

Report of 21 Cases of Neonatal Cholestasis in a Children's Hospital in Cartagena, Colombia

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Abstract

Cholestasis is an alteration in the flow of bile resulting from decreases or cessation of biliary excretion. To date, there have been only a few studies on this topic in Colombia. This article presents twenty-one cases of neonatal cholestasis from a Children's Hospital in Cartagena, Colombia that occurred between 2010 and 2013. The aim of this study is to characterize the etiology and clinical characteristics of the disease. Patients between birth and 3 months old with direct bilirubin levels over 2 mg/dl were selected. By gender, 52.4% of the patients were male, and 47.6% were female. 76.2% of the patients were full term, and 57.1% had no perinatal antecedents. Clinical symptoms presented in the first 30 days after birth in 71% of the patients, and 4 patients were referred for liver transplantation. The most common etiology was infectious (13 patients), and 4 patients had atresia. The most common cause of neonatal cholestasis in this study was infection, but obstructive disorders such as biliary atresia still account for an important proportion of the patients. They require priority study and handling because early intervention results in better prognoses.

Keywords

Neonatal cholestasis, bilirubin, biliary atresia, neonatal jaundice, neonatal sepsis.

INTRODUCTION

Cholestasis is a liver dysfunction in which the flow of bile is impaired. It is analytically defined by either a combination of elevated serum levels of bile acids and direct bilirubin over 2 mg/dl (1), or by direct bilirubin that is more than 20% of total bilirubin. It is caused by a blockage of flow through the intrahepatic or extrahepatic ducts of the biliary tree. This causes an accumulation of substances normally excreted in

the bile and usually presents with prolonged jaundice, dark urine, pale stools, hepatomegaly and itching during the first four weeks of life (2, 3). The term neonatal cholestasis covers the first three months of a newborn's life (1, 4).

Bile acids are toxic to membranes and are transported through bile ducts which protect tissues from these acids through the action of various proteins and vesicular transport within the hepatocytes (Figure 1) (5). In a cholestatic hepatocyte, the functionality of the carrier proteins is alte-

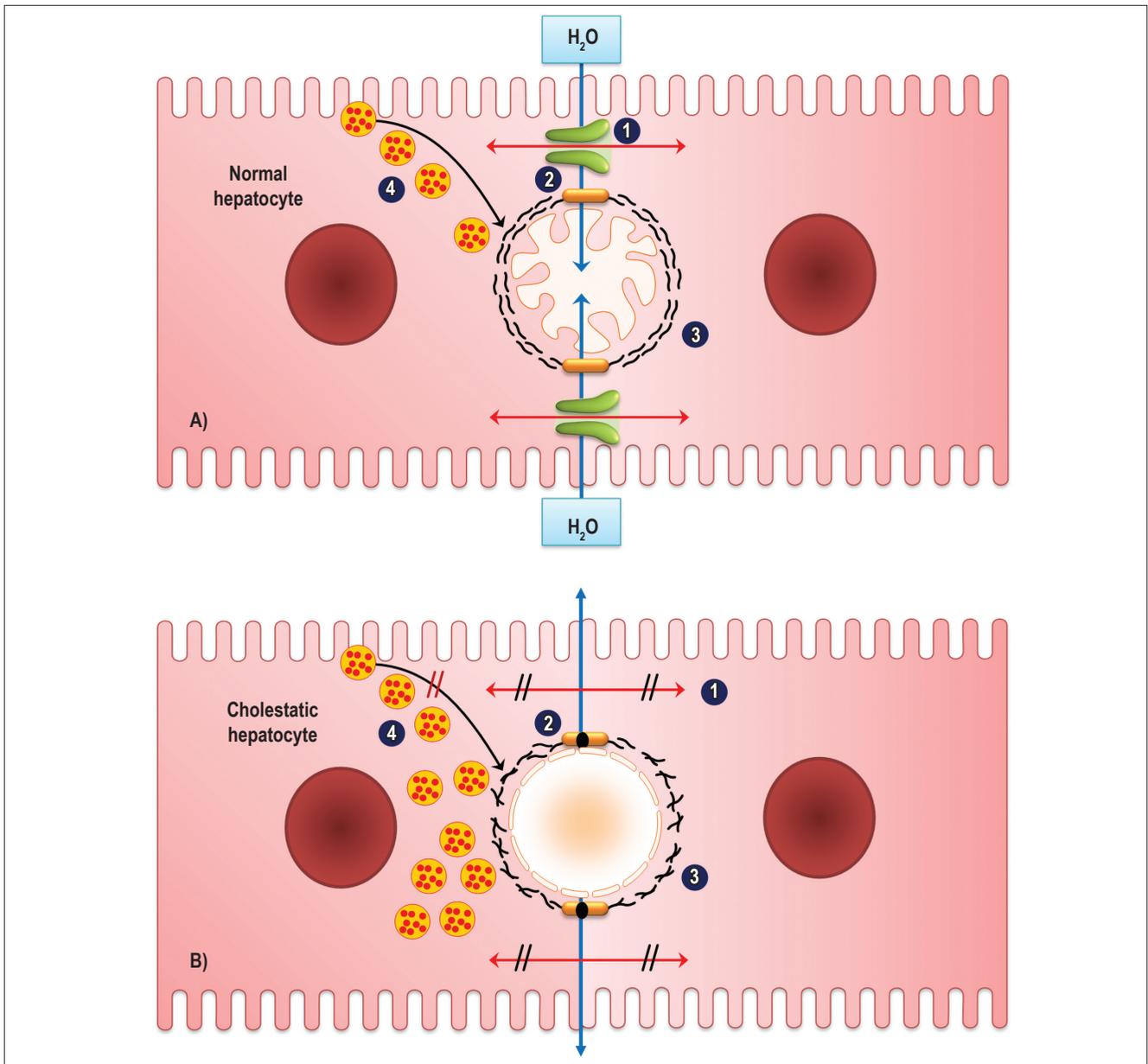


Figure 1. Bile transport in the hepatocytes. A. Normal Hepatocyte: 1) Binding protein, 2) tight junction, 3) Red actin-myosin, 4) Transcytotic vesicle pathway B. Hepatocyte with cholestasis: 1) Loss of junctions, 2) Leaking junctions, 3) Actin-myosin disorder, 4) Interruption of vesicular pathway. Source: The authors

red in ways that affect vesicular transport by disruption of microtubules in the cell. This causes accumulation of bile components (6, 7).

This clinical syndrome occurs in 1 out of every 2,500 to 5,000 live births (8). However, this rate varies according to various factors including race and gender. For example, the incidence in Europe is 1 in 18,000 (1, 9, 10).

Since global incidence of neonatal cholestasis is low, the pathology is underestimated. On the other hand, its etiology is multifactorial and can involve genetic, environ-

mental and hormonal factors (11, 12). It may be related to neonatal hepatitis, biliary obstruction, genetic cholestatic syndromes and metabolic diseases (13). For these reasons, it is important that all infants with symptoms such as prolonged jaundice are studied to achieve an accurate diagnosis which allows successful treatment that can ensure their survival (14-16). Some authors claim that it is not always possible to identify the causes of cholestasis because of the urgency of treating the patient (17). Biliary atresia and neonatal hepatitis account for 55% to 65% of all cases of neona-

tal cholestasis (1, 4). Treatment may be medical or surgical, including occasional liver transplantation, depending on the case. Transplantation is the standard therapy for acute and chronic liver failure, and over 50% of transplants are due to cholestatic diseases (18).

Since newborn babies have immature livers (19), they are at a disadvantage compared with older children. They have lower concentrations of bile acids and express less hepatobiliary transporters (20). Consequently, this condition predisposes the newborn to bleeding, encephalopathy, lack of vitamins A, D, E, and K, and jaundice (4, 21).

Neonatal cholestasis is a problem throughout the world. Its mortality rate is estimated to be between 15% and 50%. It is associated with perinatal factors whose presence can help make a proper diagnosis which can lead to optimal management. This in turn can contribute to decreases in serious consequences such as sepsis, liver failure and death (8, 22).

In cases of suspected cholestasis, the most important element of the evaluation is the color of stools. If the stools are clay-colored it is a sign of acholia and biliary atresia must be diagnosed or excluded (Figure 2). If obstruction of the extrahepatic biliary tree is excluded, a diagnosis of biliary atresia is likely. Cholangiography and should be performed and a liver biopsy should be taken. If the bile duct is not permeable, it is necessary to perform a Kasai intervention

(portoenterostomy). Conversely, if the bile duct is permeable, another diagnosis such as neonatal sclerosing cholangitis should be considered (12).

The purpose of this article is to identify the major etiological and clinical characteristics of patients with neonatal cholestasis cared for in the Hospital Infantil Napoleón Franco in Cartagena. It is important to note that few studies of this disease have been done in Colombia. Therefore, the aim of this research is to develop new knowledge, determine supporting elements for the most accurate diagnoses and to improve neonatal care.

PRESENTATION OF CASES

Twenty-one patients with neonatal cholestasis, direct bilirubin higher than 2 mg/dl, were admitted to the Hospital Infantil Napoleón Franco in Cartagena, Colombia between January 2010 and April 2013. Patients ranged in age between zero and three months old. Data were collected from interviews with families responsible for the patients, medical personnel responsible for the patients' care, and reviews of medical records. Parameters evaluated and shown in Table 1 are age, sex and clinical manifestations. Parameters evaluated and shown in Table 2 are perinatal history, lab results such as bilirubin and TORCH Infections (Toxoplasmosis,

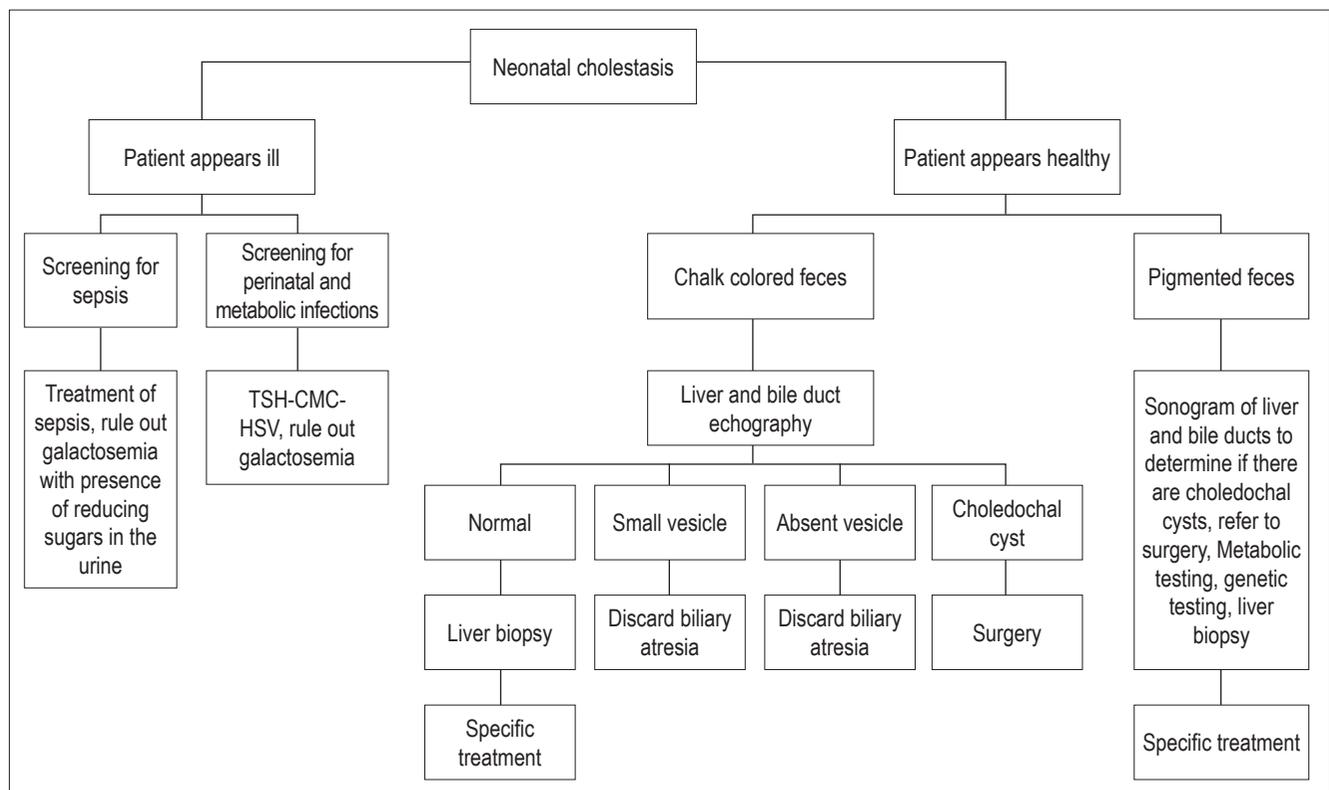


Figure 2. Diagnostic algorithm and management of neonatal cholestasis

Table 1. Basic and clinical characteristics of live births with neonatal cholestasis in the Hospital Infantil Napoleón Franco Pareja from 2010 to 2013

Patient	Sex	Gestational Age	Birth	Jaundice	Hepatomegaly	Splenomegaly	Acholia	Choluria	Fever	Age in Days
N° 1	F	Full Term	Cesarean	+	+	+	+	-	-	60
N° 2	F	Full Term	Cesarean	+	+	+	+	+	-	1
N° 3	F	Full Term	Cesarean	+	+	+	+	+	-	7
N° 4	M	Full Term	Cesarean	+	-	-	+	-	-	30
N° 5	M	Full Term	Cesarean	+	-	-	-	-	-	60
N° 6	F	Full Term	Vaginal	+	-	-	+	-	-	30
N° 7	M	Full Term	Cesarean	+	+	-	-	-	-	60
N° 8	F	Full Term	Cesarean	+	+	-	-	+	-	30
N° 9	M	Full Term	Vaginal	+	+	+	+	+	-	90
N° 10	F	Full Term	Vaginal	+	+	-	-	-	+	30
N° 11	M	Full Term	Vaginal	+	-	-	-	-	+	30
N° 12	M	Full Term	Vaginal	+	-	-	-	-	+	30
N° 13	M	Full Term	Vaginal	+	-	-	-	-	-	30
N° 14	M	Premature	Cesarean	+	-	-	-	+	-	2
N° 15	M	Full Term	Cesarean	+	-	-	-	+	-	4
N° 16	F	Premature	Cesarean	+	-	-	-	-	-	60
N° 17	M	Full Term	Cesarean	+	-	-	-	-	-	1
N° 18	M	Full Term	Vaginal	+	+	+	+	+	-	30
N° 19	F	Premature	Cesarean	+	+	+	+	+	+	30
N° 20	F	Premature	Cesarean	+	+	+	-	-	-	30
N° 21	F	Premature	Vaginal	+	-	-	-	-	-	60

Table 2. Perinatal history, laboratory tests and related etiologies of newborns with neonatal cholestasis at the Hospital Infantil Napoleón Franco Pareja from 2010 to 2013

Patient	Perinatal Antecedents	Total Bilirubin	Direct Bilirubin	Toxoplasmosis	CMV	Etiology
N° 1	-	11.53	6.01	-	-	Atresia
N° 2	-	8.7	5	-	-	Atresia
N° 3	Early neonatal sepsis	7.6	4	-	-	Atresia
N° 4	-	7.95	4	-	-	Idiopathic
N° 5	-	10.4	5.5	-	-	Idiopathic
N° 6	-	25.2	10.5	-	+	CMV
N° 7	-	19.2	7.4	-	+	CMV
N° 8	Neonatal hepatitis A	28.6	16.6	-	+	CMV
N° 9	Neonatal Jaundice	7.8	4	-	-	Atresia
N° 10	-	14.8	8.1	-	-	Neonatal Sepsis
N° 11	-	5.6	2.4	-	-	Neonatal Sepsis
N° 12	-	13.2	6.4	-	-	Neonatal Sepsis
N° 13	-	25	21	+	-	Toxoplasmosis
N° 14	Multiple	29.6	12.4	-	-	Neonatal Sepsis
N° 15	Congenital Megacolon	7.6	4.2	-	-	Neonatal Sepsis
N° 16	-	8.2	5.1	-	-	Idiopathic
N° 17	Necrotizing enterocolitis	6.4	2.8	-	-	Neonatal Sepsis
N° 18	-	7.8	4	-	-	Choledochal cyst
N° 19	Neonatal Sepsis associated with TPN	16.4	7.2	-	-	Neonatal Sepsis
N° 20	Neonatal Sepsis associated with TPN	16.4	7.2	-	+	CMV
N° 21	Anal malformation	21.8	7.6	-	-	Neonatal Sepsis

Other [syphilis, varicella-zoster, parvovirus B19], Rubella, Cytomegalovirus (CMV), and Herpes), and related etiologies. This study was classified in the category of research without risk in accordance with Article 11 of the Resolution No. 1993 008430 of the Ministry of Health.

The study group was comprised of almost equal numbers of male and female patients. Sixteen of the patients (76%) were full-term babies while five patients (24%) were premature (Table 1). The most common clinical findings were jaundice and hepatomegaly, but some presented neither acholia nor choloria. Average age at clinical onset was 33.6 ± 24 days.

It was observed that a significant proportion of these patients (57.1%) had no perinatal history of any kind. Four patients (14.3%) had histories of neonatal sepsis (Table 2). Patient No. 3 had early neonatal sepsis, patient No. 19 and patient No. 20 had neonatal sepsis associated with parenteral nutrition, patient No. 21 had neonatal sepsis associated with intestinal atresia and anorectal malformations. The remaining five patients had various histories: Patient No. 9 has neonatal jaundice, patient No. 17 had necrotizing enterocolitis, patient No. 15 had congenital megacolon, patient No. 8 had neonatal hepatitis, and patient No. 14 had severe Rh alloimmunization, Down syndrome, duodenal atresia, thrombocytopenia, septic shock, and persistent ductus arteriosus.

Most frequently, direct bilirubin levels, were about 4 mg/dl although one patient, No. 13, had a level of 21 mg/dL (Table 2). The average direct bilirubin of all the patients was 7.2 ± 4.6 mg/dL. The liver profiles of all patients were altered as measured by transaminases and prothrombin time (PT). In addition, most patients had decreased hemoglobin and hematocrit.

Etiologies included thirteen cases associated with infectious causes, four cases of biliary atresia, three with idiopathic causes, and one patient with a biliary duct cysts (Figure 3). Significantly, the direct bilirubin level of 21 mg/dl was associated with toxoplasmosis and not biliary atresia. It was also noted that the leading infectious cause was neonatal sepsis which affected eight patients (62%). Four patients (31%) had cytomegalovirus infections, and one patient (8%) had toxoplasmosis.

Infants who were referred for transplantation were characterized by being full term babies who had perinatal histories, acholia, dark urine, increased AST and ALT levels, direct bilirubin from 4 to 16.6 mg/dL, and prolonged prothrombin times. Finally, it is noteworthy that 75% of patients in the group with atresia (Figure 4) were referred for transplantation compared while only 8% of the group whose conditions were due to infectious causes were referred for transplantation.

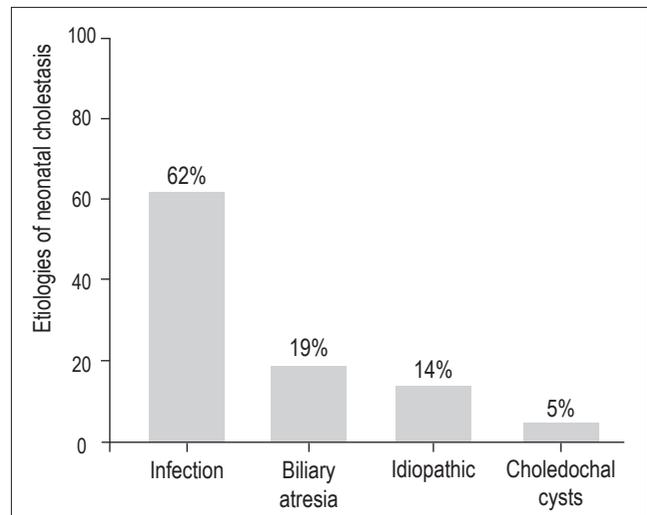


Figure 3. Distribution of newborns with neonatal cholestasis according to etiologies at the Hospital Infantil Napoleón Franco Pareja from 2010 to 2013

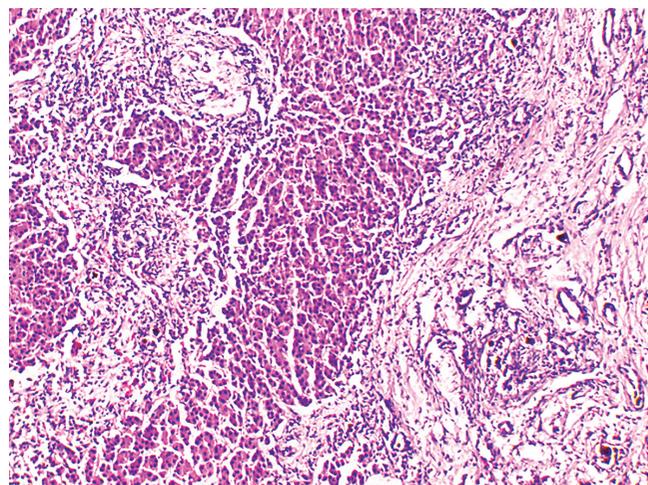


Figure 4. Liver biopsy from patient No. 1 showing biliary atresia. Cirrhosis secondary to fibrosing necroinflammatory disease of the bile ducts. Cuts show impaired histological architecture of the hepatic parenchyma in which there is a pattern of obstructive lesions, expansion of portal spaces, bile duct plugs, periportal fibrosis and bridges, enlarged sinusoidal spaces, lobular cholestasis and foci of extramedullary erythropoiesis. No granulomas, inclusions from microorganisms, giant cell transformations, or malignancies can be seen in this sample.

DISCUSSION

Worldwide, the incidence of cholestasis is very low but may vary by race and gender (23). In this study 21 patients with neonatal cholestasis were diagnosed over a period of three years. These data are representative of the newborn popu-

lation of the city of Cartagena since the children's hospital in this study is the largest in the area and it receives the largest number of pediatric referrals.

This study found no significant differences in genders, but the large majority of patients were term rather than premature. These data are similar to those in a study by Alvarez et al. in the William Soler Pediatric Hospital in Cuba (9), although a predominance of male patients with neonatal cholestasis was found in a retrospective study by Jacquemin et al. (24). In addition, most cases have no perinatal histories although those with antecedent symptoms and diagnoses including referrals for transplantation.

The results of this study demonstrate strong associations between some etiologies such as the neonatal sepsis and biliary atresia with this pathology. Our results show etiologies that are different than those in other studies in other parts of the world. For example, the main etiologies found in a study by Mendez et al. in Montevideo were hepatitis (16 patients) and atresia (13 patients) (25).

Infectious causes associated with cholestasis include cytomegalovirus, toxoplasmosis, rubella, syphilis, herpes, and bacterial sepsis (26-28). This information coincides with the result of this study. Congenital infections usually share clinical similarities including an enlarged liver and spleen, jaundice, pneumonitis and a tendency to prematurity or poor intrauterine growth (27). A clinical presentation of neonatal liver failure is possible with any of these agents, but in this study it was mostly evidenced with cytomegalovirus infections. It has been reported to be more common with herpes simplex infections.

Four patients (19% of total) with neonatal cholestasis associated with cytomegalovirus infections were found in this study. Cytomegalovirus (CMV) is the most common cause of congenital infections. They affect one to two percent of newborns most of whom are asymptomatic (27). Clinical findings include petechiae, hepatosplenomegaly and jaundice in 60% to 80% of patients. (27) Although the literature reports that it is unusual for CMV infections to cause neonatal liver failure, in this study a high proportion of patients were found with neonatal cholestasis associated with CMV.

Our finding of congenital toxoplasmosis in 5% of the patients in the study is a warning to others especially since our findings match those reported by other investigators (29, 30). A study in Brazil showed an incidence of toxoplasmosis in that country ranging from 2-20 per 10,000 births. That case study presented direct bilirubin of 35.6 mg/dl and concluded that toxoplasmosis is a disease with high morbidity which must be prevented by treatment while the patient is still alive (31).

Nevertheless, our study showed that in contrast to other reports in the literature, the most frequent etiologies encountered were those of infectious natures. Reports in the litera-

ture show that atresia of the bile ducts is the most frequent etiology (15, 18, 32), while in our population there are more cases of sepsis and CMV infections than cases of biliary atresia. This finding makes us think that the coincidence of this type of infectious etiology in cases of neonatal cholestasis is an important factor for further study in our population.

A study conducted in Medellín, Colombia coincides with our study in terms of the presence of clinical symptoms such as jaundice, dark urine, and acholia. Nevertheless, that study found atresia to be the cause in eighteen children (28%) which made it the most common cause there and which differs from the results obtained in our investigation (33).

Biliary atresia was the most common reason for pediatric liver transplantation in our study which is consistent with the literature. Nevertheless, may be other liver diseases that require transplantation (34). Up to 60% of patients with biliary atresia may require a transplant in the first 10 years of life, and even those who undergo surgery to restore bile flow may need a transplant in the second or third decade of life (18).

This study found one patient with a choledochal cyst. This type of cyst is related to a group of congenital malformations in the biliary system. The most common type is a fusiform, sometimes sausage-shaped, dilated extrahepatic bile duct. Choledochal cysts are increasingly being identified in the fetus by prenatal ultrasound and have even been found at 15 weeks of gestation (27). The diagnosis should be confirmed immediately after birth. Most of these children have conjugated hyperbilirubinemia, and surgery should be performed promptly.

Finally, the diagnostic evaluation of a newborn with cholestasis should be systematic, logical and cost-effective. A coordinated team of clinicians, surgeons, radiologists and biochemists can minimize unnecessary tests and achieve a correct diagnosis in the shortest possible period of time.

CONCLUSION

This case report indicates that the etiologic features of cholestasis reported in the literature are not accurate because there is more diversity in terms of classification. In some regions the most common cause may be biliary atresia, but elsewhere infectious causes may be more common as in this study. Diagnostic procedures for infants should include all necessary studies to determine the most prevalent cause and address treatment in the most successful way, taking into account gender, race, and geographic location.

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Conflict of interest

The authors declare that they have no conflicts of interest with respect to this research.

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