world Journal of Otolaryngology

Research Article

Variant periodic fever (VPF) is a rare syndrome characterized by episodes of recurrent fever with multiple constitutional symptoms.

Ryan D Cooperstock*
Department of Child Health, Division Infectious Disease, Immunology & Rheumatology, University of Missouri, USA

Corresponding Author
Ryan D Cooperstock, MD, Department of Otolaryngology - Head & Neck Surgery, University of Missouri, USA,
E-mail: ryandcprstock@health.missouri.edu

Received Date: Feb 27, 2022
Accepted Date: March 02, 2022
Published Date: April 01, 2022

Abstract

Background: Diagnostic criteria for periodic fever, aphthous inflammation, inflammatory disease, and cervical redness syndrome (PFAPA) are challenged, leading to imply compartmentalization. we tend to explore the explanation and treatment response among PFAPA and incomplete periodic fever variants to assess existing therapies among excluded people.

Methods: Periodic fever cases were retrospectively reviewed. A medical specialty communicable disease specialist excluded various diagnoses and phonephone follow-up confirmed knowledge fidelity.

Results: 469 charts were reviewed and thirty one potential cases known. twenty nine people were enclosed with twenty with success contacted. eleven cases met the classic definition (CD), nine had intermittent cardinal symptom(s) (IS), and nine had isolated periodic fever (IPF). Treatment enclosed observation, steroid administration, and/or surgery (tonsillectomy or adenotonsillectomy). Steroids terminated every episode altogether treated patients, 9/11 with CD and 11/18 with IS/IPF. once steroid treatment shortened the inter-episode interval, higher doses reversed this result. With observation or steroid treatment, either spontaneous resolution occurred once a mean of one hundred and five, 54, and thirty six months or episodes persisted once a mean of eighteen, 53, and fifty seven months for CD, IS, and IPF, severally. Surgery resulted during a sustained cure for four patients in every cluster. surgical procedure reduced total malady period within the CD and IPF teams p < zero.01. No individual suffered long-run adverse effects.

Conclusion: Treatment of PFAPA and incomplete variants with steroids dependably terminates acute episodes. surgical procedure alters the explanation of CD and IPF. PFAPA treatments ought to be more investigated for IS and IPF and more analysis is required to definitively characterize these teams.

Keywords

Periodic fever, PFAPA, Tonsillectomy

Key point

PFAPA is that the leading reason behind childhood periodic fever. Treatment includes steroids and/or ablation. Recently, diagnostic criteria are challenged. we tend to report corticoid effectiveness in PFAPA and incomplete variants. ablation considerably alters the malady explanation in each teams.

Introduction

First reportable by Marshall et al. in 1987, periodic fever, aphthous redness, disease, and cervical symptom syndrome (PFAPA) is that the foremost typical reason behind periodic fever in children [1-3]. whereas PFAPA is also a disorder of unknown etiology, native immune pathology or a microorganism reservoir at intervals the tonsils unit of measurement planned as possible mechanisms underlying episodes [2,4]. The incidence is reportable as
2.3 per 10,000 children below age 5 years, with male predominance [5]. identification is made on clinical findings: (1) typically revenant fevers beginning below age five; (2) constitutional symptoms whereas not higher tract infection with a minimum of 1 cardinal symptom (aphthous redness, cervical symptom, inflammatory disease); (3) exclusion of cyclic neutropenia; (4) well between episodes; and (5) ancient growth and development [6]. Periodic fever is that the hallmark of the syndrome, with temperature usually reaching 39°C or higher [4]. each case may need its own inevitable "clockwork" regularity, usually 3-6 weeks, and period, usually 3-7 days [4,5]. Cardinal symptoms, yet as aphthous redness, inflammatory disease, and cervical symptom unit of measurement gift at variable rates, with reports ranging from 38-75%, 65-100%, and 61-100%, severally [2,4,5,7]. Associated symptoms yet as headache, fatigue, vomiting, abdominal pain, and joint pain square measure reportable [4-6,8].
The explanation of PFAPA is also a benign course whereas not long-term complications [5,8]. Skipped episodes unit of measurement determined typically [6-8]. long-term follow-up has been reportable in one series with spontaneous resolution in fifty of fifty 9 patients at a mean of six.3 years [8]. nine individuals recent persisting episodes at a mean follow- up amount of eighteen.1 years [8]. Others have reportable shorter mean amount to spontaneous resolution; however a lower proportion of patients recent resolution in these series [5,6].
Treatment is usually endorsed since symptoms is also uncomfortable and disrupt family life. gastric antacid has been investigated but incontestable restricted effectiveness [6-8]. Oral corticosteroids unit of measurement extraordinarily effective, providing speedy termination of episodes in 84-97% of patients [4,7,8]. In up to 5 hundredth of cases, however, steroid treatment has been associated with shortening of disease-free interval, leading to frequent use in some individuals [4,7]. this could usually be corrected by increasing the steroid dose. Adverse effects have together been reportable in up to 3rd of children [9].

A Cochrane review of surgical treatment (tonsillectomy or adenotonsillectomy) far-famed a pair of irregular controlled studies involving sixty seven children with a four.38 pooled relative risk of symptom resolution [10-12]. Surgical effort in 2010 was planned to require: (1) onset

before age 5 years; (2) regular revenant abrupt episodes of fever lasting regarding five days with a minimum of 1 characteristic feature (cardinal symptom) but whereas not totally different signs of tract infection; (3) prompt remission of symptoms once steroid hormone administration and completely well interval; and (4) ancient growth and development [13]. A final criterion planned to select out the foremost effective candidates includes a minimum of five previous episodes defined by high fever and unknown origin [13]. The potential sensible factor concerning surgical treatment is reflected at intervals the 2011 yank Academy of medicine Head & Neck Surgery (AAO-HNS) Clinical follow Guideline: ablation in children [14]. This guideline recommends that clinicians need to assess children with perennial throat infections for PFAPA, that ablation might even be thought of in certain cases [14]. extirpation, whereas performed in conjunction with ablation in some series, is not curative severally and is felt by some to supply no any value compared with ablation alone [15,16]. Since publication of the AAO-HNS guideline, results of a literature search from 1987-2010 for ablation or adenotonsillectomy for PFAPA syndrome far-famed fifteen studies and 149 children [17]. Operation yielded a pooled complete resolution rate of eighty 3 Associate in Nursingd a meta-analysis of two irregular controlled trials disclosed Associate in Nursing odds magnitude relation for complete resolution of 13 [17]. in Associate in Nursing extremely separate series, Licameli et al. reportable complete resolution in 99/102 patients following adenotonsillectomy for PFAPA [4].

As proof for therapeutic decisions distended, the necessity for consistent diagnostic criteria has increasingly become evident. whole totally different sets of diagnostic criteria square measure used in 10 cohorts with a minimum of twenty 5 PFAPA patients since initial depicted by Marshall in 1987 [18]. individuals with onset once 5 years aged unit of measurement self-enclosed in some series Associate in Nursingd Associate in Nursing adult onset constitution has been planned [4,19]. Surgical treatment has been provided to individuals with periodic fever at intervals the absence of cardinal symptoms [11]. A web-based multicenter cohort reviewed 301 cases, method distinct phenotypic cohorts of PFAPA: a whole cluster and incomplete cluster [18]. supported review of their information, Hofer et al. reportable that the "diagnosis of PFAPA is typically based upon style of variables…that unit of measurement rather additional advanced than the mere satisfaction of the current diagnostic criteria" [18].

We retrospectively reviewed cases of periodic fever at the University of Missouri to assess clarification and treatment response among patients with PFAPA and variants excluded by existing diagnostic criteria.

Patients and ways

Protocol and knowledge assortment

Periodic fever cases were known via retrospective chart review. As no established identification code for PFAPA was out there throughout the chart review amount, Institutional Review Board approval was obtained for review of patient encounters at intervals kid health, medical specialty communicable disease, medical practice, and medicine head and neck surgery with identification codes 023.9 (Brucellosis NOS),087.9 (Relapsing fever NOS), 277.31 (Familial Mediterranean fever), or 780.60 (Fever NOS) treated at intervals the University of Missouri attention System once the implementation of the electronic medical history, from January 2004 to Sept 2013. The came back records were severally reviewed by 2 authors (MDP, RMN) to spot the utmost range of relevant cases and guarantee accuracy of recorded knowledge. Among those with disagreement, a further review was completed to reconcile variations.

Medical record review

The following knowledge points were extracted from medical records:

1. feverish episode onset, duration, interval and course;
2. Age of sure, frequently revenant fevers within the absence of infection onset;
3. Presence and frequency of cardinal and concomitant symptoms, classified as perpetually, sometimes, or ne'er present;
4. Treatment received, outcome, and adverse effects of treatment;
5. Length of follow-up;
6. Age applicable height and weight;
7. medical specialty communicable disease specialist exclusion of differential diagnoses;
8. case history of periodic fever syndrome.

Differential diagnoses were primarily excluded clinically exploitation usually accepted criteria [6,7]. Supplemental laboratory testing, applied in hand-picked cases, enclosed immune gamma globulin levels and genetic testing (Periodic Fever Panel, Gene Dx, Inc.) to exclude polymorphisms within the genes ELANE (ELA2) for neutropenia and Severe noninheritable Neutropenia; LPIN2 for Majeed Syndrome; MEFV for Familial Mediterranean Fever; MVK for Hyper-IgD Syndrome, Mevalonate enzyme Deficiency, and Mevalonic Aciduria; NLRP3 (CIAS1)for Chronic Infantile neurological body covering and body part Syndrome, Familial Cold automobile inflammatory Syndrome, Muckle-Wells Syndrome, infant Onset Multisystem Inflammatory Disease; PSTPIP1 for pathology Sterile inflammatory disease, Pyoderma Gangrenosum, and disease of the skin Syndrome; and tumor necrosis factorRSF1A for Familial Hibernian Fever and TNF Receptor-Associated Periodic Syndrome. once conflicting info regarding the presence of symptoms was documented, phonephone follow-up knowledge was wont to reconcile variations. within the case of conflicting knowledge while not phonephone follow-up knowledge, the surgical analysis was accepted. see table one for inclusion criteria.

Classification of periodic fever

Patients were classified into one amongst four teams supported chart review:

1. Complete constitution with all cardinal symptoms gift at the time of every periodic fever episode;
2. Incomplete constitution with a minimum of one amongst the cardinal symptoms gift at the time of every periodic fever episode;
3. Incomplete constitution with intermittent cardinal symptom-(s) (all cardinal symptoms absent throughout some periodic fever episodes) (IS);
4. Isolated periodic fever with no cardinal symptoms throughout periodic fever episodes (IPF). For the needs of knowledge analysis, teams one and a pair of, that meet the normal definition of PFAPA, were combined into the classic definition (CD) cluster.

Telephone follow-up

To ensure the accuracy of knowledge and extend follow-up, extra Institutional Review Board approval was obtained for phonephone follow-up with families of known cases. a regular survey script was used, and knowledge was gathered by one author (CIN). knowledge was compiled and variations were reconciled with re-review of the medical history and extra discussion with family.

Treatment

Individuals received no treatment (observation), oral sex hormone, or surgical medical aid. At the beginning of the study amount, people treated with steroids got Pediapred or Orasone one mg/kg/dose double daily for 2 days starting at the onset of symptoms. after, dosing was modified to one 1-2 mg/kg dose, with Associate in Nursing choice for a repeat dose once twelve hours. Extracapsular extirpation or adenotonsillectomy was performed in every surgical case.

Outcome assessment

Resolution was outlined because the halt of all feverish episodes. Termination was outlined because the abrupt finish of Associate in Nursing episode, no matter ulterior occurrences. return was outlined because the come back of periodic fever episodes once a hiatus of 1 or a lot of episodes. no matter past recurrences, people were classified within the resolution cluster if in progress episodes stop.

The CD, IS, and IPF teams were assessed singly. The feverish episode characteristics, clinical findings, treatment response, and explanation were documented. The impact of extirpation or adenotonsillectomy on total symptom period was compared to non-surgical treatments at intervals every diagnostic cluster.

Statistical analysis

Descriptive statistics square measure wont to summarize knowledge and stratify response to treatment. analysis of variance testing with Bonferroni correction (SigmaPlot) compared multiple teams and 2 sided t-test (Excel) compared 2 teams. applied mathematics significance was outlined by $p < zero.05$.

Results

Four hundred sixty nine records were came back and reviewed. Thirty one come-at-able cases were better-known with two excluded as a results of different etiologies of periodic fever had not been wholly dominated out (Figure 1). Genetic testing was negative altogether cases throughout that it completely was performed. All patient families were telephoned and twenty of twenty nine (69%) were successfully reached along side 7/11 inside the CD cluster, 6/9 inside the IS cluster and 7/9 inside the IPF cluster. One patient was reclassified from the IPF cluster to the IS cluster. inside the 19 different cases (95%), applicable classification was confirmed.

Patient demographics

The mean age of onset was two.2 years. Twenty 3 of twenty 9 patients (79%) were male. The mean length of febrile episodes was four.8 days and interval between episodes three.4 weeks. All febrile episodes were predictably spaced. people were well between every episode, and each patient showed traditional growth and development. alternative causes of periodic fever were excluded by one paediatric communicable disease specialist (MSC). seek advice from table two for febrile episode characteristics.

Clinical findings

Eleven patients were known within the CD cluster. One incontestible the entire composition, whereas 10 had Associate in Nursing incomplete composition with a minimum of one cardinal symptom gift at every episode. 9 patients were classified within the IS cluster and 9 within the IPF cluster. seek advice from table three for the speed of associated symptoms.

Family history

Five patients reported case history of apparently similar episodes: 2 meeting criteria for CD and 3 for the IPF cluster. The episodes were noted during a parent in 3 cases and in maternal/paternal cousins in 2 cases. case history was negative for diagnosed syndromes of periodic fever.

Treatment response

Among the eleven patients within the CD cluster, 2 were discovered and 9 received steroids. Steroid treatment like a shot terminated episodes in 100 percent of people. Frequency of episodes accrued in 2 people and minimized in one patient. within the 2 patients with accrued frequency of episodes, the anti-inflammatory drug dose was accrued from one mg/kg/dose double daily {for two|for two} days to one 2 mg/kg/dose with the choice for a second dose twelve hours later. In each cases, the first interval between episodes was renovated. No adverse effects of steroid treatment were reported . 3 patients ab initio treated with steroids went on to endure adenotonsillectomy and one underwent extirpation. Surgical medical aid was like a shot curative all told four patients. Mean follow-up length when surgical operation was ninety two months.

Among 9 patients within the IS cluster, one was discovered and 6 treated with steroids. Steroids were unfruitful in 100 percent of people treated. just one individual treated with steroids veteran modification in frequency of episodes, that was Associate in Nursing accrued interval between occurrences. there have been no reported adverse effects from steroid treatment. Adenotonsillectomy was the first treatment modality in 2 people. Two others, ab initio treated with steroids, later received adenotonsillectomy. Surgery was like a shot curative all told four people. Mean follow-up when surgery was forty one months.

In the IPF cluster, 3 patients were discovered and 5 treated with steroids. Steroids were like a shot effective all told 5 treated patients. There was no reported modification in frequency of events with steroid treatment. One patient out of print anti-inflammatory drug when experiencing hallucinations with steroid treatment; another out of print it because of parental concern for adverse effects from long- term use. Among the 5 ab initio treated with steroids, 2 later received adenotonsillectomy and one received extirpation. One further patient proceeded on to adenotonsillectomy while not steroid trial. Immediate cure was discovered in 100 percent of operated patients. Mean post-surgical follow-up was fifty two months. One patient WHO underwent observation received cutting out for Associate in Nursing unrelated reason and no impact was noted within the periodic fever episodes.

There were no complications from surgical operation in any cluster. seek advice from table four for treatment response knowledge.

Natural history

Seven patients within the CD cluster were managed only with steroids or discovered. Four of the seven veteran spontaneous resolution of symptoms throughout the study amount at a mean length of one zero five months. 3 continued to expertise episodes with mean follow-up of eighteen months. Relapse occurred in four of seven people, as well as 3 WHO later veteran spontaneous resolution. The surgically treated patients, WHO had veteran mean symptom length of thirty seven months before operation, all were like a shot cured by the procedure, $p < 0.006$, compared to those with spontaneous resolution.

Five patients within the IS cluster were managed only with steroids or discovered. 3 veteran spontaneous resolution at a mean length of fifty four months. The remaining 2 people continued to possess episodes at a mean follow-up length of fifty three months. Relapse occurred in one in all 5 people, with ensuant resolution. The surgically treated patients veteran mean symptom length of thirty one months before immediate post-procedure cure.

Five patients within the IPF cluster received steroids or were discovered while not surgical intervention. Spontaneous resolution was seen

in one individual when thirty six months. Four continued to expertise episodes at a mean length of fifty seven months. Relapse occurred all told four people with in progress episodes. The surgically treated people veteran mean symptom length of twenty three months before immediate post-operative cure, $p < 0.003$ compared to people with spontaneous resolution or in progress episodes (Figure 2).

Discussion

We report eleven cases meeting steered PFAPA diagnostic criteria and eighteen otherwise identical cases of periodic fever with partial or no expression of the desired cardinal symptoms [6,20]. curiously, the clinical presentation, explanation and, most significantly, response to treatment of the variant periodic fever cases resembled those of PFAPA.

The frequency of cardinal symptoms in our CD patients was kind of like antecedently reported rates [2,4,5,7]. Aphthous rubor, inflammatory disease and cervical inflammation were gift always/sometimes in 27/18%, 100/0%, and 55/27% of patients, severally. just one of the eleven patients had the entire cluster with all symptoms gift with each episode. In distinction, 40.8% of patients within the Hofer et al series had the entire constitution [18]. needless to say, the IS and IPF teams had lower rates of associated symptoms. as a result of symptoms in our series area unit classified as perpetually, sometimes, or ne'er as compared to less precise classification schemes, direct comparison of frequency between studies is troublesome. Further, the impreciseness of existing criteria might need light-emitting diode some patients with IS constitution to possess been reported in alternative series as a part of PFAPA whereas others were excluded for not meeting strict diagnostic criteria. There area unit few alternative cases of IS and IPF reported within the literature [11,21,22].

CD, IS, and IPF in our series every showed persistent symptoms for years, while not long complications. Among those followed till resolution, in CD, symptoms persisted for about eight.8 years from initial onset, kind of like the reported period of six.3 years within the literature [8]. IS was fifty four months and IPF was thirty six months. it's noteworthy that patients with current symptoms have old episodes for a mean of fifty seven months within the IPF cluster suggesting a extended total period of unhealthiness among these patients.

Steroid treatment was remarkably effective, with 100 percent of patients experiencing immediate termination, whether CD, IS, or IPF. at intervals the study amount, our observe pattern shifted from four steroid doses administered over 2 days to one a pair of mg/kg dose of Pediapred or anti-inflammatory, with AN choice for a repeat dose twelve hours later. each prescriptions were absolutely effective for termination of episodes. symptomless interval shortening was reversed exploitation the upper dose regime. Adverse effects were reported in barely 100 percent of patients, a rate less than reported by others [9].

Tonsillectomy, in 2 patients, or adenotonsillectomy, in 10 patients, light-emitting diode to cure in 100 percent of people in every clinical cluster. one patient underwent extirpation alone for AN unrelated reason with no impact on the course of periodic fever. These findings area unit per the speculation that tonsils and not adenoids area unit in how crucial to the pathophysiology of the PFAPA syndrome [2,4]. significantly, it additionally suggests that the tonsils can be equally concerned within the pathophysiology of IS and IPF. This seems to be the primary study to demonstrate a statistically vital cure for IPF in response to excision or adenotonsillectomy. this can be per the findings from the sole alternative series to incorporate patients with isolated periodic fever, wherever cure was achieved in 7/7 patients with excision [11].

While the pathophysiology of CD, IS, and IPF remains to be diagrammatical, we tend to believe the salient options to spot patients UN agency would possibly take pleasure in treatment ought to embrace characteristic feverish episodes, certain cyclicity, and exclusion of alternative etiologies of periodic fever by a supplier with expertise within the diagnosing of such conditions. Oral steroid treatment is extremely effective and carries an occasional risk profile. excision as an alternate provides a chance for prompt cure of the disorder. If excision is to be thought-about, it's our observe to advocate that a therapeutic trial of steroids be undertaken 1st. A positive response within the acceptable clinical setting powerfully supports the diagnosing of periodic fever and will predict surgical success.

There area unit many limitations to our information. First, the retrospective nature of our study resulted in omissions of knowledge in some cases and introduced a risk for recall bias. we tend to tried to mitigate chart review errors by employing a 2 reviewer protocol and by cross-referencing clinical findings from multiple suppliers treating every patient. Further, phonephone follow-up was accustomed make sure the accuracy of findings and extend follow-up period. Conclusions area unit restricted due to comparatively tiny sample size. yet, the info recommend a necessity to more investigate PFAPA therapeutic modalities among incomplete variants and think about whether or not IS and IPF represent a spectrum of PFAPA or distinctive entities.

Conclusion

We report 2 incomplete periodic fever variants that otherwise closely fit PFAPA, with similar clinical presentation, explanation and response to medical and surgical medical aid. more diagnostic and therapeutic analysis ought to apply well-tried PFAPA treatments to IS and IPF and that they ought to be thought-about as candidate variants of PFAPA as new classification schemes area unit outlined. For such studies, prospective cooperative efforts ought to be thought-about.

References

1. Marshall GS, Edwards KM, Butler J, Lawton AR (1987) Syndrome of periodic fever, pharyngitis, and aphthous stomatitis. J Pediatr 110: 43-46.

2. Valenzuela PM, Araya A, Pérez CI, Maul X, Serrano C, et al. (2013) Profile of inflammatory mediators in tonsils of patients with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome. Clin Rheumatol 32: 1743-1749.

3. Marshall GS (2014) Prolonged and recurrent fevers in children. J Infect 68 Suppl 1: S83-93.

4. Licameli G, Lawton M, Kenna M, Dedeoglu F (2012) Long-term surgical outcomes of adenotonsillectomy for PFAPA syndrome. Arch Otolaryngol Head Neck Surg 138: 902-906.

5. Forsvoll J, Kristoffersen EK, Oymar K (2013) Incidence, clinical characteristics and outcome in Norwegian children with periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome; a population-based study. Acta Paediatr 102: 187-192.

6. Thomas KT, Feder HM Jr, Lawton AR, Edwards KM (1999) Periodic fever syndrome in children. J Pediatr 135: 15-21.

7. Feder HM, Salazar JC (2010) A clinical review of 105 patients with PFAPA (a periodic fever syndrome). Acta Paediatr 99: 178-184.

8. Wurster VM, Carlucci JG, Feder HM Jr, Edwards KM (2011) Long-term follow-up of children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. J Pediatr 159: 958-964.

9. Tasher D, Somekh E, Dalal I (2006) PFAPA syndrome: new clinical aspects disclosed. Arch Dis Child 91: 981-984.

10. Burton MJ, Pollard AJ, Ramsden JD, Chong LY, Venekamp RP (2014) Tonsillectomy for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA). Cochrane Database Syst Rev 9: CD008669.

11. Renko M, Salo E, Putto-Laurila A, Saxen H, Mattila PS, et al. (2007) A randomized, controlled trial of tonsillectomy in periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome. J Pediatr 151: 289-292.

12. Garavello W, Romagnoli M, Gaini RM (2009) Effectiveness of adenotonsil- lectomy in PFAPA syndrome: a randomized study. J Pediatr 155: 250-253.

13. Kuppersmith RB, Schams ST, Rosenfeld RM (2010) Extracts from The Cochrane Library: Tonsillectomy for periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA). Otolaryngol Head Neck Surg 143: 473-475.

14. Baugh RF, Archer SM, Mitchell RB, Rosenfeld RM, Amin R, et al. (2011) Clinical practice guideline: tonsillectomy in children. Otolaryngol Head Neck Surg 144: S1-30.

15. Peridis S, Koudoumnakis E, Theodoridis A, Stefanaki K, Helmis G, et al. (2010) Surgical outcomes and histology findings after tonsillectomy in children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. Am J Otolaryngol 31: 472-475.

16. Wong KK, Finlay JC, Moxham JP (2008) Role of Tonsillectomy in PFAPA Syndrome. Arch Otolaryngol Head Neck Surg 134: 16-19.

17. Garavello W, Pignataro L, Gaini L, Torretta S, Somigliana E, et al. (2011) Tonsillectomy in children with periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome. J Pediatr 159: 138-142.

18. Hofer M, Pillet P, Cochard MM, Berg S, Krol P, et al. (2014) International periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome cohort: description of distinct phenotypes in 301 patients. Rheumatology (Oxford) 53: 1125-1129.

19. Padeh S, Stoffman N, Berkun Y (2008) Periodic fever accompanied by aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA syndrome) in adults. Isr Med Assoc J 10: 358-360.

20. Marshall GS, Edwards KM, Lawton AR (1989) PFAPA syndrome. Pediatr Infect Dis J 8: 658-659.

21. Abramson JS, Givner LB, Thompson JN (1989) Possible role of tonsillectomy and adenoidectomy in children with recurrent fever and tonsillopharyngitis. Pediatr Infect Dis J 8: 119-120.

22. Miller LC, Sisson BA, Tucker LB, Schaller JG (1996) Prolonged fevers of unknown origin in children: patterns of presentation and outcome. J Pediatr 129: 419-423.