22. Infection of Cytomegalovirus in Cholestasis Infant with Biliary Atresia

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Infection of Cytomegalovirus in Cholestasis Infant with Biliary Atresia

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ABSTRACT

Biliary Atresia (BA) is extrahepatic cholestasis that results in death within the first two years if the diagnosis and intervention are delayed. The etiology and pathogenesis of BA are still undetermined. Viral infections, including Cytomegalovirus (CMV), are presumed to be one of the causes. Cytomegalovirus infection is more common in intrahepatic than extrahepatic cholestasis such as BA. There are limited data about Cytomegalovirus infection in cholestatic infants with BA. This study compared the incidence of CMV infection in cholestatic infants with biliary atresia and non-biliary atresia. A cross-sectional study was performed in December 2017 - August 2018 in cholestatic infants aged 1-6 months. Liver biopsy, histopathological examination followed by PCR CMV examination were performed on cholestatic infants. The results of the PCR examination were compared between BA and non-BA infants. Statistical analysis of Chi-Square, t-test independent and Mann-Whitney U resulting in $p<0.05$ were stated as significant. Thirty-seven children were obtained during the study period, consisting of sixteen children with BA and twenty-one children with non-BA. Biliary atresia was predominantly found in female than male children, despite no differences were found between the groups ($p=0.163$). There were differences in body weight ($p=0.002$) age ($p=0.009$), birth weight ($p=0.02$) and gestational age ($p=0.03$) between children with BA and non-BA. There was no significant difference in the incidence of CMV infection in cholestatic infants with BA and non-BA ($p=0.338$). Cytomegalovirus infection in cholestatic infants with BA was less than non-BA cholestatic infants.

Keywords: Biliary atresia, cholestasis, cytomegalovirus, polymerase chain reaction

INTRODUCTION

Biliary Atresia (BA) remains a great challenge for clinicians because it has poor clinical outcomes if not early diagnosed and intervened.[1,2] Biliary atresia is a type of extrahepatic cholestasis which is frequently found in infants. However; the etiology and pathogenesis of BA are still undetermined. Particular viruses have been suggested to play a role in pathogenesis BA, including group C Rotavirus, Reovirus and Cytomegalovirus (CMV).[3]

Cytomegalovirus infection is often found in intrahepatic cholestasis; however, currently, there are several studies which showed CMV infection in extrahepatic cholestasis, including BA.[4,5] Cholestasis is classified as intrahepatic and extrahepatic cholestasis, and there are several methods for diagnosing CMV infection, including Polymerase Chain Reaction (PCR). There is no single examination that is 100% accurate in diagnosing CMV infection. Polymerase Chain Reaction examination can use blood, urine and tissue specimens, which are ideally carried out at the age of three weeks after birth.[6] The PCR examination cannot be performed at the age of three weeks because most cases of CMV infection are asymptomatic and high in cost; however, PCR can detect viral DNA with low amounts of sample and time-efficient.[7]

The gold standard of diagnosis of BA is intraoperative cholangiography; however, liver biopsy and following histopathological examination have quite high sensitivity of approximately 96.9%.[8] Several studies showed positive CMV results in PCR examination of liver biopsies of patients with AB.[9,10] However, there is no data on the incidence of CMV infection in cholestatic infants with BA in Dr. Soetomo Hospital, Surabaya. Therefore, a preliminary study is needed to determine the incidence of CMV infection in cholestatic patients with BA and without BA by using PCR in liver tissue in Dr. Soetomo Hospital, Surabaya.

METHODS

A cross-sectional study was performed from December 2017 to August 2018. Cholestasis infants aged 1-6 months old who were treated at Hepatology division were included. Cholestasis infants associated with severe infections (sepsis) or

severe multi-organ abnormalities, a history of ganciclovir treatment, and immunodeficient patients were excluded. Each subject underwent a laboratory test (complete blood count, total bilirubin, direct bilirubin, AST, ALT, albumin) and liver tissue biopsy conducted by the Pediatric Hepatology consultant. Biopsy of liver tissue was stored in a tube then sent to the Pathology Department of Dr. Soetomo Hospital Surabaya and Tropical Disease Airlangga University. The study protocol was approved by the Ethical Commission of Health Research of Dr. Soetomo Hospital with number No.729/Panke.KKE/XII/2017.

Polymerase chain reaction examination was carried out by extracting DNA using QIAampDNA Mini Kit (Qiagen) from a liver biopsy and based on manual according to the kit. Beta-globin genes were identified using PC03 + and PC04 + primers with the ability to produce 110 bp products with certain sequences (Table 1). Cytomegalovirus was identified by nested PCR with primer MIE4 and MIE5 for first-cycle which produced 435bp; while IE1 and IE2 products were used for the second cycle which produced 161bp.

Polymerization chain reaction mixtures required for β globin were mastermix (Promega): 10µL/reaction, FWD primer (PCO3 +) 10pmol: 1µL/reaction, primary REV (PCO4 +) 10pmol: 1µL/reaction, ddH2O (water): 5µL/reaction, DNA template: 3µL/reaction, with PCR conditions as follows: initial denaturation at 94°C for 5 minutes, denaturation at 94°C for 30 sec, annealing at 55°C for 30 seconds, elongation at 72°C for 45 seconds, final elongation at 72°C for 7 minutes. All of this process was performed 40 cycles.

Four microliters were taken from first-cycle products for second-cycle PCR. Polymerase chain reaction mixture in second-cycle was the same as first-cycle, the differences were only in the product used. The PCR product was visualized by electrophoresis in 2% agarose gel, stained with ethidium bromide, and viewed under ultraviolet light.

Data were collected and presented as a written explanation, tabulation, and diagrams. Descriptive analysis was used to calculate the number of BA and non-BA cases, the number of CMV infection in BA and non-BA cholestatic infants, and compare the number of CMV infection between BA and BA patients with the Chi-Square test.

RESULTS AND DISCUSSION

There were 37 cholestasis infants involved in this study, dominated by 21 male infants an average age of 2.9 (SD 1.28) months and an average body weight of 4632 (SD 1070) gram. Most patients live outside of Surabaya. Table 2 showed the basic characteristics of pediatric patients with cholestasis. It can be seen that the number of cholestatic infants with BA was smaller (43.2%) compared to without BA (56.8%).

Table 2. Baseline characteristic of cholestasis infant

Characteristic	
Age, mean (± SD)	2.9 (± 1.28)
Age, n (%)	
1 month	4 (10.8)
2 month	14 (37.9)
3 month	7 (18.9)
4 month	6 (16.2)
5 month	6 (16.2)
6 month	0 (0)
Birth weight, mean (± SD)	4632,4 (± 1070,06)
Gender (%)	
Girl	16 (43.2)
Boy	21(56.8)
Gestationalage, n (%)	
Aterm	25 (67.62)
Preterm	12 (32.4)
Type of cholestasis, n (%)	
Biliary atresia	16 (43.2)
Non-biliary atresia	21 (56.8)
Residence, n (%)	
Surabaya	11 (29.7)
Outside of Surabaya	26 (70.3)

Table 1. The primer used with the sequence and its product

Primer	Sequence	Product
MIE4	5'-CCA AGC GGC CTC TGA TAA CCA AGC C-3'	435bp
MIE5	5'-CAG CAC CAT CCT CCT CTT CCT CTG G-3'	435bp
IE1	5'- CCA CCC GTG GTG CCA GCT CC-3'	161bp
IE2	5'-CCC GCT CCT CCT GAG GAC CC-3'	161bp
PC03+	5'-CCT CTG ACA CAA CTG TGT TCA CTA GC-3'	110bp
PC04+	5'-TCA CCA CCA ACT TCA TCC ACG TTC ACC-3'	110bp

This study aimed to compare the incidence of CMV infection in BA and non-BA cholestatic infants. In addition to clinical manifestation, histopathological examination of liver tissue biopsy was used to distinguish between BA and non-BA cholestatic infants.[11] Biliary atresia is typically characterized by biliary duct proliferation, bile plugs, and portal tract edema/fibrosis in biopsy liver. A study showed that liver biopsy had a sensitivity, specificity, and accuracy of 88.2%.[12] Similar to study by Lee and Looi, biliary duct proliferation in BA showed 95% sensitivity and 88% specificity, while bile plugs showed 68% sensitivity and 86 % specificity.[13] Russo *et al.* found significant differences between BA and non-BA, indicated by more severe biliary duct proliferation, bile plugs in the ductus and canaliculi and portal fibrosis in BA cases.[14]

In this study, BA cases were predominantly found in female infants compared to male infants. Contrastingly, non-BA cases in male infants were higher compared to female infants. There were significant differences in body weight, age, birth weight and gestational age (Table 3).

The study by Bellomo-Brandao *et al.* found that from 165 infants, intrahepatic cholestasis was found in 62.64% male infants, while extrahepatic cholestasis was found in 55.25% female infants with p-value = 0.026.15 This finding was similar to this study; despite no significant differences were found, this study showed that BA or extrahepatic cholestasis was commonly found in female infants.

This study showed significant differences in birth weight between BA and non-BAcholestatic infants. The birth weight of BA infants was greater than non-BA infants, indicated by birth weight > 2500 grams was more commonly found in BA infants. This finding was similar to previous research suggesting that higher body weight and greater length at birth were found in children with extrahepatic cholestasis.[15] A study by Fischler *et al.*

Table 3. Characteristics of BA and non-BA infants

Characteristic	Biliary Atresia (BA) (n=16)	Non-Biliary Atresia (Non-BA) (n=21)	P
Age, n (%)			
Boy	7 (33.3)	14(66.7)	0
Girl	9 (56.3)	7 (33.7)	0.163*
Birth weight, mean (± SD)	5218.7 (±926.08)	4185(±966.07)	
Age (month), mean (± SD)	3.5 (±1.15)	2.43 (±1.21)	0.002**
Age (month), n (%)			
One	0 (0)	4 (100.0)	0.009***
Two	4 (28.6)	10 (71.4)	
Three	4 (57.1)	3 (42.9)	
Four	4 (66.7)	2 (33.3)	
Five	4 (66.7)	2 (33.3)	0.111*
Gestational age, n (%)			
Aterm	15 (60.0)	10(40.0)	
Preterm	1 (8.3)	11 (91.7)	0.003*
Birth weight, Mean (± SD)	2953.1 (±295.22)	2542.4 (±684.16)	0.020**
Birth weight, n (%)			
< 2500	1 (9.1)	10 (90.9)	
>2500	15 (57.7)	11 (42.3)	0.006*
IgM CMV n (%)			
Positive	9 (69.2)	4 (30.8)	0
Negative	7 (29.2)	17 (70.8)	.019*
IgG CMV n (%)			
Positive	15 (45.5)	18 (54.5)	0.435*
Negative	1 (25.0)	3 (75)	

SD= Standard Deviation *Chi-Square, ** independent t-test, *** Mann-Whitney U

found that preterm birth was superior in children with BA 3/30 (10%) compared to those without BA 5/55 (9%). However, this difference was not significant. Also, this study found that preterm birth was more frequently found in non-BA infants.[16]

The older age was found in BA infants compared to non-BA infants when patients were admitted to the hospital. This was different from the previous study which found that older infants were found in cholestatic patients without BA, supported by other studies which found that there were no significant differences between both groups.[15,16]

There were nostatistically significant differences in the onset of jaundice between cholestatic infants with BA and without BA, the onset of the yellow appearance of BA infants was longer than non-BA infants (Table 4).This was a contrast to previous studies which found the remarkably quick onset of jaundice in patients with BA.[17] The difference of the onset of jaundice in these two groups could have been different based on parents' perspective and knowledge. Parents/families sometimes do not know that the children have pathologic icteric and patients with BA still show good nutritional status at the onset of the disease.

On laboratory examination, significant differences in leukocytes count were found between the two groups (Table 4); whereas there were no significant differences in laboratory results, such as complete blood count (hemoglobin, platelets), liver function (ALT/AST), albumin, direct bilirubin, and total bilirubin levels. Higher leukocyte count was found in patients with BA and in accordance with these findings, Wibowo reported comparable

Table 4. Clinical manifestation of BA and non-BA infants

Clinical manifestation	Mean (±SD)		p
	Biliary atresia	Non-biliary atresia	
Onset of jaundice	3.4 (±0.44)	3.7 (±0.39)	0.259**
Direct bilirubin	31.4(±26.62)	25.1(±29.29)	0.646*
Total bilirubin	9.1 (±4.59)	9.6 (±4.86)	0.968**
Hemoglobin	8.4 (±6.2)	8.5 (±6.11)	0.963**
Leukocyte	10.5 (±2.07)	11.2 (±2.88)	0.034**
Platelet	14640 (±5844)	10469 (3682)	0.304*
AST	355.583(±145.052)	371.444 (156.949)	0.63**
ALT	246.2 (±95.39)	215.8 (±161.66)	0.101**
Albumin	213.9 (±133.73)	164.9(±114.27)	0.063*

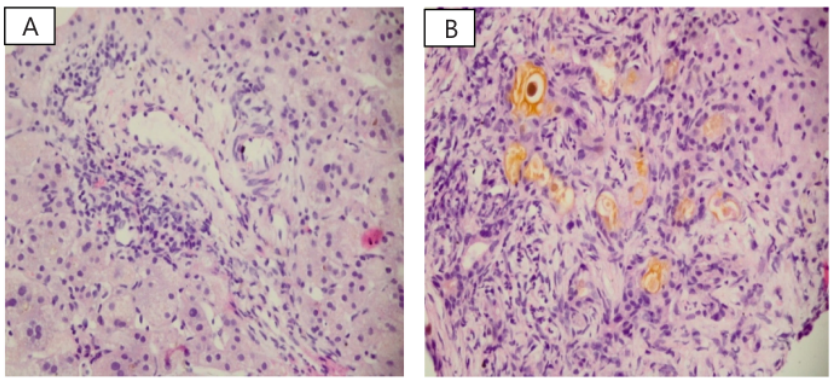

Figure 1. Histopathological features of liver tissue biopsy with a 400x magnification of a microscope. **Figure A** shows a picture of the portal track of intrahepatic cholestasis as indicated by the presence of giant cell hepatitis (red arrow) and no bile duct proliferation. **Figure B** shows a picture of BA (extrahepatic cholestasis) as biliary ducts proliferation that contains a bile plug (blue arrow) in the portal tract.

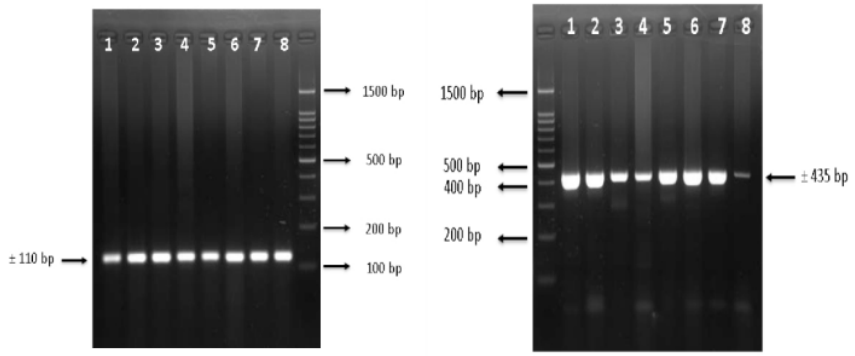

Figure 2. (A) Electrophoresis of βglobin PCR gene using PCO3 and PCO4 primers (in 8 samples) which produced 110bp products followed by (B) electrophoresis PCR results using primers MIE4 and MIE5 which produced 435 bp

Table 5. Comparison of CMV infection in cholestatic infants with BA and without BA based on the results of PCR in liver tissue

Liver Biopsy PCR CMV, n (%)	Biliary Atresia	Non-Biliary Atresia	p
Positive	9 (37.5)	15(62.5)	0.338*
Negative	7 (53.8)	6 (46.2)	

results, although the increase in leukocytes in BA remained unexplained.[18]

The diagnosis of BA was based on clinical manifestations (yellowing of the eyes and whole body, a cholic stool) and anatomical pathology examination (histopathological features such as bile plug, ductular proliferation, and portal edema with and/or fibrosis of liver biopsy tissue (Figure 1).

Biopsy samples were taken and extracted from liver tissue, then PCR was carried out with β globin using PCO3 primers to determine the quality of the samples. If a positive result (yielding a product of 100-200 bp) is obtained, the examination must be continued by PCR examination using primers MIE4 and MIE5. A positive result is reported if the product produces 400-500bp. In this study, positive results were obtained for all β globin effects; therefore, PCR was performed (Figures 2).

The detection of CMV by PCR showed positive results in 24 infants and negative results in 13 patients. The incidence of CMV infection in cholestatic infants with BA and without BA was 56.2% and 71.4%, respectively. The polymerase chain reaction is a diagnostic instrument that has high sensitivity and ability to detect the presence of CMV, despite low specificity and low CMV infection.[19]

Cytomegalovirus infection is initially more common in intrahepatic cholestasis (without BA); however, several studies have shown that CMV infection can be found in extrahepatic cholestasis (BA). The study found that viruses including CMV can be a trigger leading to dysregulation of immune mechanisms with genetic influences and eventually cause BA.[20] Cytomegalovirus infection has the ability to replicate both in hepatocytes and cholangiocytes. This virus can directly induce damage to the liver and biliary duct system and induce damage to the immune system in infected cells, leading to the formation of inclusion of bodies in hepatocyte and vascular cells of epithelial cells, especially along with biliary duct epithelial cells.[21]

There were no significant differences between BA and non-BA cholestatic infants based on the PCR of CMV in liver tissue (Table 5). This study showed that positive PCR results of CMV were only found in 9 (37.5%) BA patients. The study about PCR CMV was begun by conducting several studies on animals, and subsequently was carried out on humans.[22-25] In this study, there were no significant differences in the number of CMV infection in infants with BA and without BA. This was because BA could be caused by other viruses such as Rotavirus, Reovirus, Ebstein-Barr Virus (3.5%) and Adenovirus (5.8%).[26,27,9] Presumed role of Rotavirus and Reovirus in BA have also been studied for a long time.

Fjaer *et al.* found 4 cases of CMV infection from a

total of 9 cholestatic patients. However, positive PCR of CMV from liver tissue was only found in 2 patients from 4 cases of CMV infection. Cytomegalovirus infection in the other 2 patients was caused by Ebstein-Barr Virus.[28] The presence of the Human Herpes virus 6 in liver tissue was also demonstrated by Domiati *et al*. in their study about Human Herpes six virus in BA patients. Cytomegalovirus infection; however, was not found in the study subjects or controls.[29]

CONCLUSION AND SUGGESTION

Cytomegalovirus infection is found in intrahepatic and extrahepatic cholestatic infants like BA. In this study, the lower incidence of CMV infection in cholestatic infants with BA was found compared to non-BA. However, there was no significant difference in the incidence of CMV infection in cholestatic infants with BA or without BA. Future research with longer research time and PCR was needed to determine the causal virus of BA.

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