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COLCHICINE USE IN A CHILD WITH PFAPA SYNDROME

PFAPA SENDROMLU BİR ÇOCUKTA KOLŞİSİN KULLANIMI

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ABSTRACT

PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis) syndrome is a relatively not well-recognized periodic fever syndrome characterized by recurrent febrile episodes persisting 4-6 days in children. Fever is accompanied by aphtous stomatitis, pharyngitis, and cervical adenitis. There are several clinical similarities between familial Mediterranean fever (FMF) and PFAPA syndrome. For accurate diagnosis, increased awareness of this syndrome is essential.

We describe a three-year-old girl with PFAPA who used colchicine prophylaxis with the presumptive diagnosis of FMF. At the follow-up, she was diagnosed as having PFAPA syndrome. The interval between the febrile episodes was increased from four weeks to 12 weeks after colchicine therapy. Since there are many similarities between the FMF and PFAPA syndrome, colchicine use can be offered as an effective approach for children with PFAPA.

Key Words: PFAPA, colchicine, periodic fever, FMF

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ÖZET

PFAPA (periyodik ateş, aftöz stomatit, farenjit ve adenit) sendromu çocuklarda 4-6 gün süren tekrarlayan ateş atakları ile karakterize göreceli olarak daha az bilinen periyodik ateş sendromlarından biridir. Ateşe aftöz stomatit, farenjit ve adenit eşlik eder. FMF (familial Mediterranean fever) ve PFAPA sendromu arasında bir çok klinik benzerlikler bulunmaktadır. Doğru tanı için bu sendromun akla gelmesi gereklidir.

Burada FMF ön tanısıyla kolşisin profilaksisi kullanılan 3 yaşında bir kız takdim edilmektedir. İzleminde hasta PFAPA sendromu olarak tanı almıştır. Kolşisin tedavisiyle ateş atakları arasındaki süre uzamıştır. PFAPA sendromuyla FMF arasındaki benzerliklerden dolayı kolşisin tedavisi PFAPA sendromlu çocuklarda etkili bir yaklaşım olarak önerilebilir.

Anahtar Sözcükler: PFAPA, Kolşisin, Periodik ateş, FMF

INTRODUCTION

PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis) syndrome is one of the less recognized periodic fever syndromes in children. The main characteristic of PFAPA syndrome is the presence of a strictly periodic recurrent fever every 3-4 weeks and completely symptom-free intervals between the attacks. There is no widely accepted treatment in patients with PFAPA. Recently, Tasher et al. reviewed their experience with colchicine for the prophylaxis of PFAPA and proposed that it was beneficial to lengthen interval between the episodes (1). We also want to share our experience with this relatively unrecognized but troublesome syndrome. Colchicine prophylaxis was used in our patient with presumptive diagnosis of familial Mediterranean fever (FMF). At the follow-up, she was diagnosed as having PFAPA syndrome.

CASE REPORT

A four-year-old girl was evaluated for recurrent episodes of fever since 18 months of age in our pediatric clinic. Her febrile episodes lasting 3-5 days typically occurred every 28 days. She had no systemic symptoms except severe tonsillopharyngitis and fever ranging 39-400C. Any infectious etiology was not identified mostly in her episodes. Her prenatal, natal and postnatal history was unremarkable. Her developmental milestones were normal. During an episode, she had a mild leucocytosis (WBC: 17.700/mm3), very high C-reactive protein level (100 mg/dl), slightly elevated sedimentation rate (35 mm/h). Serum immunoglobulin levels and fibrinogen level were in normal limits including immunoglobulin D level. On review of past history, we found out that she had been treated with antibiotics for febrile episodes several times. Because of recurrent tonsillitis, she had been

started to penicillin prophylaxis every 3 weeks by her family physician and finally underwent adenotonsillectomy when she was two years old. There was no change in the frequency of episodes in spite of surgery and her attacks continued in the same manner. Although genetic analysis for FMF revealed heterozygote for E148Q mutation, our patient was suspected having FMF based on the clinical findings. Colchicine therapy was started at the dose of 0.5 mg daily. During follow-up, the interval between the episodes increased from four weeks to 12 weeks after colchicine therapy. On last admission with febrile episode, we noticed that clinical course of our case may be compatible with the diagnosis of PFAPA. A single injection of prednisolone at the dose of 2 mg/kg was administered as suggested previously. Her fever dramatically and completely disappeared within 12 hours. This dramatic response to prednisolone was also confirmed to our diagnosis. Now, she is in the follow-up with the colchicine prophylaxis and has no further symptoms for six months.

DISCUSSION

Periodic fever syndromes in children are characterized abrupt onset of fevers that occur in the absence of apparent infection and recur in a regular cyclic pattern (2). Whereas FMF and hyper Ig D syndrome are the well-known periodic fever syndromes by clinicians, PFAPA is relatively unrecognized syndrome. PFAPA syndrome has been described mostly in pediatric patients. It usually begins before the age of 5 years. However, the presence of PFAPA syndrome in adult patients has been reported recently by Padeh et al (3). They concluded that an increased awareness of this clinical syndrome would result more frequent diagnosis in adult patients.

Characteristic feature of PFAPA syndrome is periodic episodes of fever recurring in 21-28 days. Fever occurs regularly and lasts for three or five days. Aphtous stomatitis, pharyngitis and cervical adenopathy may accompany to the fever. It's been reported that most common symptoms were pharyngitis (78%), cervical adenopathy (69%), and aphtous stomatitis (51%) (3-5). During the febrile episode, an inflammatory syndrome characterized hyperleucocytosis, high CRP levels and sedimentation rate is usually observed. Diagnosis of this syndrome is based on typical clinical findings, because there are no characteristic changes in laboratory findings. Our patient completely fits the clinical picture of PFAPA according to previously reported cases. She has a clockwise periodic fever pattern, elevated acute phase reactants and severe tonsillopharyngitis during the attacks. Periodic fever syndromes such as FMF, Hyper Ig D syndrome, PFAPA syndrome may be confused with each other because of similar common features. Since FMF is relatively frequent and recognized in our country, the presence of periodic fever episodes in our patient led us to think the diagnosis of FMF.

Similar to our patient, Ataş et al. also previously reported from our country a case of PFAPA syndrome mimicking FMF (4). They proposed that colchicine therapy was administered with the diagnosis of FMF in their patient and failed to decrease the interval between the attacks. Our patient is similar to their patient in regard to confuse with FMF. But, on the other hand, Colchicine therapy is beneficial to decrease the attacks in our case unlike that patient. Tasher et al. offered prophylaxis with colchicine to the patients with frequent episodes in PFAPA syndrome (1). They concluded that the interval between the attacks was significantly increased from an average of 1.7 weeks to 8.4 weeks after colchicine. We agree with Tasher et al. that there are several clinical and laboratory similarities between FMF and PFAPA and colchicine may be beneficial in prolongation of the episodes in PFAPA (1).

Several reports proposed that tonsillectomy might induce remission in PFAPA syndrome. In a recent report by Wong et al., they proposed that their findings showed complete resolution of symptoms in 8 of 9 patients with PFAPA syndrome treated with tonsillectomy (5). On the other hand, some reports suggested that tonsillectomy was not always beneficial for patients with PFAPA. Leong et al. rewived that effectiveness of tonsillectomy in PFAPA was extremely weak and there was no role for operation in these patients (6). Similarly, adenotonsillectomy was also failed to stop the febrile episodes in our case.

The mechanisms behind this syndrome are not still well-known. There is no data regarding family history and genetic basis among patients with PFAPA. No gene specific mutations have been associated with this syndrome. It's been reported that six children with PFAPA were tested for mutations in MEFV gene and found negative (7). In only one study from Israel, Dagan et al. reported

that of the 57 children with PFAPA syndrome, 16(28.1%) carried one of the common mutations in MEFV, the gene implicated in FMF (8). Because of high carrier frequency of MEFV mutations in general population of Israel, they cannot conclude that these mutations are directly related to PFAPA. We tested our patient with the presumptive diagnosis of FMF. She showed heterozygote mutation for E148Q in MEFV gene.

In PFAPA syndrome, most effective management for the symptoms during an episode seems the usage of one dose of prednisolone (9). Prednisolone administration causes the dramatic relief of symptoms and increases the interval between the episodes. The striking response to steroids lead to think that dysregulated production of cytokines may be responsible for the febrile episodes.

In conclusion, PFAPA syndrome was common in children but not well-recognized by pediatricians. Periodic fever syndromes usually cause repeated febrile illnesses with various accompanying symptoms and usually confuse with each other. Every patient with recurrent, periodic fever should be evaluated in point of PFAPA syndrome. Even though other features such as adenopathy, aphtous stomatitis do not accompany to the fever. It is important for the clinicians to increase awareness of this clinical presentation, diagnostic approach and management. Although PFAPA has a benign clinical course, frequent episodes may cause many problems in the quality of life both patients and parents. Since there are many similarities between the FMF and PFAPA syndrome, colchicine use may be a good alternative approach in the management of problematic cases.

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