DELAYED ADMISSION IN NEONATAL CHOLESTASIS

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ABSTRACT

Delayed diagnosis of cholestasis in neonates remains a problem. Cholestatic jaundice is a pathological condition that requires immediate treatment, such as biliary atresia. This study aims to analyze the characteristics of infants with cholestasis who seek treatment at a tertiary hospital. This study was a cross-sectional study to determine the characteristics of infants with cholestasis treated at the tertiary hospital at Dr. Soetomo General Academic Hospital, Surabaya, East Java, Indonesia. Subjects were collected using medical records using the consecutive method from 2019 to 2021. The inclusion criteria in this study were infants aged >2 weeks who suffered from cholestasis. The age of the 111 infants with cholestasis involved was 4.8 ± 2.9 months old. A total of 27 (24.3%) infants visited the hospital at the age of <2 months, 36 (32.4%) at the age of 2-4 months, but most of them, consisting of 48 (43.2%) infants, came to the hospital at the age of >4 months. Jaundice was present at birth in 23 infants (20.7%), and most infants had jaundice at 1 month of age in 75 infants (67.6%). Most of the infants (75 infants) had jaundice at the age of 1 month but visited the hospital at the age of >4 months. This showed that the late diagnosis of cholestasis in infants was still quite high. This study supports education for early detection of cholestasis in primary healthcare medical personnel, community health workers, and parents.

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INTRODUCTION

Jaundice is a yellow discoloration of the skin and sclera. More than 80% of jaundice that occurs in newborns in the first two weeks is due to direct hyperbilirubinemia and resolves spontaneously. However, if jaundice persists beyond two weeks of age, it could be due to cholestasis or hepato-biliary dysfunction[1]. It can occur in 1 in 2500 births, and it is very important to distinguish between cholestasis and non-cholestatic (physiological jaundice). Cholestatic jaundice is a pathological condition that requires immediate treatment, such as biliary atresia (25-40% of cases)[2]. However, experienced physicians have a better understanding of the management of early neonatal jaundice (49%) than prolonged neonatal jaundice (16%)[3].

The recommendations suggest that infants who develop jaundice after the 14th day of life should have their total and direct serum bilirubin levels checked to evaluate for cholestasis. The infant should be referred to a hepatology for further evaluation if the direct bilirubin level is elevated >1.0mg/dL or >17 mmol/L[2]. The success of treatment depends on the time of diagnosis. The younger the infant is treated, the better the prognosis. However, delay in diagnosis remains a problem. This study aims to analyze the characteristics of infants with cholestasis treated at the tertiary hospital at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

MATERIALS AND METHODS

This study was a cross-sectional, retrospective study to determine the characteristics of infants with cholestasis treated at the tertiary hospital at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Subjects were collected using the consecutive method in 2019-2021 using medical records. The inclusion criteria in this study were infants aged >2 weeks with cholestasis. Serum bilirubin measurement establishes the diagnosis of cholestasis. Cholestasis is an increase in the direct bilirubin level of >1 mg/dL (if the total bilirubin level is <5 mg/dL) or >20% of the total bilirubin (if the total bilirubin level is >5 mg/dL[1]. Exclusion criteria in this study were the presence of congenital abnormalities and syndromes. This study was conducted after obtaining approval from the ethics committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (No. 0635/LOE/301.4.2/X/2021) on October 8th, 2021.

RESULTS

Table 1. Basic characteristics of subjects

Variable	n (%)
Sex	
Male	71 (64%)
Female	40 (36%)
Birth weight	
<2500 gram	25 (22.5%)
≥2500 gram	86 (77.5%)
Onset of jaundice	
Since birth	23 (20.7%)
≤ 1 month old	75 (67.6%)
>1 month	13 (11.7%)
First time to visit gastrohepatologist	
< 2 months old	27 (24.3%)
2-4 months old	36 (32.4%)
>4 months old	48 (43.2%)
Liver biopsy	
Extrahepatic	111 (100%)
cholestasis	0 (0%)
Intrahepatic cholestasis	
Stool color < 1 month of age	86 (77.5%)
Acholic	25 (22.5%)
Non-acholic	
Abdominal distended (bloating)	28 (25.2%)
Yes	83 (74.8%)
No	
Decreased of appetite	
Yes	22 (19.8%)
No	89 (80.2%)
Gastrointestinal symptoms	
Yes	31 (27.9%)
No	80 (72.1%)
Hepatomegaly	
Yes	93 (83.8%)
No	18 (16.2%)
Splenomegaly	
Yes	22 (19.8%)
No	89 (80.2%)
Serum Bilirubin level	Mean ± SD
Direct bilirubin (mg/dL)	9.53±5.18
Total bilirubin (mg/dL)	15.42 ± 10.99

SD: standard deviation

In this study, there were 111 infants with cholestasis, consisting of 71 (64%) males and 40 (36%) females, aged 4.8 ± 2,9 months old. They suffered from extrahepatic cholestasis based on histopathological examination with a direct bilirubin level of 9.53±5.18 mg/dL and a total bilirubin level of 15.42 ± 10.99 mg/dL.

A total of 27 (24.3%) infants visited the hospital at the age of <2 months, 36 (32.4%) at the age of 2-4 months, but most of the 48 (43.2%) infants came to the hospital at the age of >4 months. Most infants seek treatment at a late age (Table 1).

The onset of jaundice was present at birth in 23 infants (20.7%) and 75 (67.6%) infants had jaundice at 1 month of age. A total of 86 (77.5%) infants had a normal birth weight. Changes in stool color in acholic stool before 1 month of age were found in most of the infants (86 infants or 77.5%). However, most of the other symptoms have not been complained of, such as abdominal distension, which was only found in 28 infants (25.2%), decreased appetite in 22 infants (19.8%), and gastrointestinal symptoms in 31 (27.9%) (Table 1).

Table 2 shows that most of the infants (48 infants) developed jaundice at 1 month of age but were referred to hepatology at >4 months of age. Only a few infants sought treatment at an early age.

Table 2. First time to visit gastrohepatologist

	Onset of jaundice		
	Since birth	**≤ 1 month old**	**>1 month old**
<2-month-old	2	24	1
2-4 months old	10	23	3
>4-month-old	23	12	13

DISCUSSION

The primary cause of cholestasis in infants is biliary atresia. Histopathologic examination of the liver reveals extrahepatic cholestasis[2]. Previous studies have been carried out to analyze direct bilirubin levels for early detection of biliary atresia. Biliary atresia screening using direct bilirubin levels in early life has a sensitivity of 100% and a specificity of 99.9%[4]. Therefore, it is recommended to evaluate serum bilirubin levels in infants with prolonged jaundice. Immediate referral to hepatology is necessary if the direct serum bilirubin level is >1 mg/dL to prevent delay in diagnosis and management of biliary atresia[2].

Cholestasis can be caused by conditions, including infection, disorders of the immune system, genetic, metabolic, or unknown etiology[2,5]. However, previous studies have shown that biliary atresia is found in 40% of infants with cholestasis[5]. Biliary atresia is a fibro-inflammatory disease that occurs in the intra- and extrahepatic biliary tree. It is progressive, and its onset occurs in the first 3 months of life[5,6]. A previous study found that screening using direct bilirubin levels was associated with earlier treatment, with an average of 56 days before screening and 36 days after screening[4].

Biliary atresia was first discovered in the late 19th century, but biliary atresia is still a challenge in the 21st century, even though various patho-physiology have been proposed[7]. The incidence of biliary atresia is 5.000-18.000 per 100.000 live births and occurs worldwide[8]. Biliary atresia is less common in Europe than in Asian countries[7]. Biliary atresia causes cholestasis and progressive liver damage. It is the most common cause of liver transplantation in children[6,7]. Up to 60% of liver transplants in children <1 year of age are due to biliary atresia[9].

Several challenges remain in biliary atresia, including early diagnosis, prevention of fibrosis after Kasai surgery, and management of complications from

immune suppression in liver transplantation[7]. In this case, extrahepatic cholestasis was found, which showed signs of biliary atresia. Acholic stools are also found at an age before 1 month. However, clinically, the baby is healthy. Most of them had a normal birth weight and were growing well. Abdominal enlargement due to organomegaly, such as hepatomegaly, occurs in the following months of life. Splenomegaly appeared later when portal hypertension was found due to liver damage. In this case, hepatomegaly was found in 83.3% of cases, but splenomegaly was found in only 16.2% of cases. This condition often leads to delays in referral to hepatology due to misdiagnosis of physiological jaundice.

Early diagnosis at <45 days of age is associated with an increasing survival rate of the native liver[8]. Kasai surgery performed in the early 2-3 months of life aims to improve bile flow and prevent further liver damage. However, liver damage still occurs in >70% of children after Kasai surgery, requiring liver transplantation before adulthood[8]. Failure of Kasai surgery, recurrent cholangitis, hepatopulmonary syndrome, porto-pulmonary hypertension, and progressive portal hypertension are indications for liver transplantation[6]. These complications occur more frequently in cases of biliary atresia with congenital malformation[10,11]. A study in France on 743 children with biliary atresia stated that of the 695 children who underwent Kasai surgery, the survival rates at years 2, 5, 10, and 15 were 57.1%, 37.9%, 32.4%, and 28.5%, respectively. The older the patient at Kasai surgery, the lower the survival. The combination of the Kasai procedure and liver transplantation improves the prognosis of biliary atresia[12].

Several etiologies of biliary atresia have been described, such as infection, genetic factors, epigenetics, disorders of the immune system, toxic factors, and the latest, the inflammatory process triggered by a viral infection[13-15]. Although the definitive cause of biliary atresia is still unknown, recent research suggests that infections, such as cytomegalovirus infection, may induce an ongoing inflammatory process that is the most common cause of biliary atresia. Most biliary atresia begins to manifest clinically in the first month of life, which is characterized by prolonged jaundice[16]. Most of the biliary atresia is isolated. Only a small proportion of it is accompanied by congenital malformation[17].

However, the early diagnosis of biliary atresia is still a challenge today because of the similarities with common indirect hyperbilirubinemia in the newborn period[8]. As a result, the diagnosis of biliary atresia is often delayed and the management is not optimized. At first, the infant may appear clinically healthy. It is difficult to distinguish biliary atresia from the more common physiologic jaundice that may occur in the early stages of life. However, the symptoms of cholestasis, such as dark urine and pale stools that are associated with jaundice, are present only in biliary atresia[7]. Not all parents are aware of the colour of their baby's urine and stool, and the symptoms of biliary atresia often are not recognized.

The prognosis of biliary atresia increases if Kasai surgery is performed at <45 days of age. Ten-year overall survival after the Kasai surgery was 66.7% to 89%, while native liver survival at 1 to 3 years was 20.3-75.8% and at 10 years was 24-52.8%[18]. Even though Kasai surgery is performed at a young age, as many as 50%

still need a liver transplant before 2 years[6,7]. Another study stated that the native liver survival rate after Kasai surgery at the age of ≤30 days was 49% at 4 years. As many as 60% of patients who undergo Kasai surgery require a liver transplant[19].

In addition to liver damage, patients with biliary atresia who successfully survive with a native liver after Kasai surgery are at risk for developmental delay at 12 and 24 months of age. However, patients with biliary atresia who are not successfully treated with the Kasai procedure have a four times greater risk of experiencing neurodevelopmental problems[20].

Biliary atresia screening with direct (conjugated) bilirubin examination is needed to find the cases early[6,7]. Measuring direct bilirubin levels and introducing a stool color card to new parents may increase early detection of biliary atresia[8]. The study showed that routinely measuring direct bilirubin before the appearance of biliary atresia symptoms can help identify the condition early, with a 100% success rate, a 99.9% success rate, and an 18.2% success rate for predicting the condition[9]. Biliary atresia screening with direct serum bilirubin and stool color cards is cost-effective and potentially life-saving[21].

Delayed diagnosis of biliary atresia remains a challenge worldwide. The infant has prolonged jaundice and pale stools. Initially, the baby thrives, with normal growth and no complaints[22]. Late referral and late diagnosis are the causes of poor outcomes in biliary atresia[23]. Time is very crucial in diagnosing atresia. A biliary atresia screening study with a bilirubin assay in 124,385 infants showed a sensitivity of 100% (95%CI, 56.1%-100.0%) and a specificity of 99.9% (95%CI, 99.9%-99.9%). Early diagnosis of biliary atresia is still challenging. Studies are still being carried out, including regarding the opportunities for early diagnosis of biliary atresia by using blood biomarker tests[24].

Studies in animals show the possibility of treatment to prevent progression to biliary atresia which needs to be studied further[25]. The majority of infants with prolonged jaundice are considered normal and do not require further evaluation. After the appearance of obvious clinical signs such as abdominal enlargement, ascites, swelling, and increasing jaundice, the patient was referred to a referral center, but too late. This study found that the delay in the treatment of cholestasis is a cause of delay in the management of biliary atresia. More education on early recognition of biliary atresia is needed to improve the outcome of infants with the disease.

CONCLUSION

The delay rate in infants with cholestasis was very high. The delay in the early detection of cholestasis leads to a worse prognosis of the disease. The study supports the education of primary health workers, community health workers, and parents to identify cholestasis at an early stage and avoid delays in referral. Optimal treatment will decrease the need for liver transplants and decrease morbidity and mortality.

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CONFLICT OF INTEREST

All Authors have no conflict of interest

ETHICS CONSIDERATION

The research received ethical clearance from the ethics committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (No. 0635/LOE/ 301.4.2/X/2021) on October 8th, 2021.

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AUTHOR CONTRIBUTION

All authors have contributed to all process in this study, including preparation, data collecting, analysis, writing, and approval for publication of this manuscript.

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