Hepatitis A super infection as a cause of liver failure in a child with Wilson's disease

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Infection with hepatitis A virus can cause severe or even fatal illness in patients with chronic liver disease. Here we describe a seven-year-old girl who presented as acute liver failure and was diagnosed with Wilson's disease and later with coexistent hepatitis A infection. Wilson's disease was demonstrated on the basis of low ceruloplasmin, high urinary copper excretion, histological evidence of cirrhosis, and high biochemical estimation of liver copper concentration. Hepatitis A was diagnosed serologically. Our case suggests that acute hepatitis A may play a part in the acute decompensation seen in some cases of unrecognized Wilson's disease. We also emphasize the importance of prevention measures of hepatitis A infection in patients with chronic liver disease.

Key words: acute liver failure, hepatitis A infection, Wilson's disease.

Exposure to hepatitis A virus (HAV) infection occurs at a very early age in endemic areas. Turkey is a moderate endemic area with respect to HAV infection. The frequency of this infection varies due to the socio-economic differences in various regions of the country. Reports from Manisa (west) and Adana (south) have shown overall prevalence of the HAV infection in children living in these regions as 44.6% and 44.4%, respectively[1,2]. Prevalence of HAV infection was reported as 72.5% in young children and 100% in adolescents and adults in Elazig (southeast)[3]. According to the results of these studies, seropositivity increased significantly with advancing age.

Seroprevalence was significantly lower in children less than six years and of higher socio-economic status[2]. Viral hepatitis A is the leading cause of acute liver failure (ALF) in children in Turkey[4]. Even though there is evidence of specific genetic features in HAV found in ALF patients[5], why some patients infected with HAV present ALF, whereas most of them present a self-limited picture, remains unknown.

Infection with HAV in patients with chronic liver disease (CLD) has been shown to result in exacerbation of the underlying CLD and high mortality, in particular in patients with hepatitis C (35%, 6/17)[6]. Recently, there was a report on severe decompensation of CLD produced by super infection with hepatitis E virus (HEV)[7].

Wilson's disease (WD) is an autosomal recessively inherited error of copper metabolism attributed to the absence or dysfunction of a copper transporting P-type ATPase encoded on chromosome 13 and characterized by an excessive accumulation of copper in the liver and the brain[8]. WD has a broad spectrum of liver diseases such as ALF, acute hepatitis, chronic hepatitis and cirrhosis. Many of the initial clinical symptoms of WD are nonspecific and its clinical manifestations are rarely apparent prior to the age of five years; the typical young patient is at least eight years old[9]. For this reason, early severe hepatic form of WD may become unrecognized without presence of a positive family history.

Our study reports a case of hepatic failure occurring in a child with biochemical and histopathological evidence for underlying WD complicated by HAV infection. This case indicates that HAV plays a part in the acute hepatic decompensation seen in some cases of unrecognized WD.

Case Report

A seven-year-old girl was referred to the pediatric intensive care unit of Baskent University Hospital, Ankara, with encephalopathy, coagulopathy, jaundice, and biochemical evidence of hepatocellular injury. Diagnosis of the referring center was ALF due to hepatitis A. She had a one-week history of abdominal pain, fatigue, vomiting and jaundice. She had no previous signs of liver disease. Her parents were first cousins. Family history was negative for metabolic and inherited liver diseases, including WD. Her weight was 16.5 kg (10 percentile), height 112.5 cm (10-25 percentile), blood pressure 90/60 mm Hg, heart rate 104 beats/min, and respiratory rate 24 ipm. Physical examination revealed a jaundiced patient with mild ascites. Her liver and spleen were palpated 4 cm and 5 cm below the right and left costal margins, respectively. She was in grade I hepatic encephalopathy.

Laboratory investigation revealed hemoglobin, white blood cell, platelet, and reticulocyte counts of 10.3 g/dl, 4600/mm^3, 89x10^9/L and 0.5%, respectively. No hemolysis was detected in the blood smear. Serum level of glucose was 60 mg/dl (normal (N): 70-105), aspartate aminotransferase (AST) 209 IU/L (N: <40), alanine aminotransferase (ALT) 1706 IU/L (N: <40), alkaline phosphatase (ALP) 339 IU/L (N: 40-125), gamma glutamyl transferase (GGT) 74 IU/L (N: <36), total bilirubin 10.25 mg/dl (N: 0.10-1.2), direct bilirubin 9.12 mg/dl (N: 0-0.30), and albumin 2.57 g/dl. Prothrombin time was 45.6 seconds (N: 10-12.8) and international normalized ratio (INR) was 5.1 (N: 0.8-1.2). Serum level of copper was 88 µmol/L (N: 11.2-48.2) and ammonia was 59 µmol/dl (N: 70-140). Anti-HAV IgM and Anti-HAV IgG antibodies were positive.

Antibodies against hepatitis B, C, and E viruses, Parvovirus B19, human immunodeficiency virus (HIV), herpes simplex virus (HSV) types I and II, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) were all negative. Anti-nuclear, anti-smooth muscle and anti-liver kidney microsomal antibodies were negative. Urine and blood amino acid analysis revealed massive generalized aminoaciduria. Ceruloplasmin level was 18.6 mg/dl (N: 25-55). Urine copper was 470 µg/24 hours (N: 12.5-50). Liver biopsy could not be performed due to severe coagulopathy.

Patient became tachypneic one day later. Upon this symptom, a thoracal X-ray was performed and right-sided massive pleural effusion was demonstrated. Characteristics of pleural fluid were consistent with transudate, and Gram stain and culture of the fluid were negative. Acid-fast bacilli did not grow and polymerase chain reaction for tuberculosis was negative. Anti- HAV IgM was positive in the pleural fluid. Abdominal ultrasound demonstrated moderate hepatosplenomegaly and cholecystitis. During the patient's stay in hospital, liver function tests progressively deteriorated. The routine treatment for severe hepatic dysfunction was initiated, including oxygen support, lactulose and oral/systemic antibiotic therapy, fluid and electrolyte management, plasmapheresis, and continuous veno-venous hemofiltration. The patient died due to multiple organ failure on the 12th day of her admission to our unit. Unfortunately no cadaveric or living donor was available in this time period.

A postmortem core biopsy of the liver was obtained. Microscopically, basic architecture in liver tissue was distorted. Fibrosis and formation of structurally abnormal parenchymal nodules had developed. Fibrous septum contained numerous proliferating bile ductules, vascular structures and scattered inflammatory cells. Parenchymal nodules exhibited canalicular cholestasis, microvesicular steatosis, cholestatic liver cell rosettes and regenerative changes. There was no iron deposition. Biochemical estimation of liver copper concentration was 285 µg/g-dry liver weight (N: 10-35).

Discussion

Liver failure occurs as an ALF in a previously healthy liver, an acute decompensation of CLD or as chronic decompensation in end-stage liver disease. Decompensation of a patient with CLD may be caused by superimposed acute hepatitis A-E, drugs, sepsis, gastrointestinal bleeding, development of hepatic vein and portal vein thrombosis, and hepatocellular carcinoma.

Our patient presented like ALF with no previous history of liver disease. After completing the laboratory work-up for determining the etiology of liver failure, we came to the conclusion that the disease was hepatitis A super infection on a liver already affected by WD.

Symptoms of WD are nonspecific and are associated with persisting asymptomatic elevation of aminotransferase concentrations, progressive development of cirrhosis, and fulminant liver failure[9,10].

In a patient presenting with ALF, fulminant WD should also be considered in the differential diagnosis. Fulminant WD is characterized by severe derangement of liver function, encephalopathy, and hemolysis in patients with previously undiagnosed liver disease. Presence of very high serum copper levels, Coombs negative hemolytic anemia, low alkaline phosphatase levels despite high bilirubin levels, relatively low elevations of aminotransferases, and higher AST than ALT levels should alert the physician to the diagnosis of fulminant WD[10-13]. However, diagnosis of WD in a patient presenting with ALF is a diagnostic challenge because abnormal serum copper concentration, high urinary copper excretion, and low ceruloplasmin concentrations are common in ALF cases secondary to the causes of liver failure other than WD. Although liver biopsy is dangerous in patients with ALF because of clotting problems, high hepatic copper content is crucial for proper diagnosis. Early diagnosis is essential since without orthotopic liver transplantation, the mortality is virtually 100%[10]. Histologic examination of explanted livers of patients who underwent liver transplantation due to fulminant WD usually demonstrated established cirrhosis instead of massive necrosis[10,11].

Our patient had established liver cirrhosis due to WD. She had marginally low ceruloplasmin, and raised serum, urine, and hepatic copper levels. The commonly used clinical and laboratory parameters were not sufficient to exclude the diagnosis of WD in patients with liver disease of unknown origin. In 2003, Ferenci et al.[12] developed a scoring system for diagnosing WD. According to the Ferenci score, our patient had a score of 5, indicating diagnosis of WD was highly probable. It was reported that ALF with WD differed from idiopathic ALF by higher copper levels in serum, urine and liver, less pronounced elevations of transaminase levels, higher concentrations of serum bilirubin, and lower hemoglobin values[11]. Our patient had no hemolysis, her serum ALT level was very high, and her bilirubin levels were moderately high. These findings were not consistent with fulminant presentation of WD. Our patient had pancytopenia that could be related with hypersplenism.

Hepatitis A infection rarely has a fulminant course, occurring in 0.1%-0.4% of the pediatric cases[14]. It is seldom fatal, with an estimated fatality rate of 0.14 to 2%[15]. Its prevalence in pediatric ALF is reported to vary from as low as 1.5% to as high as 31%, depending on the geographical location[4,16]. Hepatitis A infection is the most common detectable cause of ALF in Turkish children[4]. Initial diagnosis of the referring center for our patient was ALF due to HAV infection. However, liver biopsy finding of established cirrhosis was not a feature of fulminant HAV infection. Patients who have ALF due to HAV infection reveal massive or submassive hepatic necrosis. This finding was not demonstrated in our case at postmortem histologic examination.

Many reports have provided information regarding the clinical course and outcome of HAV infection in patients with underlying chronic hepatitis B or hepatitis C[6,17]. Patients with chronic hepatitis are at increased risk of more severe disease including fulminant liver failure and a higher case fatality rate when infected with HAV. However, reports addressing the outcome of hepatitis A in patients with other CLDs are scarce. Akriviadis and Redeker[18] described four cases of fulminant hepatic failure occurring in patients with CLD due to drug abuse.

Sallie et al.[19] reported a case of fulminant liver failure resulting from coexisting WD and hepatitis E. This is the only article in the English literature that described a child with underlying WD who developed ALF precipitated by a viral infection. This patient had Coombs negative hemolytic anemia, and blood and urine copper studies were consistent with the diagnosis of WD. Massively raised liver copper stores with regional variation (mean 445 μg/g/dry weight) were determined in the resected liver during liver transplantation. Histopathologically there was extensive cell loss and mixed inflammatory cell infiltration, with no evidence of cirrhotic transformation. The authors reported that the acute viral insult superimposed on the underlying WD might have caused release of free copper and provoked hemolysis and severe liver damage.

In recent years, several reports from developing countries have suggested a shift in the HAV epidemiology from high to intermediate or low endemicity, presumably because of improved hygiene and sanitation[1,2,20]. Such observations have led to a recommendation for mass vaccination of all children in these countries. The Centers for Disease Control recommends routine vaccination against HAV in patients with CLD, because these individuals are at increased risk of developing ALF from acute HAV infection[21]. Consequently, the HAV vaccine is now considered the standard of care in patients with CLD.

It is possible that the severity of the liver damage in this case derives from the coincidental presence of the two conditions, hepatitis A and WD. It is conceivable that viral infections, particularly those producing hepatitis, may be responsible at least in some cases for the acute presentation of liver failure seen in patients with WD.

In conclusion, this study clearly shows that acute HAV infection in patients with cirrhosis produces decompensation of underlying liver disease and is associated with a high mortality rate. Furthermore, these results indicate the importance of HAV infection and emphasize the need for a national vaccination program. This case suggests that detectable or undetectable viral infections may play a part in fulminant presentation seen in some cases of WD.

REFERENCES

1. Tosun S, Ertan P, Kasırga E, Atman U. Changes in seroprevalance of hepatitis A in children and adolescents in Manisa, Turkey. Pediatr Int 2004; 46: 669-672.
2. Yapıcıoğlu H, Alhan E, Yıldızdaş D, Yaman A, Bozdemir N. Prevalence of hepatitis A in children and adolescents in Adana, Turkey. Indian Pediatr 2002; 39: 936-941.
3. Akbulut A, Kılıç SS, Felek S, Akbulut H. The prevalence of hepatitis A in the Elazığ region. Turk J Med Sci 1996; 26: 375-378.
4. Aydoğdu S, Özgenç F, Yurtsever S, Akman SA, Tokat Y, Yağcı RV. Our experience with fulminant hepatic failure in Turkish children: etiology and outcome. Trop Pediatr 2003; 49: 367-370.
5. Fujiwara K, Yokosuka O, Fukai K, Imazeki F, Saisho H, Omata M. Analysis of full-length hepatitis A virus genome in sera from patients with fulminant and self-limited acute type hepatitis. J Hepatol 2001; 35: 112-119.
6. Vento S, Garofano T, Renzini C, et al. Fulminant hepatitis associated with hepatitis A virus super infection in patients with chronic hepatitis C. N Engl J Med 1998; 338: 286-290.
7. Hamid SS, Atiq M, Shehzad F, et al. Hepatitis E virus super infection in patients with chronic liver disease. Hepatology 2002; 36: 474-478.
8. Tanzi RE, Petrukhin K, Chernov I, et al. The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene. Nat Genet 1993; 5: 344-350.
9. Yüce A, Koçak N, Gürakan F, Özen H. Wilson's disease with hepatic presentation in childhood. Indian Pediatr 2000; 37: 31-36.
10. Emre S, Atillasoy EO, Özdemir S, et al. Orthotopic liver transplantation for Wilson's disease: a single-center experience. Transplantation 2001; 72: 1232-1236.
11. McCullough AJ, Fleming CR, Thistle JL, et al. Diagnosis of Wilson's disease presenting as fulminant hepatic failure. Gastroenterology 1983; 84: 161-167.
12. Ferenci P, Caca K, Loudianos G, et al. Diagnosis and phenotypic classification of Wilson disease. Liver Int 2003; 23: 139-142.
13. Steindl P, Ferenci P, Dienes HP, et al. Wilson's disease in patients presenting with liver disease: a diagnostic challenge. Gastroenterology 1997; 113: 212-218.
14. Whitington PF, Spriano HE, Alonso EM. Fulminant hepatic failure in children. In: Suchy FJ, Sokol RJ, Balistreri WF (eds). Liver Disease in Children. Philadelphia: Lippincott Williams and Wilkins; 2001: 63-88.
15. Hepatitis surveillance reports no 55. Atlanta: Centers for Disease Control and Prevention 1994: 9-27.
16. Bendre SV, Bavdekar AR, Bhave SA, Pandit AN, Chitambar SD, Arankalle VA. Fulminant hepatic failure: etiology, viral markers and outcome. Indian Pediatr 1999; 36: 1107-1112.
17. Keeffe EB. Is hepatitis A more severe in patients with chronic hepatitis B and other chronic liver diseases? Am J Gastroenterol 1995; 90: 201-205.
18. Akriviadis EA, Redeker AG. Fulminant hepatitis A in intravenous drug users with chronic liver disease. Ann Intern Med 1989; 110: 838-839.
19. Sallie R, Chiyende J, Tan KC, et al. Fulminant hepatic failure resulting from coexistent Wilson's disease and hepatitis E. Gut 1994; 35: 849-853.
20. Barzaga BN. Hepatitis A, shifting epidemiology in South-East Asia and China. Vaccine 2000; 18 (Suppl) S61-64.
21. Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunization: recommendation of the Advisory Committee on Immunization Practices (ACIP). MMWR 1999; 48 (No. RR-12): 1-37.