Case Report

PFAPA syndrome: a case report

Abdal SJ[a], Yesmin S[b], Shahin MA[c], Islam MA[d], Sarkar B[e]

ABSTRACT

Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome is a complex auto-inflammatory disease characterized by recurrent episodes of fever and systemic inflammatory features. It is usually a disease of children but adult onset has also been reported. The common clinical features are aphthous stomatitis, cervical lymphadenitis, pharyngitis etc with exclusion of upper respiratory tract infection and cyclic neutropenia. The patient remains completely asymptomatic between the episodes of these clinical features with normal growth and development. Here we report a case of 20-year-old male who presented with features suggestive of PFAPA syndrome and well responded with a single dose of high dose prednisolone.

Key words: *Periodic fever, aphthous stomatitis, pharyngitis, lymphadenitis.*

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INTRODUCTION

Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome, is a recurrent fever syndrome of idiopathic etiology. It is characterized by nearly regular episodes of fever, pharyngitis, oral aphthosis and cervical lymphadenopathy. The syndrome was first described in 1987 by Marshall et al, so named after him as Marshall's syndrome.[1] Later in 1989, acronym of PFAPA was proposed.[2] The PFAPA syndrome is the most common of the periodic fever syndromes encountered in children.[3]

It is a big surprise in modern medical science that the etiopathogenesis of PFAPA syndrome is still unknown where the patients present with episodic fever and inflammation mainly restricted to the oropharyngeal tissues with a self-limited course. We report this case of a 20-year-old male patient who presented to us with features suggestive of PFAPA syndrome and with a discussion on clinical features, genetic basis, diagnosis and current trends of management of the disorder.

CASE REPORT

A 20-year-old male student presented with the complaints of recurrent fever and oral ulcer for 10 years and recurrent sore throat for 3 years. According to the statement of the patient, he started to suffer from recurrent episodes of fever starting at the age of 10 years. The fever was high grade, highest recorded temperature was 40.56°C, with diurnal variations and usually subsided sometimes with paracetamol and each episode of fever used to last for 5 to 7 days. The fever was not associated with chills and rigor nor any focal symptoms of infection and used to appear at an interval

Author Information

a. Syed Jamil Abdal, Assistant Professor, Department of Rheumatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

b. Sabrina Yesmin, Associate Professor, Department of Rheumatology, BIRDEM General Hospital, Dhaka, Bangladesh.

c. Md. Abu Shahin, Professor, Department of Rheumatology, BSMMU, Dhaka, Bangladesh.

d. Md. Ariful Islam, Associate Professor, Department of Rheumatology, BSMMU), Dhaka, Bangladesh.

e. Buddhadev Sarkar, Phase-B Resident, Department of Rheumatology, BSMMU), Dhaka, Bangladesh.

Address of correspondence: Syed Jamil Abdal, Assistant Professor, Room no. 1717, Block-D, Department of Rheumatology, *BSMMU), Dhaka, Bangladesh.* Email: sjabdal@gmail.com

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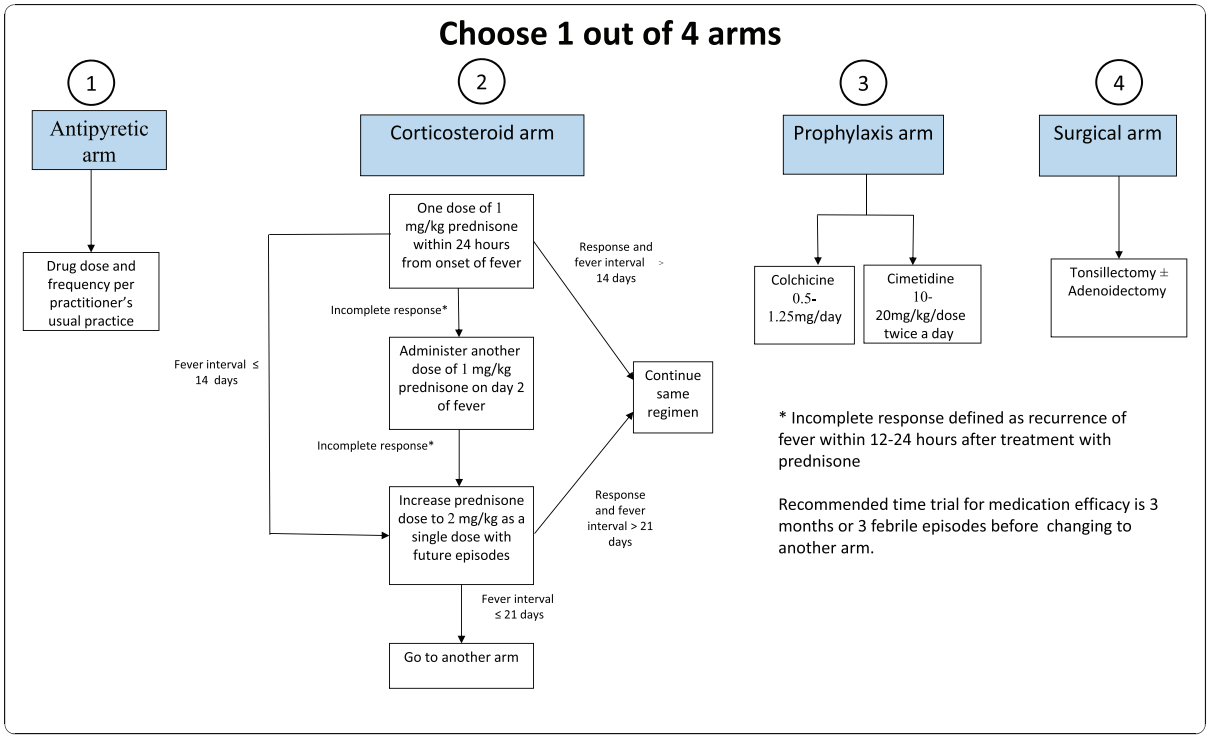

Table:1[14]

of 2 to 8 weeks. The patient gave history of recurrent multiple small oral ulcers that appeared at the onset of fever involving tongue and gum, those were painful, whitish in color had erythematous border, subsiding spontaneously following relief of fever. He took antibiotics like amoxicillin and cefixime on several occasions for sore throat. The patient used to remain asymptomatic between the episodes of fever. There was no family history of such febrile condition. He also complained of low back pain for last three weeks. The previous laboratory reports revealed raised acute phase reactants like full at first ESR, CRP during the episodes of fever without any hematological profile suggestive of cyclic neutropenia.

On physical examination, he had high fever (39.5°C) with all other his vitals were normal, had no other abnormality. There was no focal sign of fever. His physical and intellectual maturity was found to be normal. Investigational workup revealed hemoglobin 12.9 g/dl, ESR 78 mm in 1st hour, total WBC 6700/mm^3, platelet count 330000/mm^3, CRP 9.06 mg/dl (reference value <6mg/dl). His routine urine examination, x-ray chest, echocardiography, ultrasonography of whole abdomen, MRI of both sacroiliac joints found normal. His autoantibodies like rheumatoid factor, ANA were negative. His HLA-B27, viral markers like HBsAg, anti-HCV antibody were also negative. Tuberculosis screening tests were also negative. As per existing expert opinion recommendations, he had not responded well with indomethacin but responded well with a single shot of high dose dose, route? mention prednisolone and discharged with the advice of tonsillectomy that supposed to reduce the episodes of recurrent fever.

DISCUSSION

The PFAPA syndrome, still a syndrome of unknown etiology where infective origin was suspected for the cause of triggering recurrent disease flares. However, features of PFAPA such as unresponsive to antibiotics, corticosteroid induced alleviation of symptoms, unaffected family members during the flares of the patient make this explanation very unlikely. So, plausible explanation could be dysregulated immune system of a genetically predisposed individual responds to an unknown exaggerating trigger.[4] Epidemiologic data for PFAPA remains small. In a Nordic study, incidence is reported as 2.3 per 10,000 children (up to 5 years of age).[5]

Typically, attacks cease by 10 years of age in most patients but a minority continue to have episodes upto adulthood, even some have onset of fever episodes in adulthood.[6, 7] Our patient's attacks appeared at age of 10 and continued beyond 20 year of age.

There are many speculations about the etiopathogenesis of this syndrome but exact etiopathogenesis is still elusive. It is scientifically perceived that multiple genes might play a role in the pathogenesis of PFAPA syndrome as discussed below. Perko et al. reported 27% of variants in *MEFV* and *NLRP3* genes in his cohort of 62 PFAPA patients those proposed as low-penetrant variants. However, these are usually not confirmative for FMF or CAPS but could lead to auto-inflammation. As a result, they might also play a role in the pathogenesis of PFAPA. Besides this, the authors suggested that PFAPA could be associated with multiple low-penetrant gene variants accompanied by epigenetic and environmental ones. In Gattorno's study, three gene variants associated with periodic fever syndromes were analyzed in 199 Italian PFAPA patients: *MVK*, *MEFV*, and *TNFRSF1A*. Sixteen percent were positive for one of the genes whereas 18% carried low penetrance or incomplete genotypes. Explained by Theodoropoulou et al, these findings revealed a polygenic basis for PFAPA with involvement of the inflammasome related genes out of which Q703K showed significantly increased frequency in PFAPA. Similarly, the study of Stojanov et al. showed increased levels of expression in several IL-1 and inflammasome-associated genes during PFAPA flares. Haytoglu et al. found 34.3% *MEFV* gene variants in a PFAPA population though the mutation frequency was reported to be 20% in the healthy population; so, *MEFV* gene variants might be involved in the pathogenesis of PFAPA syndrome. The frequency of E148Q-L110P (a mutant variety of *MEFV* gene) was significantly higher (35%) than that observed in healthy subjects (13%). In Berkun's cohort, PFAPA patients who were carriers of *MEFV* gene mutations had shorter, less regular attacks and lower rates of oral ulcer occurrence compared with PFAPA patients without the mutation. Therefore, a conclusion likely to be reached, genes has an immense influence in the pathogenesis of FPAPA syndrome. Under the genetic influence many chemokines/cytokines have a role in the pathogenesis of FPAPA syndrome like IP10/CXCL10, MIG/CXCL9 and GCSF those are increased serum levels of the disorder and also serum IL-18 levels is found an association with PFAPA flares. Likewise, Luu's cohort of 94 PFAPA patients found transcripts for IL-1RN and TNF were significantly upregulated in PFAPA tonsils showed IL-12A (rs17753641) was found to be strongly associated with PFAPA. Similarly, Manthiram et al. proved a mutation of IL-12A (rs17753641) was found to be strongly associated with PFAPA.[8] Besides this, several class I and class II human leukocyte antigen (HLA) alleles are also significantly associated with PFAPA.[9]

This is not a well-known syndrome of family disorder. Interestingly, Sangiorgi's study in 2019 proved that variants in genes (one variant was consistently present in family members) of the PFAPA auto-inflammatory pathway observed in a family (three relatives and two generations of this family) though a Mendelian inheritance pattern has not been proven yet.[10]

Genomic analyses of familial cases by genome-wide linkage analysis and whole-exome sequencing have not revealed rare variants in a single, common gene for PFAPA.[11]

The PFAPA syndrome is a diagnosis of exclusion that is made on clinical grounds. About our patient, meticulous history taking, thorough clinical examination and extensive investigations could not reach a clinical diagnosis. So far, no universally accepted criteria for the PFAPA syndrome have developed. The criteria for PFAPA published in 1989 ref? included the following features those our patient met:

- Onset of disease in early childhood
- Regularly recurring episodes of fever
- Presence of at least one of these associated features during flares: aphthous stomatitis, pharyngitis, and/or cervical adenitis
- Asymptomatic intervals between flares with normal growth
- Absence of signs of respiratory tract infection during flares and exclusion of cyclic neutropenia, other known periodic fever syndromes, immunodeficiency, or autoimmune diseases.[3]

The management of PFAPA syndrome must be individualized according to the intensity of the damage incurred to the patient's activities of daily life. The goals of treatment are to reduce the number of attacks of symptoms and if possible, to induce remission.[12]

Treating the patients with Non-steroidal anti-inflammatory agents (NSAIDs) and anti-pyretics have shown poor results in alleviating symptoms of PFAPA syndrome. However, glucocorticoids are highly effective in aborting the attacks, but there are limited data on the effectiveness of any preventive medication in PFAPA.[13] So achieving a sustained remission is expected but many times it is difficult to achieve.

A group of expert clinicians (composed of pediatric rheumatologists, infectious disease specialists, allergists/immunologists and otolaryngologists) developed four treatment arms as described below where the group agreed that a particular regimen should be trialed for three febrile episodes to determine efficacy and, if deemed ineffective by the physician and/or family, changed to another arm:

- Symptomatic management with antipyretics, such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs)
- Abortive therapy during episodes with glucocorticoids
- Prophylactic therapy with cimetidine or colchicine
- Surgical therapy with tonsillectomy.

The primary outcome was resolution of fever, categorized as complete (no fevers for 3 months), partial (reduced total number of days with fever over a period of 3 months), and no response (no change or increase in total days of fever over a period of 3 months). The quality of life measured by missed school days and parental global assessment using a visual analog scale (a unidimensional measure of a characteristic or attitude that cannot easily be directly measured and is frequently used in populations with rheumatic diseases). The summary of the opinion is shown in Table:1.[14]

Our patient did not respond to NSAIDs, so the patient was treated with high dose of prednisolone and responded well.

Conclusion

The PFAPA syndrome is a mysterious disorder because the exact pathogenesis is still unknown. The syndrome is a disorder of exclusion since many diseases masquerade the PFAPA syndrome specially other known autoimmune/auto-inflammatory disorder, immunodeficiency (e.g. cyclic neutropenia), malignancy and infection. So, strong vigilant clinical eyes could reach a diagnosis. To date, there are no internationally recognized diagnostic criteria and treatment guidelines where experts' opinions are used for diagnosis and treatment.

Authors' contribution: SJA and SY has planned for the publication. SJA drafted the manuscript. SJA, MAS and MAI were directly involved with the management of the case. BS and SY helped in preparing the manuscript.

Consent: Informed consent has been taken from the patient for publication of this case report.

Conflict of interest: Nothing to declare.

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