CASE REPORTS

RECURRENT FEVERS IN TWO TEENAGERS

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Abstract

Fever in children is a common occurrence and is usually due to a self-limiting viral infection. However, recurrent fevers with a repetitive pattern also referred to as Periodic Fevers are usually of greater concern and require investigation to ensure appropriate diagnosis and management. We are reporting 2 cases of cyclical fevers to illustrate the need to evaluate the child with periodic fevers.

Keywords: Periodic fever, recurrent fever, children

Introduction

Fever is one of the most common symptoms of illness during childhood. The febrile period is self -limited lasting for a couple of days and associated with additional symptoms of a viral etiology. A school-aged child can have several such illnesses per year. However, recurrent fevers when associated with a periodic pattern ranging with a frequency from every 2 to 6 weeks is usually due to a non-infectious cause. A variety of diseases have been incriminated for periodic fevers in children. Specific laboratory evaluation including newly available genetic testing can aid in confirming these unusual diagnoses. Awareness of these conditions and the techniques available for their evaluation can result in timely diagnosis and management.

Case Report

CASE 1: A 17 years old male of Lebanese descent presented to the pediatric infectious diseases clinic with a history of recurrent fevers for the past one and a half years. Fever is associated with sore throat, headaches and fatigue. His maximum temperature usually rises to 1040F. The fevers are sometimes associated with chills, night sweats and mouth sores. Past medical history is significant for myelomeningocele, hydrocephalus, neurogenic urinary bladder and frequent urinary tract infections. Past surgeries include spinal closure, tethered cord repair and bladder surgery. There is a recent history of travel to Dubai. Physical examination is unremarkable. Work up for recurrent fever reveals normal erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and negative antinuclear antibody (ANA), rheumatoid factor and immunoglobulin D levels (IgD). Gene mutation study for tumor necrosis factor receptor associated periodic fever syndrome (TRAPS) is negative. Two pathological mutations in MEFV-1 gene were detected including M694V and V726A making him likely to have familial Mediterranean fever (FMF). The patient was referred to a rheumatologist and responded well to therapy with colchicine, thereafter.

CASE 2: A 15 years old previously healthy Caucasian male presented to the pediatric infectious diseases clinic with a one and a half year history of high fevers, abdominal pain, and intermittent episodes of sore throat associated with vomiting. Fevers are usually between 1000F-102.70F, mostly in the morning. There is a history of a 4 pound weight loss in last 3 months. There is a surgical history of tonsillectomy and adenoidectomy about 6 months ago. The rest of the history and physical examination are unremarkable. Laboratory studies reveal normal ESR and CRP between episodes. Chest X-ray and magnetic resonance imaging of the brain does not reveal any abnormalities. Due to concerns of periodic fever syndromes the patient is also tested for FMF and TRAPS. He was found to be heterozygous for K695R mutation in MEFV gene suggestive of FMF.

Discussion

FMF is an autosomal recessive disease characterized by recurrent episodes of fever, serosal inflammation and marked increase in acute-phase reactants. The disease predominantly affects people from the Mediterranean basin, including Sephardic Jews, Turks, Arabs and Armenians. The disease is sporadic in other populations and it has been described in Greeks, Italians, Cubans, and Belgians. It is now a worldwide disease due to widespread travel and migration(1).

In non-Ashkenazi Jews, the prevalence of FMF ranges from 1/250 to 1/500(2). The MEFV gene mutations responsible for this disease were described in 1997. Forty mutations associated with FMF have been identified so far. Five founder mutations, V726A, M694V, M694I, M680I and E148Q account for 74% of FMF chromosomes from typical cases (Armenians, Arabs, Jews, and Turks). Rare mutations are preferentially found in populations not usually affected by FMF, for example Europeans of other ancestries(3). In a study in Turkey, genetic analysis of 1090 patients revealed that M694V was the most frequent mutation (51.4%), followed by M680I (14.4%) and V726A (8.6%)(4). Our patient described in case 1 had two of the most common mutations including M694V and V726A. The K65R mutation that was detected in case 2 even though most common in the Turks, Arabs and Non Ashkenazi Jews, has been described in other ethnic populations as well(3). The MEFV gene codes for the protein pyrin which is a major regulatory component of the inflammasome, a complex of proteins that, when activated, trigger the release of IL-1β and are mediators of apoptosis. Dysregulation of the inflammasome due to mutated components may lead to increased neutrophil apoptosis in FMF(5). FMF symptoms include recurrent febrile episodes with sterile peritonitis, pleuritis, and arthritis. In a recent study in Turkey of 1090 patients clinical features included peritonitis in 93.7%, fever in 92.5%, arthritis in 47.4%, pleuritis in 31.2%, myalgia in 39.6%, and a classic erysipelas-like erythema in 20.9% of the

patients(4). The first attack usually occurs before 20 years of age in most patients(1). The episodes usually last for 1-3 days and resolve spontaneously. Other symptoms may include pericardial tamponade and constrictive pericarditis. Splenomegaly is seen in about 30% of patients and is usually not associated with amyloidosis(6). Laboratory findings may include elevated leukocytes, ESR, CRP and other acute-phase reactants during acute episodes(7). The demonstration of MEFV gene mutations is necessary to make a definitive diagnosis in clinically suspicious cases of FMF(3, 4).

Complications of FMF may include amyloidosis, glomerulonephritis and vasculitis including Henoch Schonlein purpura and polyarteritis nodosa. Amyloidosis usually affects the kidneys and may cause chronic renal failure. Differential diagnoses of hereditary periodic fevers other than FMF include TRAPS, hyperimmunoglobulinemia D syndrome (HIDS), Muckle-Wells syndrome (MWS), familial cold urticaria (FCU), chronic infantile neurological cutaneous and articular (CINCA) syndrome and periodic fever-adenopathy-pharyngitis-aphthous ulcers (PFAPA) syndrome(7). Treatment of FMF is daily colchicine therapy which helps reduce attacks and prevent as well as treat renal amyloidosis(8). Colchicine may interfere with intracellular assembly of the inflammosome complex present in neutrophils and monocytes that mediate the activation of IL-1β. Colchicine is used in doses of 0.3-1.8 mg/day in children 4-6 years of age, 0.8-1.8 mg/day in children 6-12 years of age, and 1.2-2.4 mg/day in children older than 12 years and adults.

Conclusion

FMF is one of the causes of recurrent fevers in children and adolescents and primary care providers need to have a high index of suspicion when evaluating patients with cyclical fevers.

Conflicts of Interest: None

Financial Disclosures: None

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