Familial Periodic Fever, Aphthous Stomatitis, Pharyngitis and Adenitis (PFAPA) Syndrome; is it a Separate Disease?

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Abstract

Introduction: PFAPA is the most common periodic fever syndrome in the pediatric population yet pathogenesis is unknown. PFAPA was believed to be sporadic but family clustering has been widely observed.

Objective: To identify demographic and clinical differences between patients with PFAPA and a positive family history (FH+) compared to those with PFAPA with no family history (FH-).

Methods: In a database comprising demographic and clinical data of 273 pediatric PFAPA patients treated at two tertiary centers in Israel, 31 (14.3%) of patients were PFAPA FH+. Data from patients with FH+ for PFAPA was compared to data from those with FH- of the disorder. Furthermore, family members (FMs) of those with FH+ were contacted via telephone for more demography and clinical details.

Results: FH+ group had more headaches (32% vs.2%; p= 0.016), myalgia (56% vs. 19%; p= 0.001), higher carrier frequency of M694V mutation (54% vs. 25%; p=0.053), greater family history of FMF (30% vs. 15%; p=0.096) and better outcomes with colchicine (82% vs. 52%; p=0.096) compared to those with FH-. FMs displayed almost identical characteristics to the FH+ group except for greater arthralgia during flares (64% vs. 23%; p=0.008) and compared to the FH- group, more oral aphthae (68% vs. 43%; p=0.002), myalgia/arthralgia (64% vs. 19%/16%; p<0.0001), and higher rates of FH of FMF (45% vs.15%; p=0.003).

Conclusions: Our findings suggest that FH+ likely experience a different subset of disease with higher frequency of family history of FMF, arthralgia, myalgia and better response to colchicine compared to FH-. Colchicine prophylaxis for PFAPA should be considered in FH+.

Introduction:

PFAPA is an acronym for periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome. Marshall et al. first described PFAPA in 1987 as a periodic fever syndrome (PFS), which are a set of autoinflammatory disorders defined by recurrent episodes of unprovoked systemic and specific organ inflammation interchanged with periods of normal health1.

PFAPA, the most common PFS in children, typically presents before the age of 5 with fevers over 38.9°C (102°F) that last from a few days to a week and recur every 3 to 8 weeks. Of all periodic fever syndromes, only PFAPA presents with fevers that are truly periodic—fevers appear as predictably as “clockwork”2. These fevers are accompanied by either one or more of the following symptoms: aphthous ulcers—small, relatively painless lesions on the tongue and oral mucosa, pharyngitis with or without white exudates on the tonsils, and swollen cervical lymph nodes (adenitis). Between PFAPA flare-ups, children are healthy and grow and mature naturally.

Originally, PFAPA was believed to be a sporadic disease with no genetic heritability. However, recent cohort studies have revealed that 10–78% of those with PFAPA have a family member with recurrent
fever. Manthiram et al. studied the family history in a cohort of 80 individuals with PFAPA and discovered that 18 (23%) had a family member with symptoms concurrent with PFAPA. Compared to healthy controls, these patients had a higher prevalence of parents and/or siblings with recurrent aphthous stomatitis and/or recurrent pharyngitis as well as higher rates of siblings who had undergone tonsillectomy. A longitudinal study conducted by Perko et al. found that 50/64 (78%) of their cohort had a first-degree relative who had recurrent fever or underwent tonsillectomy as children. Di Gioa et al.’s pedigree analysis of 68 PFAPA patients from 14 families found that the disorder displays autosomal dominant inheritance with estimated 50% penetrance, if Mendelian genetics assumed. As a means to uncover a causative gene, Di Gioa et al. also performed whole-genome linkage analysis on seven of these families which did not reveal a common gene mutation associated with PFAPA.

These findings are strongly suggestive that family history and heredity are involved in the pathogenesis of this disorder although a clear genetic cause or mutation has yet to be discovered.

The aim of our study is to identify demographic and clinical differences between patients with PFAPA who have a positive family history compared to those with PFAPA with no family history that can reveal if heritable and sporadic subtypes of this disorder exist.

**Methods:**

Retrospective data was collected from 273 children with a diagnosis of PFAPA who were treated at the pediatric rheumatology clinics at either Rambam's Ruth Rappaport Children's Hospital in Haifa, Israel or Schneider's Children's hospital in Petah Tikvah, Israel between March 2014-March 2019. Information regarding demography, ethnicity, diagnosis, follow-up, treatment, family history, and genetics were collected at patient clinical visits. Any patient with a concurrent diagnosis of FMF was excluded.

Of the 273 patients in the original database, 53 were eliminated from the study due to a diagnosis of FMF. Patients were then stratified into two groups based on the presence of at least one relative with a diagnosis of PFAPA. 185 patients had no family members with PFAPA while 31 (14.3%) had positive family history. Four patients were eliminated due to unknown family status (Fig 1).

Furthermore, the parents of the 31 patients identified as having FH+ for PFAPA were contacted and sent questionnaires inquiring about demography, clinical experience with PFAPA, and relation to the index case of the other family member (FM) with PFAPA. 23 questionnaires were filled out by either the parent or the FM him or herself depending on age and ability. Eight parents were unable to be contacted or declined to participate in the study.

Statistical analysis and comparison were performed between the FH- group and the FH+ group as well as the FM group compared to both FH- and FH+ groups. Data was statistically analyzed using the SPSS statistical package (SPSS, Inc, Chicago, Illinois). All data are expressed as median, mean ± standard
deviation, or as percentages. A χ² test, a Mann-Whitney U test, and Student t-test were used; P < .05 was accepted as statistically significant.

Each hospital’s local Helsinki Committee (REB no. 0318 – 16 RMB and 104-16-RMC) approved the study.

**Results:**

The 216 PFAPA patients were divided into either one of two groups, the FH- group (n = 185), where patients did not have any family members with a known diagnosis of PFAPA or the FH + group (n = 31), where each patient had at least one family member with a known diagnosis of PFAPA. None of the members of either group had clinical characteristics of FMF. Two members of the FH- group were homozygous for a mutation in one of their MEFV genes (M694V and V726A genes), however their symptomology was congruent with a diagnosis of PFAPA and not FMF as determined by expert physicians in the field.

Clinical and demographic characteristics of FH+ and FH- groups are presented in table-1. Patients in the two groups had a similar average age of symptom onset, at 3 years [1.5–4.4] in FH- and 2.8 years [1.5–4.1] in FH+ (p = 0.91) and in both groups, approximately a year and a half elapsed from symptom onset until a diagnosis of PFAPA was conferred at age 4.58 years [3-6.2] in FH- and 4.75 years [3-6.8] in FH+ (p = 0.86). Without treatment, members of both groups experienced acute attacks that lasted on average for four days (FH-: [3-4.5], FH+ [3–7]; p = 0.53) with maximum fevers reaching 39.7C ± 0.55 in FH- and 39.9C ± 0.78 in FH+ (p = 0.20). These episodes were experienced on average every four weeks in FH- and every three weeks in FH+ (FH-: [2.5-4], FH + 3 [2–4]; p = 0.29).

Table-2 lists the symptoms experienced by patients in both groups during PFAPA flare-ups. Headache and myalgia were experienced by a statistically greater percentage of patients in the FH+ group compared to the FH- group (P = 0.0016 and P = 0.001 respectively).

The vast majority of patients in both groups were treated with steroids that contributed to positive clinical outcomes such as suspending or shortening the PFAPA flare-up, although increased frequency of flares occurred in 45% of FH- and 33% in FH+ (P = 0.35) as a result of steroid usage. Colchicine was seen to be a more beneficial treatment in the FH+ group as opposed to the FH- group, although statistical significance was not reached (p = 0.096). Data on response to therapy is presented in table − 3.

Genetic testing for known mutations in FMF-causing genes was conducted in 34% of those in FH- and 41.9% of those in FH+. Of those tested, 49% of FH- members and 77% of FH+ members were found to contain at least one such mutation (p = 0.12). The M694V heterozygote mutation was the predominant mutation in both groups, representing 25% and 54% of mutations in FH- and FH+ respectively (p = 0.053). Family history of FMF was recorded in 30% of those in FH+ as opposed to 15% in FH- (p = 0.096).

Family history of tonsillectomy/adenoidectomy was similar in both groups with 34% in the FH- group and 15% in the FH+ group (P = 0.33) reporting a family member who underwent one of these procedures.
Demographic, clinical, and family history data collected from family members (referred to as FM) is displayed in Table 4.

The makeup of the FMs in relation to the FH+ group was found to be: 14 siblings (58%), 1 parent (4%), 8 cousins (33%) (one patient had 2 cousins with PFAPA), and 1 aunt (4%). Family members were found to display almost identical clinical characteristics as the FH+ group, except for arthralgia, which manifested in 64% of FMs compared to 23% of FH+ (P = 0.008). Compared to the FH- group, FMs experienced more oral aphthae (68% vs. 43%; p = 0.002), myalgia (64% vs. 19%; p < 0.0001), and arthralgia (64% vs. 16%; p < 0.0001) as well as a higher rate of family history of FMF (45% vs. 15%; p = 0.003).

Discussion:

The pathophysiology of inherited PFSs is well understood as disorders of innate immunity caused by a monogenic gene mutation. Homozygous carriers of such mutations have aberrant activation of their inflammasome that triggers dysregulated activation and release of pro-inflammatory cytokines such as IL-1β that lead to symptoms of system-wide inflammation. PFAPA possesses clinical similarities to these monogenic PFSs and PFAPA attacks have been shown to resolve with inhibition of IL-1β. However, unlike in the hereditary PFSs, no single gene mutation has been implicated as the culprit of PFAPA and its mode of heredity is unknown.

Many PFAPA patients have been found to be heterozygous carriers of gene mutations responsible for these various recessively inherited PFSs. A study in Switzerland found an increase in the expected carrier rate of NLRP3 inflammasome gene mutations, which are responsible for the majority of cases of cryopyrin-associated periodic syndrome (CAPS), in PFAPA patients compared to the general population.

In this database, as previously presented, 18.9% of the PFAPA patients had a co-diagnosis of FMF.

In our cohort, patients were tested for common MEFV mutations that are responsible for the development of FMF. In Israel, the carrier rate of FMF-associated genes is as high as 1 in 3 in Jews of Iraqi descent. Different point mutations in the MEFV gene are observed in individuals of different ethnicities and all lead to the same classic disease phenotype. The carrier rate found in this cohort (of those tested for MEFV mutations) in both the FH- and FH+ groups was found to be higher than 1 in 3 with an even higher prevalence in the FH+ group compared to the FH- group, although significance was not reached. In Israel, PFAPA is found to be most prevalent in Jews of Sephardic descent; however, this is not enough to explain the extremely high carrier rates observed in our cohort. Furthermore, studies have found that those with a family history of PFAPA are more likely to be carriers of genes implicated in PFSs.

It has been hypothesized that heterozygote carriers of PFS gene mutations are in a constant “pro-inflammatory” state and thus are susceptible to triggers that lead to symptoms of system-wide inflammation and the development of PFAPA to which a non-carrier would be immune.
The presence of PFS gene mutations has been shown to impact PFAPA's clinical presentation as well. FMF gene mutations, especially the M694V substitution (most prevalent in our cohort and associated with the most severe phenotype of FMF) has been observed to play a protective role in PFAPA symptomatology such as, shorter PFAPA flares, decreased presence of oral aphthae, and a positive response to lower corticosteroid dosage\textsuperscript{12}. Some researchers believe that the pro-inflammatory state that carriers of PFS genes find themselves in actually raises the threshold for the triggering of autoinflammatory attacks and therefore these patients experience fewer symptoms\textsuperscript{12}.

Other studies indicate that FMF gene mutation carriers have earlier PFAPA disease onset and are more likely to experience symptoms associated with FMF such as abdominal pain, rash and arthralgia during PFAPA flares compared to non carriers\textsuperscript{13}.

In our cohort, those with FH + experience greater rates of myalgia and headache and exhibit better response rates to colchicine compared to the FH- group. All other clinical characteristics between the FH + and FH- were found to be similar or did not reach statistical significance.

In a study performed by Butbul et al. which utilized the same database as in this study, it was found that patients with concurrent clinical FMF and PFAPA experienced myalgia during PFAPA attacks more often then their counterparts with a sole diagnosis of PFAPA\textsuperscript{11}. Although patients with clinical FMF were excluded from this study, the large presence of those with MEFV gene mutations in the FH + group can perhaps explain this phenomenon. Colchicine, the treatment of choice for prophylaxis of FMF flares and prevention of amyloidosis has been shown to be a more effective treatment for PFAPA flare prophylaxis in those with FMF gene mutations\textsuperscript{14}, this may explain partially the differences in the response to colchicine therapy between the FH- and FH + groups.

Data from the family members of the FH + group was collected in the hope to provide further evidence to the hypothesis that families with multiple PFAPA sufferers experience a specific genetic subtype of the disorder that differs from a non-heritable subtype. Shortcomings of the FM group include the mode of data collection and lack of genetic testing. Parents/guardians answered a telephone questionnaire about the child’s PFAPA experience without the patient ever being examined by one of the physicians involved in this study. Presence of recall and information biases has been shown to be present in parents with more than one child with the same disease. Repeat contact with the health care system instils symptom awareness and knowledge that is usually absent when a family is experiencing a disease for the first time and this can lead to over reporting of symptoms. FMs were not genetically tested for MEFV mutations (or for mutations in other PFS-causing genes) and it is not known whether FMs contain these mutations in the same proportion as their relatives in the FH + group. This information could aid in further elucidating whether a FH of PFAPA is associated with genetic mutations in FMF or other PFS genes.

**Conclusion:**
Demographic, clinical, and genetic data of patients in the FH+ and FH- groups does demonstrate differences, namely increased rates of myalgia and headache during flares, increased rates of M694V mutations, and increased response rates to colchicine in the FH+ group compared to the FH- group. When further comparing family members of the FH+ group to the FH+ group itself, the only difference discovered was that of increased arthralgia in the FM group. When comparing the FMs to the FH- group, increased rates of oral aphthae, arthralgia, myalgia, and family history of FMF were observed.

Taken together, the data does indicate that those with positive FH for PFAPA demonstrate some clinical differences from those with no FH. However, there is not enough evidence to clearly state that these two groups experience a different subset of PFAPA.

The increased rates of M694V FMF mutations in those with a positive family history should be explored further and genetic testing for family members should be completed so that a clearer picture of this association can be depicted. Prescribing colchicine as a prophylaxis for PFAPA attacks should be considered in those with a family history of the disease, and especially those who are carriers for mutation(s) in their MEFV gene.

**Abbreviations**

FH+: positive family history; meaning having at least one family member with a diagnosis of PFAPA

FH-: negative family history; meaning having no family members with a diagnosis of PFAPA

FM: Family member

**Declarations**

**Ethical approval and consent to participant**

Each hospital's local Helsinki Committee (REB no. 0318-16 RMB and 104-16-RMC) approved the study.

Verbal consent was received from the participants in the family member (FM) group.

**Supporting data:**

There is no supporting data to include.

**Competing interests:**

There are no competing interests to report.
Funding:

No funding was received for this study.

Author’s contributions:

Tamar Veres curated data from the family members, analyzed the data, and wrote the first draft of this manuscript. Gil Amarilyo M.D. and Yonatan Butbul Aviel M.D. collected data from the initial PFAPA patients and supervised the analysis and writing of this work. Yonatan Butbul Aviel M.D. reviewed and edited this manuscript.

Sabreen Abu Ahmad M.D., Maryam Abu Rumi M.D., Riva Brik M.D., Nofar Hezkelo M.D., Orly Ohana M.D., and Yoel Levinsky M.D. collected data from the initial PFAPA patients and provided professional insight. Professor Gabriel Chodick PhD was involved in the methodology and analysis of the data provided in this study.

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**Tables**

Table 1
Demographic characteristics of FH- and FH+ groups

|                | Group 1; FH- N = 185 | Group 2; FH+ N = 31 | P-value |
|----------------|-----------------------|---------------------|---------|
| Gender         |                       |                     |         |
| Male           | 111 (60%)             | 22 (71%)            | P = 0.32|
| Female         | 74 (40%)              | 9 (29%)             |         |
| Consanguinity  | 8 (4%)                | 1 (3%)              | P = 0.81|
| Origin         |                       |                     |         |
| Ashkenazi Jewish | 13 (7%)              | 3 (10%)             | P = 0.22|
| Sephardic Jewish | 66 (37%)             | 15 (50%)            | P = 1.00|
| Mix Sephardic & Ashkenazi Jewish | 57 (32%) | 9 (30%) | P = 0.099 |
| Arab           | 43 (24%)              | 3 (10%)             |         |

Table 2
Symptoms experienced during episodes

|                | Group 1; -FH N = 185 | Group 2; +FH N = 31 | P-value |
|----------------|----------------------|---------------------|---------|
| Pharyngitis    | 170 (92%)            | 29 (100%)           | P = 0.23|
| Adenitis       | 88 (48%)             | 19 (65.5%)          | P = 0.11|
| Aphthous stomatitis | 62 (33.5%)     | 12 (43%)            | P = 0.39|
| Abdominal pain | 91 (49%)             | 11 (41%)            | P = 0.54|
| Headache       | 23 (12%)             | 8 (32%)             | P = 0.016|
| Myalgia        | 35 (19%)             | 15 (56%)            | P = 0.001|
| Arthralgia     | 29 (16%)             | 6 (23%)             | P = 0.39|
| Rash           | 11 (6%)              | 2 (8%)              | P = 0.66|
Table 3
Treatment and response among PFAPA patients with and without family history of PFAPA

|                               | Group 1: -FH | Group 2: +FH | P-value   |
|-------------------------------|-------------|-------------|-----------|
| N = 185                       | N = 31      |             |           |
| Treatment with steroids       | 169 (96%)   | 28 (97%)    | P = 1.00  |
| Treatment with cimetidine     | 8 (4%)      | 1 (3%)      | P = 1.00  |
| Treatment with colchicine     | 46 (27%)    | 11 (37%)    | P = 0.28  |
| Treatment with montelukast    | 6 (3%)      | 4 (13%)     | P = 0.039 |
| Treatment with tonsillectomy (with/without adenoidectomy) | 11 (6%) | 1 (3%) | P = 1.00 |
| Episode resolves with use of steroids | 133 (87%) | 22 (92%) | P = 0.74 |
| Episode shortened with use of steroids | 149 (99%) | 22 (96%) | P = 0.25 |
| Increased episode frequency with steroids | 63 (45%) | 7 (33%) | P = 0.35 |
| Episode frequency after steroids (in weeks) | 2.5 [1.5-4] | 2.0 [2-3] | P = 0.90 |
| Episode stop/less frequent with cimetidine | 2/8 (25%) | 0 | P = 1.00 |
| Episodes stop/less frequent with colchicine | 24/46 (52%) | 9 /11(82%) | P = 0.096 |
| Episode stop/less frequent with montelukast | 3/6 (50%) | 2/4 (50%) | P = 1.00 |
| Episodes cease with tonsillectomy (with/without adenoidectomy) | 3 (21.4%) | 0 | P = 1.00 |
Table 4
Clinical and demographic data of family member of with a history of PFAPA (FM)

|                      | Family members; |
|----------------------|-----------------|
|                      | N = 24          |
| Gender               | 19:5            |
| Male: Female         |                 |
| Consanguinity        | 0               |
| Origin               | N = 23          |
| Ashkenazi Jewish     | 3 (13%)         |
| Sephardic Jewish     | 12 (52%)        |
| Mix Ashkenazi/Sephardic Jewish | 4 (17%) |
| Arab                 | 4 (17%)         |
| Age at presentation of first symptoms | 3 [2-4.5] |
| Age at diagnosis     | 4 [3-5.5]       |
| Duration of episode in days | 4 [3–6] |
| Interval between episode in weeks at presentation | 4 [3–4] |
| Maximum fever during flare | 40.2 ± 0.67 |
| Pharyngitis          | 20 (91%)        |
| Adenitis             | 14 (64%)        |
| Aphthous stomatitis  | 15 (68%)        |
| Abdominal pain       | 15 (68%)        |
| Headache             | 0               |
| Myalgia              | 14 (64%)        |
| Arthralgia           | 14 (64%)        |
| Rash                 | 1 (5%)          |
| Family history of FMF | 9 (45%)        |

Figures
Of the 273 patients in the original database, 53 were eliminated from the study due to a diagnosis of FMF. Patients were then stratified into two groups based on the presence of at least one relative with a diagnosis of PFAPA. 185 patients had no family members with PFAPA while 31 (14.3%) had positive family history. Four patients were eliminated due to unknown family status (Fig -1).