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Diagnosis of PFAPA syndrome applied to a cohort of 17 adults with unexplained recurrent fevers

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ABSTRACT

Background. *The pathophysiology of PFAPA syndrome, mainly characterised by regularly recurring periodic fevers associated with aphthous stomatitis, pharyngitis and/or lymphadenitis, and mostly occurring in the paediatric setting, resembles an acquired autoinflammatory disease. The description of PFAPA syndrome in adult patients is largely increasing.*

Objective. *To recognise PFAPA syndrome in a group of adult patients evaluated for recurrent fevers in our Rheumatology Unit.*

Methods. *To apply current diagnostic criteria for PFAPA syndrome in a group of 359 adults with unexplained recurrent fevers monitored in our Unit between January 2007 and June 2011.*

Results. *We have found 17 out of 359 patients fulfilling the diagnosis of PFAPA syndrome: these patients (10 males, 7 females) were Caucasian with a mean age of 33.3±9.5 years, had recurrent febrile episodes begun at a mean age of 25.9±8.3 years and a mean number of episodes of 8.3±5.2 per year with a mean duration of 5.5±1.8 days. In particular, 7/17 patients had the 3 cardinal signs, the other 10 had a combination of 2 signs. Corticosteroids were given in 14/17 patients; tonsillectomy was performed in 9/17 patients: corticosteroid responsiveness and tonsillectomy efficacy were observed respectively in 11 and 2 patients.*

Conclusion. *Our case highlights the importance of considering PFAPA syndrome in adults presenting with unexplained recurrent fevers and symptoms commonly encountered in general medical practice.*

Introduction

Since its first definition in 1987 by Marshall, the so-called "periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis" syndrome, named *PFAPA syndrome*, characterised by regularly recurrent fevers associated with oral aphthosis, pharyngitis and/or lymphadenitis, has been restricted to the field of paediatric age (1). Clockwork periodicity and complete wellness between febrile episodes are still two nodal points for diagnostic purposes (2). The exact culprit and pathogenesis of the disease are still to be understood, though an autoinflammatory origin with aberrant cytokine expression has been postulated and a self-limiting course within second infancy has been largely documented (3). Fever episodes, often starting before 5 years of age, usually last 4 to 6 days with a recurrence every 3 to 8 weeks (4). There are no specific diagnostic tests and PFAPA syndrome is mostly diagnosed upon the application of the "classical" clinical criteria (Table I) drafted by Marshall and modified by Thomas in 1999, requiring that the patient should not display any upper respiratory tract infection and be completely asymptomatic between febrile episodes with an overall normal growth and development (5). Many reports related to different cohorts of children have shown that small doses of corticosteroids and tonsillectomy are associated with fever vanishing and resolution of PFAPA recurrence (6, 7).

In this retrospective evaluation we have described the clinical and laboratory features of 17 adult patients with PFAPA syndrome, extrapolated from a group of 359 patients evaluated for unexplained recurrent fevers in a 4-year period.

Patients and methods

Marshall criteria were applied to 359 adult patients (194 males, 165 females) with recurrent fevers recruited in the Interdepartmental Research Center of Systemic Autoimmune and Autoinflammatory Diseases of the University of Siena in the period between January 2007 and June 2011. At the time of their first admission to our Unit the mean age of these patients was 38.1±9.6 years and their mean age at disease onset was 28.1±8.4 years.

Seventeen patients out of 359 were found to satisfy these criteria, suggesting the diagnosis of PFAPA syndrome (we have neglected the criterion of early age of onset and we have assumed that growth or development for each patient had been regular). The cohort of PFAPA patients included adults of Caucasian ancestry with a mean age of 33.3±9.5 years, 10 males and 7 females, who had presented recurrent

fevers over 39°C without any known evidence of infectious or autoimmune disease. Their medical records were accurately reviewed for demographic characteristics and past clinical history, regarding febrile episodes, duration of episodes and their periodism, associated symptoms and signs, laboratory findings, disease course, outcome following corticosteroid therapy and tonsillectomy, if performed. All patients did not present a cyclic neutropenia and were negative for mutations related to *MEFV*, *MVK*, *TNFRSF1A* and *NLRP3* genes. The HLA B5 antigen was absent in all the patients tested.

Table I. Diagnostic criteria for PFAPA syndrome

1) Regularly recurring fevers with an early age of onset (<5 years of age)
2) Constitutional symptoms in the absence of upper respiratory infection with at least 1 of the following clinical signs:
   a) Aphthous stomatitis
   b) Pharyngitis
   c) Cervical lymphadenitis
3) Exclusion of cyclic neutropenia
4) Completely asymptomatic interval between episodes
5) Normal growth and development

Results

All the patients had fevers starting at a mean age of 25.9±8.3 years and a mean number of febrile episodes of 8.3±5.2 per year, which recurred at mostly regular intervals, with a mean duration of 5.5±1.8 days. In particular, 7/17 patients had the 3 cardinal signs, the other 10 had a combination of only 2 signs. No symptom was present in the interfebrile periods. Other signs observed were: arthralgias in 12/17; myalgias in 11/17; asthenia in 10/17; cephalalgia in 9/17; macular rash or pseudofolliculitis in 6/17 and abdominal pain in 3/17 patients. Laboratory investigations performed during febrile episodes showed that the mean white blood cell count was 8.270±6.530/mm^3, mean erythrosedimentation rate was 58±30 mm/h, mean C-reactive protein was 45±25 mg/l (n.v. <3) and mean serum amyloid-A was 410±333 mg/l (n.v. <6,4). Serum IgD level was less than 100 IU/ml in the interfebrile period for each patient. All reported febrile episodes showed a poor response to acetaminophen, ibuprofen, indomethacin, naproxen or colchicine; corticosteroids (50 mg/day of prednisone or 16 mg of prednisolone) were given in 14/17 patients: in 11 with an optimal and in 3 with a partial response of fever; tonsillectomy had been performed in 9/17 patients, leading to a partial response in 2, whilst it was ineffective in the other cases.

Discussion

The attention of the scientific community to PFAPA syndrome has noticeably increased in the last years (in August 2011 a Medline search for *PFAPA syndrome* yielded 95 results and in December 2007 the same search yielded only 44 results). The rare occurrence of PFAPA syndrome in adolescents and adults could indicate that an infectious agent was the mandator of the disease, but the lack of clustering in seasons or in any geographic area combined with the long duration of the recurrent disease made infection unlikely. Conversely, the persistence of identical flares over years, the association with recurring aphthous stomatitis and the resolution after single doses of corticosteroids suggested an immunologic dysregulation (8). Several cytokines are elevated during febrile episodes of PFAPA syndrome, most notably interferon-gamma, tumour necrosis factor, and interleukin-6, and an abnormal host immune response against unidentified commensal microorganisms in the tonsils or the oral mucosae might account for the clinical picture of the disease (9). A recent report by Stojanov *et al*. has shown that specific patterns of gene expression and cytokine activation during flares of paediatric patients with PFAPA syndrome are distinct from those of other inherited autoinflammatory syndromes and suggested that the administration of the interleukin-1 receptor antagonist (anakinra: 1 mg/kg/dose subcutaneously injected at fever onset) might have a beneficial effect on fever falling (10). Different febrile diseases must be considered for the differential diagnosis, like primary or acquired immunodeficiency disorders, haematological diseases, cyclic neutropenia and the other inherited autoinflammatory diseases, with attention given to the backup of patient's ethnicity, family history, non-typical symptoms and results of simple laboratory tests, which turn to normal between febrile episodes. A set of clinical variables for predicting the risk that an adult patient with recurrent fevers might carry mutations in the *MEFV* or *TNFRSF1A* genes has been preliminarily validated in a group of 110 Italian patients to help differential diagnosis (11).

Recent medical literature has included several cases of PFAPA syndrome also in young adults: these reports highlighted the need for physicians to take into consideration PFAPA syndrome while facing recurrent episodes of unexplained fevers without other inflammatory signs localised to tissues usually involved in the hereditary autoinflammatory syndromes (12-15). In our cohort of patients, fevers began in young adulthood and the mean number of febrile episodes was 8.3±5.2 per year, which appeared fairly often as regularly-recurring and lasting on average 5.5±1.8 days per single febrile episode. The other non-cardinal clinical signs registered from the medical records during febrile flares of our patients were arthralgias, myalgias, asthenia, cephalalgia, macular rash, pseudofolliculitis and abdominal pain. During febrile flares white blood cell count was mostly normal, whilst serum amyloid-A was notably increased, unlike erythrosedimentation rate and C-reactive protein which were only moderately increased. Corticosteroid therapy was successful in 14 patients (with an optimal response in 11 and partial response in 3) and tonsillectomy led to a partial recovery in only 2 patients.

This report underscores the importance of recognising adults with PFAPA

syndrome, though family practitioners and otorhinolaryngologists are poorly confident with the disease, even if these adult patients might have suffered from PFAPA symptoms in paediatric age. Our cohort of patients emphasises that adult onset of the syndrome with continuing febrile episodes for several years is possible and suggests that diagnosis of PFAPA syndrome should not be overlooked in any adult patient with a longlasting history of recurrent, unexplained episodes of fever.

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