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Clinical Manifestation of Biliary Atresia in Bali

Merry Natalia, I Gusti Ngurah Sanjaya Putra, Ni Nyoman Metriani Nesa, I Putu Gede Karyana

Department of Child Health, Faculty of Medicine, Udayana University, Denpasar, Indonesia

Email address:
dr.merry.natalia@gmail.com (M. Natalia), sanjayaputra65@gmail.com (I. G. N. S. Putra), metriani_nesa@yahoo.id (N. N. M. Nesa), kyn_karyana@yahoo.co.id (I. P. G. Karyana)

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Abstract: Biliary atresia is a rare disease of the liver and bile ducts that occurs in infants. Biliary atresia is a condition in which the absence of a lumen in the extrahepatic biliary tract causes obstruction of bile flow. Symptoms of the disease appear or develop about two to eight weeks after birth. This study aims to describe the clinical manifestations of patients with Biliary Atresia at Sanglah General Hospital, Bali. This cross-sectional study was performed at the Sanglah Hospital Denpasar, Bali. Data was taken from medical record from January 2015 - December 2020. Study population were children who diagnosed as Biliary Atresia. Diagnosis was confirmed by cholangiography and liver biopsy. The study included 30 infants with Biliary Atresia, mostly (70%) were girl. Average age at admission was 3 months. Ninety percent subject had hepatomegaly in physical examination. Acholic stool were found in 80% subject. The average serum levels of conjugated bilirubin were 9.8 mg/dL, alanine aminotransferase (ALT) was 182 u/L, aspartate transaminase (AST) was 324 u/L, gamma-glutamyl transpeptidase (GGT) level was 671 u/L and albumin was 3.8 g/dL. Seventy percent patient showed triangular cord sign in abdominal ultrasonography. Kasai procedure was performed to all those infants. The most common clinical manifestation was icteric, dark urine, acholic stool and hepatomegaly. Triangular cord sign was the most common finding in abdomen ultrasonography.

Keywords: Biliary Atresia, Profile, Clinical Manifestation

1. Introduction

Biliary atresia is a disease of unknown etiology, characterized by progressive fibro inflammatory of the bile duct and liver that result obstruction of extrahepatic bile duct, leading to the fIbrosis and liver cirrhosis [1].

It is the most frequent surgical cause of cholestatic jaundice in this age group. Biliary Atresia occurs in approximately 1:18.000 live births in Western Europe. In the world, the reported incidence varies from 5:100.000 to 32:100.000 live births, and is highest in Asia and the Pacific region [2].

Females are affected slightly more often than males.

The etiology of Biliary Atresia remains unknown. Biliary atresia will lead to fibrosis and liver cirrhosis at a very early age, if not treated immediately. If the operation is not performed, the survival rate for 3 years is only around 10% and the average death is at the age of 12 months. Clinical features were icteric, acholic stool, dark urine, hepatomegaly. Biliary atresia is a condition in which there is no lumen in the extrahepatic biliary tract causing obstruction to bile flow. Biliary atresia occurs due to a prolonged inflammatory process that causes progressive damage to the extrahepatic biliary ducts resulting in obstruction of bile flow (cholestasis), resulting in accumulation of bile salts in the liver and blood and an increase in bilirubin. In biliary atresia, laboratory findings reveal conjugated hyperbilirubinemia and elevated transaminases, alkaline phosphatase, and c-glutamyl transpeptidase, but none of these is specific; thus, further investigative studies must be undertaken. Ultrasound is a useful adjunct because it is non invasive. It usually reveals a shrunken, atrophic gallbladder, although approximately 20% may have what seems to be a normal gallbladder that at operation is noted to be a gallbladder mucocele [3].

Biliary atresia is a cause of terminal liver disease which is the main indication for liver transplantation in children. The early symptoms of biliary atresia are often difficult to distinguish from physiological neonatal jaundice, leading to late diagnosis and management.

Another cause of delay in diagnosis is the existence of multiple differential diagnoses as a cause of direct

hyperbilirubinemia which takes time to make a diagnosis. Early detection of the possibility of biliary atresia is very important, because the success of hepato-portoenterostomy (Kasai) surgery will decrease if performed after 2 months of age. The success of the operation is largely determined by the age at the time of surgery, that is, if done before the age of two months, the success of draining bile is more than 80% while after that age the result is less than 20% [4].

Overall, the 10-year survival rate is 90%. Failures of Kasai procedure are influenced by control of nutrition and timely liver transplantation [5].

The objective of the study was to describe the clinical manifestations of patients with Biliary Atresia at Sanglah General Hospital, Bali.

2. Methods

The study was a cross sectional study conducted in 30 infants who had been diagnosed with Biliary Atresia at Sanglah General Hospital Bali. The data was taken form medical record from January 2015 until December 2020. Data including baseline characteristic, clinical manifestation, laboratory, radiology findings, abdominal ultrasound, cholangiography, liver biopsy, and Kasai procedure. Diagnosis Biliary Atresia was confirmed by cholangiography. Statistical analysis was performed by computer program.

Descriptive data presented were with table and graphs. This study was approved by the Ethics Committee of Faculty Medicine, University of Udayana with number of ethics is 980/UN14.2.2.VII.14/LT/2021.

3. Results

A total 30 cases of Biliary Atresia were included. Diagnosis was confirmed by cholangiography.

Patients were mostly girls (70%) with age of admission was 3 months (Table 1). Birth weight of the patient was 2983 gr. The patient mostly referred from pediatrician (46.7%).

The age of icteric patient was 4 weeks, with the acholic stool color was 80%. Ninety percents of the patient had hepatomegaly and most of the patient with the mild malnutrition when diagnosis confirmed was 33%. Age at kasai procedure at 11 weeks, as seen in Table 2.

The lowest conjugated bilirubin was 0.09 mg/dL dan the highest was 22.9 mg/dL. The highest total bilirubin was 29.35 mg/dL, The mean serum levels of ALT, AST and GGT increased less than 10 times of the normal value.

Table 1. *Subject Characteristics.*

Characteristic	Result
Age (months)[a]	3 (1.3)
Sex[b]	
Boy	9 (30)
Girl	21 (70)
Birth weight[a]	2983 (313)
Referred from	
Other Hospital	12 (40)
Pediatrician	14 (46.7)
General Practitioners	1 (3.3)
Midwife	3 (10)
Ethnic[b]	
Bali	25 (83.3)
Non Bali	5 (16.7)

[a]Mean (standard deviation), [b]n (%)

Table 2. *Clinical manifestation.*

Clinical Manifestation	Result
Age of icteric (weeks)[a]	4 (2.6)
Stool color[b]	
Acholic	24 (80)
Yellow	6 (20)
Urine color[b]	
Dark	23 (77)
Yellow	7 (23)
Hepatomegaly[b]	27 (90)
Hepatosplenomegaly[b]	3 (10)
Nutritional status when diagnosis was confirmed[b]	
Well nourished	6 (20)
Mild malnutrition	10 (33.3)
Moderate malnutrition	9 (30)
Failure to thrive	5 (16.7)
Age at the Kasai procedure (weeks)[a]	11 (3.3)

[a]Mean (standard deviation), [b]n (%)

Table 3. *Laboratory Characteristics.*

Characteristic	Result
Hemoglobin (g/dL)[a]	10 (1.7)
Platelet [a]	350 (164)
Conjugated bilirubin (mg/dL)[a]	9.8 (5.6)
Total bilirubin (mg/dL)[a]	11 (6.2)
ALT (u/L)[a]	182 (115.5)
AST (u/L)[a]	324 (253.4)
ALP (u/L)[a]	493 (193.7)
GGT (u/L)[a]	671 (792.8)
IgG CMV[b]	
Positive	27 (90)
Negative	3 (10)
IgM CMV[b]	
Positive	4 (13.3)
Negative	26 (86.7)
Albumin[a]	3.8 (0.6)
PTT[a]	23 (24.6)

[a]Mean (standard deviation), [b]n (%)

Table 4. *Radiology findings.*

Features	Results
Ultrasonography abdomen	
Triangular cord sign[b]	
Seen	21 (70)
Not visible	9 (30)
Gall bladder[b]	
Normal size	23 (76.7)
Small size	7 (23.3)
Contractility[a]	37 (34.6)

All patient had ultrasonography abdomen examination, with 70% of them had triangular cord sign. All those patients had cholangiography, liver biopsy and followed by Kasai procedure. Liver biopsy results of 29 patients with biliary atresia and 1 patient with neonatal hepatitis. After several

visiting, four of the subjects were not survive.

4. Discussion

The clinical presentation of biliary atresia are jaundice, alcoholic stool and dark urine, and hepatomegaly [6]. Our study found patients were mostly girls (70%) with an average age of 3 months. Wada and colleagues confirmed this association, finding a relative risk of 1.80 (95% 1.24-2.62) for girls compared to boys. This is similar with Yoon et al. study, females are affected slightly more often than males [7, 8]. Jaundice at two weeks of life is relatively common (up to 15%), however it is not always associated with liver disease [8]. In this study, most of cholestasis infants were diagnosed at the age of 3 months. About 98% of infants with white stool more than 7 days has been confirmed to have biliary atresia. In our study patient with alcoholic stool with 80% and dark urine 77% meanwhile in the other study Dehghani et al. studied 62 infants with a prevalence of acholic stools in 94.7% of patients with Biliary Atresia [9]. Meanwhile Witt et al. found that patient with alcoholic stool 87% [10]. Hepatomegaly may be present early in our study patient with hepatomegaly with 90%. Gupta et al. studied infants with 100% hepatomegaly [11]. Anemia can be found in infants with cholestasis due to reduced hepatocytes function or microhematochezia. In this study, most infants were anemic with mean level of hemoglobin was 10.5 (7.29 to 16.1) g/dL. The laboratory result of ALT serum level can be used as an indicator of hepatocyte damage. Increasing levels of GGT suggests biliary obstruction since the GGT enzymes are located in the canaliculi [12]. GGT level is more sensitive to detect obstructive jaundice than ALT, and AST. The present study demonstrated increased mean levels of ALT and AST. In our study showed significant increasing of the direct bilirubin up to more than 10 times this is different result with Carvalho research that direct bilirubin increase more than 20 times [13].

The mean serum level of GGT in this study was 671 (30-3251) u/L. The similar result was found in previous retrospective study with the biliary atresia cut-off level >250 U/L, sensitivity was 83.3% (95% CI, 55.2- 95.3%); specificity, 70.6%

The etiology and pathogenesis of biliary atresia 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 biliary atresia.

In this study the result of IgG CMV was positive is 90%. This is similar with the study Situmorang et al., 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 [14].

One of the diagnostic procedures is abdominal ultrasonography (USG). The abdominal USG was performed in two-phase procedure. The first phase was done after 12 hours fasting and the second phase was completed in 2 hours after giving breast milk or formula milk. The presence of the triangular cord sign above the portal vein bifurcation could be a sensitive radiologic marker for biliary atresia [15]. Experts in ultrasound examination could point to biliary atresia by demonstrating an irregularly shaped or absent gall bladder. Twenty-one infants (70%) in this study were diagnosed on ultrasound as biliary atresia with the triangular cord sign. In Lee et al study, only 18 of 29 patients with pathologically confirmed Biliary Atresia had positive TC signs (sensitivity 62%; specificity, 100%) [16].

Cholangiography followed by liver biopsy and Kasai procedure are mandatory in biliary atresia infants. The age at Kasai operation in this study was 11 weeks. The kasai has an effect on outcome, but it is not as clear-cut as was once thought. There is no real cut-off (e.g., six or eight weeks or 60 days) [17]. There was two-year survival rate of 65% and 80% of jaundice-free period when Kasai is performed before 60 days of age. If the Kasai is done after the age of 60 days, the survival rate is 22% and there is 20-35% of jaundice-free period [18].

Biliary atresia could be diagnosed by histopathologic examination at the age of 4-7 weeks. Percutaneous liver biopsy is highly accurate (88.2%) in diagnosing Biliary Atresia. In developing countries. This investigation should be done to decrease the frequency of negative laparotomy and to achieve cost benefit with reduced morbidity.

Thirty infants with biliary atresia had undergone Kasai procedure. Four of them died after several times of visits. Porto-enterostomy performed by an experienced surgeon would give promising results of good bile flow with normal serum bilirubin, which can be achieved in more than 80% of infants with biliary atresia operated on 60 days of age.

5. Conclusions

Biliary atresia is the most common cause of extrahepatic cholestasis in infants. Most of children with Biliary Atresia were girl. The most common clinical manifestation were icteric, acholic stool, dark urine and hepatomegaly. Triangular cord sign was the most common finding in abdomen ultrasonography.

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