

Original Article



A Comparative Study Between Cytomegalovirus Immunoglobulin M-Positive and CMV Immunoglobulin M-Negative Biliary Atresia in Infants Attending a Tertiary Care Hospital in Bangladesh

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ABSTRACT


Purpose: Perinatal cytomegalovirus (CMV) infection can lead to biliary atresia (BA) in different entities. This study aimed to compare the clinical, hematological, biochemical, and histological features of infants with BA based on their CMV immunoglobulin M (IgM) status at presentation.

Methods: This cross-sectional descriptive study was carried out between January 2019 and June 2020 at the Department of Pediatric Gastroenterology and Nutrition at the Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka. Forty-three patients with BA were selected purposively and categorized into either the CMV IgM-positive or CMV IgM-negative BA group. Categorical variables were compared using Fisher's exact test and chi-square tests, while the Student's *t*-test and Mann-Whitney U-test were used to compare continuous variables. For all statistical tests, a *p*-value <0.05 was considered statistically significant.

Results: Thirty-three (76.7%) of the cases were between 2 and 3 months of age on admission. The clinical, hematological, and biochemical parameters did not differ significantly between the CMV IgM-positive and CMV IgM-negative BA groups. Most (50.0%) of the CMV IgM-positive cases had fibrosis stage F2, while 43.5% of the CMV IgM-negative cases had fibrosis stage F3, with no significant difference between the groups (*p*=0.391).

Conclusion: Our data shows no significant distinction between CMV IgM-positive and CMV IgM-negative BA, suggesting that CMV does not contribute to BA pathogenesis.

Keywords: Biliary atresia; Cytomegalovirus; Immunoglobulin; Bangladesh

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Conflict of Interest

The authors have no financial conflicts of interest.

INTRODUCTION

Biliary atresia (BA) is a destructive cholangiopathy of the newborn, characterized by a variable degree of obliteration of both intrahepatic and extrahepatic bile ducts. It causes severe cholestasis and rapidly progresses to biliary cirrhosis. The cause and pathogenesis of BA are not well understood [1]. Clinically, BA is classified as isolated typical BA (80%), cystic BA (5–10%), cytomegalovirus (CMV)-associated BA (5–10%), and BA-splenic malformation syndrome (5–15%). Whether these variants have different causes is not clear, but their clinical course and response to hepatic portoenterostomy may differ [2]. Two pathological mechanisms have been suggested to explain the cholangiopathy that occurs in BA. One is the primary developmental defect of the bile duct and the other is the destruction of already formed bile ducts due to viral infection [3,4]. Viruses may have either cholangio-destructive effects or lead to a secondary autoimmune reaction [1,5,6]. Destruction of already formed bile ducts may be due to exposure to viral infection in late fetal or early postnatal life, as first suggested in 1974 [7]. Initially, this mechanism was supported by serological evidence of viral exposure and later by polymerase chain reaction (PCR) detection methods [8,9]. However, this has not been confirmed by direct virus isolation or inclusion bodies [10]. While CMV has been known to play a role in the etiopathogenesis of neonatal hepatitis, it has only recently been considered a possible etiologic factor in BA [11]. Serological evidence of CMV infection has been found in 30–40% of infants with BA in case series data analysis from different countries [12–14]. A Swedish study found CMV DNA in half of their infants with BA and first identified an immunoglobulin M (IgM) response evident on their hepatocyte canalicular membranes [15]. CMV IgM-positive BA has been hypothesized to be a separate clinical entity with poorer outcomes than CMV IgM-negative BA [16]. It is important to recognize that early treatment of CMV may suppress the immune-mediated response, decreasing inflammatory damage to the bile ducts. Therefore, the aim of this study was to differentiate the clinical, hematological, biochemical, and histological features of infants with BA in accordance with their CMV IgM status at presentation. A secondary aim of this study was to determine the frequency that CMV is associated with BA.

MATERIALS AND METHODS

This cross-sectional, descriptive study was conducted at the Department of Pediatric Gastroenterology and Nutrition of Bangabandhu Sheikh Mujib Medical University (BSMMU) from January 2019 to June 2020. During the study period, 50 consecutive cases of BA were initially selected. Among them, 21 (42.0%) were CMV IgM-positive and 29 (58.0%) were CMV IgM-negative. Seven patients were excluded because of a lack of information on fibrosis staging. Finally, 43 patients were selected as the study subjects. Patients with BA were categorized into either the CMV IgM-positive or CMV IgM-negative BA group. Physical examination findings and a detailed clinical history were recorded in a preformed standard data sheet. CMV IgM antibodies were detected using chemiluminescence at the Virology Department of BSMMU. After obtaining informed consent from the parents, a percutaneous liver biopsy was performed in all cases by the same person after ensuring normal vital parameters, a normal coagulation profile, normal platelet counts, and no cystic lesion of the liver on ultrasonography using a Tru-cut biopsy needle. Hepatic tissue samples obtained from each patient were sliced, stained with Masson's trichrome, and examined under a microscope at the Department of Pathology at BSMMU. Fibrosis was staged according to the Metavir scoring system [17]. According to this system, F0 indicates no fibrosis present (no

fibrosis), F1 indicates portal fibrosis without septa (mild fibrosis), F2 indicates portal fibrosis with a few septa (moderate fibrosis), F3 indicates numerous septa without cirrhosis (severe fibrosis), and F4 indicates cirrhosis (cirrhosis).

Statistical analysis

Statistical analyses were performed using SPSS software version 22.0 (IBM Co., Armonk, NY, USA). Categorical variables were compared using Fisher's exact test and chi-square tests, while the Student's *t*-test and Mann–Whitney U-test were used to compare continuous variables. For all statistical tests, a *p*-value <0.05 was considered statistically significant. Written informed consent was obtained from each parent or legal guardian after the purpose of the study was fully explained. Approval for the research protocol was obtained from the Ethical Review Committee of BSMMU (no. bsmmu/2018/1478).

RESULTS

A total of 43 infants with histologically confirmed BA were analyzed for this study. Twenty (46.5%) cases had CMV IgM-positive BA and 23 (53.5%) had CMV IgM-negative BA. A total of 23 (53.5%) were male and 20 (46.5%) were female. Most (*n*=33, 76.7%) were between 2 and 3 months of age at admission (**Fig. 1**).

Table 1 shows the clinical features that differentiate CMV IgM-positive BA from CMV IgM-negative BA. No differences between the groups were found in terms of the onset of jaundice (*p*=0.589), appropriate birth weight for gestational age (AGA) (*p*=0.566), persistent pale stool (*p*=0.230), anemia (*p*=0.692), or palpable spleen (*p*=0.345).

Table 2 shows a comparison of the biochemical and hematological parameters between CMV IgM-positive and CMV IgM-negative cases at the time of diagnosis. In addition, no differences in the total bilirubin (*p*=0.374), direct bilirubin (*p*=0.472), alanine aminotransferase (*p*=0.429), aspartate aminotransferase (AST; *p*=0.119), alkaline phosphatase (ALP; *p*=0.324), gamma-glutamyl transpeptidase (*p*=0.335), international normalized ratio (*p*=0.499), hemoglobin (*p*=0.525), total white blood cell (WBC) count (*p*=0.977), or platelet count (*p*=0.435) were observed.

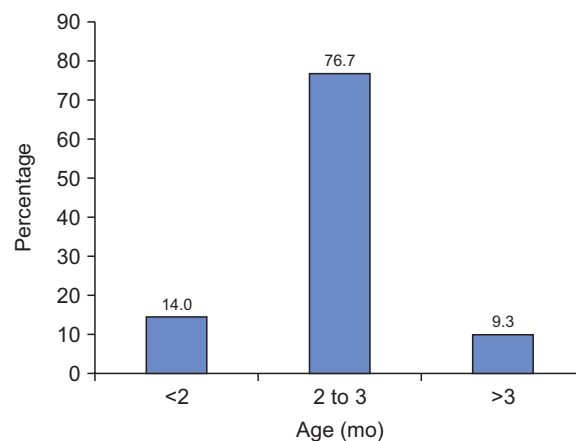


Fig. 1. Age distribution of studied subjects.

Table 1. Clinical features differentiating CMV IgM-positive BA from CMV IgM-negative BA (n=43)

Clinical variables	CMV IgM-positive BA (n=20)	CMV IgM-negative BA (n=23)	p-value
Jaundice on set			0.589*
<14 days	18 (90.0)	22 (95.7)	
>14 days	2 (10.0)	1 (4.3)	
Birth weight			0.566*
Appropriate for gestational age	16 (80.0)	19 (82.6)	
Low birth weight	4 (20.0)	4 (17.4)	
Birth history			0.553*
Term	19 (95.0)	21 (91.3)	
Preterm	1 (5.0)	2 (8.7)	
Pale stool			0.230*
Persistent pale stool	20 (100.0)	17 (73.9)	
Intermittent pale stool	0	6 (26.1)	
Anemia			0.692†
Present	15 (75.0)	16 (69.6)	
Absent	5 (25.0)	7 (30.4)	
Spleen			0.345†
Palpable	11 (55.0)	8 (34.8)	
Not palpable	9 (45.0)	15 (65.2)	

Values are presented as number (%).

CMV: cytomegalovirus, IgM: immunoglobulin M, BA: biliary atresia.

*Fisher's exact test.

† χ^2 test.

Table 2. Comparison of biochemical and hematological parameters between CMV IgM-positive and CMV IgM-negative BA at the time of diagnosis (n=43)

Biochemical and hematological parameters	CMV IgM-positive BA (n=20)	CMV IgM-negative BA (n=23)	p-value
Total bilirubin (mg/dL)	10.0	10.1	0.374†
Direct bilirubin (mg/dL)	6.5	5.8	0.472†
Alanine aminotransferase (IU/L)	130.5	110	0.429†
Aspartate aminotransferase (IU/L)	229	200	0.119†
Alkaline phosphatase (IU/L)	487.5	498	0.324†
Gamma-glutamyl transpeptidase (IU/L)	902	1,064	0.335†
International normalized ratio	1.04	1.01	0.499†
Hemoglobin (gm/dL)	9.91±2.36	11.17±8.5	0.525*
Total WBC count‡ (×10 ³ /L)	15.75	14.00	0.977†
Platelet count‡ (×10 ⁹ /L)	360	390	0.435†

Values are presented as number only or mean±standard deviation.

CMV: cytomegalovirus, IgM: immunoglobulin M, BA: biliary atresia, WBC: white blood cell.

*Independent t-test.

†Mann-Whitney U-test.

‡Median.

Table 3 shows a comparison of fibrosis staging between the subjects with CMV IgM-positive and CMV IgM-negative BA. Fibrosis stage F2 was found in 10 (50.0%) of the CMV IgM-positive cases and 7 (30.4%) of the CMV IgM-negative cases. Fibrosis stage F3 was found in 5 (25.0%) of the CMV IgM-positive cases and 10 (43.5%) of the CMV IgM-negative cases, with no significant difference between the groups ($p=0.391$).

DISCUSSION

The potential pathogenic role of viruses in BA is controversial. Perinatal CMV infection is thought to trigger BA, although clinical evidence is lacking [16]. For this study, the mean age

Table 3. Comparison of fibrosis staging between subjects with CMV IgM-positive and CMV IgM-negative BA (n=43)

Fibrosis staging (Metavir scoring system)	CMV IgM-positive BA (n=20)	CMV IgM-negative BA (n=23)	p-value
F0	0	1 (4.3)	
F1	5 (25.0)	5 (21.7)	0.391
F2	10 (50.0)	7 (30.4)	
F3	5 (25.0)	10 (43.5)	

Values are presented as number (%).

CMV: cytomegalovirus, IgM: immunoglobulin M, BA: biliary atresia.

χ^2 test.

of the patients at admission was 70.02 ± 18 days. In a previous study conducted on similar subjects at the same center, the mean age at presentation was 3.5 months (105 days) [18]. This suggests that parents may currently be more aware of infantile jaundice. In our study, the median age of patients with CMV IgM-positive and CMV IgM-negative BA was 68 and 64 days, respectively. Similarly, in a previous study, patients with CMV IgM-positive BA were found to be older by about 13 days (70 vs. 56 days at the time of Kasai portoenterostomy) than patients with CMV IgM-negative BA [16]. BA is common in female infants [19]. However, in this study, 23 (53.5%) of the patients were male. A similar male preponderance was found in a previous study at the same center in 2005 [18,20]. This male preponderance may be associated with the tendency for parents in our country to be more concerned about their male infants. In the present study, 50.0% and 43.5% of those with CMV IgM-positive and CMV IgM-negative BA, respectively, were female. In a study conducted at King's College Hospital (London, UK), 55.0% and 56.7% of those with CMV IgM-positive and CMV IgM-negative BA, respectively, were female [16].

In our study, none of the patients had petechiae, purpuric rashes, chorioretinitis, microcephaly, intrauterine growth retardation, or hearing loss, suggestive of congenital CMV infection [21]. However, the absence of these features does not exclude congenital CMV infections, as this would require samples to be tested for CMV DNA or IgM within three weeks of delivery. This was not possible for this study because our patients did not present before three weeks of age.

In this study, most of the patients (93.0%) developed jaundice before 14 days of age, while 10.0% of CMV IgM-positive patients and 4.3% of CMV IgM-negative patients developed jaundice after 14 days of age. Additionally, 86.0% of patients had persistent pale stools. A previous study similarly reported that 88.2% of patients with BA had persistent pale stool [22]. Additionally, Karim and Kamal [18] reported that 81.3% of patients with BA had persistent pale stool. In this study, 100% of CMV IgM-positive patients and 73.9% of CMV IgM-negative patients had persistent pale stool.

In the present study, 40 (93%) of the infants were term, of which 95% were CMV IgM-positive and 91.3% were CMV IgM-negative. Hamid et al. [20], in their study on 30 neonatal cases at the same center, found that 12 had BA, of which 11 (92%) were term and only one was preterm. In this study, 81.4% of the patients had a history of AGA and 18.6% had a history of low birth weight. Additionally, 55% of CMV IgM-positive patients and 34.8% of CMV IgM-negative patients had splenomegaly. However, no clinical features were significantly different between CMV IgM-positive and-negative BA.

A small study in China found no preoperative clinical differences or differences in response to surgery [14]. Regarding hematological parameters, the median total WBC count was higher in all cases, and the median platelet count was lower ($360 \times 10^9/L$) in the CMV IgM-positive BA group than in the CMV IgM-negative BA group ($390 \times 10^9/L$), though the difference was not significant ($p=0.977$ and $p=0.435$, respectively). This increase in the total WBC count may have been due to infection, which was found to be increased in 91.7% of infants with BA in a previous study [23]. Another study showed that platelet count was significantly lower in CMV IgM-positive BA ($417 \times 10^9/L$) than in CMV IgM-negative BA ($547 \times 10^9/L$) [16]. Serum bilirubin has been reported to rarely exceed 12 mg/dL in infants with BA [19]. The median total serum bilirubin level in the present study was 10.2 mg/dL. This finding is consistent with the findings of a previous study, which reported a total serum bilirubin of 10.4 mg/dL in cases of BA [18]. In this study, no significant differences in the liver enzyme levels between the CMV IgM-positive and CMV IgM-negative groups were found. However, severe biochemical disturbances were noted in a previous study with higher bilirubin, ALP, and AST levels and lower platelet counts in the IgM-positive group at presentation [16]. Although our data did not show a statistically significant difference, CMV IgM-positive cases showed slightly higher AST and ALP levels.

The patient characteristics were re-evaluated according to fibrosis staging and compared between the groups. According to the Metavir scoring system, 1 case had stage F0, 10 had stage F1, 17 had stage F2, and 15 had stage F3 fibrosis. No patient was found to have stage F4 fibrosis, which may have been because most of our patients were between 2 and 3 months of age at admission. In the present study, 50% of patients with CMV IgM-positive BA had stage F2 fibrosis and 43.5% of those with CMV IgM-negative BA had stage F3 fibrosis. These findings are directly contradictory to those of a previous study in which significantly higher fibrosis scores were found in the CMV group; however, no immunohistochemical evidence of the virus itself in the liver or biliary tissue of IgM-positive cases could be identified [16]. Another study that also reported histological findings of the liver found that the degree of inflammation and liver fibrosis in the CMV-free and CMV IgM-positive groups were milder than those in the CMV infection group [14].

Our data suggest that CMV IgM-positive BA is not distinct from CMV IgM-negative BA. Rauschenfels et al. [24] concluded that viruses play no role in the pathogenesis of BA and may simply be a secondary phenomenon. Several previous studies have also concluded that 1–2% of newborns are infected with CMV annually, which is capable of injuring the bile duct epithelium of neonates but is rarely associated with the pathogenesis of BA [25, 26]. Furthermore, in neonates with BA, the CMV genome and antigen cannot be detected [23]. In addition, the absence of demonstrable CMV DNA by in situ hybridization and PCR in extrahepatic BA biopsies suggests that it is unlikely to play a major role in BA pathogenesis [9]. In our study, we could not conduct in situ hybridization or PCR testing to detect CMV DNA in liver biopsy tissue as these studies are not available at our institution. The incidence of CMV IgM-positive infants in our study was 42% (depending on whether we count the size of the original population [$n=50$], with seven excluded due to lack of fibrosis), which is similar to the incidence reported in Brazil, Sweden, Pakistan, China, and South Africa [12, 27–30]. All these studies, however, have reported a much higher incidence of CMV IgM-positive BA, ranging from 34% to 69% [14].

The accuracy of serological testing to detect active CMV infection is low compared to that of PCR tests performed on liver tissues [11]. Therefore, one weakness of our study was that we could not perform PCR tests for CMV DNA. The results of the study would have been more accurate had this been available. However, it was cost-effective. However, the presence of CMV infections cannot be excluded by CMV DNA, as the virus may be present in a lower quantity than the PCR sensitivity limit [9].

This study did not find any clinical, hematological, biochemical, or histological differences between CMV IgM-positive and CMV IgM-negative BA. Therefore, according to the results of this study, CMV cannot be considered a cause of BA. As the present study was conducted at a single center with a small sample size, further multi-center studies with larger sample sizes will be needed for a more accurate prediction before recommendations can be offered.

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