J Compr Ped. 2023 May; 14(2):e130982. https://doi.org/10.5812/compreped-130982.

Published online 2023 April 4. **Case Report**

Periodic Fever in Children: A Report of Three Unusual Cases

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Received 2022 September 11; **Revised** 2023 January 24; **Accepted** 2023 February 11.

Abstract

Introduction: Periodic fever syndrome (PFS) is a rare monogenic autoinflammatory disease group. The innate immune system abnormalities have a characteristic onset and spontaneous inflammation without any infectious or autoimmune trigger. It differs from autoimmune disorders (e.g., systemic lupus erythematosus (SLE)) occurring due to a defect in the adaptive immune system with auto-antibodies.

Case Presentation: The clinical features of three patients presented with a periodic pattern of fever and a different constellation of symptoms were investigated. The final diagnosis of Periodic fever syndrome was reached based on standard diagnostic criteria and genetic testing. All three cases were observed to present with recurrent fever episodes at an interval of 6 - 12 weeks, 3 - 4 weeks, and one month, respectively. The first patient, presenting with a diffuse erythematous plaque-like lesion along the calf with severe calf pain and tenderness with signs of meningeal irritation, was diagnosed with a tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS) like phenotype. The genetic panel was negative in this case. The second patient presenting with recurrent pharyngitis, cervical adenitis, and tonsillitis unresponsive to antibiotics was diagnosed with periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. The last patient presenting with recurrent monoarthritis, hepatosplenomegaly, and a positive Mediterranean fever (MEFV) gene mutation was diagnosed with familial Mediterranean fever (FMF). All three patients had normal growth and development.

Conclusions: Although periodic fever syndrome was an uncommon entity, it was recommended that this syndrome should be considered when a patient presented with recurring fever episodes with a characteristic constellation of symptoms.

Keywords: PUO, Periodic Fever, Autoinflammatory Disorder, Familial

1. Introduction

Recurrent fever is defined by three or more febrile episodes (> 38°C) of fever in a 6-month period occurring at least seven days apart (1). If unexplained bouts of recurrent fever occur with a characteristic frequency and constellation of the symptoms, then a diagnosis of periodic fever syndrome can be considered after ruling out infections due to immunodeficiency and organ malformation (2).

Periodic fever syndrome (PFS) comprises a clinically distinct set of monogenic autoinflammatory disorders that occur due to defects in the innate immune system, resulting in an aberrant inflammasome and cytokine excess. It differs from autoimmune disorders such as systemic lupus erythematosus (SLE), which occurs due to defect in the adaptive immune system and has auto-antibodies directed towards self-antigens (2).

These are rare disorders that have a striking onset and spontaneous inflammation without any infectious or autoimmune etiology (1). Symptoms include recurrent febrile episodes accompanied by ocular, oropharyngeal, gastrointestinal, dermatological, musculoskeletal, and neurological manifestations. The fever recurs after a fixed interval, and usually resolves spontaneously without any medications (e.g., antibiotics, anti-inflammatory, or immunosuppressive agents) (3). Patients are generally asymptomatic between the episodes, with normal growth and development, but suffer a lot during the attack periods. Although periodic fever syndrome is a rare syndrome, its early diagnosis is essential to improve the patient's quality of life and decrease the short-term as well as long-term morbidity caused by it.

Table 1 lists the disorders included in PFS and their mode of inheritance. Periodic fever syndrome is characterized by recurrent spontaneous inflammation and elevated acute-phase reactants during and even between the attacks. Symptomatology includes inflammation of serosal surfaces (e.g., pleuritis, pericardial effusion, and joints), neutrophilic skin rashes or urticaria, lymphadenopathy,

hepatosplenomegaly, arthritis, involvement of other organs (e.g., muscles and central nervous system), and long-term risk of secondary amyloidosis (4). Periodic fever syndrome can be differentiated from chronic rheumatic disease by its typical recurrence of attacks and symptom-free intervals. Furthermore, it can be confirmed by genetic testing (5). Similar family history can be suggestive of its genetic origin.

Table 1. Periodic Fever Syndromes and Their Mode of Inheritance [a]

Disorder	Inheritance
Unknown inheritance	
PFAPA syndrome	None
Known inheritance	
FMF	AR
Cryopyrin-associated periodic syndrome	AD
Familial cold autoinflammatory syndrome	
Muckle-wells syndrome	
Neonatal onset multisystem inflammatory disease	
Mevalonate kinase deficiency	AR
TRAPS	AD
Cyclic neutropenia	AD
Pyogenic lesions	
Deficiency of interleukin -1 receptor antagonist	AR
PAPA	AD
Granulomatous lesions	
Blau syndrome	AD

Abbreviations: PFAPA, periodic fever, aphthous ulcers, pharyngitis and adenopathy; FMF, familial Mediterranean fever; TRAPS, tumor necrosis factor receptor associated periodic fever syndrome; PAPA, pyogenic arthritis, pyoderma gangrenosum, acne syndrome; AD, autosomal dominant; AR, autosomal recessive.
[a] Sources: Siroosbakht and Rezakhaniha (6) and Ozen and Bilginer (7).

A definite diagnosis is established for many PFS such as familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), and familial cold auto-inflammatory syndromes (FCAS) after respective detection of mutations in Mediterranean fever (MEFV), mevalonate kinase (MVK), tumor necrosis factor receptor superfamily member 1A (TFRSF1A), and NLRP3/NLRP12 (Nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing) gene, respectively (8). Up until recently, no genetic cause was known for periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA); however, significant familial clustering reported by many studies is suggestive of a genetic predisposition. It has polygenic or multifactorial origin. Multiple low-penetrant gene variants in MEFV or NLRP3 gene are indicative of its polygenic origin (9). Figure 1 displays the approach to diagnosing PFS when a child presents with recurrent fever (10, 11).

Therefore, three cases referring to a super-specialty tertiary care hospital with complaints of recurrent fever and diagnosed with periodic fever syndrome were investigated in our study in order to add more data on this syndrome to the available literature. It is worth mentioning that the diagnosis of these cases was difficult since they were rare and presented with various signs and symptoms, and no easy genetic testing was available at many centers to confirm the diagnosis. Diagnostic criteria for the three cases are shown in Boxes 1, 2 and 3.

Box 1. Familial Mediterranean Fever Criteria [a]

Familial Mediterranean Fever Criteria
Major criteria
Typical attacks (recurrent (at least 3 episodes), febrile (rectal temperature ≥ 38°C), and short duration (12 hours to 3 days))
1- Generalized peritonitis
2- Unilateral pleuritis or pericarditis
3- Monoarthritis (hip, knee, ankle)
4- Fever alone
5- Incomplete abdominal attack
Minor criteria
Incomplete attacks involving either or both of the following sites. (temperature < 38°C, attack duration longer or shorter than a typical attack (but no less than six hours and no more than seven days), and no signs of peritonitis during the attacks)
1- Chest
2- Joint (other than hip, knee, ankle)
3- Exertional leg pain
4- Favorable response to colchicine

[a] Source: Livneh et al. (12)

2. Case Presentation

In this study, three cases aged nine years referring to our center with recurrent fever case I and complaining of fever persisted for more than a week were reported. It was associated with diffuse erythematous, warm plaque-like lesion of the overlying calf skin and severe calf pain. Examination was performed, and the meningeal signs were found positive. The child was initially thought to have infective meningitis, and, therefore, a lumbar puncture was performed, and intravenous antibiotics were injected. However, the child showed no improvement on a complete course of antibiotics. Neuroimaging was normal.

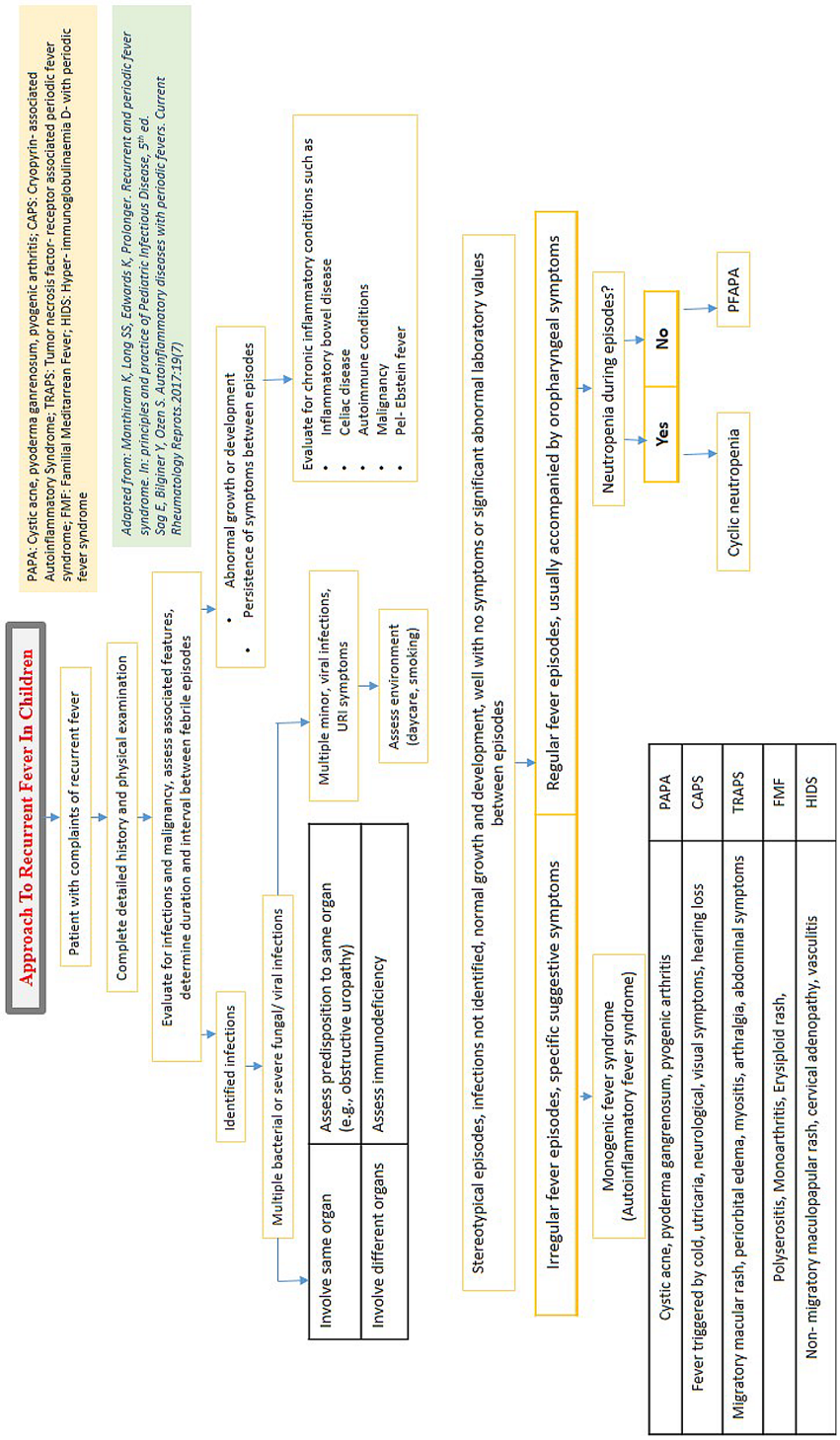

Figure 1. Approach to recurrent fever in children

Box 2. The Eurofever/PRINTO Clinical Classification for Tumor Necrosis Factor Receptor-Associated Periodic Syndrome [a]

Clinical Classification Criteria
Score $\geq$ 5 points
Presence
Fever $\geq$ 7 days (2 points)
Fever 5 - 6 days (1 point)
Migratory rash (1 point)
Periorbital edema (1 point)
Myalgia (1 point)
Positive family history (1 point)
Absence
Aphthous stomatitis (1 point)
Pharyngotonsillitis (1 point)

[a] Source: Gattorno et al. (13).

Box 3. Modified Marshall's Classification Criteria for Periodic Fever, Aphthous Ulcers, Pharyngitis and Adenopathy [a]

Classification Criteria
Onset: Early childhood, generally < 5 years
Regularly recurring abrupt episodes of fever lasting 5 days, associated with both of the following:
Aphthous stomatitis and/or pharyngitis (with or without cervical adenitis)
Elevated acute inflammatory markers
Completely asymptomatic interval periods (generally lasting less than 10 weeks), benign long-term course, normal growth parameters
Exclusion of cyclic neutropenia
Exclusion of other episodic syndromes (familial Mediterranean fever, hyper-IgD syndrome, TRAPS, Behcet disease) by family history and the absence of typical clinical features and laboratory markers
Absence of clinical and laboratory evidence for immunodeficiency, autoimmune disease or chronic infection

Abbreviations: TRAPS, tumor necrosis factor receptor associated periodic fever syndrome.
[a] Source: Marshall et al. (14).

Case II aged six years, with a complaint of recurrent fever persisting for 4 - 5 days and recurring every 3 - 4 weeks. Examination was performed, and painful ulcerated lesions were observed in the mouth, and multiple cervical lymph nodes were found palpated. The child had received multiple courses of antibiotics from outside. All the infective cultures were negative.

Case III aged four years, with a complaint of recurrent fever persisting for almost 4 - 5 days and recurring every month. Each fever episode was associated with pain and swelling of a single large joint. It subsides spontaneously and appears in different joint in the next episode. There was no residual damage. Examination was performed and the hepatosplenomegaly was determined, and the echocardiogram showed mild pericardial effusion. Further investigation indicated that *Brucella* titers were positive, but *Brucella* DNA PCR was negative.

Table 2 shows the clinical features, examination findings, investigations, and final diagnosis of the three cases in greater detail.

The given cases showed no response to antibiotics, extensive infective, immunodeficiency, rheumatologic, and autoimmune, and malignancy workup was negative. Given the typical periodic self-limiting nature of illness with highly raised inflammatory markers, a differential diagnosis of periodic fever syndrome was considered. After reviewing the literature, the periodicity and symptomatology were found to be consistent with different periodic fever syndromes.

Case I met the criteria for TRAPS according to Eurofever Printo clinical classification criteria (13), but the periodic fever genetic panel was negative. A diagnosis of tumor necrosis factor receptor-associated periodic fever syndrome-like phenotype was established. The child was treated with pulse steroid therapy followed by maintenance steroid therapy. Given sub-optimal disease control, Etanercept was added. The child showed a satisfactory response to the drug and was followed up for three years with no complications.

Case II met the criteria for PFAPA according to modified Marshall's classification (14). This diagnosis was not confirmed by the genetic test and therefore, final diagnoses of PFAPA were established. All episodes were managed symptomatically with NSAIDS and prednisolone single dose (1-2 mg per kg). The child showed improvement with the treatment.

Case III Child met the criteria for familial Mediterranean fever according to familial Mediterranean fever criteria by Livneh et al. (12). Genetic analysis showed a heterozygous missense variant in exon 10 of the MEFV gene, and a final diagnosis of familial Mediterranean fever was established. The child was treated with pulse steroid therapy followed by steroid maintenance therapy. The child was later given colchicine because of the development of steroid toxicity. The child was then followed up.

3. Discussion

Our cases were afflicted with the rare PFS from an Indian scenario and with its presentation. Familial Mediterranean fever, an autosomal recessive disorder, occurs due to gain-in-function mutations in the *MEFV gene* that encodes for pyrin. Our patient had a classical history of

Table 2. Comparison of the Cases of Periodic Fever Syndrome

	Case I	Case II	Case III
Age of onset	9 years	6 years	4 years
Attack duration	> 7 days	4 - 5 days	5 - 7 days
Interval between attacks	6 - 12 weeks	25 days	1 month
Triggers	None	Upper respiratory tract infection	None
Cutaneous manifestations	Diffuse erythematous, warm plaque-like lesion of overlying skin of the calf	Painful ulcerated lesions in mouth (aphthous ulcers in oral mucosa)	None
Musculoskeletal manifestations	Severe calf pain	No arthritis	Monoarthritis of large joints (ankle, knee, elbow) in each episode: Non-deforming
Abdominal manifestations	None	None	None
Eye	None	Conjunctival congestion	None
Pleural, pericardial manifestations	None	None	Mild pericardial effusion +
Neurological manifestations	Meningeal signs +	None	None
Lymph/spleen	None	Bilateral cervical lymphadenopathy (level I & II, 2 X 1 cm); bilateral grade II tonsillar hypertrophy with congestion	Hepatosplenomegaly
Anthropometry and development	Normal as per age	Normal as per age	Normal as per age
Hematological investigations	Normocytic normochromic anemia; neutrophilic leukocytosis; raised inflammatory markers; CRP 160 mg/dL; ESR 60 mm in 1st hour	Normocytic normochromic anemia; neutrophilic leukocytosis; raised inflammatory markers; ESR- 39 mm in 1st hour; CRP- 98 mg/dL	Normocytic normochromic anemia; neutrophilic leukocytosis; raised inflammatory markers; CRP 185.9 mg/dL; ESR 55 mm in 1st hour
Infective workup	EBV, parvovirus B19, borrelia recurrentis, brucellosis, tuberculosis, histoplasmosis, leishmaniasis negative; blood culture sterile; urine culture sterile; CSF examination-8 lymphocytes, protein 60 mg%, glucose- normal, culture sterile	Tuberculosis negative; swab culture from oropharynx- no growth; blood culture-sterile	*Brucella* abortus antibody titers- reactive 1:80; *Brucella* melitensis antibody titers-reactive 1:320; *Brucella* DNA PCR- negative; EBV- negative; tuberculosis- negative; blood culture- sterile
Special test	ANA negative; ANCA negative; CECT head-normal; doppler of lower limb- normal; NCV- normal; muscle biopsy- monocytic fasciitis; immunodeficiency workup-negative	ANA negative; immnodeficiency workup-negative	Bone marrow biopsy is cellular, showing hematopoietic elements of all three lineages with normal maturation.no granuloma/atypical cells/hemoparasite seen; anti-CCP- negative; RA factor- negative; ANA – negative; DsDNA-negative; DCT-negative; immunodeficiency workup - negative
Genetic results	Negative for pathogenic variants of periodic fever genetic panel	Not done	Heterozygous missense variant in exon 10 of the MEFV gene
Diagnosis	Mutation negative tumor necrosis factor receptor- 1- associated periodic fever syndrome (TRAPS) like phenotype	PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis)	FMF
Treatment	Pulse steroid followed by maintenance steroid therapy; etanercept	Symptomatic management with NSAIDS and prednisolone 1 - 2 mg/kg single dose	Steroid; colchicine
Follow-up duration	3 years; urinalysis- negative for micro albuminuria	5 years	2 years; urinalysis-negative for micro albuminuria

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EBV, Epstein barr virus; CSF, cerebrospinal fluid; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; NCV, nerve conduction velocity; CECT, contrast-enhanced computed tomography; Anti-CCP, anti-cyclic citrullinated peptide; RA, rheumatoid arthritis; DsDNA, double-stranded DNA; DCT, direct Coombs test; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; FMF, familial Mediterranean fever; MEFV, Mediterranean fever.

recurrent febrile episodes with monoarthritis and hepatosplenomegaly during the attack with an otherwise normal inter-febrile period with no positive family history. The genetic workup was positive for the MEFV mutation. The child was initially given steroids and low-dose colchicine, to which the child showed a response. Agarwal and Sharma reported a case of a 16-year-old boy in Jaipur who had five episodes of polyserositis and two episodes of diabetic ketoacidosis over an 8-month period with asymptomatic episodes between the attacks (15). He had no fever, no Mediterranean ancestry, and similar family history. He was diagnosed with FMF based on the clinical criteria. Gicchino et al. also investigated a 13-year-old boy with a history of T1DM for four years who presented with a periodic pattern of fever associated with abdominal pain, chest pain, and arthralgia, and had positive mutations for the MEFV gene (homozygous E148Q mutation) (16). He was initially given colchicine at 1 mg/kg. Arslan et al. documented FMF in a 5.5-month-old child who had three episodes of fever on the 22nd and 71st days as well as at 5.5 months of life with no evidence of infections and a positive family history of FMF in elder sister and recorded homozygous positive for M694V mutations (17). Familial Mediterranean fever has no cure; however, the symptoms can be controlled using NSAID for pain relief and as an anti-inflammatory drug and saline for hydration. Colchicine can be used for mild to severe inflammatory attacks. As for mild attacks, oral colchicine can be applied. In unresponsive cases, intravenous colchicine can be rarely used (18, 19).

Tumor necrosis factor receptor-associated periodic syndrome, an autosomal dominant disorder with incomplete penetrance, occurs due to mutations in the *gene TNFRSF1A* that encodes for a protein, tumor necrosis factor receptor-1 (TNFR1). This protein is present in the cell membrane and encodes for another protein called tumor necrosis factor (TNF). It sends a signal to the cells to initiate the inflammation. Mutations in the TNFRSF1A gene lead to abnormal production of TNFR1, which may not be released from the cell and may clump there. It is believed to trigger alternate pathways for inflammation. The final diagnosis is reached after performing the genetic analysis. In some cases, however, the genetic study may fail to show the confirmatory genotype due to the phenomenon of somatic mosaicism. Mutations occurring during the late stages of embryogenesis affect only the nongonadal cells and are restricted to a specific population of cells. These mutations may escape detection if screening does not involve the affected cell populations (20, 21). Our patient presented with musculoskeletal (severe calf pain and tenderness), cutaneous (erythematous rash), and neurological manifestations (positive meningeal signs). The genetic workup was negative for the PFS panel and was labeled as mutation negative TRAPS like illness (22, 23). The child was treated with pulse steroid followed by maintenance steroid therapy and later was given Etanercept at the dose of 0.8 mg/kg subcutaneously once a week, to which the child showed a response. Headache is present in 20-25 percent of patients of TRAPS. The disease, associated with the R92Q variant of TNFRSF1A gene mutation, later presents with more headaches and fewer complaints of rash and ocular features at a median age of 5.7 years (24). Hamsen et al. reported the case of a 10-year-old girl who presented with a periodic pattern of fever, skin edema, and abdominal pain (25). All infective workups and the genetic analysis for PFS were negative. There was no family history of PFS. Symptoms partially resolved using prednisolone and etanercept, and the child showed a dramatic response to anakinra.

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome is the most common autoinflammatory disorder in the childhood period, with sporadic onset and no genetic mutations associated with it. The diagnosis is usually clinical, and no genetic test is available for it (26). Our patient presented with classical recurrent episodes of fever, aphthous ulcers, pharyngitis, and cervical lymphadenopathy, and the clinical diagnosis of PFAPA syndrome was established as per modified Marshall criteria after ruling out infective etiology. Our patient was managed with single-dose steroid and symptomatic treatment. Semianchuk reported a case of a 7-year-old boy who had complaints of recurrent episodes of high-grade fever (> 40°C), sore throat, and white spots on his tonsils until the age of two; therefore, he was treated with multiple antibiotics over time and was finally diagnosed clinically with PFAPA after ruling out all the infectious causes (27). Yamahara et al. reported an adult-onset PFAPA syndrome who presented at the age of 37 years with recurrent episodes of high-grade fever, sore throat, aphthous stomatitis, and bilateral enlargement of cervical lymphadenopathy associated with tenderness (28). After ruling out the infective etiology, the diagnosis of PFAPA syndrome was confirmed based on Padeh's criteria. The patient showed no response to oral medications, and eventually required a tonsillectomy. Multiple investigations performed to find out the cause increased the parents' financial strains and the child's emotional stress of needle prick pain. It delays the diagnosis and the proper timely management of the actual disease. The timely diagnosis of PFS is limited by the lack of awareness of pediatricians about its occurrence and the unavailability of genetic testing in most setups. It is essential for a pediatrician to pay close attention to the history of the child and perform a detailed examination when s/he presents with complaints of recurrent fever; it is also necessary for him/her to consider the

differentials among periodic fever syndromes if the child shows no response to the first-line antibiotics and if the infective workup is negative. The proper management of PFS patients requires using guidelines. Furthermore, guidelines can assist pediatricians in diagnosing the issue correctly and prescribing effective antibiotic (6).

3.1. Conclusions

In sum, it was recommended that the patients experiencing recurrent fever should be evaluated for PFS even though this syndrome was generally uncommon and rare. As a frequent primary complaint, fever was commonly believed to have an exclusively infectious etiology and was treated with antibiotics. In several cases, multiple courses of antibiotics were given to the patient before a final diagnosis or suspicion of PFS was established. This caused widespread antibiotic abuse, which may have resulted in the emergence of antimicrobial resistance.

Footnotes

Authors' Contribution: AS conceived and designed the evaluation and drafted the manuscript. NG and VK collected the data with the help of AS, NG, VK, IS, and SS analyzed and interpreted the data. NG, VK, and AS drafted the manuscript. AS, IS, and SS revised the manuscript critically for important intellectual content. AS supervised the study.

Conflict of Interests: Funding or research support: None; employment: None; personal financial interests: None; stocks or shares in companies: None; consultation fees: Free of cost; patents: None; personal or professional relations with organizations and individuals (parents and children, wife and husband, family relationships, etc.): None; unpaid membership in a government or non-governmental organization: None; are you one of the editorial board members or a reviewer of this journal? No.

Funding/Support: There was no funding/support.

Informed Consent: Informed consent for publication was taken from the parents.

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