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Marshall syndrome – a challenge in medical practice

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Marshall syndrome (periodic fever, adenitis, pharyngitis, aphthae, PFAPA syndrome) is characterized by recurrent episodes of fever associated with aphthous stomatitis, cervical adenitis or pharyngitis. Although it is the most common cause of recurrent fever in children, the diagnosis is rarely established. The aim of this study was to describe a group of Romanian children with Marshall syndrome. In seven children with PFAPA, the following methods were used: patient history, clinical examination, and determination of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and tumor necrosis factor α (TNF-α). The treatment consisted in prednisone at a dose of 1 mg/kg. The age at onset was 2.2 years and at diagnosis 4.8 years. The mean interval between episodes was 3.1 weeks and the duration per febrile episode was 3.7 days. The patients presented with pharyngitis (100%), adenitis (100%) and aphthous lesions (57.1%). The mean ESR value was 31 mm/h, CRP 7.8 mg/dL and leukocytes 17700/mm^3. TNF-α remained elevated between febrile episodes. Six patients treated with prednisone had favorable evolution. In conclusion, PFAPA should be suspected in children with periodic fever associated with pharyngitis, cervical adenitis and aphthous stomatitis.

Keywords: Marshall syndrome; fever

INTRODUCTION

Marshall syndrome (periodic fever, adenitis, pharyngitis, aphthae, PFAPA syndrome) consists of recurrent episodes of fever associated with aphthous stomatitis, pharyngitis and cervical adenitis. It was first described in 1987 by Marshall and it is characterized by episodes of fever lasting for 3-6 days with recurrence every 3-8 weeks, associated with at least one of the three main signs: aphthous stomatitis, cervical adenitis and pharyngitis (1, 2). The febrile episodes can spike to 39-40 ºC, with little or no response to common antipyretics. Other symptoms may be present during fever attacks, such as headache, joint pain, myalgia, nausea, vomiting and abdominal pain. Onset of the disease is before the age of 5 years and usually lasts up to the age of 10-11 years, but there are some cases diagnosed in adults (3, 4). Patients are asymptomatic between episodes and have normal growth and development (2, 3,5). The etiology is still unknown, but studies on cytokine concentrations showed a significant increase in serum proinflammatory cytokine levels (interleukin (IL)-1b, IL-6 and tumor necrosis factor α (TNF-α)) during and between febrile episodes and reduction in anti-inflammatory cytokine levels (IL-4 and IL-10) in these patients (6-8).

There are no diagnostic tests for PFAPA syndrome. The diagnosis is based on clinical criteria and exclusion of other possible causes of recurrent fever in children. During febrile attacks, patients present elevation of white blood cells, with preponderance of neutrophils and of acute phase reactants. Procalcitonin has normal values during flares and this finding can exclude bacterial infection (9, 10). Between attacks, all inflammatory parameters are normal.

The most effective methods of treatment are corticosteroids and tonsillectomy.

Although it is the most common cause of recurrent fever in children, the diagnosis is rarely established.

The aim of the present study was to assess clinical and laboratory characteristics of seven children with PFAPA syndrome in order to review the criteria for its accurate diagnosis and to avoid unnecessary use of antibiotics.

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PATIENTS AND METHODS

Seven children (5 girls and 2 boys) with recurrent episodes of fever were evaluated for PFAPA syndrome. The diagnosis of PFAPA syndrome was established according to the criteria proposed by Thomas: (a) regularly recurrent fever; (b) onset at an early age; (c) absence of upper respiratory tract infection; and (d) at least one of the following clinical signs: pharyngitis, aphthous stomatitis or cervical adenitis. Additional criteria included completely asymptomatic intervals between febrile episodes, normal growth and development, and exclusion of cyclic neutropenia.

An informed consent was obtained from participants or their guardians prior to enrolment in the study and the principles of human research ethics were fully respected. We recorded medical data for each patient. These included demographic data and medical history of patients and their families; characteristics of febrile episodes; laboratory evaluation; and treatment used. For laboratory evaluation, we followed peripheral leukocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin, immunoglobulin and tumor necrosis factor alpha (TNF-α) concentration during and 10 days after fever attacks. The treatment consisted of prednisone at a dose of 1 mg/kg.

RESULTS

The main reason for hospitalization of children was recurrent pharyngitis for which they underwent repeated antibiotic treatments. The family medical history of the patients revealed PFAPA syndrome in one patient and autoimmune disease in another patient.

Clinical characteristics of PFAPA episodes in our patients are shown in Table 1. The mean age at onset of the disease was 2.2±0.9 years; the mean age at diagnosis was 4.8±3.2 years; the mean duration of episodes was 3.7±0.7 days; the mean maximal temperature was 39.6±0.5 ºC; and the mean frequency of febrile episodes was 3.1±0.8 weeks.

TABLE 1. **Clinical spectrum of PFAPA episodes**

Clinical characteristic		Value
Age at onset (yrs)		2.2
Age at diagnosis (yrs)		4.8
Fever	Recurrent	100%
	Duration (days)	3.7
	Periodicity (wks)	3.1
	Maximal temperature (ºC)	39.6
Pharyngitis		100%
Cervical adenitis		100%
Aphthous stomatitis		57.1%
Mean number of antibiotic courses in 12 months preceding diagnosis		6.5

TABLE 2. **Mean values of laboratory parameters in seven patients with PFAPA syndrome**

Parameter	Normal value	During PFAPA episodes	Between PFAPA episodes
Leukocytes (/mm^3)	<10 000	17 700	8 466
ESR (mm/h)	<10	31	11.2
CRP (mg/L)	<8	78	7
Procalcitonin (mg/dL)	<0.5	<0.5	<0.5
TNF-α (pg/mL)	<8.1	18.8	12.8

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; TNF-α = tumor necrosis factor α

Laboratory evaluation of the patients during and between PFAPA episodes is shown in Table 2.

Quantitative immunoglobulin levels were normal in all children.

Six children underwent treatment with prednisone at a dose of 1 mg/kg and the frequency of episodes decreased to once in 2 or 3 months. In one patient who failed to respond to prednisone administration, tonsillectomy resulted in complete remission.

DISCUSSION

We report on a group of Romanian PFAPA patients and their clinical and laboratory characteristics. Although PFAPA syndrome is nowadays considered as the most common of various auto-inflammatory fever disorders and its clinical manifestations are well known, the diagnosis is rarely established by pediatricians or primary care physicians and our patients underwent repeated unnecessary antibiotic treatments because the disease is commonly confounded with bacterial pharyngitis.

All seven patients were evaluated for recurrent acute pharyngitis and two of them had a family history of autoimmune disease and PFAPA syndrome, similar to the prevalence reported previously (11).

There are studies which suggest that PFAPA syndrome could have a genetic origin. This hypothesis is supported by the presence of MEFV (Mediterranean fever) gene mutations in a few patients with PFAPA syndrome (12). Other explanations involve the presence of this disease in siblings and clinical similarity with other periodic fever syndromes of genetic origin (12, 13). The disease occurs because of an abnormal immune response to infectious agents (virus) at the level of lymphoid organs (tonsils), which induce cell activation of innate immunity (12-14).

TABLE 3. Clinical presentation of our group of children with PFAPA episodes and results of other studies

Study		Thomas 1999	Tasher 2006	Padeh 2008	Gattorno 2009	Feder 2009	De Cunto 2010	Yazgan 2012	Present study
Number of patients		66	54	320	130	105	12	12	7
Age at onset (yrs)		-	1.9	-	1.5	3.1	1.15	1.8	2.2
Age at diagnosis (yrs)		-	3	-	-	-	3	-	4.8
Fever	Recurrent	100%	100%	100%	100%	100%	100%	100%	100%
	Duration (days)	-	5.3	-	4.5	4.1	4	5.1	3.7
	Periodicity (weeks)	-	3.7	-	-	4.2	3	5.5	3.1
	Maximal temperature (°C)	-	40.1	-	-	-	40	-	39.6
Pharyngitis		65%	96%	100%	83.8%	85%	100%	91%	100%
Cervical adenitis		77%	61%	100%	83.8%	62%	83%	78%	100%
Aphthous stomatitis		67%	39%	68%	58.5%	38%	67%	65%	57.1%
Abdominal pain		45%	65%	18%	53.1%	41%	42%	-	28.5%
Nausea, vomiting		-	35%	-	30.8%	27%	-	-	-
Diarrhea		30%	13%	-	29.2%	-	-	-	-
Arthralgia, myalgia		-	22%	11%	43.8%	-	17%	-	-
Headache		-	46%	18%	40.8%	44%	-	-	28.5%

We compared our group with the groups published in the literature (Table 3). The clinical presentation of our group showed a long period (2 years) between the clinical onset and diagnosis because general practitioners who are the first to see the patients are not well acquainted with this entity. The mean duration of febrile episodes, the frequency of episodes and the mean maximal temperature were similar to those described previously (11, 15, 16). The patients were given more than 6 unnecessary treatments with antibiotics in 12 months preceding their presentation to our service. Clinical presentation included pharyngitis in all children (57.1% of them with exudative pharyngitis), cervical adenopathy in all children, and aphthous stomatitis in 57.1% of children. During relapses, the patients presented elevation of white blood cells and acute phase reactants (ESR, CRP), which normalized between attacks. Procalcitonin did not increase during fever attacks. This indicates that an association of high serum CRP with elevated leukocyte count and undetectable levels of procalcitonin could be used to distinguish PFAPA attack from bacterial infection (10). The levels of the proinflammatory cytokine TNF-α were elevated during and between PFAPA episodes, an observation that suggests dysregulation of the immune response in PFAPA syndrome, with continuous proinflammatory cytokine activation (7, 17).

In six children, corticosteroid administration (prednisone 1 mg/kg) resulted in rapid resolution of fever, but did not prevent subsequent episodes of fever and did not change the course of the disease. A large number of studies report that febrile attacks became less frequent after the treatment with corticosteroids (7, 18, 19). Other studies report on beneficial effects of cimetidine, colchicine or thalidomide, but a small number of patients were treated (7, 18-21). The role of tonsillectomy in PFAPA syndrome is controversial. The arguments for tonsillectomy are preventing recurrence of episodes, increasing the intervals between relapses, reducing the severity of the clinical manifestations, and inducing complete remission in 56%-100% of cases. The arguments against tonsillectomy are spontaneous resolution of PFAPA syndrome, possible persistent symptoms, and possible relapses after a period of remission. Therefore, tonsillectomy should be considered in case of intolerance or failure of the standard medical treatment (18-25).

CONCLUSION

Marshall syndrome should be suspected in children with periodic fever associated with pharyngitis, cervical adenitis and aphthous stomatitis. Although it is the most common cause of recurrent fever in children, it is commonly attributed to respiratory infection and the diagnosis is established long after the onset.

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SAŽETAK

Marshallov sindrom – izazov u kliničkoj praksi

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Marshallov sindrom (periodična groznica, adenitis, faringitis, afte, sindrom PFAPA) obilježen je opetovanim epizodama groznice udružene s aftoznim stomatitisom, cervikalnim adenitisom ili faringitisom. Iako je to najčešći uzrok opetovane groznice u djece, ova se dijagnoza rijetko postavlja. Cilj ovoga ispitivanja bio je opisati skupinu rumunjske djece s Marshallovim sindromom. U sedmoro djece s PFAPA primijenjene su sljedeće metode: anamneza, klinički pregled te određivanje sedimentacije eritrocita (SE), C-reaktivnog proteina (CRP) i faktora tumorske nekroze alfa (TNF-a). Liječenje je provedeno prednisonom u dozi od 1 mg/kg. Dob pri nastupu PFAPA bila je 2,2 godine, a pri dijagnozi 4,8 godina. Srednja vrijednost intervala među epizodama PFAPA bila je 3,1 tjedan, a trajanja pojedine febrilne epizode 3,7 dana. Bolesnici su imali faringitis (100%), adenitis (100%) i aftozne promjene (57,1%). Srednja vrijednost SE bila je 31 mm/h, CRP 7,8 mg/dL i leukocita 17700/mm^3. TNF-a je ostao povišen između febrilnih epizoda. Povoljan ishod zabilježen je u šestoro bolesnika liječenih prednisonom. U zaključku, na PFAPA treba posumnjati u djece s periodičnim groznicama udruženim s faringitisom, cervikalnim adenitisom i aftoznim stomatitisom.

Ključne riječi: Marshallov sindrom; groznica