MARSHALL SYNDROME (PFAPA). EXPERIENCE OF PEDIATRIC CLINIC FROM SIBIU

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ABSTRACT

PFAPA is a chronic condition including recurrent fever episodes, aphthous stomatitis, pharyngitis and adenitis. The authors emphasize peculiarities regarding diagnosis, evolution and citokinic profile for PFAPA patients. 22 patients with PFAPA were included in study. Patients that fulfilled diagnosis criteria were analyzed regarding symptoms onset age, period of time between episodes and between disease onset and diagnosis and also data about inflammatory status. Authors compared 2 groups: "PFAPA group" including 6 patients (between febrile episodes) and "Non-PFAPA group" including 4 healty children. Both gropus were analyzed regarding serum levels of inflammatory markers and cytokines in order to identify a biological sensitive marker for PFAPA evolution pattern. Data was statistically analyzed using "independent sample t test". Results. Authors noticed a low suspicion index for PFAPA diagnosis (underdiagnosed disorder) and significant statistical differences between the 2 groups regarding C reactive protein (CRP) serum value. Conclusions. PFAPA diagnosis is established lately, so it's useful to disseminate information about disease. CRP remains a sensitive marker for disease activity in PFAPA patients, even out of fever attacks.

Key words: Marshall syndrome, child

PFAPA (Marshall syndrome) is an autoinflammatory disorder characterized by recurrent fever, aphthous stomatitis, pharyngitis and lymph nodes enlargement.

Autoinflammatory diseases features are generalized and recurrent inflammation without any autoimmune or infectious causes. Among inherited autoinflammatory diseases:

- Familial mediterranean fever (FMF) and Hyper IgM syndrome (HIDS, mevalonic aciduria): autosomal-recessive inheritance;
- TRAPS (tumor necrosis factor receptor-associated periodic syndrome), PAPA syndrome (pyogenic arthritis, pioderma gangrenosum, acne), Blau syndrome, CAPS („cryopyrin-associated periodic syndromes" including CINCA or NOMID, Muckle-Wells syndrome and Familial Cold Urticaria): autosomal-dominant inheritance.

The genetic background of Marshall syndrome is unknown (no gene defect was identified).

PFAPA

Represents the most frequent periodic fever disease in children whose cause is unknown. Infectious causes were not detected, therefore it is considered to be a non-contagious disease. Some studies have reported abnormalities of the immune system even between fever flares, respectively increasing the level of pro-inflammatory cytokines (IL-1β, IL-6, TNFα) while reducing the level of anti-inflammatory cytokines (IL-10) (1).

Although the first description of the disease dates from 1987 and is due to Marshall (2), this disease remains under diagnosed, being relatively less known among pediatricians and family doctors.

The diagnosis criteria were established in 1989 (3) and include the following: frequent periodic fever starting <5 years; at least one of the following symptoms: aphthous stomatitis, cervical adenitis, pharyngitis; exclusion of cyclic neutropenia; com-

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pletely asymptomatic patient between flares; without disorders in growth and development.

The characteristic of the disease is given by the recurrence of the fever (frequently beginning around the age of 2 years, while entering in the community), the interval between fever flares being an individual feature (2-8 weeks) (4). The fever lasts 3-7 days (5) and during fever flares, the inflammatory markers have moderate - high intensity and quasi-normal values between flares. The resolution symptoms are frequently noticed until the age of 5 years, sometimes up to 10 years (6) (although they have been reported in evolution even in adulthood).

A differential diagnosis must be done, at least in the beginning, with the following entities: cyclic neutropenia (the neutrophils number must be assessed weekly, some consecutive weeks), recurrent infections (malaria, brucellosis, Borrelia recurrentis infection, infectious mononucleosis etc.), malignancies and autoimmune diseases.

The pathogenesis is incompletely known, assigning a major part to innate immunity abnormalities. The involvement of the receptors "pattern recognition receptors" (PRR) is acknowledged, having a role in signaling dangers. From this category, the NOD-like receptors are considered to have a pathogenic role in PFAPA: receptor $NALP_3$ that can be activated by microbial toxins / bacterial RNA / uric acid / ATP as wells as NOD_2 receptor.

TREATMENT

Steroids usually stop, disease evolution in a few hours using *per os* or intravenously medication (6). The use of steroids can shorten the duration between fever flares (in 10% of the cases). Tonsillectomy determines symptoms resolution in 80-90% of the cases (7), therefore sometimes it is difficult to establish surgery case in the context of spontaneous resolution of the disease around the age of 10 years (8). In order to prevent fever flares, some authors recommend Cimetidine po dose of 20-30 mg / kg. body weight / day (unconfirmed observation in 2 cases of personal casework).

MATERIALS AND METHODS

The groups of patients diagnosed with PFAPA were subject of 2 evaluations.

1st evaluation. **Purpose**: characterization of PFAPA patients from clinical and paraclinical points of view in order to improve diagnosis.

Twenty-two pediatric patients who fulfilled the diagnosis criteria (see above) were included in the study. The evaluation of patients included: age when the symptoms for Marshall syndrome appeared; duration (weeks) between fever flares; duration of the disease start until PFAPA diagnosis was established; characterization of inflammatory profile (evaluation of C-reactive protein values) during fever flares.

2nd evaluation. Purpose: characterization of the inflammatory pattern for PFAPA patients in order to detect a biological marker that allowed the assessment of the disease evolution. The two groups were analyzed in comparison:

- "PFAPA group" included 6 patients diagnosed with Marshall Syndrome. The inclusion criteria for this group were: A. patients under 10 years old respecting diagnosis criteria; B. patients between fever flares;
- "non-PFAPA group" consisted of 4 healthy subjects (control group). The inclusion criteria in this group were similar to those in "PFAPA group", so that the 2 groups to be homogeneous (non-febrile patients aged under 10 years old).

The authors studied, for both groups, the serum procalcitonin level (in order to exclude bacterial infections) C-reactive protein, pro-inflammatory cytokines levels (tumor necrosis factor TNF-alpha and interleukin IL-8) and pro-inflammatory cytokine values (IL-10). The cytokines were analyzed (in a laboratory from Germany) using ELISA (enzyme-linked immunosorbent assay), EIA (enzyme immunoassay) and CLIA (chemiluminescent immunoassay). The data were statistically analyzed using the "sample t test".

RESULTS

1st evaluation. By analyzing the group of 22 patients with PFAPA the following results were achieved: the average age when symptoms appeared was 44.09 months; the duration from the start until the establishing of diagnosis was 52.5 months, suggesting a low index of suspicion for PFAPA diagnosis (under-diagnosed disorder); the duration between fever episodes was 7.5 weeks (range 3-20 weeks); the average values of C-reactive protein varied between 35.77 - 89.77 mg/l (normal value < 6 mg/l).

2nd evaluation. By analyzing the 2 groups, the following results were achieved:

- the subjects of both groups had normal serum levels of IL-8 and IL-10 and increased values

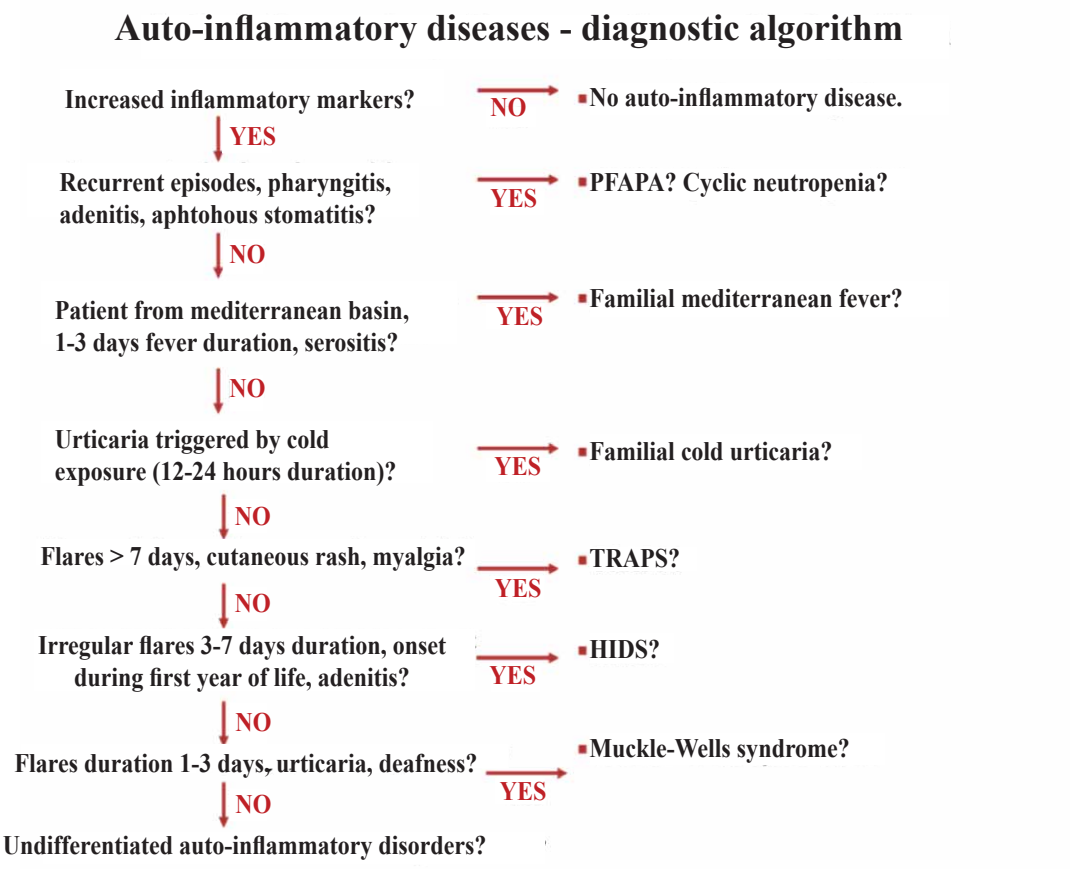
ID	C reactive protein (mg/l)	TNF-alfa (ELISA) Normal range < 8,1 pg/ml	IL-8 (CLIA) Normal range < 15 pg/ml	IL-10 (EIA) Normal range < 9,1 pg/ml
Patient 1	9,88	10,5	< 5	< 5
Patient 2	2,40	9,3	< 5	< 5
Patient 3	3,25	10,4	< 5	< 5
Patient 4	95	14,5	12,8	< 5
Patient 5	2,69	13,1	6,3	< 5
Patient 6	5,08	9,8	< 5	< 5
	Mean value = 19,71 mg/l	Mean value = 11,26 pg/ml		
Control group Subject 1	10	17,9	< 5	< 5
Subject 2	3,67	12,7	< 5	< 5
Subject 3	3,95	11,2	5,5	< 5
Subject 4	4	11	< 5	< 5
	Mean value = 5,405 mg/l	Mean value = 13,2 pg/ml		

of TNF-α; the average value of TNF-α was 11.26 pg/ml for the group PFAPA and 13.2 pg/ml for the non-PFAPA group; concerning the value of C-reactive protein, the average value of PFAPA patients was 19.72 mg/l (range 2.4 - 95 mg/l) compared with the value of 5.04 mg/l for non-PFAPA patients (see table below).

CONCLUSIONS

1st evaluation.

1. PFAPA diagnosis is established late.
2. It is useful to disseminate information about this entity in order to determine early diagnosis and avoid unnecessary use of antibiotic treatment.



2nd evaluation.

1. TNFα, IL-8, IL-10 are not useful to assess PFAPA evolution;

2. The C-reactive protein remains a sensitive marker for PFAPA disease activity, even between PFAPA flares;

3. The current study has not confirmed the literature data.

TAKE HOME MESSAGES

When should we think of PFAPA? We will consider this entity when a patient has a range of these features: fever with periodic evolution (variable interval, 2 - 8 weeks), beginning in the first 5 years of life (often after the age of 2 years), patients with a medical history with frequent episodes of tonsillitis interpreted as " purulent tonsillitis" but with repeated negative pharyngeal exudate results, lymphadenopathy, associated abdominal pain, aphthous stomatitis (in a small percentage of cases), good response to steroids (fever flares drop in 1-4 hours after oral or intravenous therapy with steroids.

It is pointed that fever is not influenced by antibiotic therapy and symptoms during flares include (besides fever, adenopathy and aphthous stomatitis), malaise, arthritis/arthralgia, abdominal pain and dysphagia. Medical history, elaborate clinical examination, information on ethnicity or origin of the patient and the patient diary card are useful for diagnosis.

An algorithm for diagnosis of auto-inflammatory diseases is presented below.

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