Diagnostic and therapeutic difficulties in PFAPA: a case report
Trudności diagnostyczno-terapeutyczne w przypadku zespołu PFAPA – opis przypadku

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Abstract
Recurrent fever syndromes are autoinflammatory diseases. In their pathogenesis, no autoantibodies or autoreactive T-lymphocytes are found. Innate immunity and adaptive immunity are of great importance in this case. In the mid-latitudes, the most common syndrome is periodic fever with aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA), which mainly affects children under 5 years of age. Fevers occur cyclically, on average every 26–36 days. Characteristic features of PFAPA include the absence of any symptoms between fever episodes and undisturbed growth and development of the child. In laboratory tests, during a fever episode, elevated white blood cell count and an increase in inflammatory markers are observed. The recommended treatment is the use of glucocorticoids. In some cases, the use of colchicine or even an interleukin-1 receptor antagonist (anakinra) may be considered. The aim of this paper is to present the case of a 3.5-year-old boy hospitalised in the Department of Paediatrics, Nephrology and Paediatric Allergology of the Military Institute of Medicine due to recurrent episodes of fever with enlarged lymph nodes, occurring at regular intervals, as well as to draw attention to the difficulties encountered during the diagnosis of recurrent febrile episodes.

Keywords: fever of unclear origin, recurrent fever syndromes, autoinflammatory diseases, lymphadenopathy, pharyngitis, aphthae

Streszczenie

Słowa kluczowe: gorączka niejasnego pochodzenia, zespoły gorączek nawrotowych, choroby autozapalne, limfadenopatia, zapalenie gardła, afthy
INTRODUCTION

Fever is one of the most common reasons for paediatric visits. Recurrent fever syndromes (RFS) are rare autoinflammatory diseases. Unlike in autoimmune diseases, no autoantibodies or autoreactive T-lymphocytes are found in RFS. In the mid-latitudes, the most common syndrome is periodic fever with aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA), which mainly affects children under 5 years of age.

PFAPA syndrome is characterised by a fever that lasts an average of 3–7 days, accompanied by symptoms such as aphthous stomatitis, pharyngitis, or enlarged neck lymph nodes. The most common symptom (present in more than 90% of cases) is erythematous or exudative pharyngitis. PFAPA is typically associated with aphthae, i.e. painful, flat, round ulcerations, with well-marked erythematous edges, up to 1 cm in size. The lymph nodes are usually symmetrically enlarged on both sides, up to 5 cm, and their consistency can be described as moderately soft. Fevers occur cyclically, on average every 26–36 days. They are resistant to antipyretic treatment. In laboratory tests, elevated inflammation markers are observed.

In addition to the typical symptoms that make up the syndrome acronym, other symptoms may also occur, such as abdominal pain, arthralgia and arthritis, headache, rash, diarrhoea, nausea, or vomiting. In approximately 60% of cases, the prodromal symptom of fever is weakness. Between fever episodes, the patient shows no symptoms. The child’s development continues as normal.

The aetiology of PFAPA is not entirely clear. No monogenic mutation associated with its occurrence has been identified. PFAPA is believed to be caused by mutations in various genes; however, it is not clear which mutations are specific to it. Elevated levels of inflammatory cytokines are also found in its course, in particular: interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), interleukins (IL): IL-6, IL-1β, IL-18, IL-12p70, and granulocyte colony-stimulating factor (G-CSF). Increased expression of CD64 on neutrophils and monocytes during febrile episodes was also observed.

In addition, family members of patients with PFAPA are more likely to have: PFAPA, other recurrent fevers, and recurrent tonsillitis. It seems that innate immunity also plays an important role in the pathogenesis of the syndrome. The risk factors for PFAPA are similar to the risk factors for childhood infectious diseases. These include: not being breastfed by the mother, smoking by the mother during pregnancy, frequent occurrence of respiratory infections, and frequent use of antibiotics. One of the more interesting risk factors for the development of the syndrome is vitamin D deficiency. Studies have indicated a relationship between vitamin D deficiency and T-lymphocyte damage in PFAPA. A reduction in the frequency of fever episodes and their duration was also observed during vitamin D supplementation in children with its deficiency.

In everyday clinical practice, cases of recurrent fevers of undetermined cause many diagnostic and therapeutic difficulties. Therefore, the authors present the case of a 3-year-old boy who was eventually diagnosed with PFAPA.

CASE REPORT

A 3.5-year-old boy came to the Department of Paediatrics, Nephrology and Paediatric Allergology of the Military Institute of Medicine due to fever up to 39°C, which had been present for 2 days and did not respond to antipyretics, as well as ineffectiveness of outpatient treatment of lymphadenitis. He had experienced recurrent (every 3 weeks) infections for 4 months and one episode of obstructive bronchitis. In addition, the boy had been hospitalised twice in the preceding 2 months due to inflammation of the cervical lymph nodes. He was then treated with cefuroxime and clindamycin. One week before the current hospitalisation, he had completed antibiotic therapy with clindamycin.

On admission, the boy was in good overall condition. Physical examination showed the following abnormalities: dry skin, swollen tonsils with white coatings, and bilaterally enlarged submandibular and cervical (anterior and posterior) lymph nodes. Complete blood count showed elevated white blood cell count (WBC 22.46 × 10⁹/L) with a neutrophil smear. Inflammatory markers were elevated: C-reactive protein (CRP) at 5.4 mg/dL (normal range: 0–0.8 mg/dL), and erythrocyte sedimentation rate (ESR) after one hour at 39 mm (normal range: 0–8 mm). Liver and kidney function indicators were normal. The level of anti-streptolysin O (ASO) specific antibodies was low (<12 IU/mL). The levels of complement components remained normal (C3 – 133 mg/dL, C4 – 29 mg/dL). Serological test excluded Toxoplasma gondii infection. Throat swab for Streptococcus was negative. No Salmonella, Shigella, or Yersinia were found in the stool culture. Urinalysis showed no signs of infection. Ultrasound examination revealed bilaterally enlarged submandibular and cervical (anterior and posterior) lymph nodes. X-ray examination of the chest revealed inflammatory changes in the pulmonary parenchyma. After a 10-day antibiotic therapy (ceftriaxone at a dose of 80 mg/kg of bodyweight/day) and normalisation of the inflammatory markers, the boy was discharged home in good condition.

One month after hospitalisation, the boy returned to the hospital due to fever present for 2 days (up to 39°C), enlargement of the neck circumference for 24 hours, and weakness. On admission, the patient was in moderately good overall condition. Physical examination revealed enlarged cervical and submandibular lymph nodes. Complete blood count showed elevated white blood cell count (WBC 22.46 × 10⁹/L) with a neutrophil smear. Inflammatory markers were elevated: CRP at 8.5 mg/dL (normal range: 0–0.8 mg/dL), and ESR after one hour at 25 mm (normal range: 0–8 mm). Ultrasound examination of the peripheral lymph nodes showed numerous enlarged cervical lymph nodes, with the largest ones located bilaterally in the area.
of the angle of the mandible (dimensions on the right side: 32 × 13 mm, on the left side: 42 × 15 mm). The visualised nodes were mostly oval in shape, some with a visible recess, with a normal vasculature pattern. Viral diseases, connective tissue diseases, parasitic infections of the gastrointestinal tract, Lyme disease, and haematologic malignancies were excluded. The test results are presented in Tab. 1. On the basis of the clinical picture and test results, inflammation of the cervical lymph nodes was diagnosed. A 10-day treatment was applied: cefuroxime (at a dose of 100 mg/kg b.w./day) and amikacin (at a dose of 15 mg/kg b.w./day), resulting in an improvement in the patient’s clinical condition. Another hospitalisation due to fever up to 39°C present for two days with accompanying enlargement of lymph nodes, mainly in the angle of the mandible, took place two months later. Additional tests showed high levels of inflammation (CRP 13.4 mg/dL, ESR 40 mm/h, WBC 18.03K). Kidney and liver function indicators were normal. Urinalysis and culture showed no signs of infection. Based on the history and the entire clinical picture, PFAPA was suspected. Prednisone was administered orally at a dose of 2 mg/kg b.w., resulting in improvement of the patient’s clinical condition, resolution of symptoms, and reduction of inflammatory markers. The patient was discharged home with the recommendation to perform a follow-up test of inflammatory parameters in 4 days and to avoid contact with other children, clusters of people, and people with infections for a period of 1–2 months. Postponement of prophylactic vaccinations by one month was also advised. In case of another fever episode, oral prednisone (2 mg/kg b.w.) was recommended.

DISCUSSION

PFAPA belongs to the group of autoinflammatory diseases. Symptoms of these diseases occur in early childhood. They are caused by a genetic defect that leads to disturbances in the pathways of the innate immune response. Currently, numerous studies indicate that a family history of recurrent pharyngitis and recurrent aphthous ulcers may be the basis for the diagnosis of PFAPA. One such study involved 80 people with confirmed PFAPA and 80 people with suspected PFAPA. The subjects were divided into groups according to the presence of the characteristic features of the syndrome: recurrent episodes of fever lasting 2–7 days, onset of symptoms before the age of 10, episodes recurring regularly every 2–10 weeks, at least 6 episodes per year, presence of aphthous stomatitis, pharyngitis and/or neck lymphadenitis, no symptoms between fever episodes, and no disturbances in growth and development. Cyclic neutropenia and monogenic fever syndromes were excluded. In patients with probable PFAPA, the above-mentioned symptoms were present, but fevers did not occur at regular intervals or were not accompanied by aphthous stomatitis, neck lymphadenitis, or pharyngitis. In this study, 23% of people with PFAPA had at least one relative with the same diagnosis. In addition, the parents of these patients were more likely to suffer from recurrent pharyngitis (36%) and recurrent aphthous stomatitis (46%) compared to the parents of the control group (16% and 28%, respectively). The study also showed that siblings of patients with PFAPA have a higher risk of PFAPA, recurrent pharyngitis and recurrent aphthous stomatitis compared to siblings of controls (10%, 24%, and 27%, respectively)\(^1\). In the case discussed herein, the patient had a twin brother who showed similar symptoms. Positive family history allowed to significantly shorten the diagnostic and therapeutic process. The clinical course in the patient described in this study was typical. The boy was 3.5 years old and had recurrent fevers (up to 39°C) lasting 2–7 days, occurring at regular intervals (every 3 weeks). Additional symptoms included enlarged cervical and submandibular lymph nodes and weakness. In laboratory tests, elevated white blood cell count was observed during the febrile episode, as well as a characteristic increase in the inflammatory parameters: CRP and ESR. Bacteriological tests (blood cultures, swabs from the throat and tonsils) gave negative results. Between fever episodes, the boy did not experience any symptoms, and his development and growth were normal. During hospitalisation, the boy underwent a broad differential diagnosis. The following were excluded: urinary tract infection, sepsis, viral infections (cytomegalovirus, human immunodeficiency virus – HIV), bacterial infections (S. pyogenes, Salmonella, Shigella, Yersinia, Mycoplasma, Chlamydia, Bartonella, Borrelia), strains: methicillin-resistant Staphylococcus aureus – MRSA; bacterial strains capable of synthesising extended spectrum beta-lactamases – ESBL; vancomycin-resistant enterococci – VRE; and Mycobacterium tuberculosis), protozoan infections (toxoplasmosis), as well as connective tissue diseases.

In the differential diagnosis of recurrent fevers, juvenile idiopathic arthritis (JIA), rheumatic fever, Kawasaki disease, and Behçet disease should also be taken into account, and neoplastic disease should be excluded. There are studies indicating the role of procalcitonin in differentiating a fever episode in PFAPA from fever of infectious aetiology. Available literature data suggest an increase in the concentration of this inflammatory marker in infections\(^11\)–\(^13\). PFAPA should be differentiated from other diseases from the recurrent fever syndrome group. These include familial Mediterranean fever (FMF) – an autosomal recessive disease characterised by a mutation in the MEFV gene, which encodes the pyrin protein. It is characterised by irregular, recurrent, short-term (2–3 days) episodes of fever, in addition to serous peritonitis and pleurisy, skin rash, and arthritis. It mainly affects people living in the Mediterranean region, which is an additional factor differentiating it from PFAPA. Recurrent fevers, typically lasting 10–14 days, also occur in tumour necrosis factor receptor-associated periodic syndrome (TRAPS). This syndrome is caused by a mutation in the TNF-α receptor gene located on chromosome 12.

\(^1\) Available literature data suggest an increase in the concentration of this inflammatory marker in infections.
Another autoinflammatory disease in relation to which PFAPA should be differentiated is mevalonate kinase deficiency (MKD). It is a rare autosomal recessive inherited disease. The duration of febrile episodes, the occurrence of episodes of aphthous stomatitis, and cervical lymphadenopathy may be common features for both entities; however, the features that distinguish MKD from PFAPA are: abdominal pain, diarrhoea, vomiting, rash, painful lymph nodes, splenomegaly, myalgia, and arthralgia.

The diagnostic algorithm for undifferentiated fever in children is shown in Fig. 1.

The recommended treatment in PFAPA are glucocorticoids, e.g. prednisone at a dose of 1–2 mg/kg b.w. This treatment was also used in the present case. Remission of fever was observed within 24 hours of the initiation of prednisone. Betamethasone at a dose of 0.1–0.2 mg/kg b.w. is considered to be an equally effective medication. Achieving remission in such a relatively short time allows to confirm the diagnosis of PFAPA. However, these drugs do not prevent fever recurrence and additionally may cause side effects, mainly vomiting, behavioural changes and sleep disturbances in children.

Butbul Aviel et al. published the results of a study concerning the use of colchicine in patients with PFAPA. Children who received colchicine at doses of 0.5 mg (<5 years of age), 1 mg (5–10 years of age) and 1.5 mg (>10 years of age) had fewer fever episodes than children not treated with colchicine.

There are also studies indicating the effectiveness of the IL-1 receptor antagonist – anakinra. Nonetheless, due to the self-limiting nature of the disease in children, drugs from this group should be reserved for strictly selected patients (especially adults).

The most effective treatment appears to be the use of glucocorticoids. These drugs quickly relieve the symptoms of the syndrome; however, they do not prevent the recurrence of the disease and can shorten the intervals between fevers (if used in the early stages of the disease). Another possible approach to therapy consists in the surgical removal of the tonsils, i.e. tonsillectomy. There are no unequivocal data to demonstrate the legitimacy of performing this procedure as a routine. Its efficiency is high, reaching up to 92%.

However, due to complications after tonsillectomy, such as bleeding, and the possibility of spontaneous remission of the disease as the child grows older, the decision whether to treat PFAPA surgically is made for each patient on an individual basis. In some patients, symptoms of the syndrome recur despite tonsillectomy. In such a situation, the differential diagnosis should be extended to include genetically determined autoinflammatory diseases.

CONCLUSION

The basis for the diagnosis of PFAPA is a thorough interview and physical examination of the child. Clinical symptoms

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**Fig. 1. The diagnostic algorithm for undifferentiated fever in children**

- **Prolonged fever**: Recurrent daily fever that lasts longer than expected for the illness
- **Recrudescent fever**: Frequent fever episodes
- **Cyclic fever**: Predictable stereotypical fever episodes that last for several days and recur after a certain period of time
- **Recurrent fever**: Unpredictable fever episodes that last for several days and recur more often than expected

**Infectious diseases**, e.g. cat scratch disease, EBV or CMV infections, toxoplasmosis, endocarditis, tuberculous

**Inflammatory diseases**, e.g. systemic vasculitis (e.g. Kawasaki disease), JIA, IBD, SLE

**Neoplastic diseases**, e.g. ALL, lymphomas, neuroblastoma, soft tissue sarcomas

**Miscellaneous**, e.g. central fever, drug fever, hyperthyroidism

**Cyclic neutropenia, PFAPA**

**Relapsing, frequent, self-limiting infections**

**Autoimmune diseases**, e.g. IBD, SLE, JIA

**Inflammatory diseases**, e.g. FMF, HIDS, TRAPS
in PFAPA and their severity are individual in nature, determining the need to repeat diagnostic tests. Correctly established diagnosis allows to avoid the use of antibiotics.

**Conflict of interest**

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