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ORIGINAL ARTICLE

Altered serum antibody levels in children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis

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ABSTRACT

Objectives: This study aimed to extend the literature by analyzing immunoglobulin (Ig) A, IgE, IgG, IgG2, IgG3, and IgM antibody levels in periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) patients.

Patients and methods: This study retrospectively analyzed the antibody test results of 20 pediatric patients (10 males, 10 females; mean age: 2.5±1.5 years; range, 0.5 to 5.4 years) with and without flare who were initially evaluated for a number of underlying diseases due to periodic fever/infectious symptoms but then diagnosed with PFAPA between January 2015 and December 2020. Antibody levels were determined by chemiluminescence microparticle immunoassay. The results were retrospectively compared with a group of healthy children after the PFAPA diagnosis was confirmed.

Results: The chemiluminescence microparticle immunoassay revealed 35%, 65%, 20%, 86.6%, and 55% of PFAPA cases with low serum levels of IgA, IgG, IgG2, IgG3, and IgM respectively, while 56.2% had high IgE levels. Moreover, low serum levels of at least two antibody classes or subclasses were reported in 80% of the PFAPA children. While cases with low IgG serum levels were with the highest incidence rates among the low IgG3 PFAPA patient population, both high IgE and low IgM cases were common in the rest of the patients.

Conclusion: Our results suggest an association between PFAPA and low serum antibody levels, particularly of IgG3. Future studies are needed to confirm our conclusion.

Keywords: Antibody, IgG3, immunoglobulin, PFAPA, serum.

The periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is an autoinflammatory disease named according to its characteristic fever flares associated with pharyngitis, adenitis, or aphthous stomatitis in the absence of any infection and is the most common cause of periodic fever among children population. It is a self-limited condition of early childhood (below 5 years of age) that can be managed most effectively by corticosteroids and tonsillectomy and generally fades away before adulthood.[1]

While the syndrome was initially thought to be a monogenic autoinflammatory disease, exome sequencing results revealed no common mutation shared by the PFAPA patients.[2] Nevertheless, the higher prevalence of the syndrome among family members with PFAPA implies the inheritance of genetic predisposition to the disorder.[3,4] Previously demonstrated risk mutations for PFAPA included those associated with inflammasome and immune dysregulation, such as NLRP3, CARD8, IL-12A, STAT4, IL10, and CCR1-CCR3.[5-12] HLA (human leukocyte antigen) alleles were also suggested as

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risk factors for PFAPA,[11] which further implies a possible role played by microbial organisms. This was further supported by studies showing altered tonsillar microbial population between PFAPA and control subjects.[13,14] Nevertheless, today there is no microorganism or external/internal factor identified as the cause of the syndrome.

PFAPA was also associated with variants of the MEFV (Mediterranean fever) gene, the causative mutation for familial Mediterranean fever (FMF). The gene encodes a pyrin protein with regulatory roles in inflammasome activity, which leads to elevated interleukin (IL)-1β levels when mutated. Both PFAPA and FMF are thought to share a common pathogenesis as the presence of MEFV variants were suggested to reduce symptom severity, delay disease onset, and shorten episode duration in PFAPA patients.[15,16] PFAPA subjects were also shown to display elevated IL-1 production during febrile episodes and exhibit prompt clinical response to recombinant IL-1 receptor antagonists.[7,17] In addition, colchicine therapy, which is an effective prophylactic treatment for FMF, has been shown to reduce the number of attacks in PFAPA patients.[6,18] Moreover, both syndromes display clinical and laboratory similarities, including episodes of fever and abdominal pain, which makes their differential diagnosis challenging, particularly in endemic countries.[19]

Flare attacks in PFAPA patients were previously associated with lymphopenia, which was thought to be due to recruitment of T cells to peripheral tissues, leading to lymphoid hyperplasia and, consequently, tonsillitis and cervical adenitis. In the same study, elevated serum levels of T helper 1 (TH1) cells, and proinflammatory cytokines were detected during symptomatic phase of the syndrome.[20] Moreover, compared to those with recurrent tonsillitis, PFAPA children exhibited elevated TH1 and reduced T helper 2 (TH2) cytokine levels during flare attacks, while the former group of patients were associated with elevated TH2 cytokine secretion only.[21] Similar oscillation in cytokine and chemokine levels, with increased production of proinflammatory mediators, was observed during afebrile phases,[22] which were also reported to display elevated tonsillar cluster of differentiation (CD)8+ T cell levels.[23] In contrast to the studies on the cellular branch of adaptive immunity, literature on antibody production in PFAPA subjects is still not consistent. While some reports demonstrated IgA, IgE, IgG, and IgM production in PFAPA patients within the normal range, others observed lowered or elevated levels in PFAPA children.[4,24-30] Furthermore, IgA deficiency was suggested as a clue for the diagnosis by recent case studies.[29,31] On the other hand, in two studies and a case report on antibody levels during afebrile periods, IgA, IgG, and IgM levels were within the healthy range.[4,27,32]

To our knowledge, no study has monitored the serum levels of IgG subclasses. The present study aimed to fill this gap in literature by analyzing antibody levels, including IgA, IgE, IgG, IgG2, IgG3, and IgM, in the blood samples collected from PFAPA patients. The obtained results would not only contribute to the literature on the immune status of the affected subjects but also to our understanding of PFAPA pathogenesis.

PATIENTS AND METHODS

All patients admitted to the department of pediatrics of the Near East University Faculty of Medicine Hospital Hospital with periodic fever/infectious symptoms are routinely evaluated for a number of underlying diseases, including recurrent beta-streptococcus tonsillitis, periodic fever syndrome (FMF, PFAPA), cyclic neutropenia, and primary immunodeficiency (PID). Data of patients admitted with recurrent fever and diagnosed as PFAPA between January 2015 and December 2020 was retrospectively gathered from the patient files and the hospital database system. Diagnosis of PFAPA and exclusion of other disorders were performed according to the Marshall criteria modified by Thomas et al.[30] Consequently, 20 PFAPA patients (10 males, 10 females; mean age: 2.5±1.5 years; range, 0.5 to 5.4 years) were included in the study.

The antibody levels in blood samples, which were obtained from later-confirmed PFAPA patients during the disease flare or at the attack free period, were retrospectively analyzed in this study. Antibody levels were detected by chemiluminescence microparticle immunoassay. The blood samples were allowed to clot at room temperature before centrifugation at 9,000 rpm

for 10 min. Serum samples were then separated and analyzed using a kit from Abbott Diagnostics (Abbott, Chicago, IL, USA) and automated immunoassay analyzer (Abbott Architect ci4100; Abbott, Chicago, IL, USA) for IgA, IgE, IgG, IgG2, IgG3, and IgM detection. The antibody levels were categorized as low (if <2 standard deviations), high (if >2 standard deviations) or normal according to the age-matched corresponding reference values from the healthy pediatric population.[33]

Statistical analysis

Data were analysed quantitatively by using Microsoft Excel.

RESULTS

No patient displayed any abnormal growth or development. The mean onset and diagnosis ages of the patients were 2.5±1.5 years and 3.6±1.6 years, respectively. None of the cases exhibited any cyclic neutropenia, clinical findings of PID, or positive throat culture during febrile attacks. All patients were asymptomatic between episodes. Tonsillectomy (TE) was performed on nine children, all of whom did not experience any flare attack after the operation. The remaining patients responded to steroid treatment during febrile attack with no need for any additional treatment (Table 1).

At the time of blood sample collection, none of the children had white blood cell and absolute neutrophil counts below the corresponding age-specific mean values. The numbers of children with lymphocyte levels lower and higher than the normal range were three (15%) and one (5%), respectively. Fourteen (70%) children had high C-reactive protein levels, and 11 (55%) displayed elevated erythrocyte sedimentation rates.

Evaluation of antibody levels in PFAPA children during afebrile period

While all 20 PFAPA patients included in the study had IgA, IgG, and IgM antibody testing, the numbers of children with IgE, IgG2, and IgG3 test results were 16 (80%), 15 (75%), and 15 (75%), respectively. The IgA, IgG, and IgM-based immunoassay analysis revealed seven (35%), 13 (65%), and 11 (55%) cases with low IgA, IgG, or IgM levels, respectively. Among the children with IgG2 and IgG3 test results, three (20%) displayed low IgG2 levels, while 13 (86.6%) had an IgG3 titer below the corresponding reference values. Serological immunoassay also reported nine (56.2%) children with high IgE levels (Tables 2, 3).

Moreover, chemiluminescence microparticle immunoassay results demonstrated 16 (80%)

Table 1. Clinical characteristics of PFAPA patients

Clinical findings	n	%	Median	Min-Max
Febrile attack frequency (day)			15-30	30
Adenitis	4	20		
Aphthous stomatitis	3	15		
Fever	20	100		
Pharyngitis	13	65		
Tonsillitis	20	100		
Familial history of tonsillectomy	2	10		
Attack frequency after steroid treatment			15-60	40
Tonsillectomy performed	9	45		
Number of attacks after tonsillectomy	0	0		

PFAPA: The periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis.

Table 2. Serum antibody levels of later confirmed PFAPA patients obtained on first admission

Antibody class	High/low	Number of cases	Number of children tested (%)
IgA	Low	7/20	35.0
IgG	Low	13/20	65.0
IgG2	Low	3/15	20.0
IgG3	Low	13/15	86.6
IgE	High	9/16	56.2
IgM	Low	11/20	55.0

PFAPA: The periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis; Ig: Immunoglobulin.

PFAPA patients with altered serum levels of two or more antibody classes or subclasses. Among the remaining four patients, data on all serum antibody levels were available only from two, who displayed only low IgM or low IgG3 concentrations. Data on serum IgG2 and IgG3 levels were not available for the other two patients, one of whom displayed only high IgE levels, while no abnormality in serum antibody levels was detected in the other (Table 3).

Table 3. Antibody test results obtained from the PFAPA patients

Patient no	IgA levels	IgE levels	IgG levels	IgG2 levels	IgG3 levels	IgM levels	Number of antibody class or classes with altered levels
1	Normal	N/A	Normal	Low	Low	Low	>2
2	Normal	Normal	Normal	Normal	Normal	Low	1
3	Normal	High	Low	Normal	Low	Low	>2
4	Low	N/A	Low	Normal	Low	Normal	>2
5	Low	N/A	Low	Low	Low	Normal	>2
6	Normal	High	Low	Normal	Low	Low	>2
7	Normal	High	Low	N/A	N/A	Normal	>2
8	Normal	Normal	Normal	Normal	Low	Normal	1
9	Low	N/A	Low	N/A	N/A	Low	>2
10	Normal	Normal	Low	Normal	Low	Low	>2
11	Low	High	Normal	Normal	Normal	Low	>2
12	Normal	Normal	Low	Low	Low	Low	>2
13	Normal	Normal	Low	Normal	Low	Low	>2
14	Normal	High	Low	Normal	Low	Normal	>2
15	Normal	Normal	Normal	N/A	N/A	Normal	0
16	Low	Normal	Low	Normal	Low	Normal	>2
17	Low	High	Low	Normal	Low	Normal	>2
18	Normal	High	Normal	N/A	N/A	Normal	1
19	Normal	High	Low	Normal	Low	Low	>2
20	Low	High	Normal	N/A	N/A	Low	>2

PFAPA: The periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis; Ig: Immunoglobulin.

Table 4. Comparison of antibody levels between the two groups of PFAPA patients

	Low IgA n/N		High IgE n/N		Low IgG n/N		Low IgG2 n/N		Low IgG3 n/N		Low IgM n/N	
IgG3 status	n	%	n	%	n	%	n	%	n	%	n	%
Low IgG3 (n=13)	4/13	30.8	5/10	50	11/13	84.6	3/13	23.1	-	-	7/13	53.8
Normal + N/A data (n=7)	3/7	42.9	4/7	57.1	2/7	28.6	0/2	0.0	-	-	4/7	57.1

PFAPA: The periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis; Ig: Immunoglobulin; N and n represent number of tests and number of samples, respectively.

The patients were broadly divided into two categories depending on the status of serum IgG3 levels. A low serum IgG3 had the highest incidence rate (n=13/15, 86.6%) detected among the PFAPA patients. Of the 13 PFAPA subjects with low serum IgG3 levels, low levels of IgA, IgG, and IgM antibodies were detected in four (30.8%), 11 (84.6%), and seven (53.8%), respectively. Moreover, IgE and IgG2 test results were available from 10 and 13 of these low IgG3 PFAPA subjects, among which five (50%) and three (23.1%) showed high IgE and low IgG2 serum concentrations, respectively (Table 4).

The second group involves seven PFAPA patients with either normal IgG3 levels or unavailable corresponding data. All seven members were tested for serum IgA, IgE, IgG, and IgM levels, whereas an IgG2 test was performed only on two children. Of these seven participants, low IgA, high IgE, low IgG, low IgG2, and low IgM concentrations were detected in three (42.9%), four (57.1%), two (28.6%), none, and four (57.1%), respectively (Table 4).

DISCUSSION

While there have been various reports demonstrating unregulated adaptive immune reaction in PFAPA patients, data on antibody production in PFAPA patients is not consistent due to studies showing both altered and unaltered antibody levels in the affected children.[4,24-30] The present study aimed to contribute to the area of research by retrospectively analyzing serum levels of IgA, IgE, IgG, and IgM in addition to that of IgG2 and IgG3 antibodies of later-confirmed PFAPA patients, which were not previously monitored.

Among the PFAPA patients studied, the rate of children with reduced IgG3 production was the highest, followed by those with low IgG, high IgE, and low IgM levels. When divided into two groups depending on the IgG3 status, most of the low IgG3 PFAPA patients were reported to display low IgG serum levels, while high IgE and low IgM serum levels had the highest rates for the rest of the PFAPA patients studied. This suggests the potential role of IgG3 in the pathogenesis of PFAPA syndrome. Studies with a higher sample size are required for confirmatory data.

In our study, all PFAPA patients except for one displayed lower antibody levels of at least one antibody class or several classes. This correlates with two previous studies demonstrating lower B-cell frequencies and smaller germinal centers in PFAPA tonsils compared to controls, which were concluded to suggest a minor role for B cells in the disease pathogenesis.[34,35] While low serum antibody levels detected in our study imply an association with PFAPA, whether they are the cause or the consequence of the syndrome needs more detailed analysis. This can be addressed by future studies evaluating antibody (particularly IgG3) specificity against specific antigens in the tonsillar microbiome by approaches similar to those using multipathogen array,[36] which would provide a valuable contribution to our understating of PFAPA pathogenesis.

IgG3 deficiencies comprise one of the most commonly diagnosed forms of IgG subclass deficiencies.[37] IgG3 is the third most dominant IgG subclass in human serum, which, together with IgG1, is also a potent activator of innate immune effector cells. However, IgG3 has higher phagocytosis and complement deposition capacity compared to the IgG1 subclass, which suggests its induction as a key marker for protection.[38]

Accordingly, IgG3 deficiency was associated with recurrent respiratory tract infections.[39]

Apart from increased susceptibility to infectious agents, deficiency in antibody production, including IgG subclasses, was also associated with atopy in the affected individuals.[40] Accordingly, high rates of asthma was previously detected in children with IgG3 deficiencies.[41] In our study, high serum IgE levels were detected in at least half of all PFAPA population and those with low IgG3 levels. While elevated serum IgE levels are detected in many conditions of immune dysregulation, they were also suggested to increase susceptibility to recurrent skin and lung infections.[42]

Nevertheless, to our knowledge, there has not been any report on the association of PFAPA with any other clinical condition. Prospective investigations evaluating any clinical consequences of disturbed antibody levels in the affected children are recommended to investigate the possible coexistance of PFAPA with other clinical conditions. Such studies may lead to the revision of clinical management guidelines to improve life quality of the affected children, which was demonstrated to be poor, with increased fatigue, by a recent study.[43] Moreover, fatigue is overrepresented in primary antibody deficiencies and was correlated with the need for immunoglobulin replacement therapy.[44]

The major limitation of our study is the low sample size and the lack of a control group. The present data on antibody levels was obtained from later-confirmed PFAPA patients among pediatric population who were screened for the underlying condition of recurrent fever/infection to rule out PID, recurrent beta-hemolytic tonsillitis, cyclic neutropenia or PFAPA, or other periodic fever syndromes. Since it was a retrospective study, it was not possible to include a control group and perform multiple measurements to see whether the reported altered levels were reverted. Therefore, future studies are required to both confirm our conclusions and evaluate the temporality of the low serum levels of antibodies detected.

In conclusion, this preliminary study suggests that there may be an association between PFAPA and low serum levels of antibodies, particularly IgG3, for the first time. Further controlled studies with a larger sample size are needed to evaluate whether hypogammaglobulinemia is the cause or the consequence of PFAPA syndrome. Moreover, studies on the association between serum antibodies and altered microbiome structure on PFAPA tonsils, the primary site for the immune dysregulation during the syndrome, are strongly encouraged to further enlighten the role of humoral immunity in PFAPA pathogenesis.

Ethics Committee Approval: The study protocol was approved by the Near East University Scientific Research Ethics Committee (date: 24.06.2021, no: YDU/2021/92-1358). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from the parents and/or legal guardians of the patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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