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Original Article

Clinic entity that should not be forgotten in children with high fever; PFAPA syndrome

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Abstract

Aim: PFAPA syndrome which we thought was not well recognized. The high fever clinic of PFAPA syndrome usually mimics infectious conditions therefore it can lead to unnecessary and costly diagnostic tests and treatments. We evaluated the medical history, clinical findings and outcomes of pediatric patients diagnosed with PFAPA syndrome

Material and Methods: In Mustafa Kemal University, Faculty of Medicine, Department of Pediatrics between September of 2016 and 2017, demographics, clinical, laboratory, diagnosis and treatment data of our patients diagnosed with PFAPA syndrome were retrospectively reviewed.

Results: 68 patients were studied in our study, of which 27 (39.7%) were females and 41 (6.2%) were males. The mean age at onset of symptoms was 21.7 months. The mean age of diagnosis was 34.9 months. The mean duration between episodes of the disease was 27.05 days and the mean duration of episodes was 4.91 days.

Conclusion: PFAPA syndrome which causes unnecessary costly examinations and treatments should be kept in mind in high fever clinic and also medical treatment was found to be effective in patients with PFAPA syndrome.

Keywords: Child; Medical Treatment; PFAPA Syndrome; Periodic Fever.

INTRODUCTION

Body temperature is normally 36.6-37.9 °C in rectal measurement and it is defined as high fever if it is above 38 degrees (1). One of the most common clinical symptoms in childhood is fever. It is unusual for infants and children to have episodes of fever that recur in certain periods. Repeated fever is defined being periodic fever attacks that higher than 38.4 ºC, three or more times in six month and no explanation of patology (2-4). Classic periodic fever syndrome is cyclic neutropenia that its recurrence every 21 days with clinic of neutropenia, fever and recurrent infections (4-6).

Periodic fever syndromes are characterized by recurrent episodes of fever, in which children are completely healthy between the episodes (3,4,7,8). PFAPA (periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis) syndrome was first reported in 1987 by Marshall et al. Characteristic feature of PFAPA syndrome; Aphthous stomatitis, pharyngitis and cervical lymphadenopathy are seen together with a high fever that starts before the age of 5, repeats every 3-6 weeks, lasts for a mean of 5 days, starts suddenly and can reach up to 41°C (3,4,8). Long-term sequelae were not identified in patients who were completely healthy between attacks (3,5,8) There are no specific laboratory findings in PFAPA syndrome and patients are clinically diagnosed (3,4,8).

PFAPA syndrome which we thought was not well recognized. The high fever clinic of PFAPA syndrome usually mimics infectious conditions therefore it can lead to unnecessary and costly diagnostic tests and treatments. We evaluated the medical history, clinical findings and outcomes of pediatric patients diagnosed with PFAPA syndrome

MATERIAL and METHODS

In faculty of medicine, department of pediatrics between October 2016 and March 2018, demographics, clinical, laboratory, diagnosis and treatment data of our patients diagnosed with PFAPA syndrome were retrospectively reviewed. This study was approved by the ethical committee. The authorization number and tha date are 18153 and March 22, 2018, respectively.

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The diagnosis of PFAPA syndrome was diagnosed according to the modified clinical criteria of Marshall et al (3), these criterias:

1) Regularly recurring fevers with an early age of onset (<5 years of age).
2) 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.
3) Exclusion of cyclic neutropenia.
4) Completely asymptomatic interval between episodes.
5) Normal growth and development

All patients' anamnesis, initial examinations and follow-up physical examinations and treatment responses were evaluated. Patients with positive MEFV mutations were not included in our study.

After diagnosis, all patients were called for clinical follow-up for 6 months. Medical records were collected.from hospital records, patients and families.

Medical data included: demographic data, medical history of patients and family members, characteristics of episodes, evaluation of laboratory findings, used drugs until diagnosis, efficacy and side effects of drugs. The family was interviewed periodically by telephone and information was obtained about clinical findings.

Initial examination findings of patients who were diagnosed with PFAPA syndrome were recorded. Hemogram parameters, liver, kidney function tests, C reactive protein (CRP), urine test, Anti streptolysin O (ASO), cultures of blood, urine and throat were evaluated.

Prednisolone (oral or intramuscular) was given during the episode. After 2-3 hour monitoring, patients with well-being were discharged. All parents were informed about illness and treatment.

RESULTS

Of the 68 patients in our study, 27 (39.7%) were females and 41 (60.2%) were males. Thirty four patients which have PFAPA findings and MEFV gene positivity, excluded from the study.

Neurodevelopmental evaluation of all patients (tonic neck reflex, ability to sit supported, ability to sit unsupported) and percentile values (height, weight, head circumference) were consistent with age.

The mean age at onset of symptoms was 21.7 months. The mean duration that from the onset of illness to diagnosis was 13.2 months. The mean age of diagnosis was 34.9 months. The mean duration between episodes of the disease was 27.05 days and the mean duration of episodes was 4.91 days. In addition, the average fever during the episode of disease was 39.4 degrees.

Patients were admitted to the hospital until diagnosis an average of 6.82 times a year. There was no difference the seasonal distribution of the attacks of the disease (15 patients in the spring, 16 patients in the summer, 18 patients in the winter, and 19 patients in autumn). We found that patients who misdiagnosed with cryptic tonsillitis and received antibiotic and antipyretic treatment 7.54 times a year in any health facility in our study were no response to treatment (Table 1).

Table 1. Demografic data and features of attacks in patients with PFAPA syndrome

Features	n
Number	68
Female	27(%39.7)
Male	41(%60.2)
Familial history of PFAPA	-
Mean age at onset of symptoms(month)	21.7(7-48)
Duration from onset of illness to diagnosis(month)	13.2(5-24)
Mean age of diagnosis(month)	34.9 (14-60)
Interval between episodes(day)	27.05 ± 6.6(15-35)
mMean duration episodes(day)	4.91 ± 1.03(3-7)
Mean grade of fever during the episode(°C)	39.4 ± 0.5(39-41)
Number of admission to the hospital(per year)	6.82(3-12)
Number of received treatment until diagnosis(per year)	7.54(5-14)

We also found that during the episodes of the patient's illness, they used antipyretics (paracetamol, ibuprofen, methimazole) for 48 to 72 hours, but no clinical response.

In the first examinations of patients; fever (100%), pharyngitis (100%), tonsillitis (100%), aphthous stomatitis (77.9%) and lymphadenopathy (76.4%) were present. In addition, 7 patients had abdominal pain and 4 patients had joint pain (Table 2).

Table 2. Clinical features in patients with PFAPA syndrome

Features	n(%)
Fever	68(%100)
Tonsillitis	68(%100)
Pharyngitis	68(%100)
Aphtous stomatitis	53(%77.9)
lymphadenopathy	52(%76.4)
Abdominal pain	7(%10.2)
Joint pain	4(%5.8)
Elevation acute phase protein	68(%100)
Response to prednisolone	62(%91.1)
Response to Colchicine	-
Response to tonsilloadenoidectomy	6/6(%100)
Number of persistant complication	-

Blood, urine and throat cultures and antistreptolysin O tests taken during high fever were negative in all of the patients. Pathologic laboratory findings such as leukocytosis and elevated CRP were detected in all of the patients.

Five patients did not respond to corticosteroid therapy and tonsilloadenidectomy was performed. No episode of the disease was seen in these patients' follow-up for 6 months. Colchicine treatment was given to a patient who had no response to treatment with corticosteroids. The patient, who had no response despite 6 months of colchicine treatment, underwent tonsilloadenoidectomy and no episode of the disease was observed during the 3 months follow-up after tonsilloadenoidectomy. In our study, 91.1% (n: 62) of all patients responded to steroid treatment.

No complication was observed during the 6-month follow-up of the patients. The follow-up of the patients is ongoing to observe the long-term outcome of the disease.

DISCUSSION

Clinical findings were reported as fever (100%), pharyngitis (88%), cervical lymphadenopathy (77%) and aphthous stomatitis (67%) in literatüre (3,4,9-11). Clinical findings were reported as fever (100%), aphthous stomatitis (68%), pharyngitis (100%) and cervical lymphadenopathy (100%) in the study conducted by Padeh et al (12). Cervical lymphadenopathies; while spreading along the anterior cervical chain, it is usually uncommon in other parts of the body (2,6).

The cryptic tonsillitis clinic with high fever and pharyngitis findings is almost entirely seen in patients. In the literature, reported that the duration between episodes is 28.2 days and the duration of episodes is 4.8 days (2-4). In our study, all patients had sudden onset high fever (mean 39.4 °C) and pharyngitis, %77.9 of patients had aphthous stomatitis, and 74.2% had lymphadenopathy. Consistent with the literature, the mean time between attacks was 27.05 days and the mean duration of attacks was 4.91 days in our patients. Headache, abdominal pain, joint pain, and mild hepatosplenomegaly may rarely accompany to clinical findings on the episodes of disease (3,4,8). In our study, 7 patients had abdominal pain and 4 patients had joint pain. The hepatosplenomegaly was not seen any patient.

Many patients are late diagnosed because of there is not a specific diagnostic laboratory test about PFAPA and the diagnosis can only be made with clinical history and physical examination findings. In addition, patients with late diagnosis are exposed to costly tests and unnecessary antibiotic treatments (3,13). In our study, until the to make of the diagnosis from initial of the clinical findings it was determined that patients applied to the health facility on an average of 6.82 times per year and taking antibiotics, antipyretic treatments on an average of 7.54 times a year.

In PFAPA syndrome episodes begin before 5 years (2.8 years on average) and repeat at 3-6 week intervals (3,8,14). In our study the average time from started of clinical findings to diagnosis of disease was 13.2 months and the mean age of diagnosis was 34.9 months.

PFAPA syndrome is more common seen in boys than in girls (2,12,15). In our study, 41 patients (60.2%) were male and 27 patients (39.7%) were female. This data consistent with the literature.

In PFAPA syndrome, patients are completely healthy between episodes (4,5,8). In addition, the growth and development rates of these children generally normal (2-5,8,14,15). In our study, the percentile values (height, weight, head circumference) of patients were normal, similar to the literature. It was also found that the neurodevelopmental evaluation (tonic neck reflex, ability to sit supported, ability to sit unsupported) of all patients were normal.

Throat culture and rapid streptococcal antigen tests are negative in tonsillitis clinic associated with PFAPA syndrome that does not respond to antipyretics and antibiotics. In addition, blood and urine cultures taken during periods of high fever are also negative. There was no difference the seasonal distribution of the attacks of the disease. It is also reported that during the episodes, the general condition of the children usually does not deteriorate. These data support the view that PFAPA syndrome is not infectious (8,10,12,15,16). In our study, there was no significant difference in the seasonal distribution of the episodes of the disease, and at the same time, throat culture and ASO tests taken during the high fever were found to be negatively similar to the literature. In addition, other culture samples (blood, urine) taken during high fever were seen to be negative in our study consistent with the literatüre (15,17).

Although the fever may fall for a short time, it generally continues high throughout the episodes during that PFAPA syndrome episodes which occurring without prodromal period. Clinical findings do not respond to antipyretics (paracetamol, ibuprofen, metamizole, acetyl salicylic acid) and antibiotics (3,4,7,8,15,18). In our study, it was determined that our patients were misdiagnosed due to high fever and upper respiratory tract infection clinical findings and thus were prescribed antibiotics 7.54 times a year and also the patients used antipyretics for 48-72 hours but no response.

There is no diagnostic laboratory findings in PFAPA (3,8,18,19). However in the literature, it has been shown that acute phase proteins increase the during episodes in patients with PFAPA syndrome and when the fever falls, these acute phase proteins rapidly return to normal levels (3,8,11,16,17,20). In our study, leukocytosis and C-reactive protein elevation were determined in patients during the episodes of the disease, similar to the literature. These data support the view that increase in acute phase proteins during episodes of PFAPA syndrome.

Familial mediterranean fever, hyperimmunoglobulin D syndrome (HIDS), cyclic neutropenia, familial cold

autoinflamatory syndrome (FCAS) and Muckle-Wells syndrome should be considered in the differential diagnosis of PFAPA syndrome. Familial Mediterranean fever was not considered because of there were no clinical signs such as abdominal pain, arthritis, arthralgia, chest pain due to the autoinflamation of serous membranes in our patients during episodes. Hyperimmunglobuline D syndrome was not considered because of normal immunoglobulin levels. Cyclic neutropenia was not considered because of normal neutrophil levels. Familial cold urticaria was not considered because of absence of urticarial rash, conjunctivitis and history of epizodes triggered by cold exposure. MuckleWells syndrome was not considered because of absence of progressive hearing loss and urticaria (3,8,16,21). Although, high-fever episodes that unresponsive to antibiotics, antipyretic treatments and benzathine penicillin protections, the control of clinical signs with single dose corticosteroids is the most important diagnostic criterion in PFAPA syndrome (3,6,7).

High fever and other clinical signs of PFAPA syndrome are not affected by antibiotics and antipyretic treatments. In therapy; it is recommended that single dose prednisolone (1-2 mg/kg/day) Prednisolone may be administered orally or parenterally depending on the clinical condition of the patients (8,13,18,21). The very high fever level in the episodes returns to normal after prednisolone treatment (3,8). At the same time, patients' aphthous stomatitis clinic is rapidly recovered with fever reduction (4). Corticosteroid use is not required again during between episodes (8,18,21).

Studies have been reported in the literature that cimetidine and colchicine may also be effective in the treatment of episodes (4,22). In clinical practice, however, there is no widespread belief that these treatments are effective (23,24).

In the literature, tonsillectomy and / or adenoidectomy is recommended in case of medical treatment failure (7,8,13,25). In various studies, tonsilloadenoidectomy has been accepted as the only permanent treatment method of PFAPA syndrome (8,13,18,21). In our study, prednisolone was administered to 68 patients. It was given as orally to 37 patients and it was given as intramuscularly to other 31 patients too. In 56 of these 68 patients were received clinical response an average of 2.4 hours after steroid treatment. In a patient with no clinical response with corticosteroid treatment, colchicine treatment was administered and no response was obtained. In our study, tonsilloadenoidectomy was applied to total 6 patients that 5 patients who did not respond to corticosteroids and 1 patient who did not respond to steroid+colchicine. There was no seen any clinical findings of the disease in these patients for 6 month follow-up.

In the literature, it has been reported that the incidence and severity of episodes usually decline after 7-8 years of age, even if no operation is performed (26). In a study conducted in our country reported that patients with spontaneous recovery had a mean age of improvement was 8.9 years (27). In our study, we followed our patients for between 6 months to 1 year. For this reason, prospective studies with longer follow-up are needed in order to evaluate the long-term outcome of the disease. Etiology of PFAPA is unclear yet, also there is not any specific diagnostic laboratory test for PFAPA syndrome and the diagnosis can only be made with clinical history and physical examination. For this reason many patients are diagnosed late and the actual incidence of the disease is unknown (3,13).

In our study, the MEFV gene mutation has not been screened despite the findings suggestive of FMF such as abdominal and joint pain. This contradiction is a limitation of the our study.

CONCLUSION

PFAPA syndrome may cause unnecessary costly examinations and treatments in repeated high fever clinic if not kept in mind. A single dose prednisolone at the onset of attacks is effective in the recovery of symptoms. Tonsillectomy or adenotonsillectomy is highly effective in remission of disease. The rate of spontaneous recovery of PFAPA syndrome without any sequelae is very high.

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