

Patient Information

PFAPA

What is PFAPA?

“**PFAPA**” is an acronym for **P**eriodic **F**ever, **A**phthous stomatitis, **P**haryngitis and **A**denitis. This condition is one of a group of diseases called the periodic fever syndromes. Most of these conditions are inherited but the cause of PFAPA is unknown. This condition was first described in 1987 in otherwise healthy American children. Since then it has been diagnosed most frequently in children of European ancestry, although it may affect children of any background, as shown by reports of a large number of cases in Israel. PFAPA affects boys and girls equally.

What are the periodic fever syndromes?

These are a group of disorders in which patients experience recurrent fevers and other symptoms, although there are no signs of infection or of any other apparent cause. These syndromes are all believed to be caused by overactivity of part of the body’s natural defence system, the immune system.



The autumn crocus flower, the source of the drug colchicine

The immune system involves a wide variety of different types of blood cells and molecular messengers. These components interact together through a variety of complex mechanisms, known as pathways. The part of the immune system affected in periodic fever syndromes is called innate immunity.

In healthy people, normal activation of the innate immune pathways occurs when the body encounters some type of tissue damage or disease. The consequent inflammation helps to fight disease and promote recovery.

PFAPA is NOT amyloidosis



If you have been referred to us because of suspicion that you or your child may have a fever syndrome such as PFAPA, this does NOT mean that you or your child have amyloidosis.

Very understandably, some patients and family members may become concerned when they are referred to us, for the following reasons:

1. We are based at the National Amyloidosis Centre (NAC), at the Royal Free Hospital.
2. Our consultants are specialists in amyloidosis as well as fever syndromes.

It is true that a few patients with longstanding, untreated periodic fever syndromes may eventually, after many years, develop amyloidosis.

However for the vast majority of our patients:

1. Referral to us is for the purposes of diagnosis and treatment of a fever syndrome.
2. Amyloidosis is not suspected at any time in the course of their illness.
3. Amyloidosis can be easily prevented by appropriate treatment.

In the periodic fever syndromes, some of these pathways are overactive. This leads to an overly aggressive immune response. The body acts as if there was a serious infection even when there is no actual disease or tissue damage acting as a stimulus. There is a state of prolonged inflammation, known as auto-inflammation. Auto-inflammation itself leads to symptoms of disease and sometimes to tissue damage.

Different pathways are implicated in different types of periodic fever syndromes. Treatment aims to “switch off” the overactive inflammatory pathway and depends on precise identification of the particular syndrome, and pathway affected.

Auto-inflammation is quite different to auto-immunity. In auto-immune diseases, the body produces antibodies against its own tissues, which then cause damage. In auto-inflammatory conditions the body does not produce antibodies against its own tissues. Auto-immune diseases are far commoner than auto-inflammatory syndromes. Auto-immune diseases include conditions such as childhood diabetes and rheumatoid arthritis.

What causes PFAPA?

Other, similar periodic fever syndromes are known to be hereditary. In recent years the precise genetic causes of most of the hereditary fever syndromes have been identified, so that they can be diagnosed by genetic testing. Studies attempting to establish a genetic basis for PFAPA have failed so far. But up to 1 in 5 of the children who fulfil the criteria for a diagnosis of PFAPA have been found to carry a known fever gene mutation. We do not yet know what the significance is of this finding.

How is PFAPA diagnosed?

The diagnosis of PFAPA, and of other periodic fever syndromes is often delayed because:

- the signs and symptoms are not specific and vary greatly
- these syndromes are rare

Some doctors have never heard of these syndromes, and most have seen few if any cases. So it may take time

What are the symptoms of PFAPA?



Symptoms usually start before age 5, most frequently at around age 2, and include **recurrent attacks of fever** lasting 3-6 days, with **one** of the following:

- mouth ulcers (**aphthous stomatitis**)
- sore throat (**pharyngitis**)
- swollen glands in the neck (**adenitis**)

There may also be chills, headache, stomach pain or muscle pains. Children are completely well between attacks, and there are no signs of respiratory infection during the attacks. Parents often report that they seem less susceptible than other children to minor viral infections.

Despite negative throat cultures, children often receive repeated courses of antibiotics for presumed recurrent pharyngitis before PFAPA is diagnosed.

Attacks are often extremely regular, and parents may learn to plan around them in advance, often knowing exactly when an attack will occur.

before the possibility is raised that a patient may have a periodic fever syndrome.

The presentation varies tremendously from patient to patient, but for many doctors, the strongest pointers to a diagnosis of PFAPA are:

- the extreme regularity of attacks
- the rapid improvement seen after a small dose of steroid treatment during an attack

Parents often report that they can organise their diary around their children’s attacks in advance, as they know just when to expect them. Keeping a symptom diary can be helpful for assessing the timing of attacks.

Although strong suspicion of PFAPA may be based on these observations, other causes of recurrent fever must be ruled out before PFAPA can be reliably diagnosed. So doctors need to ensure that the child is not experiencing

recurrent infections with viruses or bacteria. They must also make sure that blood tests rule out a condition called cyclic neutropenia. In this condition there are repeated infections because of repeated drops in the levels of the white blood cells that fight infections. So levels of white blood cells are low during attacks. In contrast, white blood cell levels are high in PFAPA.

Some specialist blood tests can support the possible diagnosis of a periodic fever syndrome. In these conditions symptoms are always accompanied by blood tests suggesting a lot of inflammation, including:

- high white cell count
- high CRP (C-reactive protein)
- high SAA (serum amyloid A protein)
- high ESR (erythrocyte sedimentation rate)

Genetic testing can rule out other periodic fever syndromes. This is difficult to do and expensive so only a very limited number of laboratories in the world (including ours) offer these tests.

How is PFAPA treated?



The treatment for PFAPA is corticosteroids, given by mouth.

When given at the start of an attack, the effect is dramatic, as the attack is usually completely prevented.

There is some evidence that tonsillectomy can cure this syndrome, especially in children with persistently enlarged tonsils.

In some cases long-term colchicine, given by mouth, can be very helpful in reducing or preventing attacks. Most children outgrow the symptoms of this condition within a decade.

Logistics

Patients with PFAPA need long-term surveillance, with regular administration of medications and specialist follow up.

Our consultants provide on-going direct management at the Royal Free Hospital for adults and at Great Ormond Street Hospital for Children.

When patients live far away, it may be possible to arrange for some treatments to be administered at their local hospitals or at other regional centres.

In these cases, we can help by providing:

- regular advice to patients and doctors involved in their treatment
- regular reviews at the Royal Free Hospital or Great Ormond Street Hospital for Children
- arrangements for hotel accommodation during visits

Children

Our consultants share a specialist paediatric fever clinic with Dr Paul Brogan and Professor Nigel Klein at the Great Ormond Street Hospital for Children. The atmosphere and environment there is child-friendly, with fun activities to occupy children while waiting for their appointment. The specialist paediatric nurses are expert at taking blood from children and putting them at ease. Therefore, most children and parents prefer to attend this clinic.

Occasionally we see children at the Royal Free Hospital if this location is more convenient, especially in the case of older children coming for repeat visits. This option should be discussed with our consultants before making the appointment.

Overseas and non-NHS entitled patients

The Royal Free Hospital welcomes overseas patients. European Union residents may be entitled to an NHS assessment in the UK under EU reciprocal arrangements for medical care that is not available locally (EU 112 form). Non-NHS entitled patients are welcome but are usually liable to charges.

Periodic Fever Service

The Inherited Periodic Fever Service is the only centre in the UK dedicated to the needs of patients with fever syndromes. We are based at the National Amyloidosis Centre. We have “state-of-the-art” clinical and research facilities and a team of highly qualified clinical, research and support staff. We are funded by the Department of Health to provide a diagnostic and management advice service for the UK’s national caseload of patients with inherited periodic fevers and related disorders. The clinical service includes:

- Detailed clinical assessment
- Genetic testing and counselling
- Recommendations for treatment and monitoring response
- Measurement and monitoring of specialised biochemical (blood) tests for C-reactive protein (CRP) and serum amyloid A protein (SAA)
- 3-12 monthly follow-up to assess response and further treatment requirements
- Providing information and support to fever patients, their families and health providers
- Systematic evaluation of existing and new treatments



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