Is there any association of extra hepatic biliary atresia with cytomegalovirus or other infections?

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Abstract

The objective of this study was to find any association of extrahepatic biliary atresia (EHBA) with a possible infectious etiology. Infants diagnosed to have EHBA were tested by blood PCR for cytomegalovirus (CMV), Ebstein-Barr virus, HBsAg, anti-HCV and IgM antibodies for CMV, toxoplasma, rubella, and herpes infections. Thirty-three infants of EHBA were included in the study, male 22, median age when diagnosed 2.5 months (range 1.0-5.0 months). On examination pallor, oedema and hepatosplenomegaly were seen in all and ascites and microcephaly in 19 (57.6%). Centile height and weight were 50th in 23 and 25th in 10. Persistent CMV infection documented by PCR was present in 14 (42%) patients. Eleven of these also had positive CMV IgM antibodies. No other above mentioned infections could be detected in our patients of EHBA. Our data suggests that CMV infection may play a role in the pathogenesis and progression of EHBA.

Keywords: Extrahepatic biliary atresia, Cytomegalovirus, PCR.
Introduction

Extrahepatic biliary atresia (EHBA) is an important cause of neonatal cholestatic jaundice. The disappearing bile ducts are thought to be a result of destructive inflammatory process which starts in the perinatal period. The etiology of biliary atresia is poorly understood. This extrahepatic obstructive cholangiopathy is progressive after birth resulting in worsening neonatal cholestasis, eventually leading to secondary biliary cirrhosis and liver failure. The process seems to be an acquired one. There is controversy about the etiological role of viruses. The studies have implicated reoviruses, rotaviruses and cytomegalovirus (CMV). The objective of this study was to find out any association of extrahepatic biliary atresia (EHBA) with exposure to TORCH infections (toxoplasma, rubella, cytomegalovirus (CMV), herpes simplex virus and Ebstein-Barr virus (EBV), hepatitis B and C.

Methods and Results

Infants presenting with cholestatic jaundice were evaluated for the presence of biliary atresia. Abdominal ultrasound and radionuclide cholecintigraphy using technetium-labeled diisopropyl iminodiacetic acid were performed in each case. Diagnosis of EHBA was made by absence of gallbladder and no biliary dilatation on ultrasound and failure of excretion of radiolabel on nuclear scintiscan. The infants diagnosed to have EHBA were further evaluated by full history taken from parents and complete physical examination. Laboratory investigations included complete blood counts, liver function tests, clotting profile, blood cultures, and presence of toxoplasma, rubella, CMV and EBV infection and hepatotropic viruses. Tests performed for this purpose included blood PCR for CMV and Epstein Bar Virus (EBV), IgM antibodies for CMV, toxoplasma, rubella, and herpes infections, HBsAg and anti-HCV antibody. All the immunological tests were performed by Chemiluminescence Microparticle Immuno Assay (CMIA) by the clinical laboratory of the hospital. Liver biopsy could be performed in 25 patients after correcting the coagulation abnormalities.

Thirty three infants of EHBA were included in the study; male 22, median age of diagnosis 2.5 months (range 1.0-5.0 months). Median birth weight 2.9 kg (2.5-3.2), median gestational age 39 weeks (38-40). These patients presented with jaundice, clay coloured stools, diarrhoea, and poor feeding. Thirty two (97%) were febrile and 31 (93.9%) were having pruritis. On examination pallor, oedema, hepatosplenomegaly and ascites were present in all patients. Microcephaly was noticed in 19 (57.6%). No other dysmorphic features were present. At the time of presentation, centile height and weight on CDC growth charts were 50th in 23 and 25th in 10. Results of the laboratory tests have been mentioned in Table-1. Liver biopsy done in 25 patients was suggestive of established biliary cirrhosis in all cases. Twenty-one patients had already undergone Kasai's portoenterostomy at the time of presentation.

Persistent CMV infection as detected by blood PCR was present in 14 (42%) patients. Eleven (33.3%) of these also had positive CMV IgM antibodies. No other TORCH infection i.e. toxoplasma, rubella, or herpes simplex could be detected in our patients of EHBA. PCR for EBV virus, HBsAg and anti-HCV were also negative.

Conclusion

Biliary atresia is the most frequent indication for liver transplantation in children. Portocenterostomy is the only available treatment, with better results when performed in the first two months of life. Transplantation has been suggested as the initial procedure of choice because of its excellent long-term survival rate and the fact that more than 60% of infants undergoing the Kasai procedure ultimately require liver transplant mention.

The etiology of EHBA is not fully understood. The inflammatory response in the livers of these patients mimics that observed during viral infections. Portal bile ductular proliferation, bile plugging, portal-portal fibrosis, and an
acute inflammatory reaction are characteristic findings in infants with biliary atresia.\textsuperscript{6} There is a possibility of primary perinatal hepatobiliary viral infection generating a secondary autoimmune-mediated bile duct injury. One study demonstrated CMV IgM immunoglobulin deposits on the hepatocellular canalicular membrane in infants with CMV infection.\textsuperscript{7} In patients with biliary atresia and cytomegalovirus infection, liver fibrosis seems to be more severe with a lower rate of jaundice disappearance after Kasai procedure and a higher post-operational reflux cholangitis.\textsuperscript{8}

CMV is known to cause intrahepatic cholestasis in infants and responds to the treatment.\textsuperscript{9} Our study indicates possible association with EHBA as well. It is important to recognize this as early treatment of CMV may suppress the immune mediated response, decreasing the inflammatory damage to bile ducts. It may delay the need for liver transplantation. Most of our patients were referred cases who were sent back to their physicians. They had already developed cirrhosis. Treatment outcome could not be assessed in these patients. There is low accuracy of serological tests for detecting active CMV infection as compared to PCR done on liver tissue.\textsuperscript{10} Though CMV infection could be documented only in one third of our patients by blood PCR, the frequency might have been higher if we had done PCR on liver biopsy samples. Our data suggests an association of EHBA with CMV infection which may play a role in the pathogenesis and progression of EHBA.

References