Outgrowing PFAPA

PFAPA patients typically outgrow the disease before adolescence, between the ages of 8 and 12, and without sequelae. However, in about 15% of cases, it may persist into adulthood with fewer flares as episodes become less frequent over time.

Vitamins and alternative therapies

Vitamin D, tart cherry, and probiotics are often used.

Siblings

PFAPA cases in siblings have been documented and studies have shown that PFAPA may run in families.

PFAPA in adults

Adult-onset PFAPA syndrome is seen in very rare cases. For the diagnosis of adult-onset PFAPA, physicians should rule out other diseases.

Labs

Laboratory tests should be undertaken during and in between flares to establish a pattern of elevated inflammatory markers including C-reactive protein (CRP), Sedrate (ESR) plus a CBC blood count, which can confirm signs of inflammation. These markers are positive during a flare and return to normal levels after the flare.

Triggers

Emotional stress (good or bad), excitement, viruses, physical activity.

Genetic testing

If a patient presents with symptoms outside of the PFAPA criteria, it would be relevant to perform genetic testing to investigate other mutations present causing a different autoinflammatory disease.
Parents should discuss testing options with the treating physician, who can order either autoinflammatory gene panels, Whole Exome Sequencing or Whole Genome Sequencing based on other factors. Relevancy may include family history of others presenting with similar symptoms.
Should no genetic mutation be found, the patient should be reclassified as uSAID (undifferentiated systemic autoinflammatory disease) and be treated accordingly with colchicine, IL-1 inhibitors, or other medications to avoid overuse of steroid medication.

Social and family impact

PFAPA is generally a self-limited condition. However, it can have a major impact on a child's quality of life, and may affect the family. It may cause children to miss days of school.
The fever episodes have a huge impact on daily activities.
The wellbeing of PFAPA children is poor, with a major impact on psychosocial functioning and increased fatigue.
Despite a benign clinical course, PFAPA syndrome is associated with a significant impact on the patients, and their families.

Educational impact

A child with PFAPA may experience disruptive educational issues in regards to school attendance, homework and related activities due to the recurrent flares. It is recommended to work with the school to develop a 504 accommodation plan based on the child's unique needs. This will ensure minimal impact to their learning and participation with broad support from teachers and administrators.

When it is not PFAPA

- Reaction to vaccines
- Urticarial rashes
- Cough and respiratory issues
- Excessive joint swelling in one or more joints
- Red eyes (conjunctivitis, uveitis)
- Hearing loss
- Developmental, growth, and neurologic delay
- Anemia
- Kidney issues
- Seizures
- Unable to walk
- Neonatal presentation
- Recurrent infections
- Standard 1-2 doses of steroids do not abort the flare

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The brochure has been reviewed and endorsed by PD Dr. Juergen Rech, Senior Physician and Head of the Autoinflammation Clinic, University of Erlangen.

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PFAPA

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Introduction

PFAPA syndrome stands for Periodic Fever, Aphthous stomatitis, Pharyngitis, and Adenitis and it is the most common periodic fever/autoinflammatory disease in children. Its cause is unknown, as it is not triggered by an infection nor is it contagious.

It is characterized by episodes of high fevers lasting approximately 4–6 days, recurring with clockwork regularity, and occurring every 2–8 weeks. Between episodes the child is asymptomatic and has continued normal growth and development. On average, most children with PFAPA will outgrow the disease within 5 years of onset or in the prepubertal years.

Diagnostic criteria

The diagnosis of PFAPA remains clinical and is based upon the following criteria:

- Recurring fevers beginning before age 5
- Constitutional symptoms in absence of upper respiratory infection with at least one of the following:
    - Aphthous stomatitis (mouth ulcers)
    - Cervical lymphadenitis (swollen lymph nodes)
    - Pharyngitis (sore throat)
- Patients have asymptomatic intervals between episodes
- Normal growth and development
- Exclusion of cyclic neutropenia

Age of onset

PFAPA usually begins in early childhood between the ages of 2 and 5 years old and slightly impacts boys at a greater percentage than girls.

Symptoms

PFAPA causes recurrent episodes of fever, mouth sores, sore throat, and swollen lymph nodes. Other symptoms include gastrointestinal manifestations (pain, vomiting, or diarrhea), headache, muscle pain, and mood/behavioral changes.

Diagnosis

PFAPA is diagnosed based on clinical symptoms that reoccur periodically. While there are no genetic tests to diagnose PFAPA, laboratory tests during flares will show elevated markers of inflammation. These blood test markers include C -reactive protein (CRP) and sedimentation rate (ESR).

It is important to note that PFAPA does not affect growth or development of the child. If failure to thrive is an issue, this would be a red flag for another autoinflammatory disease.

Lab work tests in and out of flares

Elevated inflammatory markers during flares are normal. However, they should return to normal once the flare is over. Chronic inflammation between flares is not a sign of PFAPA and should be a red flag to look for other mimicking disorders.

Treatments

All PFAPA patients present differently and treatment should be tailored based upon each case. There are several treatment options based upon response, flare intensity/ length, and parent comfort level.

Symptomatic (symptom control): NSAIDs (nonsteroidal anti-inflammatory drugs), acetaminophen, Tylenol (paracetamol), Ibuprofen (Advil, Motrin). In some patients, the fevers and other symptoms respond well to NSAIDs, which are available over the counter.

Abortive (stopping flare): corticosteroids and anakinra.
Prednisone 1-2mg/kg/day is given at onset of fever in a single dose. It can dramatically abort the fever episode within 1-4 hours. Anakinra/Kineret (IL-1 blocker) may be used should child fail all other treatment options. If this medication is required, diagnosis should be reevaluated.

Prophylaxis (preventing flare): cimetidine, colchicine.
These medications should be considered for use, when child has incomplete response to steroid treatment or if flare intervals are close together.

Surgical: tonsillectomy and adenoidectomy (T&A)
T&A should be considered if patient has either enlarged or purulent tonsillitis. Although the surgical procedure is commonly performed in PFAPA patients in the USA, studies indicate that it should only be undertaken in selected cases (see reference below). It is important to rule out other autoinflammatory diseases prior to surgical intervention.

Reference:
Consensus treatment plans for periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome (PFAPA): a framework to evaluate treatment responses from the childhood arthritis and rheumatology research alliance (CARRA) PFAPA work group. Pediatr Rheumatol Online J. 2020 Apr 15;18(1):31. *doi: 10.1186/s12969-020-00424-x.*

Common flare scenarios

Scenario 1: Child may respond to multiple doses of NSAIDs.
Scenario 2: Child may require prednisone at start of flare to abort fever and other symptoms. However, flares may increase in frequency.
Scenario 3: Child may require use of colchicine or cimetidine to reduce flare intensity and symptoms. NSAIDs may also be added to control the flare. Both drugs interact with other medications (i.e. certain antibiotics) and must be used daily.
Scenario 4: Child may require anakinra biologic due to severity of symptoms and non responsiveness to other medications.

Prednisone use in PFAPA

If prednisone is not used during a flare:
- The child will require multiple of NSAIDs during each of the 4 to 6 days and may feel miserable, be unable to eat, play, go to school, travel, etc. Additionally, parents may miss work days.
- The child may be at risk for febrile seizures.
- The child may have increased risk of drug allergy due to the recurrent use of NSAID.

Flares—fever episodes

Febrile episodes last 4 to 6 days and recur about every 28 days. It is generally a self-limited disease, and many patients will experience spontaneous resolution within 3–6 years after onset and before adolescence. However, persistent cases with onset past childhood have been reported.

Documenting symptoms

Parents should keep a diary on all symptoms during and between flares including: recurrent fevers, mouth sores, sore throat, swollen lymph nodes, etc. The length of the flares should be noted and can be helpful to diagnose PFAPA and rule out other autoinflammatory diseases.

Keeping this symptom and fever diary over time will also allow parents to spot trends and report to their pediatricians. Additionally, it is important to take pictures of any visible symptoms such swollen joints, rashes, eye issues, as they may be a sign of other autoinflammatory diseases.