RESEARCH ARTICLE

PREVALENCIA Y CARACTERIZACIÓN CLÍNICA DE COLESTASIS NEONATAL EN UN HOSPITAL DE TERCER NIVEL DE ATENCIÓN EN UN PERÍODO DE 4 AÑOS.

PREVALENCE AND CLINICAL CHARACTERIZATION OF NEONATAL CHOLESTASIS IN A TERTIARY CARE HOSPITAL OVER A 4-YEAR PERIOD.

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Received: June 15, 2024. **Approved:** November 15, 2024

RESUMEN

Introducción: La colestasis neonatal se define como la disminución del flujo y/o excreción biliar que conlleva a la acumulación de sustancias que normalmente son excretadas por la bilis hacia el intestino. Desde el punto de vista bioquímico, se caracteriza por un nivel de bilirrubina directa en sangre > 1 mg/dl (17 µmol/L). La incidencia oscila entre 1 de cada 2500 recién nacidos a término. Las enfermedades que causan colestasis incluyen un gran número de etiologías las cuales varían desde desórdenes genéticos hasta patologías infecciosas. Un diagnóstico oportuno y el inicio del tratamiento para causas tratables de colestasis son cruciales para limitar el daño hepático progresivo y prevenir las lesiones en otros órganos. **Objetivo:** Establecer la prevalencia y las características clínicas de la colestasis neonatal en un hospital universitario de tercer nivel de atención en Cúcuta, Colombia. **Materiales y métodos**: Estudio observacional, retrospectivo y descriptivo. Se realizo la revisión total de seiscientas un historias clínicas de las cuales se incluyó 42 historias clínicas para nuestro estudio. A las variables cuantitativas se les calculo media y desviación estándar y a las cualitativas frecuencia y porcentajes. El análisis estadístico se realizó con Epi Info™ Versión 7.2. **Resultados**: El número de nacidos vivos en los 4 años fue de 25447, alcanzando una proporción de 4 casos por cada 2500 nacidos vivos, predominio el género masculino en el 69 %. Entre las etiologías las infecciosas en un 59.5%, nutrición parenteral y sin etiología especifica representado el 21.4%, causas

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obstructivas en el 16.7% y metabólicas en el 2.4%.**Conclusión**: En nuestro estudio identificamos que la etiología infecciosa representó la principal causa de colestasis así mismo como la exposición a antibióticos y exposición a nutrición parenteral.

PALABRAS CLAVE : colestasis neonatal, bilirrubina directa, hepatobiliar, nutrición parenteral.

ABSTRACT

Introduction: Neonatal cholestasis is defined as decreased bile flow and/or excretion leading to accumulation of substances that are normally excreted by bile into the intestine. Biochemically, it is characterized by a direct blood bilirubin level > 1 mg/dl (17 µmol/L). The incidence ranges from 1 to 2500 term newborns. Diseases causing cholestasis include a large number of etiologies ranging from genetic disorders to infectious pathologies. Timely diagnosis and initiation of treatment for treatable causes of cholestasis are crucial to limit progressive liver damage and prevent injury to other organs. **Objective:** To establish the prevalence and clinical characteristics of neonatal cholestasis in a tertiary care university hospital in Cúcuta, Colombia. **Materials and methods:** Observational, retrospective, and descriptive study. A total review of six hundred and one medical record was conducted, of which forty-two medical records were included in our study. Mean and standard deviation were calculated for quantitative variables and frequency and percentages for qualitative variables. Statistical analysis was performed with Epi Info™ Version 7.2. **Results:** The number of live births in the 4 years was 25447, reaching a proportion of four cases per 2500 live births, with a male predominance of 69%. Among the etiologies, infectious causes accounted for 59.5%, parenteral nutrition and without specific etiology represented 21.4%, obstructive causes 16.7% and metabolic causes 2.4%. **Conclusion:** In our study we identified that infectious etiology represented the main cause of cholestasis as well as exposure to antibiotics and exposure to parenteral nutrition.

KEY WORDS: neonatal cholestasis, direct bilirubin, hepatobiliary, parenteral nutrition.

INTRODUCCIÓN

Neonatal cholestasis is defined as an increase in serum bilirubin (>1 mg/dl) or more than 20% of total bilirubin when it exceeds (5 mg/dl); it occurs secondary to an alteration of bile flow, either intrahepatic or extrahepatic, as a consequence, bile acids increase causing clinical jaundice, dark urine, acholic stools, hepatomegaly, and pruritus within the first 4 weeks of life. This term refers to the period from birth to the first three months of life, and can represent up to 100 different types of pathologies or metabolic disorders (1–4).

According to epidemiological studies, the incidence ranges from 1 in 2500 (0.4%) live births per year, although this varies depending on the

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geographical area; in Spain, the incidence can reach up to 1 in 5000 live births, and in up to 30% of cases, other congenital abnormalities may be present. On the other hand, in India, neonatal cholestasis accounts for approximately 30% of hepatobiliary disorders, a fact that is directly related to genetic and environmental factors (5, 6).

Neonatal cholestasis includes a large number of etiologies, comprising infectious causes, anatomical abnormalities of the biliary system, endocrinopathies, genetic disorders, metabolic abnormalities, exposure to toxins and drugs (parenteral nutrition), cardiovascular dysfunction, and neoplastic processes (7,8). Among the most frequent causes are biliary atresia (25-40%); genetic and metabolic diseases such as α1-antitrypsin deficiency (A1AT) (10-20%), Alagille syndrome (2-14%), cystic fibrosis; progressive familial intrahepatic cholestasis, hypopituitarism (5%), idiopathic neonatal hepatitis (INH), transient neonatal cholestasis (TNC), and cholestasis associated with the administration of parenteral nutrition in premature infants and those with intestinal failure (9). Historically, neonatal cholestasis associated with INH and TNC represented the second most frequent cause of neonatal cholestasis (10). However, the discovery of many genetic causes of cholestasis that share the clinical and histological phenotype of INH/TNC has significantly reduced the number of neonates currently diagnosed with INH/TNC. Recently, heterozygous mutations in genes associated with bile transport (ATP8B1, ABCB11, and ABCB4) have been described in INH/TNC (11–13).

Infants with cholestasis usually present with generalized jaundice indistinguishable from that of infants with indirect hyperbilirubinemia; however, the presence of acholic stools, dark urine, or hepatomegaly should suggest cholestasis. We must emphasize that acholic stools signify biliary obstruction and should always be a reason for medical evaluation (14, 15). Among obstructive causes, biliary atresia represents a frequent cause of liver transplantation (LT) and has specific indications such as dysfunction of the Kasai portoenterostomy, malnutrition, recurrent cholangitis, and progressive manifestations of portal hypertension. Extrahepatic complications of this disease, such as hepatopulmonary syndrome and portopulmonary hypertension, are also indications for LT. The optimal treatment of these potentially fatal complications before transplantation and the optimization of nutritional status requires the experience of a multidisciplinary team (15).

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GENERAL OBJECTIVE

To establish the prevalence and clinical characteristics of neonatal cholestasis at the Erasmo Meoz University Hospital during the period from January 2019 to December 2022.

MATERIALS AND METHODS

Observational, retrospective, and descriptive study. Data were obtained by reviewing medical records of newborns and infants under 3 months of age during the period from January 1, 2019, to December 31, 2022, using a data collection instrument with information from digital medical records that included the analysis of 14 variables. Children were included according to CIE-10 diagnoses ((Q440, Q441, Q442, Q443, Q444, Q445, Q447, K710, K820, K828, K829, K835, K38, K839, P580, P581, P582, P583, P584, P585, P588, P589, P590, P592, P593, P598, P599) and medical records outside the specified time period, medical records that did not include newborns or infants under three months, and medical records without the aforementioned CIE-10 diagnoses were excluded. Mean and standard deviation were calculated for quantitative variables, and frequency and percentages for qualitative variables. Statistical analysis was performed with Epi Info™.

RESULTS

During the period from January 2019 to December 2022, a total of 601 medical records were reviewed, of which 42 medical records were included in our study.

Regarding the year of birth, 20.9% (9) were from 2019, 11.6% (5) were from 2020, 41.8% (18) were from 2021, and 23.6% (10) were from 2022. The number of live births in the 4 years was 25,447, corresponding to a prevalence of 4 cases per 2,500 live births (table 1).

Regarding maternal age, between 18 and 35 years old represented 51.2% (22) of the cases, 18.6% (8) of the cases were from mothers younger than 18 years, and 16.3% (7) of the cases were from mothers older than 35 years; in 13.9% (5) of the cases, this information was not found in the medical records.

With respect to parity, 55.8% (24) of the cases were products of multigravida mothers and 37.2% (16) of the cases were products of primigravida mothers; in 6.9% (2) of the medical records, this information was not found.

Adherence to prenatal controls showed that 30.3% (13) of mothers had between one and three prenatal controls, 25.5% (11) had no prenatal controls, 20.9% (9) had between 4 and 6 prenatal controls, 9.3% (4) had more

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than 7 prenatal controls, and 13.5% (5) of cases had no information.

The route of delivery by vaginal birth represented 62.8% (27) of cases, 32.5% (14) of cases were by cesarean section, and 4.6% (1) had missing data. in the medical records. With respect to fetal well-being, 25.8% (10) reported fetal distress, while 74.4% (32) did not present fetal distress.

Term gestational age represented 60.4% (26) of cases, less than 37 weeks (preterm) a total of 34.8% (15) of cases, and greater than 40 weeks (post-term) 4.65% (1).

The most frequently found weight for gestational age was adequate weight for gestational age with a total of 51.2% (21), low birth weight 44.2% (19), very low birth weight 2.3% (1), and extreme low birth weight 2.3% (1).

Regarding gender, 69% (29) of participants were male and 31% (13) were female; regarding gestational age, term was 59.5% (25), preterm 35.7% (15), and post-term 4.8% (2) (figure 1).

Among the identified etiologies of neonatal cholestasis, we have infectious causes in 59.5% (25) of cases, others including blood incompatibility, parenteral nutrition, and without specific etiology represented 21.4% (9) of cases. Obstructive etiologies (figure 2) such as biliary atresia and choledochal cyst were 16.7% (7), and finally metabolic etiologies such as inborn error of metabolism and familial intrahepatic cholestasis were 2.4% (1).

In the distribution of associated infectious etiologies, we identified syphilis in 52.4% (22), neonatal sepsis in 14.3% (6), cytomegalovirus in 2.4% (1), toxoplasmosis in 2.4% (1), and dengue in 2.4% (1), with 26.2% (11) having no associated infection. (Figure 3). 81% (34) had exposure to antibiotics (figure 4), 83.3% (35) had exposure to breast milk substitutes, and 35.7% (15) had exposure to parenteral nutrition (figure 5).

BIRTH YEAR	NUMBER OF LIVE BIRTHS	CHOLESTASIS CASES	PREVALENCE
2019	6997	9	0.13%
2020	6137	5	0.08%
2021	6765	18	0.26%
2022	5548	10	0.18%
TOTAL	25447	42	0.17%

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Table 1. Live births and relation to the number of cases.

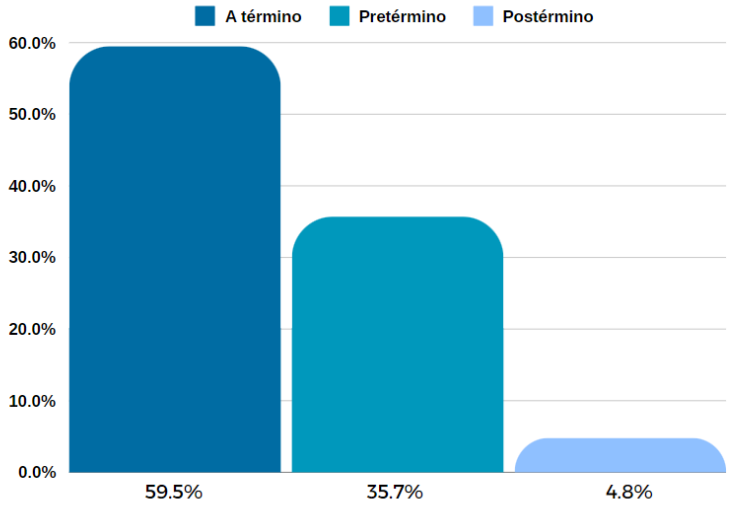

Figure 1. Distribution of gestational age.

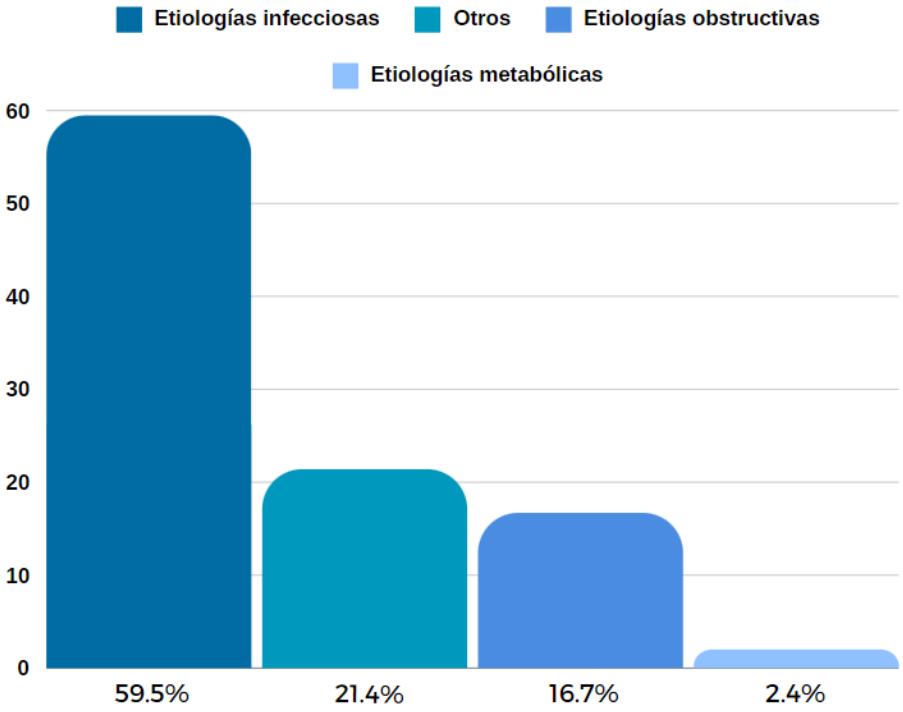

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Figure 2. Distribution by etiology group.

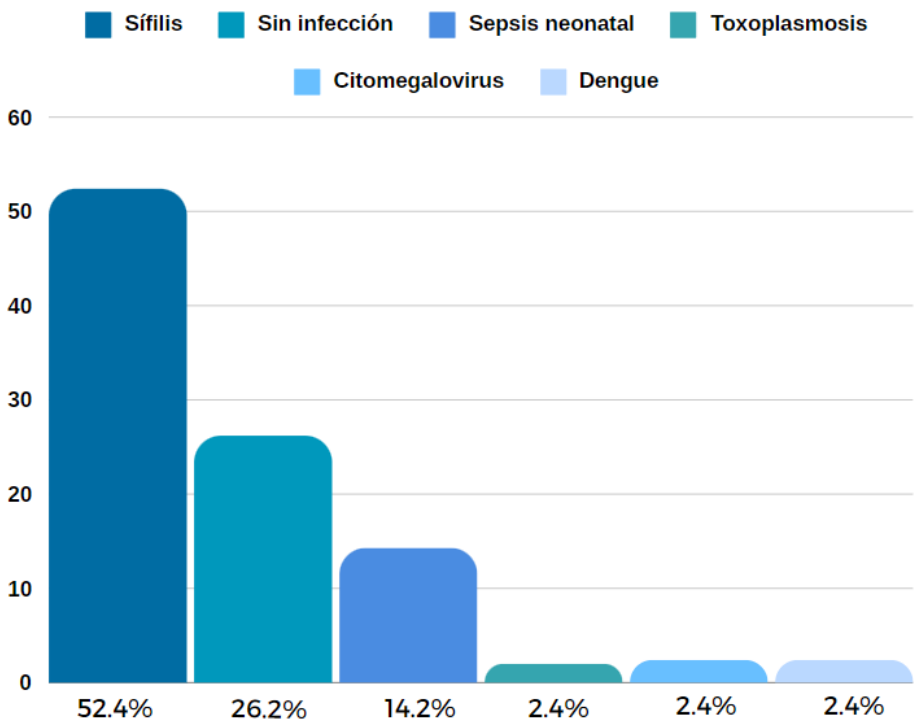

Figure 3. Infectious diseases.

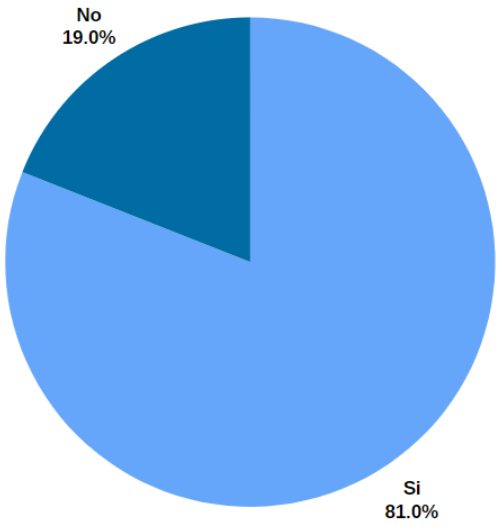

Figure 4. Distribution of antibiotic exposure.

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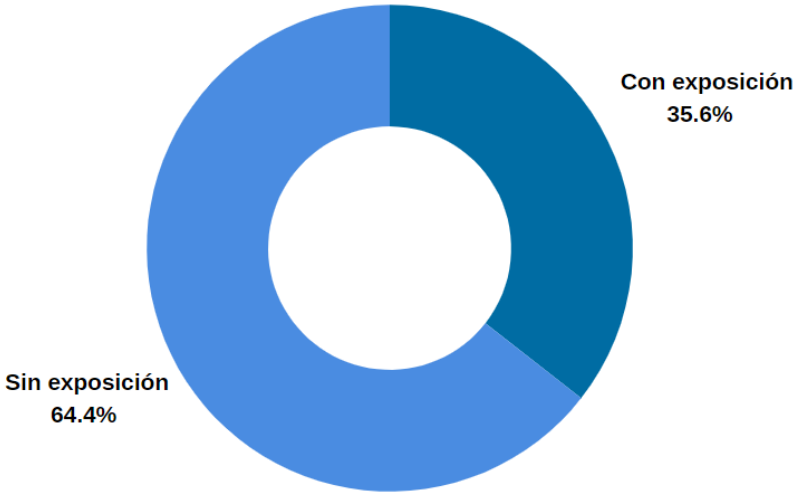

Figure 5. Exposure to parenteral nutrition.

DISCUSSION

As previously mentioned, neonatal cholestasis occurs due to the accumulation of biliary substances in blood and extrahepatic tissues, with elevated conjugated bilirubin levels as a consequence of a canalicular alteration of bile flow with variable etiology. The neonatal period represents the time of greatest susceptibility to deterioration of bile formation, because metabolic demands exceed the functional capacity of the first weeks of life (16). In this study, a total of 42 cases of neonatal cholestasis were found over a four-year period, with a proportion of 4 out of every 2500 live births, which is higher than the worldwide reported incidence of 1 in 2500 cases, probably associated with the fact that the Erasmo Meoz University Hospital serves a high-risk obstetric population associated with a large proportion of migrant population and represents a referral center in the department of Norte de Santander. Although gender is generally a 1:1 variable in a large number of studies, as is the case in the research conducted by Jorge Mendoza and collaborators at the Cartagena Hospital in Colombia, our results showed a higher number of male cases with 67.4%, which is similar to a retrospective study conducted by Jacquemin and collaborators (17, 18). Regarding fetal distress present in 25.8% of cases, gestational age less than 37 weeks in 34.8% of cases, and low birth weight in 44.2% of cases, These are risk factors that often coexist in cases of cholestasis, as evidenced in the study by Tufano and collaborators conducted in the neonatal ICU, in which they found these factors in 92.5% of cases (16). Carol Jean and collaborators conducted a review

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article in 2020 in which they concluded that merely having a preterm neonate is an indicator of liver dysfunction or a reduced ability to respond to the noxae that these patients will be exposed to while reaching adequate metabolic development (19).

Among the most frequently identified etiologies, we found infectious etiologies in 59.5% of cases, other undefined causes and etiologies in 21.4%, and to a lesser extent obstructive etiology at 16.7% and metabolic at 2.4%. These results vary according to those reported in more complex centers where the main causes are obstructive and metabolic (1, 20, 21).

The role of parenteral nutrition in neonatal cholestasis has been an identified risk factor in multiple studies conducted in intensive care, with a direct relationship to the duration in our study with a significant percentage of association (20, 22–25).

CONCLUSION

In our study, we found that infectious etiology was the most frequent cause of cholestasis, as well as exposure to antibiotics and parenteral nutrition, thus highlighting the importance of strengthening mother-child care with the aim of reducing the incidence of infectious pathologies from the TORCH group. However, we emphasize that biliary atresia is recognized as the most frequent treatable cause of neonatal cholestasis and as the main cause of pediatric liver transplantation worldwide.

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