Not just another fever

Recognising recurrent fever syndromes in children

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Fever in children is common, with infection being the cause in most cases. When infection is excluded, broader causes of recurrent and periodic fevers in children include rheumatic disease, malignancy and immunodeficiency. Autoinflammatory periodic fever syndromes are rare but important to consider, as targeted treatments can improve quality of life and prevent long-term morbidity.

KEY POINTS

- Most children with recurrent fevers do not have a periodic fever syndrome; infection is the most common cause of fever, regardless of the fever pattern.
- Periodic fever syndromes should be considered if fever episodes are recurrent, have a predictable pattern and are not explained by infection, and if the child is well between episodes.
- Measurement of inflammatory markers and a full blood count during a fever episode can help guide the diagnostic process.
- Referral of the patient to a paediatric rheumatologist or other specialist experienced in these conditions is appropriate in the setting of a suspected periodic fever syndrome.

Fever is one of the most frequent paediatric presentations in primary care and is most often caused by infection, particularly respiratory infection, which accounts for the majority.[1] Fevers can be acute or chronic, and can occur in various patterns such as prolonged, recurrent or periodic (Box 1).[2] When infection is excluded, the differential diagnosis of recurrent fever in children includes rheumatic disease, malignancy and immunodeficiency, requiring careful assessment (Box 2).[3,4]

When assessing a child with fever, taking a thorough history is important, as the pattern of fever, associated symptoms and family history may provide important diagnostic clues. A thorough clinical examination, with attention paid to findings in the oropharynx, lymph nodes, musculoskeletal system and skin, can also be helpful. In cases of recurrent or periodic fevers, assessing organ involvement, the suspected aetiology and whether the child returns to baseline health between fever episodes can assist in directing further assessment. A diagnostic and management approach to recurrent fever is presented in the Flowchart.

A small proportion of children with recurrent fevers have a rheumatic disease, of which a smaller proportion have an autoinflammatory periodic fever syndrome. Autoinflammatory periodic fever syndromes are a group of rare disorders of the innate immune system characterised by unprovoked episodes of systemic inflammation. Management varies between specific syndromes and early recognition is important to prevent complications. This article reviews the clues that may suggest an autoinflammatory cause of recurrent fevers.

Understanding autoinflammation

The immune system can be broadly divided into two components: the innate and adaptive systems. The innate immune system provides a 'first line of defence' involving a rapidly activated, nonspecific response to pathogens. It acts via myeloid cells (e.g. macrophages and neutrophils), cytokines (particularly interleukin-1, interleukin-6 and tumour necrosis factor-alpha) and chemical mediators (e.g. complement). This is in contrast to the adaptive immune

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Australian Rheumatology Association

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1. PATTERNS OF FEVER IN CHILDREN[2]

- **Prolonged:** a single episode of fever that is longer in duration than expected for the clinical syndrome
- **Recurrent:** repeated, unrelated fever episodes at irregular intervals, either in a single organ system or involving different organ systems
- **Periodic:** recurring episodes of fever (which may occur regularly or irregularly) where the associated symptoms are predictable, a return to normal health between episodes and no identifiable infectious cause

2. DIFFERENTIAL DIAGNOSES OF RECURRENT OR PERIODIC FEVERS IN CHILDREN[3,4]

Infection
- Viral (e.g. Epstein–Barr virus, cytomegalovirus or recurrent viral respiratory infections)
- Bacterial (e.g. recurrent urinary tract infections, abscesses or occult bacterial infections)
- Parasitic (e.g. malaria)

Inflammatory or immunological
- Systemic lupus erythematosus
- Inflammatory bowel disease (e.g. Crohn's disease)
- Behçet syndrome
- Systemic juvenile idiopathic arthritis
- Periodic fever syndromes
- Vasculitis (e.g. antineutrophil cytoplasmic antibody-associated vasculitis)

Malignancy
- Leukaemia
- Lymphoma
- Solid organ cancers

Immunodeficiency
- Cyclic neutropenia
- Congenital or acquired immunodeficiencies (e.g. HIV) manifesting as recurrent infections

Other
- Drug fever
- Castleman disease
- Central nervous system abnormalities (e.g. hypothalamic dysfunction)
- Factitious fever

system, which is slower to respond but highly specific, involving lymphocytes (T and B cells) and immunological memory.[5]

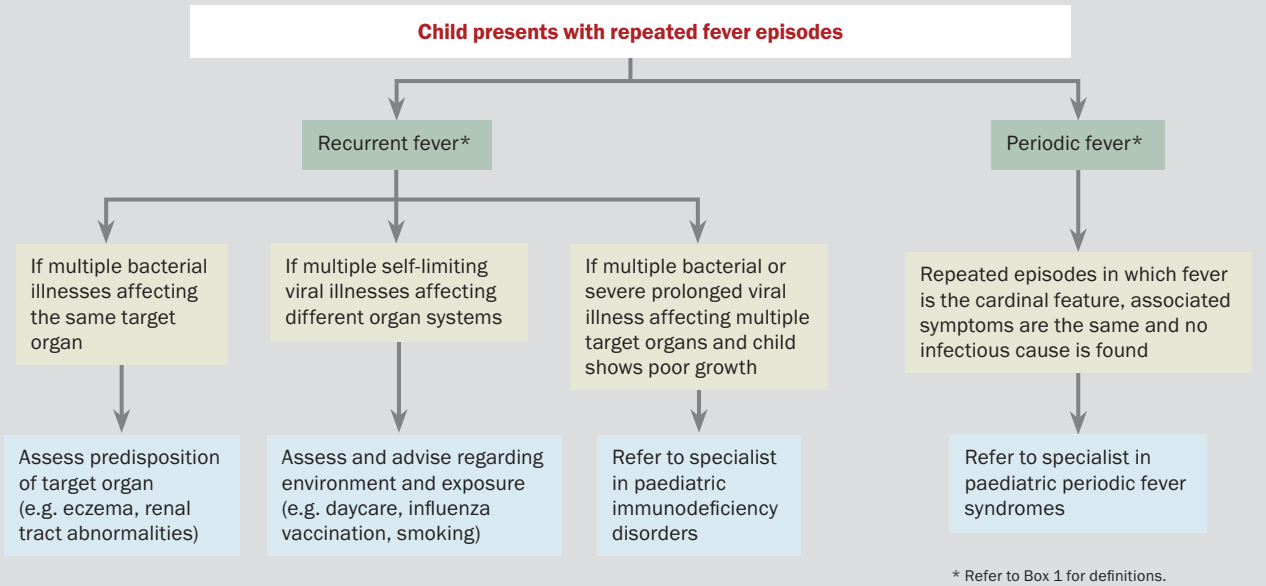
The term 'autoinflammatory' has been used to differentiate diseases of the innate immune system from those that arise primarily from the adaptive immune system, which we call autoimmune diseases. Autoinflammatory diseases result from dysregulation of the innate immune system, leading to inflammatory episodes characterised by fevers and stereotyped symptoms, typically lasting a predictable duration and often with a predictable frequency.[6]

Clinical features of autoinflammatory periodic fever syndromes

The following clinical features are suggestive of an autoinflammatory periodic fever syndrome.

- **Recurrent fevers:** a proposed definition of recurrent fever is the presence of three or more episodes of fever in a six-month period (with no alternative cause such as infection), with an interval of at least seven days between episodes.[7] The episodes often occur with a predictable pattern of duration and frequency and are termed 'periodic'.
- **Associated symptoms:** these may include rash, serositis (including pleuritis, peritonitis and myocarditis), arthritis or mucosal ulcers. The

MANAGEMENT APPROACH TO REPEATED FEVER EPISODES IN A CHILD



* Refer to Box 1 for definitions.

TABLE. COMMON AUTOINFLAMMATORY PERIODIC FEVER SYNDROMES[5,9-11]

Syndrome	Onset	Prevalence	Key features	Fever pattern	Genetic association	Management	Prognosis
PFAPA	• Early childhood, especially <5 years of age	• Limited data	• Recurrent fever, mouth and pharyngeal ulcers, pharyngitis, cervical lymphadenitis • Well between episodes • No ethnic predilection	• 3–6 days every 4–6 weeks • Highly predictable in each child ('like clockwork')	• Unknown	• Prednisolone at onset • Tonsillectomy • Colchicine	• Usually resolves spontaneously several years after onset
FMF	• Usually <20 years of age	• Up to 1 in 500 in certain populations	• Recurrent fever, serositis, arthritis, erysipelas-like rash • Common in Mediterranean populations	• 12–72 hours • Variable frequency	• *MEFV* gene (AR inheritance)	• Daily colchicine • IL-1 inhibitors if needed	• Lifelong • Risk of amyloidosis
TRAPS	• Childhood or adulthood	• 1 in 100,000 in populations of Northern European ancestry	• Prolonged fever, rash, myalgia, serositis, conjunctivitis, periorbital oedema, arthritis • No ethnic predilection	• ≥7 days • Variable intervals	• *TNFRSF1A* gene (AD inheritance)	• Corticosteroid • Etanercept (tumour necrosis factor receptor antagonist) • IL-1 inhibitors	• Amyloidosis in about 10%
MKD (formerly HIDS)	• Infancy	• Very rare • About 200 known cases worldwide	• Fever, lymphadenopathy, gastrointestinal symptoms, rash, ulcers, myalgia • More common in Northern European populations	• 3–7 days • Variable intervals (usually 1–2 months)	• *MVK* gene (AR inheritance)	• IL-1 inhibitors (as needed or continuous)	• Improves in adolescence
CAPS (FCAS, MWS, NOMID)	• Infancy	• 1 in 300,000 to 1,000,000 (based on European and North American data)	• Cold-induced urticaria, rash, arthritis, hearing loss, central nervous system involvement (varies by subtype) • No ethnic predilection	• FCAS: 12–24 hours post-cold exposure • MWS: variable • NOMID: continuous	• *NLRP3* gene (AD inheritance)	• IL-1 inhibitors	• Depends on severity and subtype

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; CAPS = cryopyrin-associated periodic syndrome; FCAS = familial cold autoinflammatory syndrome; FMF = familial Mediterranean fever; HIDS = hyperimmunoglobulin D syndrome; IL-1 = interleukin-1; MKD = mevalonate kinase deficiency; MWS = Muckle–Wells syndrome; NOMID = neonatal-onset multisystem inflammatory disease; PFAPA = periodic fever, aphthous stomatitis, pharyngitis and adenitis; TRAPS = tumour necrosis factor receptor-associated periodic fever syndrome.

episodes are typically stereotyped and have a similar constellation of symptoms each time.

- **Absence of coryzal symptoms:** no signs or symptoms of an intercurrent respiratory infection, such as cough and coryza, are present.
- **Return to baseline:** patients are generally well between episodes, with resolution of all signs and symptoms that manifest during a febrile episode.
- **Raised levels of inflammatory markers:** there is typically a marked elevation of C-reactive protein levels and erythrocyte sedimentation rate during an episode of fever, which typically normalise between episodes.[4]

Common autoinflammatory periodic fever syndromes

There are many rare autoinflammatory periodic fever syndromes described in the paediatric literature, and the list continues to grow as further discoveries of their genetic and biochemical aetiology are uncovered.[8] A subset of the more common autoinflammatory periodic fever syndromes that are more likely to be encountered in the primary care setting are outlined in the Table.[5,9-11]

Investigations

If historical and clinical features of a periodic fever syndrome are present, initial workup that may assist in the diagnostic process is uncomplicated and should include:

- inflammatory markers (e.g. C-reactive protein and erythrocyte sedimentation rate):
  - at least moderately raised levels

of inflammatory markers during an episode are consistent with the diagnosis
  - normal inflammatory markers during an episode make the diagnosis unlikely
  - between fever episodes, inflammatory markers may normalise
- full blood count and blood film:
  - may show leukocytosis during fever episodes
  - consider haematological malignancy or immunodeficiency when interpreting abnormal cell counts, particularly cytopenia
  - serial full blood counts may be requested in cases of suspected cyclic neutropenia, an important differential for recurrent fevers
- liver function tests and urea, electrolytes and creatinine:
  - abnormal findings may indicate an alternative systemic disease, for which further investigations may be needed.

If the diagnosis of a periodic fever syndrome is suspected, a specialist may order serum amyloid A or genetic testing. Serum amyloid A is an acute phase reactant that is a sensitive but nonspecific marker of inflammation. It can be used to monitor disease control, assess for the risk of developing amyloidosis and detect subclinical inflammation in the setting of familial Mediterranean fever (FMF).[12]

Genetic testing is considered when clinical features are suggestive of a monogenic autoinflammatory syndrome. Patient or parental consent is required, and the method of testing and list of candidate genes should be carefully considered before the test is requested. Specialist interpretation of the result is required, as a negative or inconclusive result does not always exclude the diagnosis, and treatment may still be indicated.[13]

Management

Patients with a suspected autoinflammatory periodic fever syndrome should be referred to a specialist with experience in the diagnosis and management of these conditions. This may include a paediatrician, paediatric rheumatologist, immunologist or infectious disease physician.

Treatment aims to reduce the frequency and severity of episodes; improve the quality of life by reducing time spent away from school, recreational activities and parental workplaces; and prevent long-term morbidity.

Corticosteroids are often used for a very short duration at the start of an episode with the aim of reducing the severity of symptoms and episode duration. The chronic use of systemic corticosteroids is limited by the long-term adverse effects.

Colchicine can be taken regularly to reduce the episode frequency and severity in several conditions (including FMF and periodic fever, aphthous stomatitis, pharyngitis and adenitis [PFAPA]). Importantly, it also reduces the long-term risk of developing amyloidosis in cases of FMF.[14]

Biological disease-modifying antirheumatic drugs, which act via the blockade of proinflammatory cytokines (e.g. interleukin-1 using anakinra or canakinumab), can be highly effective for some autoinflammatory conditions.

Tonsillectomy can be curative in children with PFAPA.[7]

Prognosis and long-term care

The course of periodic autoinflammatory fever syndromes varies between the different conditions. Amyloidosis is a severe complication of several autoinflammatory conditions including FMF, tumour necrosis factor receptor-associated periodic fever syndrome and cryopyrin-associated periodic syndrome, and can lead to long-term morbidity. Optimised disease control and regular assessment are essential for the prevention of this complication, which generally manifests clinically with renal involvement after many years of active inflammation.[15] In the case of PFAPA, symptoms can resolve or reduce in severity as children enter adolescence or adulthood.[16]

Conclusion

Although the cause of most recurrent fevers in children is benign and self-limiting, such as viral infections, autoinflammatory periodic fever syndromes are rare but treatable conditions that should be considered when episodes are stereotyped and have no identifiable infectious cause. A targeted history, focused examination and simple investigations (such as measurement of inflammatory markers and a full blood count during a febrile episode) can help guide initial assessment. Early recognition and referral can prevent long-term complications such as amyloidosis, reduce the impact of repeated investigations and missed days of school, and improve the quality of life for children and their families. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

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