



C-reactive protein and procalcitonin during febrile attacks in PFAPA syndrome

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ABSTRACT

Objectives: To assess the levels of procalcitonin (PCT) and C-reactive protein (CRP) in children diagnosed with PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis) during their febrile attacks.

Methods: 23 patients with diagnosis of PFAPA included into the study prospectively during a three years period. In these patients, CRP and PCT values were recorded during 78 febrile episodes. Furthermore, 20 patients with diagnosis of pneumonia were chosen as a control group and their CRP and PCT values were measured. Normal reference values for CRP and PCT were 0–10 mg/L and 0–0.5 ng/mL, respectively.

Results: Mean CRP and PCT values of patients with PFAPA were 94.8 ± 71.6 mg/L and 0.29 ± 0.14 ng/mL, respectively. In control group, mean CRP value was 153.2 ± 26 mg/L and PCT was 1.59 ± 0.53 ng/mL. CRP and PCT were high in control group. CRP was detected high and PCT was normal in PFAPA. Compared to control group, in PFAPA group, CRP values were not significantly ($p > 0.05$) and PCT values were significantly lower ($p < 0.001$).

Conclusion: During febrile episodes in the patients with diagnosis of PFAPA, CRP values were substantially elevated, whereas PCT values were within normal levels. Concomitant assessment of CRP and PCT in addition to clinical diagnostic criteria may be of help in making diagnosis and distinguishing febrile attacks from infections. However, studies in larger groups are required.

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1. Introduction

PFAPA syndrome is a clinical entity of unknown etiology characterized by periodic episodes of high fever accompanied by aphthous stomatitis, pharyngitis/tonsillitis, and cervical adenitis [1] (Table 1). High fever usually occurs in every three to eight weeks on a regular basis. The fever often last for three to six days. The other symptoms may include nausea, vomiting, headache, abdominal pain, muscle pain, diarrhea, arthralgia, cough, coryza, and rash [2,3]. Diagnosis of PFAPA is based on the presence of suggested clinical criteria in addition to the exclusion of other periodic fever syndromes [2]. Although the clinical manifestations of this condition have been well-described, the lack of specific laboratory results complicates the making of proper diagnosis [4–7]. In PFAPA patients, distinguishing a fever attack due to bacterial infection from a fever attack due to noninfectious inflammation is a major difficulty [7]. Early diagnosis and treatment of PFAPA can help avoid the unnecessary use of antibiotics. It can also make the

patient comfortable. Therefore, cost-effective, rapid and reliable tests are needed. CRP and PCT proved to be promising in some studies [7,8]. There is limited number of studies where CRP and PCT are evaluated together. We aim to assess CRP and PCT values together in patients diagnosed with PFAPA during their febrile episodes (Figs. 1 and 2).

2. Material and method

Twenty-three patients diagnosed with of PFAPA followed up at the pediatric clinic of Private Sema Hospital between June 2008 and January 2011 were enrolled in the study. The ethical committees of our institutes approved the study protocol and the guardians of all the patients gave their informed consent. Diagnosis was made in accordance with the international criteria suggested by Thomas et al. [1]. At least three febrile episodes of the recruited patients were followed up. Demographic, clinical, and laboratory data of the patients were recorded (total 78 febrile attacks). Means of obtaining samples differed according to the patients' day of admission. Patients who had infections and were suspected to have other causes of periodic fever were excluded from the study. Twenty patients who had definite diagnosis of infection (pneumonia, $n: 20$) were selected as control group. The CRP and PCT values of these patients were also measured. The CRP

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Table 1
Diagnostic criteria for Marshall's/PFAPA syndrome (Thomas et al. [1]).

Regularly recurring fevers with an early age of onset (<5 years of age)
Symptoms in the absence of upper respiratory tract infection with at least one of the following clinical signs:
a) Aphthous stomatitis
b) Cervical lymphadenitis
c) Pharyngitis
Exclusion of cyclic neutropenia
Completely asymptomatic interval between episodes
Normal growth and development

levels were assessed using the nephelometric method (Image Immunochemistry System, Beckman Coulter), and the PCT levels were measured using fully automated electrochemiluminescence immunoassay (ECLIA) (Hitachi Cobas 6000). Normal reference values for CRP and PCT were 0–10 mg/L and 0–0.5 ng/mL, respectively. SPSS 13.0 package program was used in data analysis. The CRP and PCT levels of both groups were compared using the

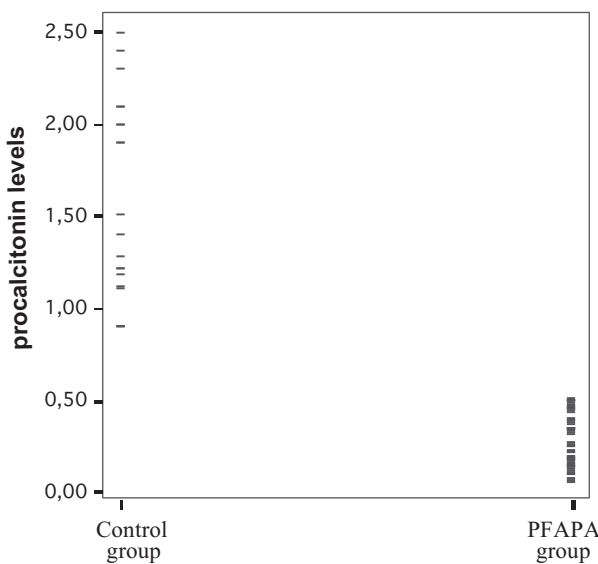


Figure 1. The distribution of PCT in PFAPA and the control group.

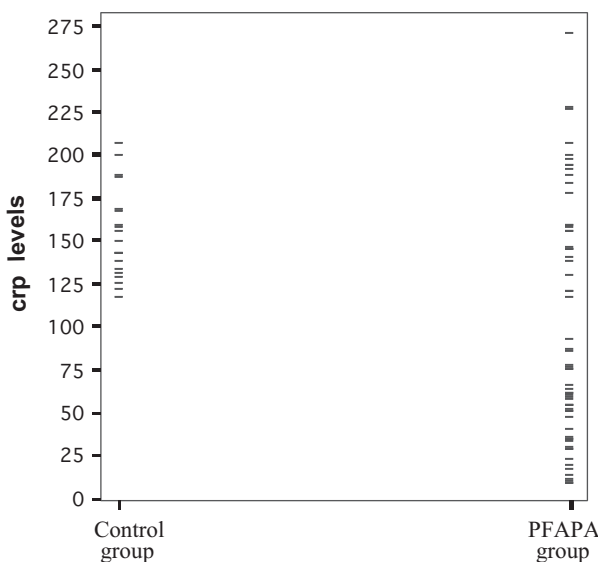


Figure 2. The distribution of CRP in PFAPA and the control group.

Table 2
Signs and symptoms in 23 patients who were associated with PFAPA febrile episodes.

Symptoms	n	%	Signs	n	%
Fever	23	100	Fever	23	100
Throat pain	19	82.6	Pharyngitis	21	91.3
Neck swelling	13	56.5	Exudative tonsolitis	18	78.2
Agitation	12	52.1	Cervical lymphadenitis	18	78.2
The other symptoms	9	39	Aphthous stomatitis	15	65.2
			The other signs	12	52.2

Mann–Whitney *U* test. A *p* value of <0.05 was considered to be statistically significant.

3. Results

Of the 23 patients enrolled in the study, 13 were male and 10 were female. The mean age was 4.1 ± 3.8 years and the mean duration of diagnosis was 2.3 ± 1.0 years. The average duration of fever was 5.11 ± 1.26 days and average time between attacks was 5.55 ± 1.01 weeks. The symptoms and signs of the condition are shown in Table 2. In the laboratory investigation, the throat cultures showed no growth. Epstein Barr Virus (EBV) serology, adenovirus and influenza virus pharyngeal swab results were negative. There was no significant elevation in the serum immunoglobulin levels. Chest X-rays were normal. White blood cell numbers were $14.6 \pm 5.3 \times 10^3/\text{mm}^3$. The mean CRP value was 94.8 ± 71.6 mg/L and the mean PCT value was 0.29 ± 0.14 ng/mL. 12 of the patients in control group were female and 8 were male. Their mean age was 3.70 ± 1.56 years. The average number of leukocytes was $15.6 \pm 4.3 \times 10^3/\text{mm}^3$. The mean CRP and PCT values were measured as 153 ± 26 mg/L and 1.59 ± 0.53 ng/mL, respectively.

4. Discussion

Diagnosis of PFAPA is made in accordance with the clinical criteria after exclusion of other syndromes associated with periodic fever [1]. The clinical signs and symptoms are defined better with each passing day [9–12]. Nevertheless, there are no special tests to help with diagnosis [9]. Moderate leukocytosis ($13.6 \pm 4.5 \times 10^3/\text{mm}^3$) with prominence of neutrophils in PFAPA was reported in the literatures [1,9]. An increase in the number of monocytes and a decrease in the numbers of eosinophils during febrile episodes and thrombocytosis during afebrile period were reported as a new finding [13]. The erythrocyte sedimentation rate (ESR) can be normal at the beginning of feverish period but it can increase in consequent days [9]. The immunoglobulin levels are usually found to be normal [9]. In some studies Ig D levels were reported to be high [1,14]. There were no significant increases in the immunoglobulin levels of our patients in whom immunoglobulin levels were measured. CRP is increased during the entire feverish period and it made a peak in the 2nd and 4th days compared to the first day of episode in FAPA [8,9,13]. In our study, the CRP values were found to increase during the episodes of fever of PFAPA patients and in the control group. These tests are not specific for PFAPA. PCT correlates with bacterial load and severity of the infection [15,16]. Procalcitonin concentrations do not increase in correlation with the increase of other acute-phase reactants during an attack, a finding that may be unique to PFAPA patients [7,13]. Yoshihara et al. found that the levels of CRP were moderately elevated while procalcitonin was normal during the febrile attacks in children with PFAPA [7]. In our study, PCT values were found to be within normal limits during the fever attacks of our PFAPA patients. In the control group, these were increased ($p < 0.001$).

In conclusion, during the febrile episodes of the patient diagnosed with of PFAPA, the CRP values increased while the PCT level remained within normal limits. Concomitant assessment of CRP and PCT in addition to clinical diagnostic criteria may help in

coming up with a diagnosis and in distinguishing febrile attacks from infections. However, studies in larger groups are required.

Conflict of interest

The authors confirm that there is no conflict of interest in relation to this paper.

Financial disclosure

None.

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