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Genetics-Proven Familial Mediterranean Fever: A Case Report and Review of the Literature

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Abstract

Familial Mediterranean fever (FMF) is an auto-inflammatory disease characterized by relapsing and remitting episodes of fever and serositis. We have a case of a 35-year-old male who presented with nausea, abdominal pain and myalgia for several months. He underwent an extensive workup to rule out diabetic ketoacidosis, celiac disease, gastroparesis, rheumatoid arthritis and porphyria. It was determined that he had heterozygous V726A mutation for the MEFV (Mediterranean fever) gene, suggesting possible FMF. His symptoms responded well to colchicine.

Keywords

Familial Mediterranean Fever, Abdominal Pain

1. Introduction

Although periodic fever has been described since antiquity, familial periodic fever syndromes were identified in the latter half of the twentieth century with description of the various symptoms and organ involvement. Heberden wrote a book in 1802 and mentioned fits of pain in bowels, stomach and limbs [1]. Later, Osler in 1895 described 11 cases, which periodically presented with different visceral manifestations and various rashes [2]. Janeway in 1908 reported a young girl with intermittent fever and abdominal pain. The case was reported as "an unsolved diagnostic problem" [3]. The first accurate description of FMF was published in 1945 by Siegal under the name "benign paroxysmal peritonitis" [4]. The syndrome since then appeared under several other names, including periodic peritonitis, familial recurring polyserositis, Cattan-Mamou disease, Siegal-Cattan-Namou syndrome, and periodic disease. The actual modern name "familial Mediterranean fever" was

coined by Heller in 1958, who emphasized the genetic nature of the disease [5]. It was not until 1997 that the gene causing FMF (MEFV gene) was finally identified. The discovery of a caspase-activating complex by Martinon *et al.* in 2002, "the Inflammasome", provided the precise molecular mechanisms whereby pyrin participates in the disease process [6]. Five years later, in 2007, Papin *et al.* in Switzerland showed that pyrin binds to several components of the inflammasome, particularly caspase-1 and interleukin-1β. This was a breakthrough discovery that finally uncovered the precise disease process at the molecular level [7]. The introduction of colchicine in 1972 as a prophylactic treatment in FMF has dramatically reduced the frequency of attacks as well as the incidence of the dreaded complication of amyloidosis.

2. Case Presentation

A 35-year-old male with past medical history of type 1 diabetes mellitus, on insulin pump, presented to the medicine clinic with nausea, abdominal pain, headache and myalgia. His symptoms started almost a year ago. Over the course of time, the frequency of his symptoms increased and would last 1 - 4 days, every 2 - 3 weeks. The physical exam was mostly significant for mild diffuse abdominal tenderness. His symptoms were initially attributed to diabetic ketosis as home checks for ketonuria were mostly 1+ with these episodes. He had an emergency room visit for one episode; laboratory results were significant for bicarbonate 22 mmol/L, blood glucose 160 mg/dL, creatinine 0.80 mg/dL, beta-hydroxybutyrate 11.5 mmol/L, hemoglobin 13.5 g/dL and urine ketones 15 (1+). He was managed supportively with intravenous hydration only as presentation was not suggestive of diabetic ketoacidosis.

He was referred to specialists on increasing frequency of symptoms. Gastrointestinal (GI) workup included normal tissue transglutaminase IgA and IgG levels. He also had endoscopy, colonoscopy and gastric emptying study, which ruled out celiac disease, gastroparesis, and structural anomalies. Rheumatology workup included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibodies (ANAs), rheumatoid factor (RF), Vitamin B12, Vitamin D, thyroid stimulating hormone (TSH), cyclic citrullinated peptide (CCP) antibodies and Lyme screen, all of which were unremarkable.

The patient himself was concerned about common variable immunodeficiency based on web search. He was referred to hematology and immunology. Normal IgA, IgM and IgG levels ruled out common variable immunodeficiency. Other workups included immunofixation, kappa lambda ratio, and peripheral flow cytometry ruled out hematopoietic malignancies. Although the patient had no cutaneous findings, given possible neurovisceral symptoms, porphyria workup, including 24-hour urine collection, total porphyrins and coproporphyrins levels were checked, but all came unremarkable. On further history, patient was found to have Eastern European ethnicity. Genetic testing for FMF showed heterozygous V726A mutation for the MEFV gene. He was started on colchicine 1.2 mg daily with improvement of his symptoms.

3. Discussion

Familial Mediterranean fever is an auto-inflammatory disease that sometimes is categorized as periodic fever syndrome. Most common occurs in Middle East, Turkey, Eastern Europe, but cases have been reported as far as Japan and the United States. Five founder mutations, V726A, M694V, M694I, M680I, and E148Q for MEFV gene have been found, which encodes for pyrin [8]. It is a protein found in innate immunity cells like neutrophils, monocytes, and dendritic cells. Normally in response to toxins or external stimuli, this protein gets hypo-phosphorylated, leading to generation of inflammasome and IL-1β. Hence, causing inflammation-like state [9]. In FMF, gain-of-function mutation in pyrin results in proinflammatory state. Symptoms include fever, abdominal pain, chest pain, arthralgias, erysipelas-like skin lesions, headache and myalgias. Before the age of 20, fever is the most common presentation in about 90% cases, but after the age of 20, abdominal pain is more common up to 96% cases [10]. FMF is usually inherited as an autosomal recessive trait, but some heterozygotes can be symptomatic too. It is hypothesized that additional genetic and environmental modifiers such as vigorous exercise, emotional stress, infections, exposure to cold, surgery, and menses influence the phenotypic expression of the disease [11]. Several criteria have been reported to diagnose, but Tel Hashomer Medical Center criteria are widely used [12]. This is mostly a clinical diagnosis, but newer classification criteria consider including genotype [13]. Most common complications are secondary (AA) amyloidosis, small bowel obstruction and infertility. Treatment is colchicine with recommended maximum dose of 2 mg for children under 12 years and 3 mg for adults [14]. Anti-inflammatory biologics: Canakinumab, Rilonacept, Anakinra and etanercept are second-line to those who are unresponsive to colchicine.

4. Conclusion

FMF is an uncommon clinical entity that may have been overlooked in patients presenting with abdominal pain. An extensive history and systematic workup can provide early diagnosis and treatment. This case adds to the importance of unusual diagnosis and recognizing the zebras among the horses.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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