 23 for Windows (IBM, Armonk, New York). Descriptive statistics are reported as mean and SD or number and percentage. Heterogeneity among the various subgroups was evaluated by 1-way ANOVA with the Tukey post hoc test. For categorical parameters, we used Pearson χ^2 test with comparison of column proportion and adjusted the *P* value with Bonferroni methods. A *P* value of ≤.05 was considered significant.

Results

Of the 354 patients being treated for PFAPA during the study period, 53 were excluded from the study because of suspected concomitant FMF. (All had PFAPA manifestations with 2 *MEFV* mutations and all but 1 fulfilled the pediatric Yalcinkaya-Ozen criteria for FMF) The final cohort of 303 patients was compared with 475 patients with asthma. Table I summarizes the demographic and ethnicity data of the 2 groups. Among the patients with PFAPA, 178 (58.7%) were of Mediterranean descent, including 106 Sephardic Jews and 72 Israeli Arabs; no other ethnic groups from the Mediterranean region were represented in the cohort. Of the remainder, 96 (33.0%) were multiethnic, all Ashkenazi/Sephardic Jews, and 17 (5.8%) were of non-Mediterranean descent, all Ashkenazi Jews. Among the patients with asthma, about one-third each was of Mediterranean, non-Mediterranean, and multiethnic descent. The non-Mediterranean asthma group included 7 Ethiopian Jews in addition to Ashkenazi Jews. The patients with PFAPA were significantly more likely to be of Mediterranean descent than the patients with asthma (58.7% vs 35.8%; $P < .0001$), even when the Sephardic Jewish and Arab subgroups were analyzed separately.

Table I. Comparison of demographic data between patients with PFAPA and control patients with asthma

Variables	PFAPA (n = 303)	Asthma (n = 475)	*P* value
Female sex, n (%)	120 (39.6%)	207 (43.8%)	.26
Age at symptom onset (y), mean ± SD	2.96 ± 1.84	7.29 ± 5.63	**<.001**
Ethnic group, n (%)			
Non-Mediterranean	17 (5.8%)	142 (30.3%)	**<.0001**
Mediterranean	178 (58.7%)	170 (35.8%)	**<.0001**
Sephardic Jews	106 (36.4%)	104 (22.2%)	**<.0001**
Arabs	72 (24.7%)	66 (14.1%)	**.0003**
Multiethnic	96 (33.0%)	156 (33.3%)	.94

Significant statistical differences ($P < .05$) were bolded.

As expected, the patients with PFAPA had an earlier onset of disease than the patients with asthma (2.96 ± 1.84 vs 7.29 ± 5.63 years, $P < .001$).

Table II summarizes the demographic data of the patients with PFAPA by ethnic group. PFAPA was more common in male patients (61.2%). The Mediterranean group had a significantly earlier onset of symptoms than the non-Mediterranean group (2.75 ± 1.7 vs 3.78 ± 1.9 years, $P < .04$) and were younger at disease diagnosis (4.77 ± 2.3 vs 6.27 ± 2.9 years, $P < .04$). In all 3 ethnic groups, there was an average delay of about 2 years between symptom onset and diagnosis. Twelve patients, all Muslim Arabs, had parents who were first-degree cousins. Almost one-fourth of the patients of Mediterranean descent (in both the Mediterranean and multiethnic groups) had a family history of FMF, and almost one-fourth had a family history of symptoms compatible with or equivalent to PFAPA. A similar percentage had a family history of tonsillectomy in childhood.

Table III shows the results of Sanger sequencing for the 9 most common *MEFV* mutations. One of the 2 patients of non-Mediterranean (Ashkenazi Jewish) descent who were tested was found to carry an *MEFV* mutation. The rate of positivity for *MEFV* mutations was 59.2% for the screened patients of Mediterranean descent compared with 53.1% of the screened patients of multiethnic descent. All affected patients were heterozygous for the mutation. The most common mutation identified in both groups was M694V.

At presentation, there were no significant differences in mean duration of flares and in mean interval between flares among the ethnic groups with PFAPA (Table IV). The most common symptom (except for fever, which is mandatory for diagnosis) in all 3 groups was pharyngitis (about 90%). Abdominal pain during attacks was reported by 54.5% and 63.8% of the Mediterranean and multiethnic groups,

Table II. Comparison of demographic data of patients with PFAPA by ethnic group

Variables	Non-Mediterranean (n = 17)	Mediterranean (n = 178)	Multiethnic (n = 96)	*P* value
Female sex, n (%)	7 (41%)	67 (38%)	39 (41%)	.87
Age at symptom onset (y), mean ± SD	3.78 ± 1.9	2.75 ± 1.7	3.20 ± 1.9	**.042***
Age at diagnosis (y), mean ± SD	6.27 ± 2.9	4.77 ± 2.3	5.23 ± 2.4	**.041***
Parental consanguinity, n (%)	0	12 (7%)	0	NA
Family history of FMF, n (%)	0	40 (22.7%)	23 (24.5%)	.76†
Family history of PFAPA/PFAPA- equivalent symptoms, n (%)	2 (11.8%)	42 (24.3%)	24 (25.8%)	.46
Family history of tonsillectomy, n (%)	2 (25%)	26 (22.8%)	11 (23.9%)	.98

Significant statistical differences ($P < .05$) were bolded.
*Non-Mediterranean vs Mediterranean.
†Non-Mediterranean vs multiethnic.

respectively, compared with 23.5% of the non-Mediterranean group ($P < .008$). Similarly, corresponding rates of arthralgia during attacks were 15.9% and 28.7% compared with 5.9% ($P < .008$).

More than 90% of patients received treatment with corticosteroids (1 dose), and almost all showed defervescence within a few hours (Table V). In 43% of the patients treated with corticosteroids the interval between flares was shortened. After treatment, the mean interval between flares was significantly shorter in the Mediterranean and multiethnic groups than in the non-Mediterranean group ($P < .036$ and $P < .041$, respectively). The most commonly used prophylactic agent was colchicine, administered to 37% of the total patients. Rates of response were 78% in the Mediterranean group compared with 54% in the multiethnic group ($P < .04$). A positive response was also noted in the sole patient treated with colchicine in the non-Mediterranean group (Ashkenazi Jewish). Too few patients were treated with cimetidine and montelukast for statistical analysis. Overall, 17 patients (5.8%) underwent complete tonsillectomy, with a 76% success rate in terms of full resolution of the disease. No partial responses were observed.

Discussion

Although, PFAPA was found by us and by others to be associated with FMF,[5,6] we describe an ethnic predisposition for non-FMF-associated PFAPA manifestations. The main finding was the high frequency of patients with PFAPA of Mediterranean descent (59%), namely Sephardic Jews and Israeli Arabs, relative to patients with asthma, who were equally represented in the 3 ethnic groups. Another 33% of the patients with PFAPA had at least 1 parent of Mediterranean descent, for a total of 93% of patients. Only 6% were solely of non-Mediterranean origin. The differences in distribution between the PFAPA and patients with asthma were strongly significant for all ethnic groups. These findings are striking given that they were calculated after exclusion of 15% of the total patients with PFAPA identified in our databases who had a concomitant diagnosis of FMF, all of whom were of Mediterranean origin.

The Israeli population (native-born and immigrant) is comprised roughly of 74% Jews and 21% Arabs.[10] Among Jews, an estimated 40% are Ashkenazi (Jews whose ancestors had settled in Central and Eastern Europe) and 35% are Sephardic (Jews whose ancestors had settled mainly in the Middle East and North Africa region); about 1.5% are of Ethiopian ancestry.[10,11] Studies have shown that about 28% of native-born Israeli children are multiethnic, and their percentage in the Jewish population is growing.[12] The rate of children from mixed Arabic and Jewish families is negligible.[11] Taken together, the findings suggest that the Israeli population can be divided into approximately 40%-45% Mediterranean ancestry and approximately 30% each multiethnic and non-Mediterranean ancestry. Unfortunately, we did not have an external control arm because of the lack of

Table III. Comparison of genetic data of patients with PFAPA by ethnic group*

Variables	Non-Mediterranean (n = 17)	Mediterranean (n = 178)	Multiethnic (n = 96)
Total screened†, n (%)	2 (11.8%)	76 (42.7%)	32 (33.3%)
No mutation‡, n (%)	1 (50%)	31 (40.8%)	15 (46.9%)
M694V heterozygous§, n (%)	0	25 (27.8%)	11 (28.9%)
E148Q heterozygous§ n (%)	0	11 (12.2%)	1 (2.6%)
M680I heterozygous§, n (%)	0	3 (3.3%)	2 (5.3%)
M694I heterozygous§, n (%)	0	1 (1.1%)	0
V726A heterozygous§, n (%)	1 (100%)	5 (5.6%)	3 (7.9%)
Total heterozygous§, n (%)	1 (50%)	45 (59.2%)	17 (53.1%)

*Genetic testing was performed by Sanger sequencing for the nine most common MEFV mutations (M694V, M694I, M680I, K695R, R761H, A744S, P369S, V726A, and E148Q).
†Total screened patients within each ethnic group.
‡Calculated for screened patients only.
§Calculated for heterozygous patients only. None of the patients was homozygous for an MEFV mutation.

Table IV. Comparison of clinical data at presentation of patients with PFAPA by ethnic group

Variables	Non-Mediterranean (n = 17)	Mediterranean (n = 178)	Multiethnic (n = 96)	*P* value
Mean duration of flares (d), mean ± SD	4.84 ± 1.8	4.25 ± 1.9	3.85 ± 1.5	.10
Mean interval between flares (wk), mean ± SD	4.71 ± 3.3	3.53 ± 1.9	3.86 ± 2.3	.089
Symptoms, n (%)				
Pharyngitis	15 (88.2%)	168 (95.5%)	85 (89.5%)	.13
Aphthous stomatitis	5 (29.4%)	66 (37.5%)	31 (33%)	.65
Adenitis	8 (47.1%)	90 (51.1%)	44 (46.8%)	.78
Abdominal pain	4 (23.5%)	96 (54.5%)	60 (63.8%)	**.008***
Myalgia	6 (35.3%)	45 (25.6%)	33 (35.1%)	.22
Arthralgia	1 (5.9%)	28 (15.9%)	27 (28.7%)	**.014***

Significant statistical differences ($P < .05$) were bolded.
*Mediterranean and Multiethnic vs Non-Mediterranean.

recent accurate ancestry data. Nevertheless, previous studies[10-12] support our finding that PFAPA is much more common in individuals of Mediterranean descent.

Manthiram et al presented genetic risk variants for PFAPA (rs17753641 variant upstream of IL-12A gene and variants near STAT4, IL10, and CCR1-CCR3 genes) that were associated with Behçet disease, another autoinflammatory disease which involves the oral mucosa and has a predisposition for a particular ancestry.[13] Batu et al, in a comparative study of 71 Turkish and 60 American children with PFAPA, found that the Turkish patients had an earlier onset of symptoms, shorter duration of attacks, higher frequency of pharyngitis, and less frequent adenitis during attacks.[14] There were no between-group differences in frequency of abdominal pain or arthralgia. In our cohort, the Mediterranean group was characterized by significantly earlier symptom onset and disease diagnosis than the non-Mediterranean group ($P < .04$; Table II) and higher rates of abdominal pain and arthralgia (Table IV). However, because the non-Mediterranean group was composed of only 17 patients, we cannot draw definitive conclusions.

Similarly, we could not reliably compare the carriage rate of *MEFV* variants among the ethnic groups because only 2 non-Mediterranean patients were screened (Table II). All patients who were positive for *MEFV* on screening were heterozygous for the mutation, owing to our exclusion of patients with concomitant FMF. Furthermore, more than one-half the tested patients with PFAPA who were of Mediterranean or partly Mediterranean (multiethnic) descent carried 1 variant of the *MEFV* gene. By contrast, studies reported an overall carriage rate in individuals of Mediterranean origin ranging from 6% to 39%,[15] and these findings were found to be comparable with results for the Israeli population.[5] Although our exclusion of patients with suspected FMF created a selection bias, as these patients were more likely to be tested, it remains unclear if there is a correlation between phenotypic presentations of PFAPA alone, without other autoinflammatory manifestations, and

Table V. Treatment and treatment response of patients with PFAPA by ethnic group*

Type of treatment	Non-Mediterranean (n = 17)	Mediterranean (n = 178)	Multiethnic (n = 96)	*P* value
Corticosteroids				
Patients treated, n (%)	16/17 (94%)	160/178 (89.9%)	88/96 (92%)	1.00† 1.00‡ .83§
Response to initial dose, n (%)	13/14 (92.8%)	128/148 (86.5%)	70/78 (89.7%)	.65
Patients with shortened intervals (%)	13/13 (100%)	139/147 (94.5%)	74/75 (98.7%)	.90
Mean post-treatment interval between flares, (wk, median; 25%-75%)	4 [3-6]	2 [1-4]	2 [1.5-3.5]	**.036**† **.041**‡
Increase in flares post-treatment, n (%)	5/13 (38.5%)	49/126 (38.8%)	36/69 (52.2%)	.55
Prophylactic treatment				
Colchicine Patients treated, n (%)	2	74	32	
Response* (no/fewer flares), n (%)	1/1	49/63 (77.8%)	14/26 (53.8%)	**.039**§
Cimetidine Patients treated (%)	1	3	6	
Response (no/fewer flares), n (%)	1/1	1/2	0/5	1.00
Montelukast Patients treated (%)	0	7	8	
Response (no/fewer flares)* (%)	0	2/5	3/7	1.00§
Tonsillectomy Patients treated (%)	4	9	4	
Response (no/fewer flares) (%)	3	7	3	.99

Significant statistical differences ($P < .05$) were bolded.
*One patient who was treated concomitantly with colchicine and montelukast was excluded from the analysis.
†Mediterranean vs non-Mediterranean.
‡Non-Mediterranean vs multiethnic.
§Mediterranean vs multiethnic.

the *MEFV* variant genotype. A positive family history has been previously reported in 10%-15% of patients with PFAPA.[5,16] We found that about 25% of the patients of pure or mixed Mediterranean ethnicity had a family history of PFAPA or PFAPA-equivalent symptoms compared with 11.8% of the non-Mediterranean (Ashkenazi Jewish) patients. However, these numbers were not sufficiently powered to achieve statistical significance.

More than 90% of the patients with PFAPA were treated with corticosteroids, and about 90% of the treated patients exhibited a decrease in fever in response to the first dose. There were no differences among the ethnic groups in the percentage of patients who experienced an increase in attack frequency after starting corticosteroid treatment (overall 46%). However, among the patients with an increased attack frequency, the frequency was significantly higher in those of Mediterranean than non-Mediterranean descent. Indeed, only 3 patients (18%) in the non-Mediterranean group were treated with a prophylactic drug, whereas 27% of the patients in the Mediterranean and multiethnic groups received colchicine, which is also used for the prophylactic treatment of FMF. The response rate to colchicine was 76% which is considerably higher than the reported rate of 50% in patients with PFAPA.[2,3] Although cimetidine is extensively used for prophylaxis of PFAPA in North America,[17] it is generally unavailable in Israel. Montelukast has been shown to be effective for PFAPA,[18] but these findings were never published in a peer-reviewed journal. In our cohort, only a few patients received montelukast, and about one-third of them responded. Tonsillectomy was used in less than 5% of patients by physician and parental preference, and the response rate was 80%, which is comparable with other studies.[19,20]

In a survey study, Manthiram et al investigated the practice patterns of 277 North American specialists in pediatric infections, rheumatology, and allergy and immunology in the diagnosis and treatment of PFAPA.[17] Most (72%) reported seeing 1-5 patients with PFAPA yearly in their clinics. Only 3% of the clinics (including 1 Israeli) had had more than 20 patients per year. The 4 pediatric rheumatologists who were among the authors of the present study from 2 pediatric rheumatology clinics in central and northern Israel, had a similar experience. We, therefore, speculate that PFAPA is more common in Israel than in North America, probably owing to the higher frequency of individuals of Mediterranean origin in the Israeli population.

This study was limited by the retrospective design which has inherent biases. Furthermore, the non-Mediterranean group was relatively small (only 17 patients), making comparisons difficult. The study was conducted in tertiary medical centers, which may see patients with a more severe phenotype, whereas patients with milder disease might be managed by their primary care physician. Therefore, our findings may not be generalizable to the whole Israeli population.

To ensure the integrity of the study results, there were several potential biases we needed to address. (1) Although low socioeconomic status has been linked to lesser access to quality care in Israel, every resident is insured by 1 of the 4 national healthcare funds and can be referred for consultation to any pediatric rheumatologist (all are hospital-affiliated) in an outpatient clinic with minimal co-pay that can be waived in case of low income.[21] Therefore, we did not identify a potential referral bias on a socioeconomic basis. (2) The higher rate of patients of Mediterranean descent in the PFAPA group could have been a consequence of the similar symptoms of PFAPA and FMF. Therefore, we reviewed the primary physician referral letters of a random sample of 30 patients in the Mediterranean study group and found that in only 3 was the possibility of FMF mentioned. (Fifteen were a consult request for diagnosis and follow-up of the disease, and 12 were referrals for evaluation because of an increased frequency of attacks in patients who had already been diagnosed by the primary physician.) Therefore, any potential referral bias, if present at all, was small, and the differences in ancestry distribution were sufficiently striking to support our conclusion. (3) For the same reason, patients of Mediterranean ancestry may be referred by pediatricians specifically to pediatric rheumatologists and not to infectious diseases and pediatric ear nose and throat specialists. Indeed, in our institutions, tonsillectomies performed for indications of PFAPA are extremely rare (1-2 per year per center), as can be seen in **Table V**. In the event that an infectious disease specialist encounters a patient with PFAPA in our institutions, he/she will eventually refer the patient to our clinic. (4) To avoid the risk of a nonhomogeneous study population owing to the high proportion of Arabs that reside in the catchment area of Rambam Medical Center, we used patients with asthma as a control group. (5) The patients with PFAPA had an earlier disease onset than the patients with asthma. To determine whether age acted as a confounder, we stratified the analysis of ethnicity between PFAPA and asthma by age group. The observed association between ethnicity and PFAPA remained significant, and there was still no association of ethnicity with asthma (data not shown). Therefore, our results cannot be explained by differences in age distribution.

In conclusion, the present study shows that PFAPA may be more common in patients of Mediterranean descent. This group was characterized by earlier disease onset and earlier diagnosis than patients of mixed or non-Mediterranean descent, in addition to a possibly higher frequency of *MEFV* variant carriage than the general population of Mediterranean descent. Future prospective studies such as the Childhood Arthritis and Rheumatology Research Alliance PFAPA Working Group consensus treatment plans initiative[22] are needed to better define the disease, tailor specific treatments based on patient characteristics, including ancestry, and to explore the relationship to the pathogenesis and genetics of FMF, another

autoinflammatory disease common to patients of Mediterranean ancestry. ■

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