CLINICAL VIGNETTE

Mediterranean Fever: A Pain and Fever Disease Often Overlooked

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Case Presentation

A 42-year-old female from Iran presented with intermittent joint pains. She described the pain as severe episodic leg pain, accompanied with fever and abdominal pain. Her earliest memory of these episodic "attacks' was when she was 4 years old. She was called "crazy" and labeled a liar at school, and eventually was diagnosed with ADHD and panic attacks. She was given medication for her behaviors. Her mother witnessed the attacks and always believed they were a behavioral disorder. By age 5 her mother had taken her for multiple evaluations including at neighboring countries of Greece and Turkey.

The patient continued to experience attacks described as sudden in onset, with waves of abdominal pain and joint pain, which usually involved ankles and knees, accompanied by the rash below the ankle. The episodes lasted from a few hours to a few days with a frequency of weeks to months.

She was born in Iran with mixed Greek, Italian, and Iranian ancestry. Her family left Iran and moved to the United States when she was 5. She continued to experience the attacks throughout her life causing her to frequently miss school and work. She was evaluated by several physicians including rheumatologists, gastroenterologists, and psychiatrists. She married at age 30 and had 2 children. Marriage was challenging because of her inability to maintain employment and difficulty taking care of her children when she experienced the "attacks". One of their 2 children also begins to experience similar attacks.

Physical Exam

Overall, the patient appeared healthy and in no distress. She had no symptoms on the day of exam and her vital signs, joints, skin and abdominal exams were unremarkable.

A Familial Mediterranean Fever test was ordered and returned Positive for Homozygous FMF mutation.

Initially she was started on Non-Steroidal Anti-Inflammatory Drugs as needed during attacks. Colchicine was also initiated. Colchicine has been shown to be effective in reducing attacks, and can improve quality of life. It also delays development of amyloidosis in kidney, heart, and gastrointestinal systems, which is a common complication of FMF.[1]

Discussion

Mediterranean fever is rare in the general population, but not so rare in certain ethnic groups. This inflammatory disorder is classically identified by intermittent bouts of fever and serosal inflammation. Joints are the most common sites of inflammation but the peritoneum, pericardium and pleura are also frequently affected. The initial episode usually occurs in childhood but has been reported in adults greater than 50. Patients diagnosed later in life may have had prior symptoms for many years, but not striking enough to raise suspicion for this disease. Mediterranean Fever is thought to be an autosomal recessive disease affecting the MEFV gene on chromosome 16. Five mutations of MEFV account for 60-80 percent of all Mediterranean fever patients.[2] The MEFV gene codes for Pyrin protein. Pyrin stimulates the creation of an inflammasome, a multi-protein oligomer ultimately responsible for the secretion of many inflammatory mediators including IL-1, IL-18. This inflammatory pathway is normally activated by toxins or infectious pathogens, but with MEFV mutation no trigger is needed to initiate the inflammatory cascade. Thus the mutation is considered a gain of function mutation.

The typical clinical presentation is fever and pain which lasts for days. Patients may have repeat episodes days, weeks, months or even years in between. Occasionally, fever is the only symptom but is often associated with abdominal pain due to inflammation of the peritoneum, chest pain (pleura, pericardium), joint pain, and scrotal pain. Occasionally patients describe a restless sensation in a region (pleura, pericardium, joint, scrotum) just prior to inception of pain.

This disorder is most prevalent among people of Jewish, North African, Turkish, Greek, Arab and Italian descent. Diagnosis can be confirmed by genetic testing for the most common MEFV mutations. Negative genetic screening does not completely rule this disease out as there are mutations and gene modifiers that may contribute to the disorder that are yet to be characterized. Other laboratory markers suggestive of this disease include elevation of inflammatory markers, leukocytosis/ leukopenia, and elevated serum amyloid protein. Successful treatment of symptoms is usually achieved by regular administration of Colchicine. Serious long term complications of untreated Mediterranean Fever are related to the persistent elevation of amyloid and subsequent deposition in different organs. Disruption of normal kidney function and ultimate ESRD is of the most serious complications of amyloidosis in

Mediterranean Fever patients. Small bowel obstruction and infertility are also pervasive. Lastly, an early diagnosis can save time and cost for patients with this disease as they often undergo many invasive diagnostic procedures prior to eventual diagnosis.

REFERENCES

1. **Magaki S, Parks R, Vinters HV, Khanlou N**. A 44-year-old female with familial Mediterranean fever, cardiomyopathy and end stage renal disease. *Brain Pathology*. 2017;29(2) Wiley Online Library. https://doi.org/10.1111/bpa.12581
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