Fever in Pediatric Rheumatological Disorders

Moderator:

Prof. Dr. A. V. Ramanan

Professor of Pediatric Rheumatology, University of Bristol,
Consultant Pediatric Rheumatologist,
Bristol Royal Hospital for Children, UK

Introduction

Fever represents a cardinal manifestation across pediatric rheumatological disorders, encompassing both autoinflammatory and autoimmune etiologies, and frequently poses significant diagnostic and therapeutic challenges.[1,2] In any febrile child, infectious causes and malignancy, particularly acute lymphoblastic leukemia, must be systematically excluded as foundational principles of differential diagnosis.[2,3]

Among non-infectious, non-neoplastic rheumatological causes in children younger than five years, Kawasaki disease predominates, followed by systemic-onset juvenile idiopathic arthritis (sJIA) and periodic fever syndromes. Of these, periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome remains significantly underdiagnosed.[3-7] In children aged five to ten years, Kawasaki disease and PFAPA continue to be the principal considerations, with few alternative diagnoses. Systemic lupus erythematosus (SLE) is uncommon before eight years of age in the absence of monogenic variants, and non-Kawasaki vasculitides rarely present with fever before seven years.[3,6,7]

In contrast, children aged 10–15 years demonstrate increased susceptibility to SLE and vasculitic disorders, including ANCA-associated vasculitis and monogenic vasculitis.[8,9] This age-stratified framework underscores the need for diagnostic restraint; for example, diagnoses such as SLE or medium-vessel vasculitis in four- to five-year-old children should prompt consideration of robust genetic or molecular corroboration.[10] Subsequent sections present illustrative cases to adopt these principles in clinical practice.

Case 1: Kawasaki disease

A four-year-old boy presented with a three-day history of fever and right-sided cervical lymphadenopathy.

Initial evaluation by a general pediatrician revealed marked fever with a documented temperature of 40°C; systemic examination was otherwise unremarkable, prompting a working diagnosis of acute bacterial cervical lymphadenitis and empirical antibiotic therapy. Laboratory investigations showed leukocytosis with neutrophilia and markedly elevated C-reactive protein (CRP) levels of 254 mg/L, findings consistent with bacterial lymphadenitis, yet several atypical features were evident. Serum albumin remained normal (approximately 38–39 g/L), whereas hypoalbuminemia in the absence of gastrointestinal or renal losses would suggest a more protracted systemic inflammatory process; additionally, deranged liver transaminases are atypical for uncomplicated bacterial lymphadenitis.

Despite broad-spectrum antibiotic therapy, the child continued to have persistent high-grade fever and elevated inflammatory markers. Neck ultrasonography was non-diagnostic, prompting escalation of antibiotics under the presumption of refractory bacterial lymphadenitis. On meticulous re-examination, additional clinical features were identified, including bilateral non-purulent conjunctivitis and a characteristic "strawberry" tongue. This case illustrates a variant presentation in which prominent unilateral cervical lymphadenopathy, more marked than typically observed, diverted attention from the classical features of Kawasaki disease and prolonged an infectious diagnostic pathway. Delayed consideration of Kawasaki disease resulted in echocardiographic detection of a giant coronary artery aneurysm.

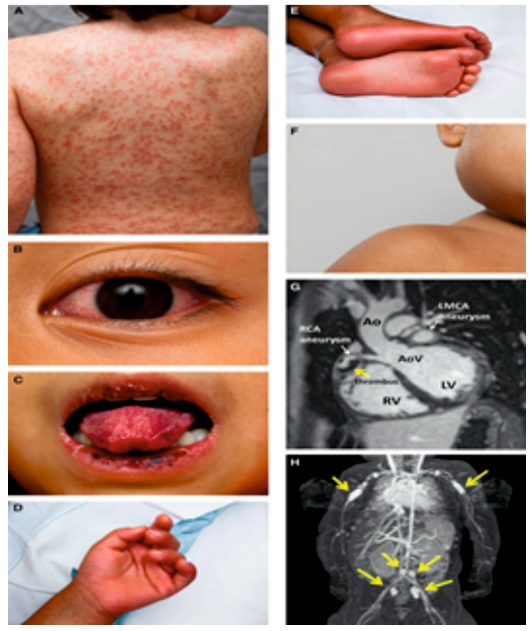
This case illustrates that Kawasaki disease may manifest atypically, underscoring the need to consider the diagnosis in any child with prolonged fever. The presentation is consistent with node-first Kawasaki disease, a term denoting predominant initial lymph node involvement. Fever with cervical lymphadenopathy should not be assumed to be of bacterial origin, particularly when subtle accompanying features are present.[11] Kawasaki disease remains the leading cause of acquired coronary artery disease in children in Western countries and is presumed to be similarly prevalent in India.[12]

Epidemiology and diagnostic criteria of Kawasaki disease

Kawasaki disease affects boys and girls equally. Although most cases occur in children younger than five years, the diagnosis can be established in older children, including those aged eight to twelve years. Recurrence is exceedingly rare; however, siblings of affected children have a modestly increased risk.[13,14] Children with comorbidities such as inflammatory bowel disease, atopic disorders, or immunodeficiency are susceptible and are at greater risk of diagnostic delay.[15,16]

The diagnostic criteria require fever persisting for at least five days in addition to four of five principal clinical features: bilateral non-purulent conjunctival injection, polymorphous rash, cervical lymphadenopathy (≥1.5 cm), oral mucosal changes, and extremity changes, including erythema, oedema, or periungual desquamation (Fig. 1).[4] Complete Kawasaki disease fulfils these criteria. Incomplete Kawasaki disease refers to cases with strong clinical suspicion that do not meet the full criteria, often supported by echocardiographic findings. Atypical Kawasaki disease describes presentations with incomplete clinical criteria accompanied by coronary artery abnormalities. Infants younger than six months and children older than six years are at increased risk of developing coronary artery aneurysms, frequently due to delayed diagnosis.[17,18]

Fig. 1. Classic clinical features of Kawasaki disease



Treatment strategies and outcomes in Kawasaki disease

Therapeutic strategies for Kawasaki disease have evolved since the 1960s and 1970s, progressing from high-dose aspirin monotherapy to combination therapy with aspirin and intravenous immunoglobulin (IVIG). Landmark clinical trials established a single dose of IVIG at 2 g/kg administered with aspirin as the current standard of care. Aspirin now serves primarily as an adjunct, while IVIG functions as the principal immunomodulatory agent; its continued use reflects historical practice rather than a primary disease-modifying effect. Contemporary management commonly employs either moderate- to high-dose aspirin (approximately 30 mg/kg/day) or low-dose antiplatelet therapy (5 mg/kg/day), particularly in the presence of transaminitis (Fig. 2).[19]

Fig. 2. Effect of IVIG dosage on coronary artery lesions in Kawasaki disease

Treatment	CAL < 30 days of illness	CAL 6-8 weeks of illness
ASA alone	23.5%	14.7%
ASA + <1g/kg IVIG	12.2%	8.6%
ASA + 1-1.2g/kg IVIG	13.7%	7.0%
ASA + 1.6g/kg IVIG	5.7%	3.7%
ASA + 2g/kg IVIG	3.6%	2.6%

Treatment failure is uniformly defined in clinical trials as persistent or recrudescent fever exceeding 38 °C beyond 48 hours after completion of IVIG infusion; fever occurring during the infusion or immediately afterward does not meet this definition. Primary IVIG resistance occurs in approximately 15–20% of patients and is associated with poorer clinical outcomes.[20-22]

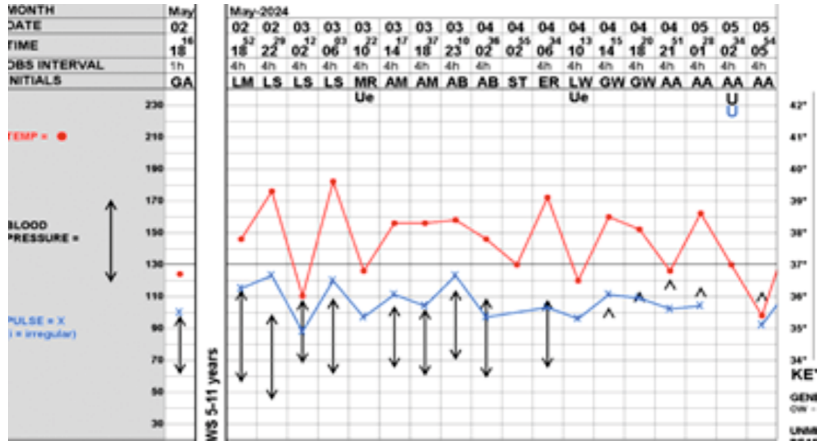
Several alternative therapeutic agents have been evaluated. A randomized trial comparing IVIG plus intravenous methylprednisolone with IVIG alone demonstrated no additional benefit, a finding that was later criticized for the absence of risk stratification. Infliximab has shown anecdotal efficacy in refractory cases; however, a phase III trial in unselected patients found no superiority of infliximab over IVIG plus placebo. Infliximab may have a role in refractory Kawasaki disease but lacks evidence for routine use.[23]

In contrast, the Kobayashi trial, which enrolled high-risk patients defined by adverse prognostic features such as low baseline platelet counts and prolonged fever (≥20 days), demonstrated significantly improved coronary outcomes with upfront combination therapy using IVIG and corticosteroids compared with IVIG alone. The incidence of coronary artery aneurysms was reduced from 23% to 3%, supporting selective treatment intensification in patients with high-risk features.[24]

Case 2: Systemic-onset juvenile idiopathic arthritis

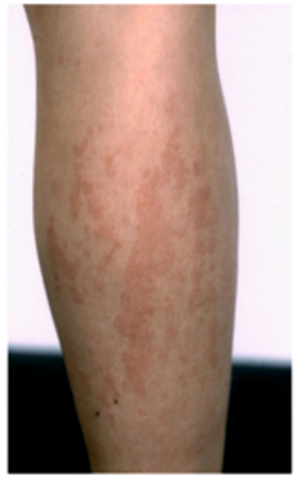
An 11-year-old boy presented with a two-week history of rash that manifested exclusively during febrile episodes. The fever pattern characteristic of sJIA, when documented on a fever curve, can be differentiated from sepsis or infectious etiologies by its typical occurrence as one or two spikes daily, predominantly in the late evening or occasionally morning; by contrast, genuine infectious fevers demonstrate multiple spikes throughout the day. A distinctive feature of sJIA fever is the post-spike temperature nadir, which frequently falls to subnormal levels of 35–36°C. This patient exhibited fever, evanescent rash, and arthralgias; physical examination revealed modest lymphadenopathy, faint macular rash, mild arthritis, and hepatomegaly. The fever chart corroborated subnormal inter-spike temperatures with only one or two daily peaks (Fig. 3).

Fig. 3. Fever chart demonstrating a double quotidian pattern with one to two daily spikes and intervening subnormal temperature



Laboratory findings revealed marked leukocytosis (35,000/µL) with neutrophilia and profoundly elevated C-reactive protein levels, consistent with the interleukin-6–driven pathogenesis of sJIA. Malignancy was excluded by a normal bone marrow aspiration performed prior to steroid initiation; certain investigations, such as whole-body MRI, yielded essentially normal results. This case exemplifies sJIA as an important cause of prolonged fever lasting weeks, frequently following multiple courses of antibiotics. The rash may be subtle in children with darker skin phototypes, and arthritis may not be clinically apparent at initial presentation (Fig. 4). The patient demonstrated an excellent clinical response to corticosteroid therapy.

Fig. 4. Faint maculopapular rash of sJIA showing Koebner phenomenon and characteristic histological features



- Faint maculopapular rash
- Koebner phenomenon
- Pruritus is seen in 10%
- Histology - sparse perivascular infiltrate with predominance of polymorphs

Cardinal features of sJIA fever include its quotidian pattern with one or two daily spikes, subnormal temperatures between spikes, and rash accentuation concurrent with fever. The rash is characteristically macular, though urticarial in approximately 20% of cases; the presence of urticaria does not preclude the diagnosis.[5,25] In adults, sJIA manifests across the lifespan, including the second through fifth decades as adult-onset Still's disease, with onset possible from infancy to 60–70 years of age, and a predilection for wrist involvement among affected joints (Fig. 5).[25-30]

Fig. 5: Systemic-onset Still's disease across the lifespan with characteristic wrist-predominant arthritis

The potential severity of untreated disease in a boy who tragically succumbed to sJIA complications. Close inspection reveals fixed elbow flexion contractures, massive axillary lymphadenopathy, marked hepatosplenomegaly, a protuberant abdomen, and ascites. Without intervention, sJIA can progress to macrophage activation syndrome or hemophagocytic lymphohistiocytosis, often with catastrophic outcomes, as observed in this case.

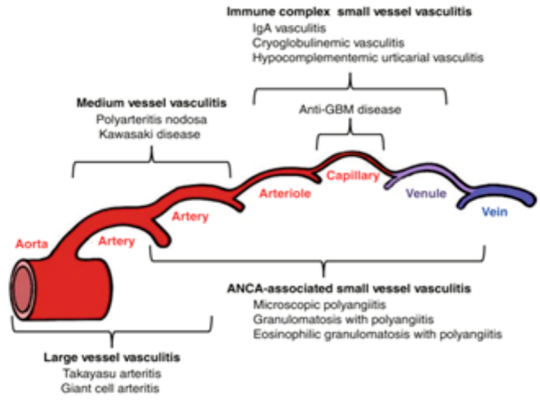
Simple laboratory parameters are sufficient for initial evaluation, including anemia, leukocytosis, and thrombocytosis. CRP generally outperforms erythrocyte sedimentation rate (ESR) as an inflammatory marker in most rheumatological conditions, except SLE, while ferritin levels exceed 1,000 µg/L in approximately 80% of sJIA cases.[31,32]

Case 3: Pediatric vasculitis

An 8-year-old girl presented with fever, sore throat, and arthritis, accompanied by a non-blanching purpuric rash; the remainder of her physical examination was unremarkable. Laboratory evaluation revealed mild leukocytosis with neutrophilia, alongside markedly elevated ESR and CRP levels. Given the pharyngitis, streptococcal infection was initially suspected, with serological confirmation of recent streptococcal exposure. A skin biopsy performed by an experienced dermatologist demonstrated fibrinoid necrosis, a hallmark histological feature of vasculitis, leading to a diagnosis of vasculitis provisionally classified as polyarteritis nodosa, which was clinically appropriate. She received a course of corticosteroids and was commenced on mycophenolate mofetil as a steroid-sparing agent, achieving clinical remission for 18 months. At that juncture, she elected to discontinue mycophenolate, a reasonable decision, and remained in remission for approximately four years. However, she subsequently presented with an identical constellation of symptoms: fever, sore throat, and recurrent non-blanching purpuric rash, accompanied by arthralgias without objective synovitis and evident pharyngeal congestion. Inflammatory markers were again elevated, with persistently high antistreptolysin O titres, consistent with a well-described entity in which streptococcal infection triggers systemic vasculitis beyond isolated cutaneous involvement. On this occasion, she proved refractory to corticosteroids and mycophenolate alone, necessitating rituximab therapy. The principal teaching point is that an infective trigger, such as streptococcus, can precipitate immunological sequelae manifesting as streptococcus-associated vasculitis, representing classic polyarteritis nodosa rather than post-streptococcal vasculitis; she continues on disease-modifying antirheumatic drugs.

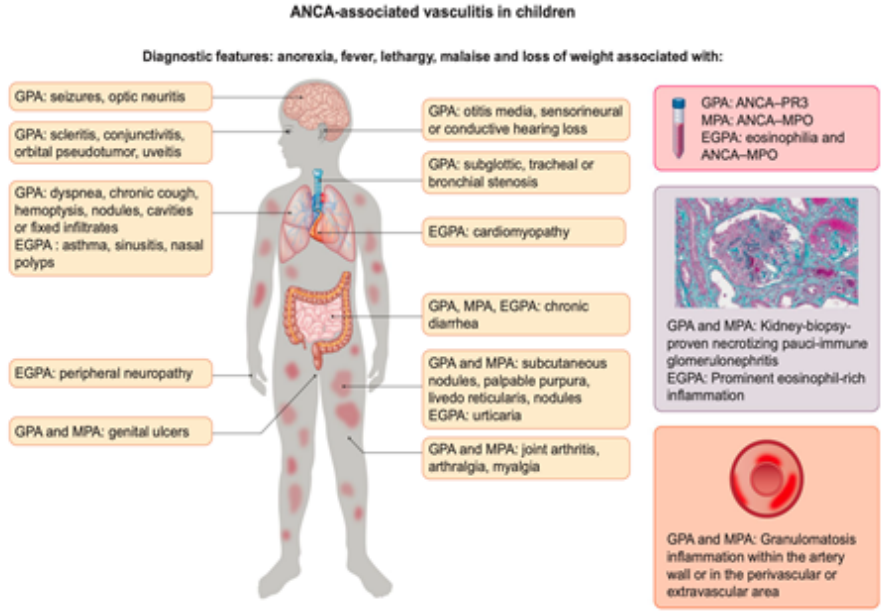
Vasculitis is conventionally classified according to the predominant vessel size as large, medium, or small vessel. In pediatric practice, large- to medium-vessel vasculitis is exemplified by Kawasaki disease, while polyarteritis nodosa, characterized by its classic purpuric rash, may present with a streptococcal association, potentially leading clinicians to attribute symptoms to infection alone rather than to an underlying immunological process. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis remains rare, with an incidence of approximately 1–2 per million, warranting consideration primarily in atypical or refractory cases (Fig. 6).[33]

Fig. 6. Vessel-size-based classification of vasculitis from aorta to small vessels



ANCA-associated vasculitis may exhibit protean manifestations, although it occurs infrequently in pediatric populations. When encountered, presentations may involve central nervous system or cardiac complications, while vasculitic rash and fever remain the principal clinical pointers. A non-blanching purpuric rash accompanied by fever and elevated inflammatory markers mandates immediate assessment of blood pressure and urinalysis for proteinuria. Clinicians frequently pursue advanced investigations while neglecting fundamental evaluations such as blood pressure measurement or urine protein-to-creatinine ratio (Fig. 7).[34]

Fig. 7. Multisystem clinical manifestations of ANCA associated vasculitis in children



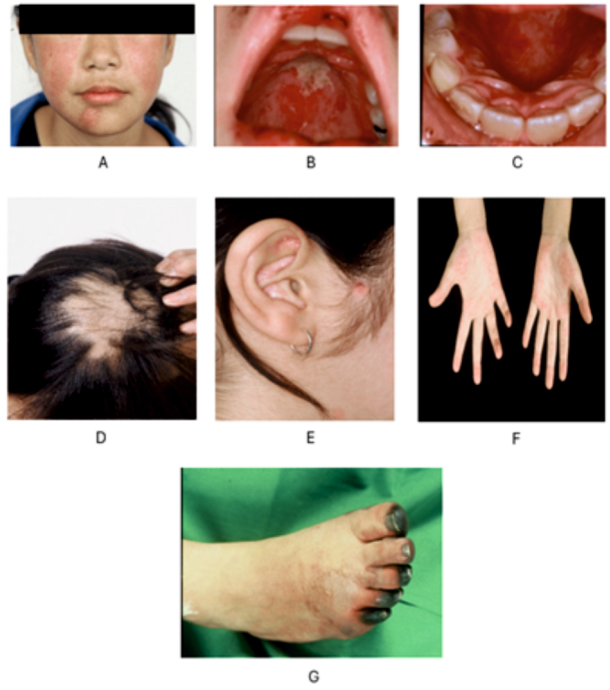
Life-threatening manifestations include end-stage renal disease, rapidly progressive glomerulonephritis, or pulmonary-renal syndrome; affected patients may deteriorate rapidly if not managed aggressively. Central nervous system involvement, although possible, is uncommon. By contrast, non-life-threatening, skin-limited presentations are more frequent. Key diagnostic principles include the value of tissue biopsy for histopathological confirmation, the recognition that negative ANCA serology does not exclude the diagnosis, and the recommendation that confirmed cases be managed at specialized centers with expertise in pediatric vasculitis.[35,36]

Case 4: Systemic lupus erythematosus

A 10-year-old girl presented with a one-week history of fever, rash, oral ulcers, and polyarthritis, with the diagnosis confirmed by characteristic laboratory findings. In contrast to the neutrophilia and leukocytosis observed in most other conditions, this unwell child exhibited neutropenia and thrombocytopenia approaching pancytopenia. A pivotal diagnostic clue is the presence of fever in an adolescent girl with dissociation between ESR and CRP, in which CRP remains disproportionately low despite markedly elevated ESR, a finding that is nearly pathognomonic for SLE. SLE is distinctive among rheumatological disorders, with the notable exception of certain complications, such as infection, in that CRP is rarely substantially elevated. Additional supportive features included hypoalbuminemia indicative of prolonged disease activity, hypocomplementemia, and a positive direct Coombs test. This constellation represented classic SLE, further corroborated by autoantibody profiling revealing ANA positivity, anti-double-stranded DNA antibody positivity, and evidence of lupus nephritis. She was successfully managed with steroids, mycophenolate mofetil, and rituximab. The key teaching point is that a teenage girl presenting with fever, rash, cytopenias, and low CRP merits urgent consideration of SLE, prompting evaluation of complement levels, urinalysis, and blood pressure.

SLE manifests with remarkable phenotypic heterogeneity and multisystem involvement (Fig. 8). In sun-exposed regions, cutaneous manifestations such as rash are prominent; however, in temperate climates such as the United Kingdom, particularly during winter, patients more commonly present with fever, hematological abnormalities, and visceral organ involvement without overt dermatological features. Ultraviolet exposure may unmask the malar rash, which is often more conspicuous in fair-skinned individuals (Fig. 8A). In patients with darker skin phototypes, discoid lesions or depigmentation predominate over erythema or hyperpigmentation. Meticulous examination of the palate frequently reveals ulceration or petechiae (Fig. 8B and 8C). Adolescent girls may underreport patchy alopecia due to social embarrassment, yet this remains a frequent manifestation (Fig. 8D). Vasculitic lesions characteristically favor the ears (Fig. 8E), while palmar erythema is a distinctive early feature (Fig. 8F). Delayed diagnosis or fulminant vasculitis may culminate in digital gangrene (Fig. 8G).[37]

Fig. 8. Mucocutaneous and vascular manifestations of pediatric SLE



Cytopenias are prominent, including Coombs-positive hemolytic anemia, with rare thrombotic thrombocytopenic purpura-like presentations. Nearly all patients test ANA-positive with contemporary assays; ANA negativity virtually excludes lupus. Anti-double-stranded DNA positivity occurs in only 50-80% of cases. Thus, ANA positivity is required, but other autoantibodies are variably present.[38]

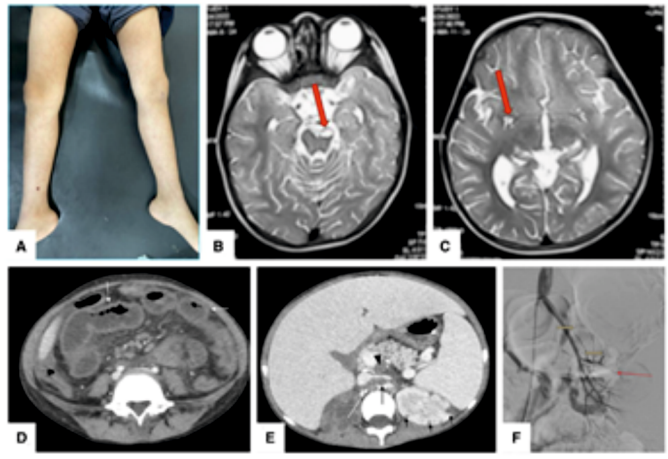
Case 5: Monogenic vasculitis

A 4-year-old boy presented in early childhood with chronic diarrhea, failure to thrive, and recurrent infections, accompanied by cytopenias. Low B-cell and natural killer cell counts, coupled with inadequate vaccine responses, raised suspicion for an underlying primary immunodeficiency, prompting management by immunology specialists. His clinical course from birth until his untimely death at 12 years of age involved extensive evaluation for recurrent infections and neutropenia, with trials of multiple therapies including intravenous immunoglobulin and various immunomodulatory agents. Progressive complications included encephalitis and invasive fungal infections, ultimately revealing profound immune dysregulation characterized by hypogammaglobulinemia and impaired vaccine immunogenicity. A delayed diagnosis of monogenic vasculitis secondary to adenosine deaminase 2 (ADA2) deficiency was established; notably, he never manifested the classic vasculitic triad of recurrent fever, vasculitic rash, or cerebrovascular events. Although a hematopoietic stem cell transplant was attempted, he did not survive.

The patient's sibling presented at two months of age with severe anemia (19 g/L), attributable to pure red cell aplasia, a recognized manifestation of ADA2 deficiency, and was promptly initiated on etanercept

therapy at 10 weeks of age, achieving excellent outcomes following successful hematopoietic stem cell transplantation. This familial case, subsequently published, underscores the phenotypic heterogeneity of monogenic vasculitis and emphasizes the need for a high index of clinical suspicion.[39] The spectrum of deficiency of adenosine deaminase 2 (DADA2) in the Indian population has been characterized, revealing diverse presentations including recurrent fever and livedo racemosa. Strokes, however, represent the most frequent neurological manifestation. Accordingly, DADA2 and other monogenic vasculitides warrant consideration in any child presenting with unexplained fever and stroke (Fig. 9).[40]

Fig. 9. Multisystem vasculitic and aneurysmal manifestations in a child with DADA2



Periodic fever syndromes and periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA)

PFAPA and related periodic fever syndromes are now well recognized as important causes of recurrent fever in childhood, and pediatricians increasingly encounter these entities in routine practice. Very rare syndromes with an incidence of approximately 1-2 per million are beyond the scope of this discussion; instead, emphasis is placed on the more frequently observed disorders. Recurrent fevers without a clear infectious etiology, a poor or absent response to appropriate antibiotic therapy, and a strikingly predictable periodicity, typically every 4-6 weeks with febrile episodes lasting 2-3 days followed by spontaneous resolution, should raise suspicion of an autoinflammatory or periodic fever disorder. Ethnic background is a well-recognized risk factor in European cohorts, particularly for hereditary monogenic periodic fevers, but appears to play a less prominent role in India, although regional clustering may occur; robust epidemiological data from the Indian subcontinent remain limited.[1,41,42]

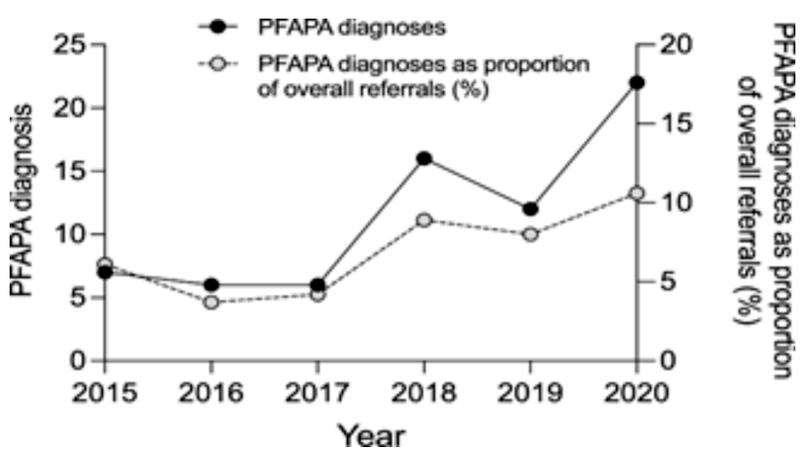
Among the periodic fever syndromes, PFAPA is the most common diagnosis in young children and should be particularly suspected in those under five years of age presenting with clockwork-like febrile episodes. These children frequently exhibit markedly inflamed tonsils and are often repeatedly treated for presumed recurrent tonsillitis; a subset also reports abdominal pain during episodes. Acute-phase reactants such as CRP are typically elevated during attacks but normalize rapidly as the fever resolves spontaneously within a few days, and children remain entirely well between episodes.[41,43]

PFAPA is classically defined using the modified Marshall criteria, which include onset before five years of age, regularly recurring fever episodes, the presence of at least one of aphthous stomatitis, pharyngitis, or cervical adenitis, and complete clinical well-being with normal growth and unremarkable investigations between attacks. Routine laboratory tests outside of febrile episodes are generally normal, and growth parameters are typically preserved, supporting the benign systemic impact of the syndrome. During the coronavirus disease 2019 (COVID-19) pandemic, with substantial reductions in nursery and school attendance, several tertiary pediatric centers reported that the true burden of PFAPA became more apparent, as fewer episodes were misattributed to community-acquired infections (Fig. 10). This experience highlighted that many children had previously been labelled as having recurrent viral infections and had been exposed to multiple unnecessary courses of antibiotics before PFAPA was recognized (Fig. 11).[44]

Fig. 10. Incidence rate of children diagnosed with PFAPA syndrome and their characteristics before and during the COVID-19 pandemic

	Pre-COVID-19 pandemic Jan 2015 to Dec 2019 (n=51)	COVID-19 pandemic Jan 2020 to Mar 2021 (n=26)
PFAPA incidence rate (per 1 000 000 person-years)*	9.85	24.67
Gender (male:female)	28:23 (55%:45%)	15:11 (58%:42%)
Age (years), median (range)	4.8 (1.3–12.8)	5.4 (1.3–15.5)
Colchicine treatment	25 (51%)	17 (65%)
Tonsillectomy	24 (49%)	Insufficient time elapsed to assess
Clinical resolution	41 (89%)	Insufficient time elapsed to assess

Fig. 11. Rise in children presenting with PFAPA syndrome during the COVID-19 pandemic



Tonsillectomy is a key therapeutic option in PFAPA and has been shown in multiple cohort studies and controlled trials to result in complete or near-complete remission in a substantial proportion of patients, with reported cure rates often in the 80–90% range. In many Western health systems, the indications for

tonsillectomy have become more restrictive over the last two decades, moving away from liberal use for recurrent tonsillitis, as was common in the 1970s and 1980s, toward targeted surgery for well-defined conditions such as PFAPA or obstructive sleep apnea. This shift in practice has likely contributed to increased recognition and diagnostic labelling of PFAPA, as recurrent febrile episodes previously "treated" with tonsillectomy are now more often evaluated and characterized as autoinflammatory syndromes.[45,46]

For general pediatric practice, a pragmatic diagnostic approach is essential. Autoinflammatory or hereditary periodic fever syndromes should be considered in children with early-onset recurrent fever, a positive family history of similar febrile illnesses (for example, parental episodes resolving in early adulthood), recurrent fevers without documented infection, and characteristic accompanying features such as abdominal pain suggestive of familial Mediterranean fever or rash and urticaria-like lesions suggestive of cryopyrin-associated periodic syndromes. In selected settings, a therapeutic trial of colchicine for approximately three months may be informative, as a favorable response can be both diagnostically and therapeutically useful in familial Mediterranean fever and some PFAPA-like phenotypes, given its generally favorable safety profile in pediatric patients. Clinical assessment should incorporate documentation of age at onset, the pattern and severity of inflammatory episodes, and systematic use of a symptom diary to delineate periodicity, while laboratory evaluation should confirm systemic inflammation using acute-phase reactants during attacks and exclude alternative infectious or immunodeficiency causes.[47]

In middle-income countries such as India, the expanding availability of next-generation sequencing, including clinical exome sequencing offered by commercial providers, has substantially improved the diagnostic work-up of suspected monogenic autoinflammatory conditions by enabling parallel analysis of multiple candidate genes at comparatively lower cost. Management of rare, non-PFAPA periodic fever syndromes is best centralized in specialized centers with expertise in pediatric rheumatology and clinical immunology, given the complexity of interpretation and the potential need for biologic therapies targeting interleukin-1 or other cytokines. By contrast, in children with a typical PFAPA phenotype characterized by a clear cyclic pattern, fulfilment of clinical criteria after exclusion of alternative diagnoses, and frequent misclassification as recurrent tonsillitis-tonsillectomy remains a highly effective and often definitive intervention, making PFAPA one of the few periodic fever syndromes in which cure is routinely achievable.[1,45-47]

Take-home messages

- Recurrent fevers without an identifiable cause, persisting despite multiple evaluations, require a structured diagnostic approach prioritizing infectious and malignant causes, with rheumatological and auto inflammatory disorders as key differentials; factitious fever, though rare, should also be considered.
- Parental accounts of recurrent fever may be unreliable; objective inpatient monitoring is essential to confirm episodes.
- Periodic fevers do not always follow strict regularity; atypical patterns should prompt consideration of less common autoinflammatory syndromes.

- PFAPA syndrome remains underdiagnosed in children under five, despite tonsillectomy being a highly effective curative intervention.
- In children under five years of age, Kawasaki disease and PFAPA are most common; between five and ten years, these remain possible but less frequent; from ten to fifteen years, SLE and vasculitides become more prominent.
- A systematic, age-stratified approach incorporating fever pattern analysis, targeted genetic testing, and immunological evaluation facilitates timely diagnosis and optimal management.

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