Review

The liver in familial Mediterranean fever: is it involved?

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ABSTRACT

Objectives. *Familial Mediterranean fever (FMF) is characterised by recurrent attacks of fever and serositis. It may affect the peritoneum, pleura, synovia and the skin. Usually the liver is intact in FMF. Recently, this concept was challenged by some groups which claimed that hepatitis is a feature of FMF and that non-alcoholic liver disease (NAFLD) and cryptogenic cirrhosis are more common among FMF patients.*
Scope of this paper is to critically review the relevant literature and to answer the question whether or not the liver is involved in FMF.

Methods. *We used Medline, Embase, Scopus and Web of Science database for searching articles dealing with FMF and the liver since 1960. We also reviewed some manuscripts which were not identified by the above search engines.*

Results. *Some cases reported that hepatitis is a feature of FMF based upon transaminase elevations without liver biopsy. Due to this questionable diagnosis and the paucity of similar reports, it seems that hepatitis is not a feature of FMF. Cryptogenic cirrhosis is considered as the end stage of NAFLD. Since NAFLD is prevalent in 25% of the general population it is more plausible to relate the occurrence of cryptogenic cirrhosis in FMF patients to NAFLD rather than to FMF. M694V mutation carriage was relatively more frequent among FMF patients with cryptogenic cirrhosis or "hepatitis".*

Conclusions. *The literature review indicates that FMF and liver disease are not generally associated. However, carriage of M694V mutations may play a role in the pathogenesis of liver disease.*

Introduction

Familial Mediterranean fever (FMF) is an auto-inflammatory disease characterised by recurrent attacks of fever, peritonitis, pleuritis arthritis or erysipelas like erythema (1). It is prevalent mainly in the Middle East but also in other areas in the world (2). Colchicine is the drug of choice for the disease since 1972 (3, 4). It can prevent the attacks of FMF and fend off the development of amyloidosis which is the most devastating complication of this disease (5).

FMF affects mainly, serous tissue of many organs. However, the liver is not considered as a typical organ involved in FMF unless hepatic amyloidosis is develops in uncontrolled disease.

Mild hepatomegaly has been reported by many authors but in view of the difficulties in clinical assessment of liver size in borderline cases a doubt was raised that liver enlargement indeed occurs in FMF (6). Liver biopsies have been performed on numerous occasions and with a few exceptions were found to be normal (7-12). Peri-portal infiltration in one case has been reported by Siegal (13) and in two more cases by Reimann (14). Liver function tests excluding serum proteins were found to be normal in many studies (9, 12, 15-18). However, we still see some cases with elevated transaminases with no clear explanation.

In recent years the concept that the liver remains intact in patients with FMF was challenged. Korkmaz *et al*. studied 41 consecutive FMF patients with acute attacks (19). Bilirubin levels, liver transaminases, erythrocyte sedimentation rate and C-reactive protein (CRP) levels were determined within the first 72 h after the onset of attacks. Hyperbilirubinaemia was detected in 11 of the 41 patients (26.8%). Levels of liver transaminases slightly increased in 4 patients with FMF during the attack and two of them had also mild hyperbilirubinaemia. The authors concluded that mild hyperbilirubinaemia

may occur in one-fourth of the patients with FMF during an attack.

Some authors proposed that hepatitis may be a feature of FMF (14, 20) while others reported that there is high prevalence of non-alcoholic liver disease among FMF patients compared with healthy controls (21). Tweezer-Zaks *et al*. added that cryptogenic cirrhosis is also more common among FMF patients and is associated specifically with the carriage of M694V mutation (22).

Based upon these observations it was suggested that FMF should be considered in the differential diagnosis of cryptogenic chronic hepatitis or cirrhosis – especially – in regions where this inflammatory disease is prevalent (22, 23).

In this manuscript we aim to critically review the available literature on this subject in order to try answering the questions whether or not hepatitis is a clinical feature of FMF and whether steato-hepatitis and cryptogenic cirrhosis are more prevalent among FMF patients.

Methods

We performed a literature search of series and case reports in the English and non-English medical literature – published since 1960. We used Medline, Embase, Scopus and Web in Science - in order to look for articles dealing with the following key words combinations: Liver and FMF, hepatitis and FMF, FMF and cryptogenic cirrhosis and FMF and fatty liver. We also reviewed relevant publications cited in the references of the articles – which had not been identified by the above searching engines. We excluded studies dealing with FMF and amyloidosis since this is a complication of uncontrolled disease rather than a primary clinical feature of FMF.

Results

We found more than 53 publications most of which dealt with general recommendations for treating FMF, FMF and secondary amyloidosis and others described liver complications of colchicine toxicity. Only seven series and 6 case reports dealing with hepatitis, cryptogenic cirrhosis or NAFLD and FMF, were included in this review. Apart from two case reports all articles were published in English. Most series did not have control groups and all of them were retrospective. Following is a critical review of the relevant articles.

Hepatitis and FMF

In 1961, while looking for the abdominal findings of 30 laparotomies in FMF Armenian patients, Reimann obtained 8 liver biopsies (14). Degenerative changes of the hepatic cells and foci of necrosis were seen with invasion of lymphocytes, monocytes and plasma cells into the portal space – in two of them. There was no information as to the clinical presentation of these patients. Based upon this observation Reimann claimed that "hepatitis is a feature of periodic peritonitis". In these cases one cannot exclude an incidental finding of hepatitis due to numerous causes in patients with FMF who underwent laparotomy. Furthermore, if it is a feature of FMF why it was found in only 2 of the 8 biopsies?

Since then several authors described sporadic cases of FMF patients with hepatitis. Neequaye and Jelly described in 1994 two children of Yemenite origin who have FMF (24). In one of them they claim that FMF was characterised by hepatitis. In this patient – at presentation the AST, ALT, LDH and CPK (1380) were elevated while the alkaline phosphatase was normal. Moreover, no liver biopsy was available and the diagnosis of hepatitis was proposed based on the transient elevations of serum transaminases. It should be emphasised that elevation of CPK is not a feature of hepatitis raising a question as to the source of the enzymes; muscles or liver. The second reported patient with FMF who was his cousin did not present with "hepatitis".

In 2008 Migita *et al*. described a 45 year old lady with Sjogren's syndrome who presented with elevated liver enzymes and a history of recurrent periodic fever episodes (20). A liver biopsy taken during laparotomy showed multiple foci of liver cell necrosis. In proximity to these necrotic foci, an assortment of inflammatory cells such as neutrophils, lymphocytes and macrophages accumulated. However, there were no findings consistent with interface hepatitis or bile duct disease. The histological findings were summarised as "nonspecific reactive hepatitis". Two years after the episode of the hepatitis, genetic analysis revealed that the patient was homozygous for M694I and a diagnosis of FMF was made. The authors related the hepatitis to her FMF though the diagnosis was made two years later. This case raises several questions related to the diagnosis. Could this hepatitis be related to her Sjogren's disease? Could it be related to medications she had taken for her Sjogren's syndrome? Were there other causes for this association?

In 2009 Khatibian and Arab described a 32 year-old man with recurrent attacks of fever, abdominal pain and arthralgia that had moderate increase in liver transaminases only during disease flares (25). FMF was diagnosed based on the clinical picture, carriage of *MEFV* mutations and response to colchicine. Liver enzymes normalised after colchicine treatment. Despite a thorough work up, no known underlying liver disease was found to account for the transaminases elevation. Therefore, they claim that the only explanation for abnormal liver enzymes in this case is transient hepatitis during the FMF attacks. Again this is a single case with transient elevation of liver enzymes which we have to assess without the benefit of a liver biopsy.

In a retrospective study from 2012, Unal *et al*. found hepatic involvement in 11 of 58 patients (18.9%) which were followed in their dedicated liver clinic (23). Two patients (3.4%) had abnormal liver enzymes during the diagnostic evaluation, while 9 patients (15.5%) had been admitted with features of liver disease, and had a final diagnosis of familial Mediterranean fever. Two had Budd-Chiari syndrome, 5 had chronic hepatitis/cirrhosis, and two had acute hepatitis. The two patients with clinical and laboratory findings of acute hepatitis were admitted to the hospital. No cause was found for the acute hepatitis in either patient. After clinical and laboratory recovery, these patients were followed in the outpatient paediatric unit. Two years later a diagnosis of FMF was made based upon clinical features and further ge-

netic confirmation. Comparison of patients with and without liver involvement in FMF, disclosed no difference in the demographic factors or laboratory findings between the groups. However, M694V allele was more common in patients with liver involvement but this was not statistically significant ($p = 0.21$). Again the patients described in this study had had hepatitis before a diagnosis of FMF was made. This suggests that the two diseases were probably not related.

In 2014 Tzifi *et al*. reported a case of FMF patient heterozygous for the mutation I259V (26). At the age of 2.5 years he presented with FMF clinical phenotype with 2 consecutive episodes of acute hepatitis during fever attacks, which spontaneously resolved. It should be stressed that the patient had had experienced many episodes of recurrent fever since the age of 6 months (Two years before the episode of hepatitis). These attacks lasted 3–4 days, while asymptomatic periods usually lasted 40–50 days. During asymptomatic periods and in previous episodes of fever no liver dysfunction had been noted. A therapeutic trial with colchicine was successful with no further fever attacks or acute hepatitis episodes. A liver biopsy was unavailable. In this child serum liver enzyme returned to normal values without treatment within 15 days while a usual FMF attack resolves within 3–4 days. Therefore the association between FMF and transaminase elevation may still be debated in this patient, as well, unless it was the hepatic component that prolonged the FMF attacks.

In 2015 Salehzadeh screened 403 FMF patients in a single centre in Iran (27). He found 2 female siblings who were homozygous for M694V mutations and who had massive ascites, abdominal pain, and idiopathic hepatitis. No data about other background of the patients or liver histology were given. The fact that the two patients were siblings may raise an underlying genetic factor which could contribute to this unusual clinical picture.

Cryptogenic cirrhosis and FMF

In 2007 Tweezer-Zaks *et al*. investigated the association between FMF and chronic liver disease (22). Among 6000 FMF patients – in one centre – they found 16 patients with liver cirrhosis. One had an autoimmune hepatitis, 6 had amyloidosis and 9 were designated as cryptogenic cirrhosis since no specific cause for cirrhosis was found. It should be stressed that in 4 out of the nine patients liver biopsy was not performed and in one of the patients liver biopsy revealed only fatty changes. Therefore, an unequivocal diagnosis of cryptogenic cirrhosis based upon liver biopsy was made in only 4 of the 9 patients. The authors found that 5 of the 7 patients with cryptogenic cirrhosis and who had genetic analysis – were homozygotes for M694V. Therefore they suggested that M694V mutation may play a role in the pathogenesis of cryptogenic cirrhosis.

In a poster presented by Baskin *et al*., a 9 year-old boy was found to have cryptogenic cirrhosis and genetic analysis disclosed homozygosis of M694V supporting the above observation (28).

In 2012 Unal *et al*. described 2 children with cryptogenic cirrhosis of whom one underwent a liver biopsy showing severe fibrosis (23). Genetic analysis disclosed M694V homozygosity in one patient and carriage of M694V and M680I mutations in the other. The authors did not find association between the severity of FMF, the response to colchicine and the development of liver disease. The rate of homozygosity for M694V among FMF patients with liver disease was high but did not reach statistical significance. Nevertheless, they suggested that every patient with cryptogenic cirrhosis should be investigated for *MEFV* mutations.

Non-alcoholic liver disease and FMF

Rimar *et al*. investigated 27 FMF patients who were referred to a liver clinic due to hepatic function disturbances which lasted more than 6 months (21). In 15 patients, there was evidence for nonalcoholic fatty liver disease (NAFLD) by liver biopsy. Five patients had "simple" steatosis, 3 had non-alcoholic steatohepatitis (NASH), and 7 had NASH-cirrhosis. Patients with FMF and NAFLD were compared to matched controls from a cohort of 150 patients with NAFLD with no associated FMF and all diagnosed by liver biopsy. An additional 5 patients had "cryptogenic" cirrhosis, which in most patients probably represented the end result of unrecognised NASH. Comparing FMF patients with NAFLD and the controls with NAFLD but without FMF, did not reveal any excess of metabolic syndrome among the FMF patients. Due to the extremely high proportion of NAFLD in this cohort of FMF patients without overt metabolic syndrome the authors concluded that this finding may indicate an unappreciated novel association between FMF and NAFLD. A possible support for this impression can be found in a case report by Moretti *et al*. who described a patient with FMF and fatty liver (29). Following treatment with colchicine for several years, serum triglycerides were reduced leading the authors to conclude that FMF was the cause for the fatty liver. Regarding the study by Rimar *et al*. it should be bear in mind that the patients' cohort was chosen from a dedicated liver unit and there might be a selection bias towards a higher rate of liver involvement in the FMF population studied.

In a later study by Sarkis *et al*. the clinical findings and treatment information of FMF patients were obtained from outpatient files (30). Weight, height, blood pressure, blood C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, glucose, low-density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), creatinine, alanine aminotransferase (ALT), and insulin levels were determined in all subjects. In addition, liver ultrasonography was also performed in order to detect signs of hepatosteatosis. Fifty-two age- and gender-matched patients with FMF, and 30 healthy controls were included in the study. The prevalence of metabolic syndrome in the patient group was found to be significantly higher compared with the healthy group. On the other hand, 11 patients (21%) with FMF were found to have grade 1–2 hepatosteatosis, and 6 of healthy subjects (20%) had grade 1 hepatoseatosis (p=0.901). These results led the authors to conclude that

when compared with healthy controls, the prevalence of NAFLD was not increased in patients with FMF while the rate of metabolic syndrome was higher among these patients. Thus these results did not support the previous contentions by Rimar *et al*. (21).

Colchicine and the liver

Since FMF patients are treated continuously with colchicine, a question may be raised regarding its potential role for liver damage. In our clinical experience we have not seen that colchicine – in therapeutic dose – causes liver injury. Furthermore, in patients with elevated transaminases continuous colchicine treatment did not increase their serum levels. Thus, chronic therapy with colchicine is uncommonly associated with serum aminotransferase or alkaline phosphatase elevations. Furthermore, colchicine has, indeed, been used off label for the treatment of liver diseases such as; alcoholic hepatitis and primary biliary cirrhosis (31, 32).

Colchicine overdose due to liver or kidney failure or due to receiving concurrent drug which may inhibit the functions of the P-glycoprotein multidrug transporter ABCB1, or that of cytochrome P450 3A4 isoenzyme, can cause multi-organ injury including the liver (33). In this case the hepatic abnormalities are probably secondary to ischemic injury to the liver or sepsis.

Discussion

The literature search resulted in a few articles half of which were case reports. Most series were retrospective and uncontrolled.

Regarding the issue of hepatitis as a feature of FMF, in most reported cases the diagnosis of hepatitis was made based upon transaminase elevations without histological confirmation by liver biopsy. Furthermore, in many cases the diagnosis of FMF was made several years after the episode of hepatitis suggesting that both diseases were not associated.

A recent report presented two patients who suffered from recurrent fever and severe episodes of liver involvement characterised by considerable anicteric hepatitis in one case and significant increase in the values of bilirubin and liver function tests (LFTs) in the other case (34). Mutational analysis revealed that the first patient carried the R202Q/R202Q homozygous alteration in exon 2 of the *MEFV* gene, while the other was heterozygous for the M694V and homozygous for the R202Q/R202Q mutation. These patients did not have typical FMF and represent a totally different phenotype of MEFV associated diseases - as described previously (35). Therefore, they do not support the notion of increased prevalence of hepatitis in the classical phenotype which is defined as FMF.

Cryptogenic cirrhosis is a medical condition of liver fibrosis of unknown aetiology. Therefore, the diagnosis is actually one of exclusion. Today we know that the most common cause for cryptogenic cirrhosis is nonalcoholic liver steatohepatitis (NASH) (36). Recently, a large study proposed that a quarter of the general population, worldwide, have non-alcoholic fatty liver disease (NAFLD) (37). Since NAFLD prevalence is this high in the general population while FMF is a relatively rare disease, it is more plausible to relate the occurrence of cryptogenic cirrhosis to this underlying fatty liver disease rather than to FMF. Thus, cryptogenic cirrhosis is also not a feature or a complication of FMF.

Regarding NAFLD and FMF there were only 2 studies from liver units with contradictory results. The study by Sarkis *et al*. differed from that of Rimar *et al*. on two accounts: a. FMF patients did not have an increase in the frequency of metabolic syndrome; and b. Even so, NAFLD was more prevalent among these patients. Based upon only these two studies it is quite difficult to conclude a definite conclusion.

Regarding colchicine and liver disease, no convincing instances of acute liver failure, vanishing bile duct syndrome or chronic liver injury due to this medication have been reported. Moreover, in some of the above mentioned case reports starting colchicine treatment resulted in complete control of FMF attacks and remission of "hepatitis" (25, 26). Therefore, it seems that colchicine in therapeutic dose does not harm the liver.

Finally, it should be emphasised that since the articles reviewed were either case reports or retrospective uncontrolled studies the conclusions should be taken carefully. Furthermore, the fact that some of them were conducted by physicians working in a gastrointestinal and liver unit may lead to a selection bias towards a high percentage of liver involvement in FMF patients.

In brief, our literature review indicates that FMF and liver disease are not generally associated. Due to the high prevalence of NAFLD in the general population it is reasonable to suggest that, in most cases, FMF patients with liver enzyme disturbances have a fatty liver. Having said that, the observation of high carriage rate of M694V mutations- especially – in the homozygote state – among FMF patients with cryptogenic cirrhosis or "hepatitis", may suggest a role for this mutation in the pathogenesis of liver disease.

Prospective studies including follow-up of liver functions, liver ultrasound and – where possible – liver histology, in large cohorts of FMF patients - are needed in order to sort out the exact relationship between hepatic diseases and FMF.

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