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PFAPA: a periodic febrile syndrome afflicting children

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Abstract

- Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA).
- Auto-inflammatory disorder occurring in affected children every 3-8 weeks.
- Onset around age 2; lasting into second decade of life.
- A current pathophysiologic theory is PFAPA is a disorder of the innate immune system involving interleukins, chemoattractants, and cytokines that stimulating the inflammatory response causing symptoms associated with PFAPA.
- Early diagnosis of PFAPA may help prevent the unnecessary use of antibiotics.
- Biomarker CD64, galectin-3 and the MPV may be useful in the diagnosis of PFAPA along with other laboratory values during the febrile attack period of PFAPA.
- Traditional and current treatment of PFAPA is single dose of corticosteroids at onset of symptoms.
- Treatment with tonsillectomy was found to have an 80% cure rate.
- No statistical difference between corticosteroid and tonsillectomy treatments.
- Treatment of PFAPA with antibiotics was found ineffective.
- Treatment of PFAPA with vitamin D, was found by one study to have promising results.

Introduction

- First describe by Marshall et al. in 1987 as a self-limiting disorder in which affected children experience febrile episodes every 3-8 weeks with the episodes lasting 2-6 days.
- Slight increased prevalence of males being inflicted.
- PFAPA can be mistaken for recurrent tonsillitis with treatment of antibiotics.
- PFAPA is an auto-inflammatory syndrome therefore antibiotics do not succeed as a treatment.
- Financial and educational burdens occur due to missed days of school for affected child and missed days of work for parent(s).
- Early diagnosis and proper treatment of PFAPA can help reduce the financial and educational burdens.

Statement of the Problems

- PFAPA may be misdiagnosed as an illness such as recurrent tonsillitis.
- Unnecessary treatment with antibiotics.
- Disorder is not well known.

Research Questions

- What is the pathogenesis of PFAPA?
- Are there biomarkers or diagnostic tests that can aid in the early diagnosis of PFAPA?
- What are the different treatment options of PFAPA and how do they compare to the current traditional treatment?

Literature Review

- An article search of electronic medical databases from PubMed and The Cochran Library was conducted.

Pathophysiology

- Stojanov et al. and Forsvoll et al. observed an elevation of CXCL10 during the febrile attack period of PFAPA indicating activation of T-lymphocytes accounting for cervical adenitis and pharyngitis observed.
- A decrease in levels of IL-4 and eosinophils were found by Valenzuela et al. The authors theorized the decrease in IL-4 and eosinophils, decreases the number of Th2 cells.
- According to Ling et al., there were elevated levels of CXCL8 during the febrile attack period of PFAPA. CXCL8 is thought to bring neutrophils to the site of inflammation accounting for the elevated neutrophil count observed.

Diagnostic studies

- Sundqvist et al. found the addition of galectin-3 to PMNs during the febrile attack period of PFAPA produced icROC and ecROC, this does not occur during the afebrile period or in control groups; indicated the primed state of PMNs during the febrile attack period.
- The MPV was lower in both the febrile and afebrile period of PFAPA patients compared to the control groups, as discussed by Tekin et al.
- Yamazaki et al. found during the febrile attack period of PFAPA there was a significant increase in expression of CD64 compared to afebrile period and the control groups.

Treatments

- Krol et al. found that 94% of patients with PFAPA had resolution of symptoms when treated with prednisone.
- Also, no statistical difference in remission of PFAPA patients treated with prednisone compare to those who chose the “watch and wait” option, was found by Krol et al.
- Perdisis et al. found treatment of PFAPA with antibiotics to be ineffective, treatment with tonsillectomy and steroids to be effective, and no statistical difference between tonsillectomy vs. steroids for treatment.

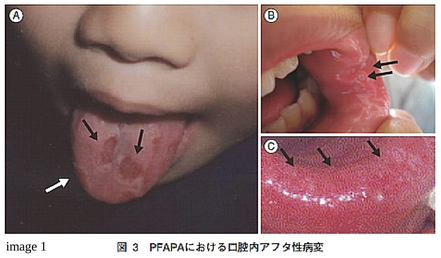


image 1 図 3 PFAPAにおける口腔内アフタ性病変

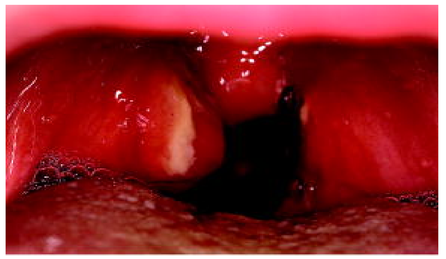
- The treatment with tonsillectomy vs. expectant management of PFAPA was found, by Gravello et al., to be significantly higher.
- Burton et al. also found there was a 92% reduction of symptoms with adenotonsillectomy or tonsillectomy and by the end of the trial period all PFAPA patients who had the surgical management experienced complete remission.
- It was concluded by Stagi et al. that supplementation with vitamin D helped reduce the length of episodes of the febrile attack period of PFAPA when initial levels of 25(OH)D were insufficient.
- Stojanov et al found that the use of recombinant IL-1R antagonist (anakinra) caused the resolution of symptoms during the febrile attack period of PFAPA.

Discussion

- Whereas Velenzueal et al. suggests that there are less Th2 cells differentiated in the circulation, Forvoll et al. and Stojanov et al theorized that the T-lymphocytes are brought to lymph nodes via chemoattractants which accounts for the decrease in lymphocytes observed during the febrile attack period of PFAPA.
- It is suggested by Ling et al. that the heterogeneity of cytokines may be due to the different triggers to the innate immunes system leading to symptoms of PFAPA.
- To better identify the pathophysiology of PFAPA, research with larger study groups are needed to identify the involvement of interleukins, cytokines and chemoattractants, including IL-1β, IL4, CXCL10 and CXCL8.
- It is unclear how specific and sensitive galectin-3, biomarker C64 and the MPV (mean platelet volume) would be in the diagnosis of PFAPA, therefore more research is needed.
- Although steroids do not shorten the disease course, steroids do relieve symptoms in many of those who suffer from PFAPA.
- Tonsillectomy appears to not only resolve symptoms of PFAPA but approximately 80% of PFAPA patients experience remission.
- More research is needed to verify the effects vitamin D has on PFAPA patients.
- Anakinra appears to be promising in the treatment of PFAPA but further research and studies are needed to confirm the findings of Stojanov et al.

Applicability to Clinical Practice

- Diagnostic criteria described by Esposito et al.:
  - First, onset prior to age five.
  - Second, febrile episodes occur with regularity with one or more of the following cardinal symptoms: aphthous stomatitis, pharyngitis, or cervical adenitis.
  - Third, between febrile episodes the child is asymptomatic with normal growth and development.
  - Forth, cyclic neutropenia and other autoimmune or auto-inflammatory syndromes are excluded.
- PFAPA can occur after the age of 5.
- General presentation of PFAPA is fever, enlarged tonsils with exudate, enlarged cervical lymph nodes and pharyngitis with several other possible symptoms.
- Strep test is negative.
- WBC, neutrophil, ESR or CRP will be elevated during the febrile attack period of PFAPA.
- Lymphocyte count and eosinophil count will be decreased during febrile attack period of PFAPA.
- PFAPA could be mistaken for bacterial infection or recurrent tonsillitis with subsequent antibiotic treatments.
- PFAPA is self-limiting with episodes lasting 2-6 days which may mislead providers and parents into believing the antibiotic treatment worked, leading to continued unnecessary treatment with antibiotics.
- Traditional and current treatment of PFAPA is 1 mg/kg of prednisone at onset of symptoms.
- The single dose of prednisone could be used to help diagnose PFAPA however other illnesses such as pneumonia should be ruled out first.
- Tonsillectomy is another treatment option but the surgical risks need to be assessed along with the fact that PFAPA is typically a self-limiting disorder.



Pharyngitis. image 2

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