Cytomegalovirus in biliary atresia: coincidental or causal?

***Devdeep Mukherjee[1], Ritabrata Kundu[1], Prabal Niyogi[1], Joydeep Das[1]**

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Introduction

Neonatal cholestasis (NC) has been documented in 19–33% of neonates with chronic liver disease attending tertiary care hospitals in India[1-3]. Of these, almost one third have been attributed to biliary atresia[3]. Cytomegalovirus (CMV) is known to cause intrahepatic bile duct paucity and destruction and has been suggested to cause extra hepatic biliary atresia (EHBA) in a few case series[4]. We present a series of 4 cases admitted to our hospital over the last 18 months having EHBA with CMV infection.

Case 1: A 3 month old female baby was admitted with yellowish discolouration of eyes and urine since 3 weeks of age. She was having pale stools since 1 month of age. Investigations were suggestive of NC (table 1).

Table 1: ***Investigations in the 4 cases***

Investigation	Case 1	Case 2	Case 3	Case 4
Total bilirubin	8.4 mg/dl	7.3 mg/dl	12.2 mg/dl	13.4 mg/dl
Conjugated bilirubin	7.0 mg/dl	4.4 mg/dl	7.4 mg/dl	9.8 mg/dl
Aspartate aminotransferase	150 IU/L	108 IU/L	186 IU/L	156 IU/L
Alanine aminotransferase	156 IU/L	121 IU/L	194 IU/L	174 IU/L
Gamma glutamyl transpeptidase	1099 IU/L	970 IU/L	1170 IU/L	1236 IU/L
Alkaline phosphatase	896 IU/L	786 IU/L	982 IU/L	1049 IU/L
International normalised ratio	1.7	1.5	2.8	2.1
Albumin	3.3 g/dl	3.2 g/dl	2.6 g/dl	2.7 g/dl
Alpha 1 antitrypsin	Negative	Negative	Negative	Negative
Galactosaemia	Negative	Negative	Negative	Negative
Ultrasonography of abdomen	Hepatosplenomegaly with ascites	Hepatosplenomegaly	Hepatosplenomegaly	Hepatosplenomegaly with ascites
Liver biopsy	Biliary atresia	Biliary atresia	Cirrhosis	Biliary atresia
CMV IgM (<0.9)	2.96	1.71	2.10	2.87
CMV IgG (<6)	33	25	28	36
CMV DNA PCR copies/ml	11,626	7,250	13,328	18,258

CMV: cytomegalovirus, IgM: immunoglobulin M, IgG: immunoglobulin G, DNA: deoxyribonucleic acid, PCR: polymerase chain reaction

As she had CMV immunoglobulin M (IgM) and immunoglobulin G (IgG) reactive (table 1), a CMV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) was sent to assess the viral load. Liver biopsy was suggestive of EHBA. Gancyclovir was started because of the high viral load and child being symptomatic. As even after 3 weeks the jaundice was persisting, Kasai portoenterostomy was done. The child continues to have conjugated hyperbilirubinemia with progressive enlargement of liver and spleen at 21 months of age.

Case 2: A 6 week old male infant was admitted with yellowish discolouration of eyes and urine and occasional whitish stools since 3 weeks. On examination, he had hepatosplenomegaly. CMV DNA PCR was suggestive of infection and liver biopsy of EHBA (Table 1). Liver transplant was advised but not done due to financial constraints. Kasai portoenterostomy was done within 2 weeks of diagnosis. At 8 months, child has conjugated jaundice with deranged liver enzymes and firm and enlarged liver and spleen.

Case 3: A 7 month old girl was admitted with jaundice since 1 month of age and clay coloured stools. She had a distended abdomen, ascites and hepatosplenomegaly. Hepatic technetium-99m-mebrofennin iminodiacetate (HIDA) scan was suggestive of biliary atresia. Liver biopsy showed cirrhotic changes. CMV DNA PCR was significantly elevated (table 1). She was given supportive management and died after 1 month.

Case 4: A 5 month old girl presented with jaundice and clay coloured stools since 2 weeks of age. She had hepatosplenomegaly. Liver biopsy was suggestive of EHBA and CMV DNA PCR was significantly elevated (Table 1). Gancyclovir was

[1]*Department of Pediatric Medicine, Institute of Child Health, Kolkata, West Bengal, India*
**Correspondence:* devdeep_dm@rediffmail.com
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administered for 2 weeks. Her jaundice persisted and she was lost to follow up.

All 4 cases were diagnosed as having EHBA with concomitant CMV infection. None had hearing or vision abnormalities. Head circumference was normal for age in all 4 babies.

Discussion

Viral infection has been proposed as a cause of EHBA. In a study from Pakistan, patients with EHBA were searched for evidence of infection with CMV, Epstein Barr virus, toxoplasma, herpes, hepatitis B and C. It was concluded that CMV may play a role in pathogenesis of EHBA[5]. In a study from Brazil on 76 patients with NC, CMV IgM was positive in 28.5% patients with extra hepatic cholestasis and 29.4% with intra hepatic cholestasis[6]. All our 4 patients had CMV IgM positive along with significantly detectable copies of CMV DNA PCR. The liver enzymes, HIDA and liver biopsy were suggestive of EHBA.

Cases 1 and 2 underwent Kasai portoenterostomy without any improvement in follow up. Case 1 underwent the operation after 3 months and case 2 underwent it early. A study from London found CMV IgM positive cases with biliary atresia as a distinct entity with late presentation and a poor response to Kasai operation. Except case 2 who presented early, all other patients presented late. Two patients underwent operation with poor response in follow up. Cases 1, 3 and 4 also had significant inflammation and fibrotic changes on liver biopsy as has been documented in this study[7]. A study from China reports a strong association between CMV and lower rate of jaundice disappearance following operation. They also found increased fibrosis as we found in our patients[8]. However a study from Canada, with CMV DNA analysis on bile duct biopsy specimens showed negative results ruling out any association of CMV involved in the pathogenesis of EHBA[9].

There is still no consensus on whether the association between CMV and EHBA is causal or coincidental. A study by Tarr et al has stated that infants with cholestasis with CMV infection should also be investigated for EHBA and monitored accordingly[10]. Till further data are available, CMV should be considered as a potential aetiological agent for EHBA with poor prognosis even after operative intervention.

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