Turk J Gastroenterol 2003; 14 (1): 71-73

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

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

Yusuf YAZGAN, Levent DEMİRTÜRK, Melih ÖZEL, Mustafa ERCAN

GATA Haydarpaşa Training Hospital Department of Gastroenterology, istanbul

Familial Mediterranean fever is a multisystem disorder, usually seen in subjects of Mediterranean and Middle Eastern origin, characterized by recurrent bouts of fever and pain due to inflamation 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-existant or a feature of the disease.

Ailevi Akdeniz Ateşi, genetikle Ortadoğu ve Akdeniz kökenli kişilerde görülen, periton, sinovya veya plevrayı tutan inflamasyona bağlı olarak gelişen ateş ve karın ağrısı atakları ile karakterize bir hastalıktır. Bu makalede, Ailevi Akdeniz ateşi ataklarına eşlik eden bilirubin yüksekliği ile karakterize bir olguyu, literatür bilgilerini gözden geçirerek bu bulgunun rastlantısal mı yoksa hastalığın bir özelliği mi olduğunu irdelemeye çalıştık.

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).

We report a FMF case admitted to our department with recurrent abdominal pain and concurrent jaundice during the course of the attack.

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 discoloration 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

Address for correspondence: Yusuf Yazgan
GATA Haydarpaşa Eğitim Hastanesi Gastroenteroloji Servisi Üsküdar - Istanbul / Turkey
Phone: +90 2163885838 - +90 2163462600-Fax: +90 2163487880
E-mail: yuyazgan@turk.net

Manuscript received: 6.8.2002 **Accepted:** 7.1.2003

discoloration. Rectal examination was normal. Liver transaminases, gama glutamil 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/lst hour) and an increse 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 similiar signs, symptoms and laboratory findings were observed during the one month hospitilization 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, coproporfirin 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 erisipelas-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 aggrevated 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 it may be that these cases are in fact silent hyperbilirubinemia syndome. 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 occasionaly 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 hyperbiliru-

binemia syndrome (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, coproporfirin levels and hepatobiliary scan, to evaluate the association of FMF and hyperbilirubinemia.

REFERENCES

1. Sohar MJ, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med 1967; 43: 227-53.
2. Barakat M, Karnick A, Majeed HA, et al. Familial Mediterranean fever (recurrent hereditary polyserositis) in Arabs. A study of 175 patiens and review of the literature. Q J Med 1986; 60: 837-46.
3. Ozdemir AI, Cavit S. Familial Mediterranean fever among the Turkish people. Am J Gastroenterol 1969; 51: 311-6.
4. Rogers DB, Shohat M, Petersen GM, et al. Familial Mediterranean fever in Armenians. Am J Med Genet 1989; 34: 168-72.
5. Özel AM, Demirtürk L, Yazgan Y, et al. Familial Mediterranean fever. A review of the disease and clinical and laboratory findings in 105 patients. Digest Liver Dis 2000; 32: 504-9.
6. Çattan R. Maladie periodique. Dix observations at deux hypotheses. Bull Mem Soc Med hop Paris 1954; 70; 43-50.
7. Bloede G. Maladie periodique at rhyles Biologiques. Maroc Med. 1954; 33: 7-14.
8. Neequaye J, Jelly AE. Acute hepatits in recurrent hereditary, polyserositis (familial mediterranean fever). J Trop Pediatr. 1994; 40: 243-5.
9. Majeed HA, Halabi I, Al-Taleb O. Recurrent hyperbilirubinemia, a feature of familial Mediterranean fever: report of a child and review of the literature. Ann Ped Trop. 1998; 18; 13-6.
10. Schwabe AD. Recurrent polyserositis (Familial Mediterranean fever). In: Haubrich WS, Schaffner F, berk JE, editors Bockus Gastroenterology. Philedelphia. WB Saunders Co. 1995. p. 3097-105
11. Eshel G, Zemer D, Bar-Yochai A. Acute orchitis in familial Mediterranean fever. Ann Intern Med. 1988; 109: 164-5.
12. Tutar HE, Imamoglu A, Atalay S. Recurrent pericarditis in familial Mediterranean fever. Acta Paediatr 1999; 88: 1045-6.
13. Zimans S, Tauber T, Hegesch T. Familial Mediterranean fever presenting with massive cardiac tamponade. Clin Exp Rheumatol 1994; 12: 67-9.
14. Glikson M, Galun E, Schlezinger M,et al. Polyarteritis nodosa and familial Mediterranean fever. A report of two cases and review of the literature. J Rheumatol 1989; 16: 536-9.
15. Longewitz P, Zemer D, Linveh A, et al. Protracted febrile myalgia in fatients with Familial Mediterranean fever. J Rheumatol 1994; 21: 1708-9.
16. Said R, Hemzeh Y, Said S, et al. Spectrum of renal involvement in Familial Mediterranean fever. Kidney Int 1992; 41;414-9.
17. Reiman HA. Hepatitis: a feature of peritonitis. JAMA 1961; 178: 334-5
18. Siegal S. Familia paroxysmal polyserositis. Analyses of fifty cases. Am J Med 1964; 36: 893-918.
19. Priest RJ, Nixon RK. Familial recurring polyserositis: a disease entity. Ann Int Med 1959: 51; 1253-74
20. Berk PD. Pathophysiology, diagnosis and treatment of hereditary bilirubinemias. In: Williams R, Maddrey WC, eds. Butterworth's international medical reviews: gastroenterology, vol. 4: liver. London: Butterworths, 1984:1.
21. Berg CL, Crawford JM, Gollan JL. Bilirubin metabolism and the pathophysiology of jaundice. In: Eugene R. Schiff, Michael F. Sorrell, Willis C. Maddrey, eds. CD-ROM version of Diseases of the Liver, 8th Edition on CD-ROM. Philadelphia, Pennsylvania. Lippincott Williams & Wilkins. 1999.
22. Bar-Meir S, Baron J, Seligsohn U, et al. 99mTc-HIDA colescintigraphy in Dubin-Johnson and Rotor syndromes. Radiology 1982;142:743.