CASE REPORT

Severe liver involvement in two patients with long-term history of fever: remember familial Mediterranean fever

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SUMMARY

Familial Mediterranean fever (FMF) is characterised by recurrent, self-limited fever attacks and serositis. Severe liver involvement has rarely been reported. We present two FMF cases of a 55-year-old man and a 20-year-old woman in whom the prevailing manifestations were recurrent unexplained episodes of anicteric hepatitis (man) and recurrent severe jaundice (woman). A long-term history of recurrent self-limited episodes of fever was also claimed in both. After exclusion of infectious, malignant, autoimmune, and liver and biliary diseases, a diagnosis of FMF as confirmed by molecular analysis was established. The patients started colchicine 1 mg/day with immediate resolution of symptoms. During follow-up, no new episodes of fever and exacerbation of liver biochemical parameters have been recorded for 5 and 1 years. Physicians must keep FMF in mind in patients with recurrent episodes of unexplained severe liver impairment and fever and especially in regions like Mediterranean basin where hereditary periodic fever syndromes are common.

BACKGROUND

Familial Mediterranean fever (FMF) is the most common among the hereditary periodic fever syndromes (HPFS) worldwide, an autosomal recessive disease that mainly affects inhabitants living around the Mediterranean basin, such as Jews, Armenians, Turks and Arabs, but nowadays it is not considered rare in Italy, Spain and Greece.[1 2] The disease is characterised by recurrent, unpredictable self-limited flares of fever associated with polyserositis including not only peritonitis, synovitis and pleuritis but also pericarditis, orchitis and meningitis.[1 3] In 1997, the MEditerranean FeVer (*MEFV*) gene was identified on chromosome 16p13.3. Its product, named pyrin (also known as marenostrin), was found to play a pivotal role in the regulation of inflammation and specifically interleukin-1β (IL-1β) production. *MEFV* gene is consisted of 10 exons, and most patients have mutations in exon 10, the longest exon of this gene. Although the diagnosis of FMF remains mainly clinical and requires information about family history and response to colchicine, the availability of the molecular approach to the diagnosis improved the global identification of the disease by identifying apart from patients carrying the typical manifestations of the full-blown disease also patients with mild or atypical forms of the disease.[1]

Under this context, we present herein two atypical adult FMF cases who suffered from recurrent severe episodes of liver involvement characterised by considerable anicteric hepatitis in the first case and significant increase in the values of bilirubin and liver function tests (LFTs) in the second case, which after molecular analysis of the *MEFV* gene proved to be caused by the presence of FMF. The latter analysis was decided as after a careful and in-depth history both patients had, along with liver involvement, a long-term past history of recurrent self-limited episodes of fever accompanied by abdominal pain.

CASE PRESENTATION

Two patients (55-year-old man and 20-year-old woman) were referred for consultation to the Department of Medicine, Medical School, University of Thessaly, Larissa, Greece because of recurrent episodes of anicteric hepatitis and recurrent significant increase in the values of bilirubin and LFTs, respectively. Both patients had many hospitalisations because of their above-mentioned symptoms in other academic and regional hospitals in the past 3 and 12 years, respectively. Their current diagnosis and treatment was autoimmune cholangitis under 100 mg/day azathioprine, 1000 mg/day ursodeoxycholic acid and low-dose prednisolone (5 mg/day) for the male patient and recurrent severe cholangitis managed with intravenous antibiotics and subsequently by oral antibiotics for the young female patient.

On admission, both patients had high fever (39°C) of 1-day duration and diffuse mild abdominal pain accompanied by generalised arthralgias, whereas the female patient was also significantly jaundiced. The remaining physical examination was unrevealing. Both patients denied ever consumption of herbal agents and/or dietary supplements, intravenous or nasal illicit drugs, or alcohol use.

INVESTIGATIONS

The laboratory work-up (abnormal values) was as follows: for the male patient, leucocytes 18 000/μL, aspartate aminotransferase (AST) 526 IU/L, alanine aminotransferase (ALT) 489 IU/L, gamma-glutamil-transpeptidase (γ-GT) 128 IU/L, urea 45 mg/dL, creatinine 1.43 mg/dL, C reactive protein (CRP) 24 mg/dL and serum amyloid A (SAA), 10.2 mg/dL and for the female patient, leucocytes 12 100/μL, AST 118 IU/L, ALT 257 IU/L, γ-GT 231 IU/L, total bilirubin 7.3 mg/dL, direct bilirubin 2.9 mg/dL,

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erythrocyte sedimentation rate (ESR, 76 mm/1 hour) and CRP 18.3 mg/dL. The remaining haematological, microbiological, virological and biochemical parameters including blood cultures and investigation for hepatitis viruses, tuberculosis, leishmaniasis, brucellosis, leptospirosis, autoantibodies related to autoimmune rheumatic diseases, serum IgG, IgA, IgM, C_3 and C_4 complement components and ferritin levels were within the normal limits. Abdominal ultrasonography, chest X-ray, MRI of the abdomen and retroperitoneal space and MR cholangiography were also normal. Liver autoimmune serology, according to our standard protocols,[4] for the diagnosis of autoimmune liver diseases including autoimmune hepatitis and its variants as well as autoimmune cholestatic liver diseases was repeatedly negative.

During the fourth day of hospitalisation, the fever and abdominal pain were subsided spontaneously in both patients, whereas abnormal laboratory markers became normal in 1 week without any specific treatment. Of note, their history was very interesting. The male patient had undergone liver, kidney and bone marrow biopsies 3 years ago during the investigation of a similar episode of self-limited fever, abdominal pain and polyarthralgia syndrome accompanied by increased laboratory markers of acute-phase reactants and considerable elevation of LFT values; no specific findings were found in liver biopsy apart from mild to moderate portal inflammation consisting of lymphocytes, neutrophils and rare eosinophils with mild focal interface hepatitis and cholangiolar hyperplasia in association with mild inflammatory lymphocytic infiltrate of the bile ducts.

The previous episodes in the female patient were characterised at onset by severe sore throat with negative cultures followed by high self-limited fever, arthralgias and abdominal pain. In most instances, the latter symptom was predominant in the upper right quadrant of the abdomen. For these reasons, the patient had undergone cholecystectomy 10 years ago after a similar episode thought to be due to acalculous cholecystitis, though repeatedly sets of MRI of the abdomen and MR cholangiographies were unrevealing. Both patients' grandfathers and grandmothers were refugees from Asia Minor but without any known history of confirmed FMF. Interestingly, the female patient was claimed that attacks were more common during menstruation.

DIFFERENTIAL DIAGNOSIS

Taking carefully into account the previous in-depth history of both patients, a molecular analysis of the *MEFV* gene was decided. A rapid screening test of the entire coding sequence of *MEFV* gene,[5 6] combined with targeted sequencing, revealed that both patients suffered from FMF as no other aetiology had been identified thus far, whereas there was an appropriate exclusion of infectious, malignant, autoimmune, rheumatic, and liver and biliary diseases at their last submission. Actually, the mutational analysis revealed that the male patient carried the *R202Q/R202Q* homozygous alteration in exon 2 of the *MEFV* gene, while the female young patient was heterozygous for the *M694V/0* conservative mutation in exon 10 and homozygous for the *R202Q/R202Q* mutation in exon 2.

TREATMENT

Current treatment schedules discontinued, and both patients started immediately colchicine 1 mg/day.

OUTCOME AND FOLLOW-UP

During follow-up, no new episodes of sore throat, fever in association with abdominal pain, polyarthralgia syndrome and exacerbation of liver biochemical parameters or remarkable jaundice have been recorded in both patients for 5 and 1 years, respectively.

DISCUSSION

The following major points have been raised from the present case series: (a) using the molecular approach for FMF diagnosis, it is now obvious that the disease is clinically heterogeneous reflecting probably the complexity and multiplicity of pyrin functions;[7] (b) contrary to the known conservative mutations clustered in exon 10 (*M694V, V726A, M680I, M694I*) and exon 2 (*E148Q*), the presence of *R202Q* in exon 2 further supports this mutation as disease-related in Greek patients with FMF; and most importantly, (c) although severe liver involvement is extremely rare in FMF cases, this possibility should be considered if there are recurrent episodes of unexplained severe liver impairment including remarkable jaundice accompanied by fever and in particular in regions like Mediterranean basin where HPFS are common as attested by our two cases who characterised by a significant delay of diagnosis.

Indeed, various studies have now shown that the spectrum of the disease-associated signs and symptoms is broader than previously believed.[1 3 6 8 9] In general, a typical attack lasts 12–72 hours with well-being intervals of few weeks to months or years.[1] The age of onset is typically below 20 years in most cases, although in Western countries only a minority of them will have a final FMF diagnosis within the age of 20 years with almost half of the patients having the diagnosis between 25 and 55 years.[1 2 5 6 9–11] Under this context, the diagnostic delay in our patients could be justified by the fact that FMF has been considered a rare disease in Greece for a long time.

The attacks may be triggered by usual precipitating factors like emotional or physical stress, cold exposure, vaccinations and menstruation. The latter factor was characteristically claimed by our young female patient. It has been proposed that oestrogens normally inhibit IL-6 production and mimic the effects of colchicine. During menstruation, the protective effects of oestrogens disappear, and this in turn may provoke the acute attack. Recurrent episodes of high fever, which may be the only manifestation of FMF, can partially respond to paracetamol or corticosteroids, while antibiotics do not have any effect as also shown in both of our patients. Abdominal pain is also very common and usually involves the entire abdomen with rigidity, rebound tenderness and abdominal distension resulting in a diagnosis of 'acute abdomen' and therefore, to unnecessary surgery and biopsies of many organs without resolution of the symptoms as observed in our patients. During the course of the attacks, a typical acute-phase response characterised by neutrophilic leucocytosis and elevated ESR, CRP, SAA and fibrinogen is usually present, which disappears in intercurrent well-being periods. Other manifestations include articular involvement, chest attacks due to pleura or pericardium inflammation, protracted febrile myalgia, erysipelas-like erythema and aseptic meningitis. On the other hand, cases with proteinuria or renal failure due to AA amyloidosis before the clinical onset of FMF or 'silent' carriers of FMF gene mutations who may suffer from a mild or incomplete form of FMF ('FMF-like disease') have also been reported further supporting the large phenotypic variability of the disease.[1 12]

To date, FMF phenotype has been linked, by several groups, with *R202Q* alteration.[5 6 13 14] The presence of *R202Q* homozygosity in both of our FMF patients is in parallel with previous findings from our group where almost 10% of Greek FMF patients carry only this mutation, which is extremely rare in the healthy Greek population.[5 6] In addition, the favourable

response to colchicine in both patients further enhances the mutational role of *R202Q* in FMF. How this mutated variant of pyrin leads to an inappropriate or prolonged inflammatory response is still not understood.[15]

In general, changes in LFT values may occur in almost 25% of FMF patients with mild hyperbilirubinamia being the most common abnormality during the attacks.[16] However, severe or acute liver injury, such as acute hepatitis, or acute cholestatic attacks similar to that observed in our patients are extremely rare.[17–19] The prolonged and exaggerated inflammatory response in undiagnosed FMF cases may lead to the acute liver injury via a pro-inflammatory cytokine network. IL-1β and/or autophagy-driven inflammatory responses are crucially involved in the pathophysiology of FMF[20] and have also been linked with liver inflammation and fibrosis in many studies.[21–26] On the other hand, cytokine stimulation during FMF attacks may cause a decrease in bile excretion and UDP-glucuronosyltransferase activity, while it may also increase the permeability of tight junctions in intrahepatic bile duct-derived epithelial cells leading finally under some circumstances to considerable hyperbilirubinemia.[27]

In conclusion, as FMF diagnosis is mainly clinical, an accurate and detailed history along with otherwise unexplained self-limited acute-phase determinants (CRP, SAA, ESR, white cell count) seems mandatory to build up a correct and timely diagnosis of suspected cases. Prompt diagnosis contributes to avoid further unnecessary investigations and therefore, to reduce the cost but also to promise our compliant patients an almost normal life expectancy if remission under treatment is achieved with a good quality of life. However, after the use of reliable genetic tests for FMF confirmation, it became obvious that the disease-related manifestations are broader than previously believed. Under this context, our cases further support the concept that physicians must keep FMF in mind even in patients with recurrent episodes of unexplained severe liver impairment which is not as common as other FMF manifestations, particularly when periodic episodes of fever are also present and the patient resided in regions like Mediterranean basin where HPFS are common.

Learning points

- Familial Mediterranean fever (FMF) diagnosis is mainly clinical, and therefore, an accurate and detailed history along with otherwise unexplained self-limited acute-phase determinants (CRP, SAA, erythrocyte sedimentation rate, white cell count) seems mandatory to build up a correct and timely diagnosis of suspected cases.
- Prompt diagnosis contributes to avoid further unnecessary investigations and therefore, to reduce the cost but also to promise our compliant patients an almost normal life expectancy with a good quality of life.
- The availability of the molecular approach to FMF diagnosis improved the global identification of the disease by unmasking apart from patients carrying the typical manifestations of the full-blown disease also patients with mild or atypical forms.
- Our cases suggest that physicians must keep FMF in mind even in patients with recurrent episodes of unexplained severe liver impairment and periodic episodes of fever, especially in regions like Mediterranean basin where hereditary periodic fever syndromes are not uncommon.

Contributors GND, KR and NKG had the original idea, designed the study and wrote the first draft of the manuscript. NKG and PS collected and summarised the published literature and the data of the patients. GND was the principal treating physician, while PS and KR made the genetic analysis. GND and KR made the final critical revision of the manuscript for important intellectual content. All authors have seen and approved the final version of the manuscript.

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Patient consent Patient consent was obtained.

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Reminder of important clinical lesson