

BENIGN RECURRENT INTRAHEPATIC CHOLESTASIS (BRIC): IS IT REALLY AS BENIGN AS ANTICIPATED?

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ABSTRACT

We report an 18 year old male patient with a known diagnosis of BRIC who presented with acute renal failure secondary to hyperbilirubinemia in three successive episodes. Renal replacement therapy was required in all three episodes but his renal function recovered to baseline creatinine on discharge. Proposed pathophysiology of ARF in the setting of hyperbilirubinemia includes direct tubulotoxicity and sequestration of pigment casts within the tubular lumen causing tubular obstruction aggravated by dehydration. We emphasize the importance of vigorous hydration to be started with the impending attack to prevent progression to ARF.

Key Words : Acute Renal Failure, BRIC

INTRODUCTION

Benign recurrent intrahepatic cholestasis (BRIC) is an autosomal recessive inherited liver disease,

characterized by intermittent attacks of cholestasis without progression to chronic liver disease (1). Each cholestatic attack begins with increasing serum bile acids followed by hyperbilirubinemia, resolves spontaneously without residual biochemical abnormalities and hence merits the suffix "benign".

We report a case of BRIC developing acute renal failure (ARF) during a so-called 'benign' cholestatic attack and discuss the possible pathogenetic mechanisms and protective measures that can be applied in this setting.

CASE REPORT

An 18 year old male patient with a previous diagnosis of BRIC presented with severe jaundice accompanied by acute renal failure on three subsequent cholestatic attacks. He was diagnosed to have BRIC in 1993 following two previous resolving attacks of cholestatic jaundice. The viral and autoimmune serology including hepatitis B(HBV), hepatitis C (HCV),

antinuclear antibody (ANA), antiDNA antibody, anti-smooth muscle antibody(ASMA), anti-mitochondrial antibody (AMA) and anti-liver kidney antibody (ALKM) were all negative as well as the hemolytic parameters. Hepatic nuclear scanning revealed markedly decreased hepatic uptake and delayed biliary excretion. The liver biopsy revealed focal absence of bile ducts accompanied by minimal septal fibrosis and hence he was diagnosed to have BRIC.

He had a history of 6 previous episodes of cholestatic jaundice by 1997 when he presented for the first time to our clinic with additional symptoms of anuria, confusion and drowsiness accompanying severe jaundice. He had no history of additional therapy with diuretics, laxatives, radiocontrast, nonsteroidal antiinflammatory drugs and/or antibiotics. On initial assessment, he was clearly icteric with no clinical evidence of ascites or peripheral edema. Serum BUN was 160mg/dl, Creatinine(Cr): 9,8mg/dl, total bilirubin(TB): 66,7mg/dl and direct bilirubin(DB) was 55,78mg/dl with a daily urine output less than 500 ml. Ultrasound scan showed a normal renal size and structure with no additional abnormalities. Following vigorous hydration, 500 mg furosomide tid iv, and dopamine infusion of 2 µg/kg/h were started. Due to failure in response and in view of worsening renal function he was dialyzed in two successive sessions after which his renal function recovered over a couple of days. By the seventh day, his Cr was 1,3mg/dl and BUN:17mg/dl with a daily urinary output of 3000 ml. Bilirubin levels were still high but started to resolve and they were back to normal over the next fortnight. The second episode was in October 1999 when he presented with oliguria, total bilirubin of 128 mg/dl and direct bilirubin of 56 mg/dl, Cr:2,8mg/dl, BUN: 40mg/dl, K: 3,1mEq/L. The daily urine output once more decreased to less than 500 ml. The time period between the beginning of the cholestatic attack and oligoanuria was 12 days. He was promptly put on intravenous hydration and dopamin and frusemide in the above stated doses were added to his treatment. However, his creatinine reached 5,2 with a BUN of 70mg/dl, developed signs of overvolemia accompanying complete anuria and he was dialyzed in two successive episodes. His renal function recovered once again over a couple of days and he was discharged on the

15th day with a Cr of 1,4 mg/dl and BUN:22mg/dl while his TB was 70mg/dl and DB was 47mg/dl. On follow up a month later his Cr was 0.8mg/dl; BUN:13mg/dl; TB:7.43mg/dl and D.Bil:5.17mg/dl. The third episode occurred three months later when his total and direct bilirubin increased to 77mg/dl and 58 mg/dl respectively. Due to a decrease in daily urine output accompanied by an increase in serum Cr and BUN levels to 7mg/dl and 98 mg/dl respectively, he required three sessions of hemodialysis after which he again recovered his renal function and was discharged on the twelfth day with a creatinine of 1.7 mg/dl and BUN of 30 mg/dl. On follow up a month later his creatine and BUN were 1.1 mg/dl and 24 mg/dl respectively.

DISCUSSION

Benign recurrent intrahepatic cholestasis was first described by Summerskill and Walsh in 1959 and since then more than 100 cases have been reported (2). Despite its benign quality, the disease causes substantial morbidity in afflicted patients, mainly due to pruritus and malabsorption (1). To our knowledge acute renal failure in the setting of BRIC has not been previously reported.

In the case reported, ARF seems to be secondary to ATN supported by the urinary Na being above 40 mmol/L although preexisting dehydration could have had an additive effect on the development of ATN. We were unable to perform a renal biopsy due to the coagulopathy accompanying severe cholestasis which could cause bleeding complications during the acute setting.

Hyperbilirubinemia with a predominant increase in conjugated fraction is the usual outcome in obstructive jaundice, although a moderate increase in unconjugated fraction could also be seen in severe cases. The predisposition of patients with obstructive jaundice to ARF has been well recognized in the surgical literature (3-4). The proposed underlying pathogenetic mechanism has been direct tubulotoxicity of high bilirubin levels as well as cardiovascular instability (3-4). Extremely high conjugated bilirubin levels could result in sequestration of pigment casts within the tubular lumen, causing

tubular obstruction. Griffin et al have reported tubular epithelial damage with pigment containing casts, early interstitial fibrosis and ischemic glomerular changes in the setting of prolonged anuria, complicating primary sclerosing cholangitis (5).

On the other hand, obstructive jaundice has been associated with increased reabsorption of endotoxins from the gastrointestinal tract and shunting of the reabsorbed endotoxin into systemic circulation. Endotoxin has been associated with acute tubular necrosis in experimental animals and men (6).

Hyperbilirubinemia also has indirect effect on renal function, through impairment of vascular reactivity to vasoactive agents, resulting in adverse influence on cardiac function and thus further compromising renal performance.

Bilirubin nephrotoxicity due to unconjugated hyperbilirubinemia has also been described with renal medullary deposition resulting in medullary necrosis and formation of bilirubin crystals in the renal papillae, as has been shown in rats and hyperbilirubinemic infants. Although conjugated hyperbilirubinemia predominated in our case, unconjugated bilirubin fraction was also substantially increased. Additionally bile and bile salts have been shown to impair renal tubular cell membrane transport, modify membrane composition and alter renal cellular metabolism.

ARF could also have prerenal components in the setting of the cholestatic episode with severe jaundice, including the syndrome of BRIC. Vigorous rehydration corrects volume deficits, reduces circulating concentrations of the toxic hepatic metabolites as well as bile, bile salts and direct and indirect bilirubin.

The underlying pathophysiology of ARF in the setting of a jaundiced patient therefore seems to be very complex and further studies are needed for a better understanding.

Our case clearly demonstrates that ARF requiring renal replacement therapy may complicate the so-called 'benign' recurrent

intrahepatic cholestasis and in the clinical setting, starting vigorous hydration with the first signs and symptoms of the impending attack may be vitally important to avoid this complication. On the other hand, hemodialysis also helped to remove conjugated bilirubins from the circulation and probably decreased further damage to the kidney as well as other organs caused by hyperbilirubinemia.

In the case reported all three episodes of ARF seemed to resolve without much long term renal dysfunction as assessed by clinical and laboratory means. It would be worthwhile to perform a renal biopsy in the attack free period to have an objective assessment of the kidneys.

In conclusion, we report a case of BRIC with acute renal failure most likely due to acute tubular necrosis which emphasizes the importance of prompt hydration during the cholestatic episode and suggests that BRIC is not as benign as has hitherto been thought.

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