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Araştırma

Procalcitonin Levels in PFAPA Syndrome

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Procalcitonin Levels in PFAPA Syndrome

Objective: *To investigate procalcitonin (PCT) levels during febrile attacks in children diagnosed with the Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis Syndrome (PFAPA).*

Material and Method: *A total of 39 cases with 91 febril episodes and 35 cases with bacterial septicemia were included in the study. Demographic, clinical, and laboratory data were collected. Hemogram, C-reactive values (CRP) and PCT values of all patients were measured.*

Results: *In the study group with PFAPA, average duration of fever was 4.6±0.85 days, and the average time between attacks was 25.06±9.76 days. The mean white blood cell (WBC), CRP and PCT values were found to be 15.959±5.737/mm^3, 76.88±47.63 mg/L, and 0.18±0.10 ng/mL respectively. Throat cultures in the PFAPA group showed no growth. Twenty patients in the control group were female and 15 were male. The average WBC count was 16.700±5.820/mm^3. The mean CRP and PCT values were measured as 34.64±18.2 mg/L and 2.12±1.95 ng/mL, respectively. While the mean WBC values did not significantly differ between the two groups (p>0.05), PCT levels were significantly higher in the controls compared to the PFAPA group (p<0.001).*

Conclusion: *During febrile episodes in patients diagnosed with PFAPA syndrome, CRP values increased, while PCT values remained within normal levels. Concomitant assessment of CRP and PCT, in addition to clinical diagnostic criteria, may help distinguish febrile attacks from infections.*

Keywords: *C-reactive protein, fever, PFAPA, procalcitonin*

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PFAPA Sendromunda Prokalsitonin Düzeyleri

Amaç: *PFAPA sendromu tanısı konan çocuklarda febril atak sırasında prokalsitonin (PCT) düzeylerinin araştırılması.*

Gereç ve Yöntem: *Çalışmaya 91 ateşli atak geçiren toplam 39 vaka ile bakteriyel septisemi tanısı konan 35 vaka kontrol grubu olarak alındı. Demografik, klinik ve laboratuvar bulguları kaydedildi. Her iki grupta hemogram, CRP ve PCT değerleri araştırıldı.*

Bulgular: *Çalışma grubunda atak süresi ort 4,6 ±0,45 gün olup atak sıklıkları arasındaki süre ort 25,06±9,76 gün olarak saptandı. Çalışma grubunda ortalama lökosit, CRP and PCT değerleri sırasıyla 15,959±5,737/mm^3, 76,88±47,63 mg/L ve 0,18±0,10 ng/mL bulundu. PFAPA sendromlu hastalarda boğaz kültürlerinde üreme saptanmadı. Kontrol grubundaki vakaların 20'si kız, 15'i erkekti. Ortalama lökosit sayısı 16,700±5,820/mm^3 saptanırken, CRP değeri ise 34,64±18,61 mg/L, PCT düzeyi 2,12±1,95 ng/mL ölçüldü. Lökosit değerleri açısından iki grup arasında fark bulunamazken (p>0,05), PCT değerleri kontrol grubunda anlamlı düzeyde yüksekti (p<0.001).*

Sonuç: *PFAPA sendromunda ateşli epizodlar sırasında PCT değeri yükselmemektedir. Tanı kriterlerine ek olarak CRP ile eşzamanlı PCT düzeyinin bakılması febril atağın bakteriyel enfeksiyonlardan ayıredilmesinde kullanılabilir.*

Anahtar kelimeler: *Ateş, CRP, PFAPA, prokalsitonin*

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INTRODUCTION

First described by Marshall in 1987, PFAPA is characterized by episodes of fever lasting three to six days, with a recurrence every three to eight weeks, and is associated with at least one of three main signs: aphthous stomatitis, cervical adentitis, and pharyngitis [1]. Usually, it is clinically diagnosed after other probable causes of fever, such as infection, have been excluded.[2]. Studies on PFAPA's pathogenesis are ongoing and no monogenic trait or other specific laboratory marker has been found [3]. Early diagnosis and treatment of PFAPA can help to avoid the unnecessary use of antibiotics; therefore, cost-effective, rapid, and reliable diagnostic tests are needed. Both CRP and PCT levels increase in

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response to proinflammatory cytokines such as 1β, IL-6 and TNF-α, which are also involved in the pathomechanism of PFAPA attacks [4]. Besides, elevated CD64 serves as a potential biomarker for the diagnosis of PFAPA [5]. Lastly, CXCL10 was shown to be elevated during febrile episodes of PFAPA but not during other periodic fever syndromes or infectious conditions [6]. CRP and PCT proved to be promising in the diagnosis of PFAPA in some studies [7-10]. A limited number of studies exist where CRP and PCT have been evaluated together to diagnose this syndrome. To aid in the development of objective criteria for diagnosis, the aim of our study is to assess CRP and PCT values during febrile episodes associated with PFAPA syndrome.

MATERIAL and METHODS

Between October 2012 and October 2017, 39 patients with 91 febrile attacks diagnosed with PFAPA syndrome according to the international criteria suggested by Thomas et al, were enrolled and followed up in this prospective study conducted at the Istanbul Medipol University, Department of Pediatrics, outpatient clinic. Demographic, clinical, and laboratory data were collected. Throat cultures were obtained from all participants. Patients who had infections and were suspected to have other causes of periodic fever were excluded from the study. From the cardiovascular intensive care unit (ICU), 35 patients who were diagnosed as bacterial sepsis due to growth in hemoculture were included as control group, and the CRP and PCT values of these patients were measured. The CRP levels were measured using the nephelometric method (Image Immunochemistry System, Beckman Coulter), and the PCT levels were measured using fully-automated electrochemiluminescence immunoassay (ECLIA) (Cobas). The detection limit was 0.02 ng/ml for PCT. Normal reference values for CRP and PCT were 0–6 mg/L and 0–0.5 ng/mL, respectively. MEFV mutation determination was planned in the patients with PFAPA syndrome.

The local ethics committee approved the study protocol, and informed consent was obtained from all patients' parents or guardians.

In statistical comparisons between the two groups, independent sample t-tests, for equal variances or non-equal variances, were used when the distribution was normal. The statistical significance level was considered as $p<0.05$. All analyses were performed using Windows® statistical software package (SPPS).

RESULTS

We determined the serum PCT concentrations in 39 patients (21 males and 18 females with a median age of 2.66 years [range 1.5–7.1 years]) with the PFAPA syndrome, and in 35 controls (median age of 2.1 years [range 1–4 years]) with septicemia. In the study group with PFAPA, average duration of fever was 4.6±0.85 days, and the average time between attacks was 25.06±9.76 days. Selected demographic characteristics and laboratory findings in both groups are shown in Table 1. Throat cultures in the PFAPA group showed no growth. The WBC count was 15.959±5.737/mm^3, the mean CRP value was 76.88±47.63 mg/L, and the mean PCT value was 0.18±0.10 ng/mL. Twenty patients in the control group were female and 15 were male (median age of 26.2±15.7 months). The average WBC count was 16.700±5.820/mm^3. The mean CRP and PCT values were measured as 34.64±18.2 mg/L and 2.12±1.95

Table 1. Characteristics of study and control groups.

Item	Study Group	Control Group	P
Age, mean±SD	2.66±1.12 (1.5–7.1)	2.2±1.3 (1–3.5)	0.84
Gender, n (%)			
Female	18 (48.5)	20 (57.1)	0.24
Male	21 (51.5)	15 (42.9)	0.29
Leucocyte (WBC)/mm^3	15,959±5,737	16,700±5,820	0.21
C-reactive protein (CRP), mg/dl	76.88±47.63	34.64±18.61	0.054
Procalcitonin (PCT), ng/ml	0.18±0.10	2.12±1.95	0.0003

ng/mL, respectively (Table 1). While the mean WBC values did not significantly differ between the two groups (p=0.21), PCT levels were significantly higher in the controls compared to the PFAPA group (p=0.0003).

MEFV mutation in four cases could be investigated and in two cases heterozygous MEFV gene mutation was detected.

Intravenous or oral 1 mg/kg metilprednisolon were used in all of cases. Fever attacks were stopped after this therapy in twelve patients. Twenty-one subjects had significantly longer fever free intervals with corticosteroid treatment. Six patients didn't respond to metylprednizolon therapy and underwent tonsillectomy. PFAPA symptoms at 3 months follow-up in patients who underwent operation didn't appear again.

DISCUSSION

PFAPA syndrome represents the most common type of recurrent fever in childhood. Diagnosis of PFAPA is made when the clinical criteria of other syndromes, associated with periodic fever, are excluded [1,12]. Symptoms of our patients are shown in Table 2.

Table 2. Signs and symptoms of patients in the PFAPA group.

Sign/Symptom	n (%)
Fever	39 (100)
Tonsillitis	37 (94.2)
Pharyngitis	30 (85.7)
Throat pain	22 (62.5)
Lymphadenitis	21 (60.0)
Abdominal pain	8 (22.8)
Vomiting	7 (20.0)
Aphthous stomatitis	7 (20.0)
Headache	6 (17.1)

Although the clinical manifestations of this condition have been well-described, no specific diagnostic tests for the PFAPA syndrome are available [13-15]. The origin of fever, bacterial or not, in PFAPA is important [15]. During flares, patients usually present with an elevation of WBC with preponderance of neutrophils and acute-phase reactants [12]. In our study, the CRP and WBC values increased during the fever episodes in PFAPA patients and in the control group. None of these tests are specific for PFAPA.

PCT is a more accurate biomarker than traditional screening tests for identifying young febrile infants and children with serious bacterial infections [16].PCT concentrations do not rise in correlation with the increase of other acute-phase reactants during an attack, a finding that may be unique to PFAPA patients [17]. Yoshihara et al. found that levels of CRP were moderately elevated while PCT was normal during febrile attacks in children with PFAPA [10]. In our study, while PCT values were found to be within normal limits during the fever attacks in the study group, they were significantly increased in the control group.

MEFV mutation in four cases could be investigated and in two cases heterozygous MEFV gene mutation was detected. PFAPA syndrome is an immune mediated disease characterized by a cytokine dysfunction moreover, the strong familial clustering suggest a potential genetic origin of the syndrome [3,9-11]. The presence of variants in inflammasome related genes, mostly in NLRP3 and MEFV, suggest a possible role of these genes in PFAPA pathogenesis. In our study, 4 patient had heterozygote MEFV mutation [18]. In a study conducted in our country, heterozygote MEFV mutation was detected at 66%. When compared to the non-mutated group, there was no difference in symptoms and clinical course [19].

Since PFAPA has a benign and self-limiting course, treatment should be limited to glucocorticoids or other symptomatic antipyretic drugs. One or two doses of prednisone (1-2 mg/kg) or betamethasone (0.1-0.2 mg/kg) can dramatically stop fever attacks in a few hours [20,21]. Some studies have shown that prophylaxis against fever attacks with colchicine or cimetidine may be effective [16,22]. In a small series, five children with PFAPA were treated with a single dose of anakinra [interleukin-1 (IL-1) receptor antagonist] on the second day of fever, and all showed a prompt clinical and laboratory response [20]. In another study, treatment with montelukast (leukotriene receptor antagonist) was empirically shown to reduce the frequency of fever cycles in some patients with PFAPA [23]. All of these cases had methylprednisolone therapy during acute attacks (12 responded to this treatment and 6 did not). The non-responsive group (six cases) underwent tonsillectomy. Tonsillectomy should be reserved only for selected indications [24,25].

In conclusion, during the febrile episodes of patients diagnosed with PFAPA in our series, CRP values increased while PCT levels remained within normal limits. Concomitant assessment of CRP and PCT levels, in addition to clinical diagnostic criteria, may help in the differential diagnosis of febrile attacks from infections.

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