



# The Impact of Hypo Allergic Diet to Control of Fever Attacks in Children with Periodic Fever, Aphthous Stomatitis, Pharyngitis, Cervical Adenitis (PFAPA)

Shiari R<sup>1,\*</sup>, Khave LJ<sup>2</sup>, Mirzaee AZ<sup>3</sup>, Shiari S<sup>3</sup> and Babaei D<sup>4</sup>

<sup>1</sup>Mofid Children's Hospital, Department of Pediatric Rheumatology, Shahid Beheshti University of Medical School, Iran

<sup>2</sup>Shahid Beheshti University of Medical School, Faculty of Medicine, Iran

<sup>3</sup>Masih Daneshvari Hospital, Shahid Beheshti University of Medical School, Faculty of Medicine, Iran

<sup>4</sup>Mofid Children's Hospital, Department of Immunology and Allergy, Shahid Beheshti University of Medical School, Iran

\*Corresponding author: Shiari R, Professor of Pediatric Rheumatology, Department of Pediatrics, Mofid Children's Hospital, Shahid Beheshti University of Medical Science, Tehran, Iran; Tel: +98-21-22227033; E-mail: [shiareza@yahoo.com](mailto:shiareza@yahoo.com)

## Abstract

**Background:** Periodic Fever, Aphthous stomatitis, Pharyngitis, and Cervical Adenitis (PFAPA) is the most common cause of periodic fever syndrome in childhood.

**Objectives:** Although steroids are effective in controlling fever episodes, no medication has proved to be helpful for the prophylaxis of febrile episodes.

**Methods:** Herein, we evaluated the allergic profile in 33 confirmed cases of PFAPA and its correlation to PFAPA occurrence, symptoms, and role in treatment.

**Results:** In the skin prick test studies, a few allergens demonstrated a larger proportion in the study population and probably stronger associations with PFAPA occurrence.

**Conclusions:** It is essential to educate patients and their families on the management of food allergies and to review their risk of developing fever attacks in PFAPA patients..

**Keywords:** Periodic fever; Aphthous stomatitis; Pharyngitis; PFAPA; Allergy

## Introduction

The syndrome of periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) is the most common auto inflammatory periodic fever disorder first described in 1987 for the first time [1-2]. The condition is characterized by regular episodes of high fever ( $\geq 39^{\circ}$ ), often mentioned as clockwork mechanism [3], every 3 to 8 weeks with completely asymptomatic intervals in between generally starting before the age of five (2). The fever is accompanied by at least one of the three cardinal signs: aphthous stomatitis, pharyngitis, and cervical adenitis.

Other heterogeneous clinical features such as headache, skin rashes, arthralgia, gastrointestinal symptoms and others may be present [4]. In fact, PFAPA seems to have a broader spectrum of manifestations than previously assumed [5]. The incidence has been reported 2.3 cases per 10000 in a Norwegian study, yet the worldwide epidemiologic patterns may differ [6]. The pathogenesis of the disease is yet to be discovered. Though numerous studies have explored the hereditary patterns of the disorder [8-9], genetic background [10-17], inflammatory and prop-inflammatory cytokines role in the diseases course, environmental factors associated with the syndrome [18] and

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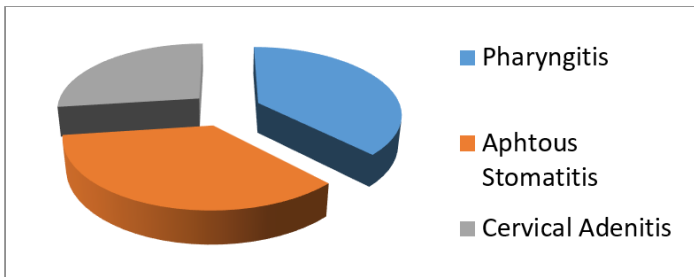
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potential involvement of microbiological agents [19], the precise cause of PFAPA remains unclear and with no specific diagnostic biomarker, the diagnosis is only based on clinical judgments and criteria [20,21]. Considering the unclear role of inflammation in the development of the syndrome, there may be a link with other disorders involving dysregulated immune responses and inflammation namely allergies which has not yet been studied in the medical literature. Allergy is defined as an abnormal atypical immune response directed against non-infectious environmental substances (allergens), characterized by the role of allergen-specific IgEs, T helper 2 cells and other cytokines [22] and correlation to many disorders is coming to light every day. Despite the benign and self-limited nature of the disease, maintaining normal growth and development [23,24], adulthood relapses have been reported [25] and symptoms may persist for years. Also, notable negative impacts on life quality and psychosocial functioning are worrisome. [26] In this study, we aimed to assess the allergic profile (via prick test) in 33 confirmed cases of PFAPA and its correlation to PFAPA occurrence, symptoms and role in treatment.

## Methods

### Study population and Design

Thirty-three patients with confirmed PFAPA diagnosis, treated in a Clinic of Pediatric Rheumatology were enrolled in the study retrospectively between 2020 and 2021. All patients were less than 10 years of age. Patients were selected if they met the Thomas, 1999 criteria as described in (Table 1).



**Figure 1:** Frequency of cardinal signs in patients with PFAPA.

All other diagnosis was excluded through the course of routine check-ups. Serum cytokine profiles, neutrophil activation during attacks and genetic profiles were taken into consideration in diagnostically difficult cases. The medical records gathered included demographic data, medical history, disease onset and course, signs and symptoms, family history, laboratory findings and treatment measures. All patients went through a prick test and had a complete genetic and allergy analysis profile under investigation. A large wheal was considered as a true allergy. If no wheal appears, it was unlikely that there was allergic to the test. The study was approved by the Shahid Beheshti University of Medical Sciences Ethics Committee.

## Results

The study reviewed medical records of 33 patients diagnosed with PFAPA based on the Thomas et al, 1999 criteria. The baseline characteristics of the patients are presented in (Table 1). A total of 18 patients were male (54.54%). The mean age of patients was 3.29 (SD 1.28) at the onset of fevers (87.8% under the age of 5) and 4.48 at the time of final diagnosis of PFAPA. The mean interval between each flare up is 31 days (ranging between 2 to 7 weeks) and the mean duration of fever was 4.07 days with mean body temperature measuring 39.9°. All patients had at least one of the three cardinal clinical manifestations. Aphthous stomatitis presented in 78.7%, pharyngitis in 84.8% and cervical adenitis in 60.6%. Other symptoms included exudative pharyngitis (69.6%), arthralgia (27.2%), myalgia (12.1%), skin rashes (12.1%), and headache (18.1%). Gastrointestinal symptoms included abdominal pain (81.8%), nausea and vomiting (12.1%) and diarrhea (6.06%) (Table 2).

**Table 1:** Thomas criteria for PFAPA diagnosis.

1	Regular recurrent fevers with <5 years of age of onset
2	Constitutional symptoms in the absence of upper respiratory infection, malignancies, autoimmune diseases, or hereditary autoinflammatory Diseases with at least 1 of the following cardinal signs: Aphthae Cervical lymphadenitis Pharyngitis
3	Exclusion of cyclic neutropenia
4	Completely asymptomatic interval between episodes
5	Normal growth and development

**Table 2:** Frequency of cardinal signs in patients with PFAPA.

Clinical findings	Pharyngitis	Aphthous stomatitis	Cervical adenitis
Percentages	84.40%	78.80%	60.60%

**Table 3:** Prick test Results.

Allergen	Proportion	Std. Err.	[95% Conf.	Interval]
Trees	0.193548	0.072131	0.046237	0.34086
Birch	0.032258	0.032258	-0.03362	0.098138
Grass mixture	0.225807	0.076337	0.069907	0.381706
Weeds mixture	0.129032	0.061205	0.004034	0.25403
Rye grass	0.032258	0.032258	-0.03362	0.098138
Bermuda grass	0.032258	0.032258	-0.03362	0.098138
Timothy	0.032258	0.032258	-0.03362	0.098138



Ragweed	0.032258	0.032258	-0.03362	0.098138
Russian thistle	0.032258	0.032258	-0.03362	0.098138
Sycamore	0.032258	0.032258	-0.03362	0.098138
Cladosporiom	0.032258	0.032258	-0.03362	0.098138
Aspergillus	0.064516	0.044853	-0.02709	0.156118
Alternaria	0.032258	0.032258	-0.03362	0.098138
Penicillium	0.032258	0.032258	-0.03362	0.098138
Pteronyssinus	0.258065	0.079889	0.09491	0.42122
Farina	0.258065	0.079889	0.09491	0.42122
Cat	0.096774	0.053978	-0.01346	0.207012
Dog hair	0.129032	0.061205	0.004034	0.25403
Cockroach	0.096774	0.053978	-0.01346	0.207012
Mosquito	0.032258	0.032258	-0.03362	0.098138
Corn moth	0.032258	0.032258	-0.03362	0.098138
Feather mix	0.032258	0.032258	-0.03362	0.098138
Egg-Y	0.225807	0.076337	0.069907	0.381706
Egg-W	0.193548	0.072131	0.046237	0.34086
Beef	0.193548	0.072131	0.046237	0.34086
Walnut	0.193548	0.072131	0.046237	0.34086
Peanut	0.290323	0.082873	0.121074	0.459571
Almond	0.129032	0.061205	0.004034	0.25403
Garlic	0.096774	0.053978	-0.01346	0.207012
Pepper green	0.032258	0.032258	-0.03362	0.098138
Pepper black	0.096774	0.053978	-0.01346	0.207012
Shrimp	0.096774	0.053978	-0.01346	0.207012
Tuna	0.096774	0.053978	-0.01346	0.207012
Banana	0.096774	0.053978	-0.01346	0.207012
Strawberry	0.032258	0.032258	-0.03362	0.098138
Cereals	0.16129	0.067151	0.024151	0.29843
Potato	0.16129	0.067151	0.024151	0.29843
Tomato	0.322581	0.085347	0.148279	0.496882
Cocoa	0.064516	0.044853	-0.02709	0.156118
Wheat	0.129032	0.061205	0.004034	0.25403
Rice	0.290323	0.082873	0.121074	0.459571
Soya	0.193548	0.072131	0.046237	0.34086
Chicken	0.096774	0.053978	-0.01346	0.207012
Sesame	0.258065	0.079889	0.09491	0.42122
Cow milk	0.129032	0.061205	0.004034	0.25403
Barley	0.129032	0.061205	0.004034	0.25403
Hazelnut	0.032258	0.032258	-0.03362	0.098138
Pistachio	0.032258	0.032258	-0.03362	0.098138

The past medical history of patients with a higher focus on disorders with an allergic pathophysiologic basis was gathered and showed a considerable co-occurrence with PFAPA: 81.8% had previous allergies; 24.2% reported Dermatitis and 66.6% reported GERD; 9% had Asthma. History of similar signs and

symptoms in first and second degree family members was 12.1% and only one case of autoimmune disorders (3%) in the family was reported. In the skin prick test studies, a few allergens demonstrated a larger proportion in the study population and probably stronger associations with PFAPA occurrence. These allergens are as followed: Overall allergy to trees was 0.19 (SD 0.072), to grass mixture was 0.22 (SD 0.076) and to weed mixture was 0.12 (SD 0.061). Birch, Rye grass, Bermuda grass, timothy, ragweed and Russian thistle and sycamore among botanical allergens all had a proportion of almost 3% each in our study population. In the animal, dust and danders allergies, allergy to mites (d pteronyssinus and d farina was reported in one-quarter of patients followed by dog hair with 12% in the second place and other allergens showed in (Table 3). In the food allergen category, tomato was the most common (32.2%), followed by rice and peanut (29.03%), sesame (25.8%), egg yolk (22.58%) – vs egg white (19.35%) - and other allergens seen in (Table 2). Positive allergy test for cow milk was seen in 12.9% of the population and green paper, strawberry, hazelnut and pistachio had the lowest distribution: approximately 3%.

## Discussion

In this study we analyzed the frequencies of various allergens in children with PFAPA. In the food allergen category, tomato was the most common (32.2%), followed by rice and peanut (29.03%), sesame (25.8%), egg yolk (22.58%) – vs egg white (19.35%)- and other allergens seen in Table 2. Positive allergy test for cow milk was seen in 12.9% of the population and green paper, strawberry, hazelnut and pistachio had the lowest distribution: approximately 3%. These results suggest that there is considerable association between allergies and attacks of fever in PFAPA which need for further investigation. In 27 patients, treatment (Singular and cimetidine) along with allergen contact cessation resulted in complete regression of fever episodes, suggesting the effective role of allergy control of fever in PFAPA patients. The baseline characteristics of the patients are presented in Table 1. A total of 18 patients were male (54.54%), compatible to the slight male sex preference of the disorder in the previous studies [27-29].

## Conclusions

Although food allergy is rarely the etiology of PFAPA, it is important to monitor allergic diet because they have a higher risk of developing PFAPA. It is essential to educate patients and their families on the management of food allergy and to review their risk of developing fever attacks in PFAPA.

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