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Relationship of diagnosis and treatment directed to the causes of Neonatal Cholestasis

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ABSTRACT

Objective: To identify the relationship between diagnosis and treatment directed to the causes of neonatal cholestasis. Methods: A search was carried out in February 2023, using the PubMed database, using the following syntax: cholestasis AND neonatal AND causes NOT (Review OR qualitative studies OR theoretical study). Results: From the search carried out, 59 articles were found, of which 52 were excluded by consensus of the authors. The reasons for this fact were: because they did not address cholestasis as the main object (X=40), because they were eminently theoretical articles (X=8) and because they did not present data regarding the causes of the variables that were the object of this study (X=4). After the methodological procedures described, the 07 articles were assiduously read and only 04 articles were selected for systematic review. Conclusion: Through the analysis of the data presented, the importance of early diagnosis of NC and identification of its etiology is shown, as some causes lead to the death of patients if not treated early.

Keywords: Cholestasis, Neonatal Cholestasis, Jaundice, Etiology.

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INTRODUCTION

Neonatal cholestasis (NC) is defined as decreased bile formation or flow due to hepatobiliary dysfunction or obstructive cholangiopathy in the neonatal period. Screening for NC is by identifying bilirubin (BD) and elevated direct (or conjugated) bile acids. It occurs in about 1 in 2,500 full-term newborns. (CHOI HJ, et al., 2022). For Cochran WJ (2021), the management of neonatal cholestasis requires caution, as its etiology can be determined by laboratory tests, hepatobiliary imaging, and sometimes liver biopsy and surgery. Treatment depends on the cause.

NC is never physiological, but a sign of hepatobiliary and/or metabolic disorders, some of which can be fatal if not detected and treated promptly. Prompt evaluation is essential to identify a treatable cause and provide an accurate prognosis (WANG H et al., 2022).

It usually presents with jaundice, clay-colored stools, pruritus, dark urine, hepatosplenomegaly, developmental delay, and, in some cases, congenital malformations such as polysplenia/asplenia, congenital heart disease, bowel malrotation, and skeletal anomalies (BILAL H, et al., 2022).

According to Lane E and Murray KF (2017), the most common identifiable etiologies are biliary atresia (BA) (25–35%), hereditary intrahepatic cholestasis (25%), and metabolic disease (20%), with other risk factors including small gestational age (SGA), alloimmune hemolytic disease, neonatal history of surgery, and any neonatal adverse events (asphyxia, sepsis, total parenteral nutrition).

Jaundice becomes clinically apparent when serum bilirubin concentrations exceed 2 to 3 mg/dL in older children and 5 mg/dL in neonates. Cholestatic jaundice is characterized by direct hyperbilirubinemia - direct bilirubin > 20% of total bilirubin (or > 1 mg/dL, if total bilirubin < 5 mg/dL) (FISCHER HS, et al., 2020).

According to the studies of Fawaz R, et al. (2017), biochemically, it is characterized by elevated serum levels of direct bilirubin, transaminases, and alkaline phosphatase. Gamma-glutamyl transpeptidase (GGT) is usually high, but it can be normal or low. Liver biopsy plays a key role in diagnosing various etiologies of NC. Common histological findings on liver biopsy are bile duct hyperplasia, bile duct embolism, and periportal edema with intact lobular architecture in biliary atresia. Idiopathic neonatal hepatitis presents with giant cells, mixed inflammatory infiltrates, and lobular lesions, PFIC presents intrabiliary cholestasis, and Alagille syndrome presents features of bile duct dispersion. Early diagnosis and timely management generally reduce mortality and morbidity in the long term (AMATO MD, et al., 2016).

The diagnosis of cholestasis by the detection of hyperbilirubinemia in newborns (NB) who develop jaundice after 14 days of life is a milestone that can change the prognosis of several diseases caused by CN (Melo A, et al., 2018).

The objective of this study was to identify the relationship between diagnosis and treatment directed to the causes of neonatal cholestasis. The research was systematically organized based on a theoretical framework designed to synthesize several published studies to advance the understanding of the topic presented.

Thus, the relevance of the present study aims to advance knowledge based on the diagnosis and effective treatment of the causes of neonatal cholestasis and its relationship in the population to a certain extent.

METHODS

To achieve this goal, it was decided to conduct a systematic review to describe and synthesize the available evidence on this topic and research questions in the literature using retrospective studies.

The inclusion criteria for these studies were: (a) original and quantitative articles (therefore, editorials, letters to the editor, theoretical articles, case studies, and qualitative studies were excluded); (b) the research was based on causes of neonatal cholestasis; (c) is complete and available free of charge; (d) is published between 2022 and 2023 and in English.

Regarding the search strategy, a search was carried out in February 2023, using the PubMed database, using the following syntax: cholestasis AND neonatal AND causes NOT (Review OR qualitative studies OR theoretical study).

From the search carried out, 59 articles were found, of which 52 were excluded by consensus of the authors. The reasons for this fact were: because they did not address cholestasis as the main object (X=40), because they were eminently theoretical articles (X=8) and because they did not present data regarding the causes of the variables that were the object of this study (X=4). After the methodological procedures described, the 07 articles were assiduously read and only 04 articles were selected for systematic review.

RESULTS

Chart 1 presents the results of a systematic review of four articles selected to better present the data and answer the central question. The articles will be presented in chronological order.

1. In 2022, authors Huanhuan Wang, Lin Yang, Jin Wang, aimed to investigate the etiological diagnosis for newborns with cholestasis during the neonatal period after emerging molecular tests comprehensively. The most commonly identifiable etiologies in the article were: biliary atresia (BA) (25–35%), genetic intrahepatic cholestasis (25%), and metabolic diseases (20%), other risk factors include small gestational age (SGA), neonatal surgery, alloimmune hemolytic disease, and a history of some neonatal harmful

event (asphyxia, sepsis, and total parenteral nutrition). It is concluded that the causes of cholestasis in neonates are complicated, molecular diagnosis can improve the etiological diagnosis for newborns with cholestasis. But even so, a large number of causes are remediable and transient during the neonatal period, genetic testing can help rule out genetic causes and increase confidence in judging the prognosis.

2. Researchers Ho Jung Choi, Inki Kim, Hye-Jin Lee, Hyun Ju Oh, Mi Kyoung Ahn, Woo Im Baek, Yeong Eun Kim, SeakHee Oh, Byong Sop Lee, Jung-Man Namgoong, Dae Yeon Kim, (2022), investigated the etiology and outcome of neonatal cholestasis in a tertiary hospital, developing an NCM prediction model for these patients. Management of neonatal cholestasis requires caution because its causes are known to be biliary atresia (BA) and monogenic liver disease in approximately 25–40% and 25% of cases, respectively. It was concluded that several etiologies of neonatal cholestasis were identified in a tertiary hospital, resulting in unfavorable results of great proportion.

3. According to the study by authors Hazrat Bilal, Muhammad Irshad, Nagina Shahzadi, Hashmi Souls, and Hashmat Ullah (2022). The objective of this study was to determine the frequency of clinical presentation and laboratory profile in the diagnosis of the etiological spectrum of neonatal cholestasis. The most common causes of neonatal cholestasis are biliary atresia and idiopathic neonatal hepatitis. Other causes can be attributed to infections such as sepsis, urinary tract infection, TORCH (toxoplasmosis, rubella virus, cytomegalovirus, herpes simplex virus, and HIV), metabolic disorders such as galactosemia, tyrosinemia, hereditary fructose intolerance, and progressive familial intrahepatic cholestasis (PFIC), and endocrine diseases. Common causes of neonatal cholestasis in this study are galactosemia, idiopathic hepatitis, and biliary atresia.

4. As for the study by Xiufang Yang, Guosheng Liu and Bing Yi (2022). The aim of this study was to investigate the relationship between PNAC and *Mdr3* through the detection of Mdr3 gene mutations and *Mdr3 P-gp* expression in hepatocytes. PNAC can cause irreversible liver damage, liver cirrhosis, liver failure, and even death. The results of this research show that these four mutations of the *Mdr3* gene may be closely related to the development of PNAC.

Table 1. Main results of the included studies

Authors	Country	Objectives	Causes

WANG H et al.	China	To investigate the etiological diagnosis for newborns with cholestasis during the neonatal period after emerging molecular tests.	Biliary atresia, genetic intrahepatic cholestasis, metabolic diseases, small gestational age (SGA), neonatal surgery, alloimmune hemolytic disease and asphyxia, sepsis, and total parenteral nutrition.
CHOI HJ, et al.	South Korea	They investigated the etiology and outcome of neonatal cholestasis in a tertiary hospital, developing a model to predict NCM for these patients.	Biliary atresia (BA) and monogenic liver disease in approximately 25–40% and 25% of cases.
BILAL H, et al.	Pakistan	To determine the frequency of clinical presentation and laboratory profile in the diagnosis of the etiological spectrum of neonatal cholestasis.	Common causes of neonatal cholestasis in this study are galactosemia, idiopathic hepatitis, and biliary atresia.
YANG X, et al.	China	To investigate the relationship between PNAC and *Mdr3* through the detection of Mdr3 gene mutations and *Mdr3 P-gp expression* in hepatocytes.	It has been shown that these four mutations of the *Mdr3* gene may be closely related to the development of PNAC.

Source: Prepared by the authors

DISCUSSION

In cholestasis, the main failure is the excretion of bilirubin, resulting in excess conjugated bilirubin in the blood and decreased bile salts in the gastrointestinal tract. Malabsorption of fats and fat-soluble vitamins (A, D, E, and K) due to insufficient bile in the gastrointestinal tract leads to vitamin deficiencies, nutritional deficiencies, and poor growth (YANG X, et al., 2022).

Cholestasis (jaundice) can be a result of intrahepatic or extrahepatic dysfunction, although some conditions may overlap. The most common extrahepatic disease is biliary atresia (BA) (CHOI HJ, et al., 2022).

Second Harpavat S, et al. (2020), BA is an obstruction of the biliary system caused by progressive sclerosis of the extrahepatic bile ducts. In most cases, BA develops in the first few weeks of life, possibly after inflammation and scarring of the extrahepatic (and sometimes intrahepatic) bile ducts. It rarely occurs in premature babies or newborns at birth. The cause of the inflammatory response is unknown, but several infectious organisms have been implicated, including reovirus type 3 and cytomegalovirus.

Regarding the study by Fabris L, et al. (2019), cholangiocytes rarely present as neonatal cholestasis; these cysts are more common in patients with autosomal recessive polycystic kidney disease. Large bile duct syndrome can also be a cause of extrahepatic neonatal cholestasis and is more common in infants with cystic fibrosis.

Intrahepatic causes can be infectious, alloimmune, metabolic/genetic, or toxic. Infection can cause cholestasis. Infections can be viral (herpes simplex virus, cytomegalovirus, rubella), bacterial (gram-positive and gram-negative bacteria, urinary tract infection due to E. coli), or parasitic (toxoplasmosis). Neonatal sepsis receiving parenteral nutrition can also cause cholestasis (WANG NL, et al., 2020).

As corroborated by Feldman AG, Sokol RJ. (2019), alloimmune liver disease of pregnancy involves the passage of maternal IgG antibodies through the placenta, inducing complement-mediated membrane-attacking complexes to damage the fetal liver. Among the metabolic causes, there are many inborn errors of metabolism, such as galactosemia, tyrosinemia, alpha-1-antitrypsin deficiency, lipid metabolism disorders, bile acid deficiencies, mitochondrial diseases, and fatty acid oxidation deficiencies. Other genetic defects include Alagille syndrome, cystic fibrosis, and arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome. There are also genetic mutations that interfere with the normal production and excretion of bile; the resulting diseases are called familial progressive intrahepatic cholestasis.

For Wang NL, et al. (2020), the cause of poisoning is mainly due to the long-term use of parenteral nutrition in extremely premature newborns or newborns with short bowel syndrome. Idiopathic neonatal hepatitis syndrome (giant cell hepatitis) is an inflammatory liver disease in newborns. Its incidence has decreased and is becoming less common, as better diagnostic research has made it possible to identify the specific cause of cholestasis.

DIAGNOSIS OF NEONATAL CHOLESTASIS

Neonates have immaturity of the mechanisms related to bile production, especially in the metabolism of bile acids. For this reason, diseases that do not cause cholestasis in adults can also cause it in children, such as urinary tract infections. Thus, in the neonatal period, the differential diagnosis of cholestasis is broad and includes disorders with different prognoses (QUEIROZ TCN, et al., 2013).

Harpavat S, et al. (2020) reported that about 70% to 80% of childhood cholestasis is caused by idiopathic neonatal hepatitis and biliary atresia. Clinically, the manifestations of idiopathic neonatal hepatitis are similar to those of BA. However, while the first patients are usually male, small for gestational age, and with growth defects, the latter are predominantly female and have

better nutritional status. The clinical manifestations of extrahepatic obstructive disease are indistinguishable from BA, with choledochal cysts being the most common example.

According to the studies by Hertel PM, et al. (2021), Any child with jaundice should be evaluated for cholestasis after the second week of life and bilirubin levels measured fully and directly. Some experts argue that babies who receive exclusive breastfeeding with jaundice only need to be evaluated after 3 weeks of age. The initial approach should aim to diagnose treatable diseases (e.g., extrahepatic biliary atresia, where early surgical intervention improves short-term outcomes).

Cholestasis is recognized by the elevation of total and direct bilirubin. The tests needed to better assess liver function are serum albumin, prothrombin time/partial thromboplastin time (PT/PTT), liver enzymes, bilirubin fraction, and ammonia (these cholestasis). Once cholestasis is confirmed, determine its etiology (diagnostic evaluation of neonatal cholestasis) and evidence of malabsorption (low levels of fat-soluble vitamins A, D, E, and K or prolonged PT indicating low vitamin K levels) (BIL H, et al., 2022).

Abdominal ultrasound is usually the first test; It is non-invasive and can assess the size of the liver and certain abnormalities in the gallbladder and common bile duct. However, it is not specific. Hepatobiliary mapping should also be performed using iminodiacetic hydroxy acid (HIDA scintigraphy); intestinal excretion of contrast medium excludes BA, but BA and severe neonatal hepatitis and other causes of cholestasis may lead to insufficient excretion. Infants with cholestasis are usually given phenobarbital for 5 days prior to the HIDA scan in an attempt to increase excretion (RASHED YK, et al., 2013).

According to the studies of Boskovic A, et al. (2014), when a diagnosis is not made, liver biopsy and sometimes surgical cholangiography are usually done early. Patients with BA often present with dilation of the portal veins, bile duct hyperplasia, and increased fibrosis. Neonatal hepatitis is characterized by lobular development with multinucleated giant cells. Alloimmune liver disease registers high iron deposits in the liver.

TREATMENT OF NEONATAL CHOLESTASIS

Specific treatment is targeted with the cause. If there is no specific therapy, supportive therapy and nutritional therapy, including supplementation of vitamins A, D, E, and K, should be prioritized. For infants who use formula milk, formula should contain chain triglycerides, because absorption is better when bile salts are deficient. Caloric intake should be adequate and infants may require >130 calories/kg/day. In infants with bile discharge, ursodeoxycholic acid at a dose of 10 to 15 mg/kg once or twice daily may relieve pruritus (BILAL H, et al., 2022).

For Harpavat S, et al. (2020), infants with suspected BA require surgical exploration with intraoperative cholangiography. If BA is confirmed, a portoenterostomy (Kasai technique) should be

performed. Ideally, this procedure should be done in the first 1 or 2 months of life. After this period, the short-term prognosis deteriorated significantly. After surgery, many patients develop significant chronic problems, including persistent cholestasis, recurrent ascending cholangitis, and poor weight gain. Prophylactic antibiotics (trimethoprim/sulfamethoxazole) are usually prescribed one year after surgery to prevent ascending cholangitis. Despite optimal treatment, most children develop cirrhosis and require liver transplantation.

As there are no established markers and/or tests for alloimmune liver disease in pregnancy, treatment with IV immunoglobulin (IVIg) or exchange transfusion should be performed early to reverse ongoing liver injury, given that no definitive diagnosis has been made (FISCHER HS, et al., 2020).

Stool color grading card, with different color numbers, which parents choose according to their child's stool up to one month of age, is a simple and efficient method for screening for AB. This method was started in the 90s in Japan. It has been used in Taiwan since 2002 and has been perfected and spread throughout the country since 2004 and the results have been motivating. The child's health booklet, distributed by the Ministry of Health to all parents of Brazilian newborns, has a colored card with the color grading of the stool for parents to compare with the feces of their children, in order to make them aware that when they are clay-colored, whitish, it is abnormal and they should seek medical help as soon as the abnormal color is identified - it is expected that in the initial phase of the disease (LIEN TH, et al., 2011).

Yellow Alert is a campaign by the Brazilian Academy of Pediatrics and the Pediatric Hepatology Research Group (GEHPed) to guide parents and doctors on the need for early recognition of liver diseases in newborns and infants, the Yellow Alert booklet, in addition to general information also, provides a colored card with stool color classification, a tool to help parents and clinicians identify faecal hypobiliary or insufficient bile (MELO A, et al., 2018).

Evaluation of the color of the stool and urine is part of the examination of a baby with jaundice. Fecal acholia and choluria are indications of a cholestatic process that requires medical evaluation and measurement of serum bilirubin (VAZ MA et al., 2018). Disseminating the importance of analyzing stool color, whether through campaigns such as the yellow alert or by color scale, is essential not only for parents, but also for health professionals (LIEN TH, et al., 2011).

The biggest challenge for the physician is to distinguish between intrahepatic and extrahepatic cholestasis in the newborn, and success in this initial distinction by several different investigation methods allows the physician to focus their research on the possible etiology of the condition (MELO A, et al., 2018).

CONCLUSION

Late referral of patients with suspected NC is one of the main factors for the failure of surgical correction. Therefore, it is a general guideline to measure bilirubin in every newborn who remains jaundiced two weeks after birth, with the goal of promptly diagnosing the cause of cholestasis and, more importantly, initiating treatment. Through the analysis of the data presented, the importance of early diagnosis of NC and identification of its etiology is shown, as some causes lead to the death of patients if not treated early. In addition, the importance of further research on NC is recognized, as few recent publications on this topic are specific to each etiology of the disease.

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