Is hyperbilirubinemia a component or just a coincidence of familial Mediterranean fever: A case report and review of the literature

Hiperbilirubinemi ailevi akdeniz ateşinin bir özelliği mi yoksa rastlantısal bir bulgusu mudur: Bir olgu takdimi ve literatürün gözden geçirilmesi

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Familial Mediterranean fever (FMF) is a genetic multisystem disorder of unknown etiology characterized by recurrent episodes of fever and pain due to acute inflammation of the peritoneum, synovia, or pleura. In this article, we report a case of Familial Mediterranean fever with recurrent abdominal pain and hyperbilirubinemia, review the literature and discuss whether the hyperbilirubinemia is co-existent or a feature of the disease.

INTRODUCTION
Familial Mediterranean fever (FMF) is a genetic multisystem disorder of unknown etiology characterized by recurrent episodes of fever and pain due to acute inflammation of the peritoneum, synovia, or pleura (1). Patients are symptom-free between episodes, which usually occur at irregular and unpredictable intervals. The disease is restricted mainly to certain ethnic groups of Mediterranean and Middle Eastern origin (2-5).

The rare and acute involvement of various organs have been described in case reports. Recurrent hyperbilirubinemia is a very rare feature of FMF which was first described in the 1950s and early 1960s (6, 7) but since then there has been only two further case reports with this feature (8, 9).

CASE REPORT
A 22 year-old boy was admitted to our department with acute abdominal pain, fever and jaundice. He had been well until the age of 16, when acute abdominal pain with concurrent fever and jaundice had developed. Since then he had experienced one or two attacks monthly of abdominal pain, lasting from a few hours to two days, accompanied by fever and jaundice each time. He had, however, remained well except for slight yellowish discolouration of the sclerae between the pain episodes, with no pruritus, diarrhea, vomiting or change in stool color either between episodes or during the attacks. He had four brothers and four sisters, two of whom had a diagnosis of FMF without a history of jaundice. At presentation, he had severe abdominal pain with rebound tenderness, distension, and rigidity. His temperature was 39°C. His sclerae and skin had a marked yellowish

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discoloration. Rectal examination was normal. Liver transaminases, gamma glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase, prothrombin time, serum glucose, renal function tests, albumin, total protein, cholesterol, triglycerides, hemoglobin level, reticulocyte count, serum amylase, Coombs tests, serum heptoglobulin, serum free hemoglobin levels and serum electrolytes were normal. Mild leucocytosis (13200/mm\(^3\)), mild elevation in serum fibrinogen levels (690 mg/dl), elevation of erythrocyte sedimentation rate (80 mm/1st hour) and an increase in bilirubin levels (direct bilirubin 3 mg/dl, indirect bilirubin 3.2 mg/dl) were observed during the attack. Twelve hours after the pain episode, all abnormal results returned to normal except direct and indirect bilirubin levels, which decreased to 2.1 mg/dl and 1.9 mg/dl respectively. Two more bouts of pain with similar signs, symptoms and laboratory findings were observed during the one month hospitalization period of the patient. His upper abdominal ultrasound was normal and percutaneous liver biopsy showed normal histological findings. Serology for Hepatitis B and C virus infection was negative. Hepatobiliary scan, coproporfin levels and bromosulphophatelein test could not be performed because the patient refused further investigations.

The patient was prescribed oral colchicine 0.5 mg b.i.d., which reduced the number of attacks to one in six months.

**DISCUSSION**

The presentation of FMF is characterized by fever, acute abdominal pain, pleural pain and arthralgia due to inflammation of the peritoneal, pleural and synovial membranes. Other less common acute manifestations are skin-related signs such as erysipelas-like erythema, nodular erythema and urticaria, angio-edema (1, 5, 10), acute orchitis (11), pericarditis (12, 13) meningitis (10), Henoch-Schönlein purpura (1), polyarteritis nodosa (14), protracted febrile myalgia (15), and glomerulonephritis (16). Recurrent hyperbilirubinemia as a feature of FMF was first described by Çattan and Bloede in the late 1950s and early 1960s (6, 7, 17, 18). No large series since that time has indicated that jaundice is a feature of FMF. (1, 2, 5, 10) Only two case reports of FMF mentioning transient hyperbilirubinemia during a peritoneal attack lasting one or two days have been published. (8, 9). Some investigators reported hepatitis with concurrent FMF attacks, (8, 17) while others found normal hepatic histology in biopsy specimens obtained during the attack (19). Our case with characteristic features of FMF had recurrent hyperbilirubinemia aggravated by abdominal pain and normal hepatic histology.

Plasma bilirubin concentration varies according to bilirubin generation and is inversely associated with hepatic bilirubin clearance. (20) Some genetic defects in the UDP-glucuronosyltransferase gene complex have been found to be responsible for unconjugated hyperbilirubinemia such as in Gilbert's syndrome and a defect in the ATP-dependent organic anion transporter at the level of the biliary epithelium has been found to be responsible for conjugated hyperbilirubinemia such as that of Dubin-Johnson syndrome (21). Although the hyperbilirubinemia of FMF has been interpreted as a distinct clinical entity, occurring only during a peritoneal bout in previous reports (8, 9, 17, 18), it may be that these cases are in fact silent hyperbilirubinemia syndrome. In Gilbert syndrome, subclinical individuals may first be detected in association with calorie withdrawal due to febrile illness, "morning sickness" of pregnancy, achalasia, postoperatively, behavior change such as fasting intravenous nicotinic acid administration: This generally results in a two- to threefold rise in plasma bilirubin level, even if the initial bilirubin concentrations are normal (21). In Dubin Johnson syndrome, many patients are anicteric at the time of diagnosis. (21). It should also be noted that congenital hyperbilirubinemic cases such as Rotor's syndrome may occasionally present with fever and frank abdominal pain, although they are usually asymptomatic. (21). In the case reported by Majeed et al, the subject seemed to also have a conjugated hyperbilirubinemia syndrome because 9mTc-labeled dimethyliminodiacetic acid cholescintigraphy showed delayed observation of the gallbladder (9), a finding which is a feature of Dubin-Johnson syndrome. (22) Although further studies and genetic testing for bilirubin metabolism could not be performed, the findings in our case led us to believe that the association of FMF with a conjugated hyperbilirubinemia syndrome was coincidental, although the latter was probably aggravated by fever and abdominal pain attacks.

In conclusion, the findings of our case suggest that other cases with recurrent abdominal pain and concurrent hyperbilirubinemia, as reported in the literature, might have been a form of hyperbilirubinemia.
Hyperbilirubinemia in familial Mediterranean fever (Such as Gilbert's, Rotor's Dubin-Johnson's) coincidental to the FMF. Further studies with larger numbers of cases are needed, including genetic testing, bromosulfophthalein test, coproporphyrin levels and hepatobiliary scan, to evaluate the association of FMF and hyperbilirubinemia.

REFERENCES