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A rare cause of myalgia and muscle stiffness in an adolescent: a Heterozygous case of familial Mediterranean fever

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ABSTRACT

Familial Mediterranean fever (FMF) is a hereditary, autoinflammatory disease that causes recurrent fever, arthritis, and serositis. The diagnosis of FMF is based on the presentation of typical clinical symptoms and the Mediterranean fever gene (*MEFV*) test. However, the challenge lies in diagnosing atypical cases. We describe the case of an 18-year-old male patient with heterozygous FMF whose dominant clinical features were recurrent myalgia and muscle stiffness with or without fever. He had intermittent attacks of muscle aches and muscle stiffness with and sometimes without fever for which he was on regular non-steroidal antinflammatory medications. His acute inflammatory markers and serum amyloid A was found high and The diagnosis heterozygous FMF was done after *MEFV* gene analysis revealed heterozygous *MEFV* mutation. Recurrent, prolonged, and unresolved muscle aches that was refractory to nonsteroidal anti-inflammatory drugs.so the diagnosis of heterozygous FMF was done and started on colchicine 1mg/day. The muscle aches and muscle stiffness improved dramatically after starting colchicine therapy 1mg/day and the inflammatory markers returned to normal levels. We present an adolescent who is a case of heterozygous FMF presented with history of recurrent myalgia and muscle stiffness and back pain with and without fever since childhood. The patient was treated with colchicine. Based on this case, we suggest that FMF should be kept in mind in the differential diagnosis of patients with myalgia, back aches, muscle stiffness with or without fever.

1. INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessively inherited disorder caused by genetically inherited mutations. Familial Mediterranean fever (FMF) is a common, autoinflammatory disease that is mainly characterized by periodic fever and polyserositis [1]. FMF is seen more frequently among Arabs, Armenian, Turkish, and Jewish, populations and in other ethnic groups living in the Mediterranean region [2], [3]. Mutations in the Mediterranean fever gene (*MEFV),* which encodes the protein called pyrin are responsible for FMF. Mutant pyrin causes hyperactivation of inflammasomes and interleukin-1β (IL-1β)

hypersecretion [4]. The M694V, M694I, M680I, V726A, and E148Q mutations in *MEFV*, the gene responsible for FMF, account for most FMF cases in Mediterranean populations [5]. Incidentally, FMF diagnosis might be difficult since it exhibits diverse clinical manifestations, and the majority of *MEFV* variants are classified as variants of unknown significance [6], [7].

Clinical symptoms are fever, abdominal, chest, or joint pain recurring with irregular intervals, erythema like erysipelas in the lower extremities, myalgia, orchitis, and aseptic meningitis. The common characteristic of these symptoms is unresponsiveness to analgesics or antipyretics and complete resolution spontaneously in 24 to 72 hours [1]. Course of attack may be with only one symptom or multiple symptoms [8]. These symptoms appear before 20 years of age in more than 90% of cases, and in 60% of cases, the age of onset is less than 10 years of age [9]. The most frequently observed symptoms of FMF in children are fever and abdominal pain, and however, some clinical, molecular, and prognostic characteristics may differ between patients with early and late (adulthood) onset [10]. In a study, 6.2% of children with FMF had attacks of isolated fever alone without any serositis [4]. The probability of attacks with isolated fever alone increases with decreasing age, and the frequency of arthritis and erysipelas like skin eruptions increases in patients with early onset of FMF [10].

Usually, FMF presents clinical symptoms namely recurrent fever and serositis, and its occurrence is confirmed by genetic analysis. However, due to the variants of unknown significance in *MEFV*, an accurate diagnosis of FMF might be difficult. In this case unexpected heterozygous mutations in *MEFV at codes E148Q, 1692del, V726A*., *MEFV* ^{I692del}, and its function has not been completely analyzed [11], [12]. Therefore, functional analysis of *MEFV* variants along with an assessment of the patient's peripheral blood can help to diagnose FMF.

2. Case presentation

An 18-year-old Egyptian male high school student who is resident in Saudi Arabia presented to our clinic with the complaints of muscle aches, back pain and weakness for 14 days. The condition was associated with on and off fever, anorexia, headache, and malaise. The condition was associated with mild abdominal discomfort and loose stool. The patient gave history of recurrence of myalgia, back pain, muscle weakness and muscle stiffness with or without fever since childhood for which he is taking non-steroidal anti-inflammatory drug (Ibuprofen) regularly. He sought medical advice and performed EMG and NCV, plain x-ray and MRI of lower limbs and spine which was normal and he is taking pain killer when his muscle aches. The patient's vital signs at presentation included a body temperature of 36.3°C, pulse rate of 75bpm, blood pressure of 120/70mm Hg and respiratory rate of 18 breaths/min. There were no notable abnormal findings in the physical examination except for the lower limb muscles were tender and the patient cannot walk few steps. Muscles were tender, rigid to palpation. Abdominal pain was mild. Any slight movement was enough to aggravate the muscle pain. There was no particular social or environmental history. There were no obvious cardiac, chest, or abdominal and neurological findings.

The patient was born to Egyptian parents. There was no consanguineous marriage. The patient's mother had uneventful pregnancy with the patient. his father`s sister had rheumatoid arthritis. The patient had been experiencing recurrent episodes of muscle aches with or without fever since childhood. Sometimes he develops arthralgia that was associated with fever and he took regularly analgesics for pain. The patient has underwent many laboratory investigations when he was a child including CBC, ESR, CRP, LDH, liver function tests, and renal function tests. There were increased acute phase reactants without explanation. The patient had chronic pain in the lower limbs sometimes with and sometimes without fever. EMG and NCV were done and came normal. Pediatric neurologist adviced the patient to do EMG, NCV and both results were

normal.

We considered the history of recurrence of the patient symptoms and we requested for him full laboratory work up including CBC, routine biochemistry, urine analysis, stool microscopy and culture, markers of hepatitis, thyroid function tests, urine albumin/creatinine ratio, Vitamin D3 level, LDH, iron profile(serum iron, Iron binding capacity), serum immunoglobulin levels, and HIV serology, brucella antibodies level, ANA, CCP, rheumatoid factor IgM, anti-double stranded DNA, extractable nuclear antigen antibodies, anti-tissue transglutaminase antibody, gliadin IgG, and the results were normal or negative. Antinuclear antibody, Antineutrophil cytoplasmic antibody, rheumatoid factor, and *Brucella* agglutination tests were negative. His tests results revealed high inflammatory markers, Erythrocyte sedimentation rate was 75mm/h (normal range, 0–20) and C-reactive protein level was 122mg/L (0.2–5)., serum amyloid A= 210 mg/L(1-10), serum iron was low, urine albumin/ creatinine ration was moderately elevated (0.63). all laboratory results were normal except for high ESR, CRP, and SAA. Follow up of the patient after 2 weeks of conservative management with analgesics revealed persistently elevated inflammatory markers (ESR,CRP,SAA) while the pain improved. According to the previous data we did genetic analysis for familial Mediterranean fever and Ankylosing spondylitis. His *MEFV* gene mutation analysis revealed positive at heterozygous state at codon E148Q mutation, 1692 del and V 726A, while HLA-B27 for ankylosing spondylitis was negative. The diagnosis of heterozygous familial Mediterranean fever was considered and Colchicine was started 2×0.5 mg/day. After the colchicine treatment, the patient's complaints markedly improved and the inflammatory markers returned to normal levels after two months.

FMF was considered in the patient due to the presence of recurrent attacks and heterozygous mutation in the FMF gene analyses. Colchicine was started 2×0.5 mg/day. The patient's symptoms were successfully controlled by administration of colchicine. After the colchicine treatment, there was a marked improvement in his complaints and the inflammatory markers returned to normal levels. The patient provided written informed consent to have the case details published.

3. Discussion

FMF is a disease that is characterized by recurrent fever and serositis. The majority of patients (80%) present before 10 years of age and 90% present before the age of 20 years. Onset of the disease is rare after 40 years old. Acute episodes may last from 24 to 72 h and have variable frequencies. Some commonly reported precipitating causes include viral illness, emotional stress, excessive/intense physical activity, high-fat diet, extremes of temperature. The frequency of attacks may range from once a week to every 5–10 years, with the median frequency being approximately once a month [1], [4], [13], [14]. Our case was diagnosed in adolescence because of atypical presentation.

The first attack appears before the age of 20 in >90% of the patients. Fevers are generally accompanied by symptoms of inflammation in one or more sites. These may include abdominal pain, chest pain, joint pain, and skin rashes, and other characteristic findings. Abdominal pain is the most frequent clinical complaint in FMF. The diagnosis of FMF is based on the clinical criteria, family history, geographic and ethnic considerations, response to colchicine treatment, and genetic analysis of known mutations. Analysis of MEFV gene is the only method to be confirm the diagnosis of the disease. Colchicine is the gold standard and still the only recommended drug for treating FMF [1], [4], [6], [7], [10], [15]. Here, we present a case heterozygous of FMF accompanied by myalgia and muscle stiffness.

The majority of patients with FMF (95%) experience abdominal pain, and this may be the first finding in half of the patients. Acute episodes of FMF are associated with acute inflammatory markers, such as CRP, ESR

and SAA protein. However, elevated levels of SAA, CRP are nonspecific. Molecular genetic diagnostic testing is used to provide a confirmation of the FMF diagnosis as it is obviously more specific than ESR and CRP. Also, some researchers use SAA protein levels as an important marker of chronic inflammation in between attacks of FMF [4], [16- 18]. In our case, an increase in SAA suggested FMF.

Several diagnostic criteria have been shown in the literature. The most widely used criteria are the so-called Tel-Hashomer criteria [16]. A favorable response to colchicine may be one of the most valuable criteria for diagnosing FMF [4]. Genetic analysis plays a certain role in the diagnosis of the disease. The gene responsible for FMF (*MEFV*) is localized on chromosome 16p13.3 and includes 10 exons. FMF exhibits an autosomal recessive pattern of inheritance, and patients are either homozygous or compound heterozygous for *MEFV* mutations. Most of these mutations are in exon 10. The most commonly observed mutations ie, M694V, M680I, M694I, V726A, and E148Q, are responsible for a large percentage of mutations in different ethnic groups. The relationship between FMF and mutations such as M694V, M694I, M680I, V726A, and E14Q has been clearly established [19- 23]. In our case, genetic analysis demonstrated His *MEFV* gene mutation analysis revealed positive at heterozygous state at codon E148Q mutation, 1692 del and V 726A.

Various muscle symptoms during the course of FMF disease may emerge, and the incidence is about 20–40% [24], [25]. Types of myalgia that may occur during the course of FMF can be categorised as (i) muscle pain occurring in childhood after exercising; (ii) disseminated muscle pain due to fibromyalgia; (iii) protracted febrile myalgia (PFM); (iv) muscle pain accompanying the attack; and (v) myalgia and myopathy related to colchicine treatment. Post-exercise muscle pains occur particularly in the lower extremities. These are not accompanied by fever or acute phase response, last for 2–3 days on average, may follow a severe course, and usually begin in the evening [26]. The incidence of fibromyalgia syndrome, which causes generalized pain, has increased in both paediatric and adult FMF patients. The basic cause of this situation is that the pain threshold decreases as a result of chronic illness. Acute phases and muscle enzymes in myalgia resulting from this are normal, and trigger points with pain can be detected during examination [27], [28]. Generalised muscle pain that accompanies fever and other clinical findings during attacks is another type of myalgia. This situation ends when the attack ends [29]. Another finding relevant to muscles is myopathy, which develops due to colchicine treatment. As is previously known, colchicine is the gold standard treatment for FMF.

Another type of muscle pain is PFM. Its incidence has been stated to be 1–3% in various case series [30], [31]. It occurs particularly in the lower extremities, continues with intense pain and sensitivity, and seriously affects the patient's quality of life. Contrary to most FMF clinical findings, PFM can last for up to 6 weeks. Some authors have suggested that to be able to say that a pain is PFM, it should last for at least 5 days [32]. PFM can occur before or after a serositis attack. Approximately 70% of cases are accompanied by fever [33]. In PFM, muscle enzymes are at normal levels, and no abnormality is detected in muscle biopsy and EMG [26]. However, in magnetic resonance imaging (MRI) examinations, findings of oedema have been reported in the involved muscles [34]. A higher ratio of female patients in the case series is noteworthy (25]. Studies of the genotype-phenotype relationship suggest that PFM is seen more frequently in M694V homozygous individuals [35].

The diagnosis of FMF is made based on patient history, inflammatory markers, and genetic testing [36]. Several clinical diagnostic criteria sets have been proposed for diagnosis of FMF. The Tel Hashomer criteria, Livneh criteria, and Turkish pediatric criteria all rely on clinical symptoms, family history, and colchicine response [37- 39]. modified Tel Hashmer criteria have been suggested [40]. These include: recurrent febrile episodes (three or more episodes lasting 12 h to 3 days with fever ≥ 38 °C), and eight minor criteria. A diagnosis of FMF is determined if the patient exhibits the major criteria and one or more minor criteria.

Differential diagnoses include infections, malignancy, and autoinflammatory diseases. In the present case, we diagnosed heterozygous FMF because of recurrent myalgia and muscle stiffness and a genetic analysis together with favorable response to colchicine.

Treatment of FMF is focused on the prevention of painful attacks and the development of amyloidosis. Non-steroidal anti-inflammatory drugs may be used to treat individuals during acute episodes, although they are not always effective. Colchicine has been the mainstay of FMF treatment since 1972. It reduces the frequency, severity, and duration of attacks and prevents amyloidosis in almost all patients when used regularly on a lifelong basis at optimal doses. However, despite using maximum doses, 5%–10% of patients do not respond well to colchicine and 30% have partial response. These patients are either intolerant or resistant to colchicine. Interleukin-1 and tumor necrosis factor inhibitors may be effective in these settings [4], [6], [9]. Our patient was diagnosed as heterozygous FMF, and colchicine 1 mg/day was prescribed. At his follow-up visit myalgia and muscle stiffness had improved. And acute phase reactant has returned to normal levels.

4. Conclusion

FMF is characterized by self-limiting fever episodes, usually accompanied by serositis, arthralgia, and arthritis. We describe this case of heterozygous FMF accompanied by myalgia and muscle stiffness sometimes with or without fever as a disease among the rare causes of myalgia in an adolescent who was treated with colchicine. Based on this case, we propose that FMF should be kept in mind in the differential diagnosis of the patients with myalgia and muscle stiffness with or without fever. We present an unusual case of heterozygous FMF with excellent response to colchicine. Colchicine treatment is usually prescribed in FMF cases. Clinicians should consider FMF in the differential diagnosis of myalgia and muscle stiffness with and without fever.

Disclosure

The authors report no conflicts of interest in this work.

I have taken written consent from the patient to present his case.

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