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Review Article

Neonatal Cholestasis: Definition, Clinical Manifestations and Management; A Mini Review

Shirin Mohammadi[1], Shiva Mohammadi[2*], Maliheh Kadivar[3]

[1] Division of Neonatology, Department of Pediatrics, Shohadaye Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2] Hepatology and Nutrition Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3] Division of Neonatology, Department of Pediatrics, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

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Abstract

Physiological jaundice of the newborn is a complex benign disease that rarely persists in the second week of life. Neonatal cholestasis (NC) is caused by a disorder in the formation of bile by liver cells or obstruction of the flow of bile through the intrahepatic or extrahepatic biliary tree, which leads to the accumulation of bile substances in the liver, blood, and extrahepatic tissues. This state may continue until the first six months of infancy, and its vulnerability to other cholestatic agents increases. This fact makes NC an uncommon feature of neonatal liver disease rather than a late manifestation. The aim of this paper is to review the definitions, etiologies, clinical manifestations, treatment, and management strategies for NC infants.

Keywords: Bile Metabolism Disorders; Infant Liver Disease; Neonatal Cholestasis; Physiological Jaundice

***Corresponding Author:** Shiva Mohammadi, MD
Hepatology and Nutrition Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran
E-mail: dr.shv.mohamadi.ped@gmail.com

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Introduction

Physiologically, cholestasis is defined as stopping or reducing the flow of bile in the bile canaliculi, which is mainly caused by an increase in serum conjugated bilirubin to more than 2mg/dl or an increase in conjugated bilirubin to more than 20% of total bilirubin. Unlike unconjugated hyperbilirubinemia, which may be physiological and normal in the first two weeks of birth, the increase of conjugated bilirubin is always pathological and abnormal.(1-3). Neonatal cholestasis (NC) determined by conjugated hyperbilirubinemia is never benign and indicates a severe underlying disease.(4, 5). Cholestasis is never physiologic and should always prompt immediate evaluation to determine the specific cause. Certain causes, including galactosemia, tyrosinemia, choledochal cysts, bacterial and viral sepsis, and biliary atresia (BA), are amenable to medical or surgical interventions that may prevent progression to

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liver failure or the development of serious extrahepatic diseases.(6-8).

Conjugated hyperbilirubinemia in infancy always needs to be evaluated, and the type of bilirubin should be determined for every infant with prolonged jaundice. The main goal of evaluating cholestasis in infancy is to distinguish internal and external liver disorders(3, 9).

Extrahepatic biliary obstruction should be differentiated from intrahepatic disorders for intervention such as surgery or appropriate supportive treatment. In various studies conducted on cholestasis in the early months of life, extrahepatic biliary atresia and neonatal idiopathic hepatitis have been assigned the most common causes(9, 10). Since there are common features between cholestasis with intrahepatic and extrahepatic etiology, and on the other hand, the separation of these causes usually leads to the adoption of two different treatment processes, early diagnosis of etiology can be effective in the patient's prognosis. Despite data suggesting that early detection of cholestasis and its causes is potentially life-saving, delayed diagnosis remains a problem(11). Premature discharge of infants from the hospital, inadequate follow-up of persistent jaundice, false assurance of the appearance of pigmented stools, fluctuating serum bilirubin levels, and misdiagnosis of jaundice associated with human milk have all been cited as reasons for late referral for evaluation of cholestasis(6, 11). The purpose of this article is to review the causes, diagnosis, and management strategies for neonatal cholestasis.

Definition

Cholestasis is defined as a biliary excretion disorder that can be caused by defects in intrahepatic bile production, transmembrane bile transport, or mechanical obstruction to bile flow. The biochemical characteristics of cholestasis reflect the retention of bile components in the serum, such as bilirubin, bile acids, and/or cholesterol. (3, 12). The severity and pattern of each of these abnormalities are different from the underlying disorder. Increased conjugated bilirubin is the overcoming feature in most reasons for neonatal cholestasis.(13).

Neonatal cholestasis: The term " Neonatal cholestasis" is often used to refer to cholestatic liver disease that is present at birth and/or develops within the first few months of life rather than specifically referring to the neonatal period (14). Neonatal cholestasis occurs in 2.4% to 15% of newborns.(15). The overall incidence of NC is estimated to be approximately 1 in 2,500 live births.(15, 16).

Etiology

Cholestasis may be caused by extrahepatic or intrahepatic disorders, although some conditions overlap. The most prevalent extrahepatic disorder is Biliary atresia (BA)(17-19).

Biliary atresia is obstruction of the biliary tree due to progressive sclerosis of the extrahepatic bile duct. In most cases, biliary atresia appears several weeks after birth, possibly after inflammation and ulceration of the extrahepatic (and sometimes intrahepatic) bile ducts. It is rarely present in premature infants or in infants at birth. The cause of the inflammatory response is unknown, but several infectious organisms have been implicated, including reovirus type 3 and cytomegalovirus. (20, 21).

Biliary cysts: rarely manifest as neonatal cholestasis; these cysts are more common among patients with autosomal recessive polycystic kidney disease(22). Inspissated bile duct syndrome can also be a cause of extrahepatic neonatal cholestasis and is more common among infants with cystic fibrosis.(4, 23). Intrahepatic causes can be infectious, alloimmune, metabolic/genetic, or toxic. Infections can cause cholestasis. Infections may be viral, bacterial, or parasitic. Sepsis in neonates receiving parental nutrition can also cause cholestasis.(24).

The gestational alloimmune liver disease involves the transplacental passage of maternal IgG that induces a complement-mediated membrane attack complex that injures the fetal liver.(25).

Prompt identification of infants with medically treatable forms of cholestasis as well as causes amenable to surgical intervention is critical.(26). Metabolic causes include numerous inborn errors of metabolism, such as galactosemia, tyrosinemia, alpha-1 antitrypsin deficiency, disorders of lipid metabolism, bile acid defects, mitochondrial disorders, and fatty acid oxidation defects.(17). Toxic causes are due mainly to the use of prolonged parenteral nutrition in extremely preterm neonates or infants with short bowel syndrome.

Newer generations of lipid emulsions in parenteral nutrition appear to have decreased the risk of cholestasis.(27). Idiopathic neonatal hepatitis syndrome (giant cell hepatitis) is an inflammatory condition of the neonatal liver. Its incidence has decreased, and it is becoming rare because improved diagnostic studies allow the identification of specific causes of cholestasis.(28, 29).

Clinical manifestations

Infants may have immature bile acid excretion, leading to cholestasis.(30). This state may continue until the first 6 months of infancy, and its vulnerability to other cholestatic agents increases. This fact makes NC an uncommon feature of neonatal liver disease rather than a late presentation. (31, 32). NC is suspected when jaundice is prolonged and requires further workup for cholestasis.(33). Patients' complaints are usually related to fat-soluble vitamin deficiency, i.e., prolonged prothrombin time. (34). Common findings in neonates with cholestasis are long-term jaundice, dark yellow urine, hysterics sclera, hepatomegaly, and acholic stools(15, 27).

It is likely that jaundice subsides in the first few weeks after birth, as the indirect bilirubin component decreases, giving false reassurance that jaundice is resolving and no further examination is needed. One of the items that can be evaluated in an NC is acholic stool. Neurological abnormalities such as irritability, hypotonia, seizures, lethargy, and poor nutrition can indicate sepsis, intracranial hemorrhage, mitochondrial disorders, metabolic disorders, or severe liver dysfunction that leads to hyperammonemia and encephalopathy(35, 36). However, 20% of biliary atresia (BA) patients will have other extrahepatic congenital anomalies, such as cardiac malformations, intestinal malrotation, malrotation of the gut, and polysplenia or asplenia, and midline liver; most patients with BA appear well within the first month after birth.(37).

Diagnostic methods

In cases of prolonged neonatal jaundice, the fractionated bilirubin needs to be determined as a first step. A conjugated bilirubin of more than 1 mg/dL in combination with a total bilirubin of <5.0 mg/dL or a conjugated bilirubin fraction of >20% of the total, if total bilirubin is >5.0 mg/dL, indicates NC. A parenteral report of depigmented feces suggests an extrahepatic obstructive process. For clarification, the stool should be seen by a physician in any case.(2, 38).

First of all, conditions or complications that require immediate treatment should be detected. Therefore, a series of basic blood tests need to be performed. Further important initial steps are a fasting ultrasonography, a liver biopsy, and a hepatobiliary scintigraphy. If these tests are inconclusive, then the next step is to undertake an intraoperative cholangiogram or ERCP. In some cases, the liver biopsy may need to be repeated 3–4 months after birth because several of the diseases follow a dynamic course.(3, 39). In patients with advanced disease, insufficient hepatic synthetic function, and hypovitaminosis, a vitamin K-dependent bleeding disorder may occur. Therefore, an oral supplementation with vitamin K (1 mg/day), vitamin A (1500 U/kg/day), vitamin D (cholecalciferol; 500 U/kg/day), and vitamin E (50 U/kg/day) should be initiated immediately(40).

Biochemical testing for Neonatal cholestasis

The current approach to evaluating an infant with cholestasis focuses on early exclusion of BA, looking for "red flags" that suggest a specific cause, and searching for other treatable conditions(41, 42). If this evaluation is not helpful, special tests are done for less common and rarer conditions. Initial evaluation should include serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), and albumin, although these rarely differentiate between causes (28, 32, 42).

Management

The first goal in the management of infants with cholestasis is to identify diseases that are subject to specific medical treatment or primary surgical intervention(28, 41, 43).

General medical management

Most children with NC are malnourished. To prevent and treat malnutrition associated with steatorrhea and malabsorption, adequate caloric

intake is required. Affected patients should receive 125% of the recommended dietary allowance based on ideal body weigh(4, 44). In non-breast-feeding, a mixture of puffed rice powder and medium chain triglycerides (MCT) in the milk can thicken the food. Essential fatty acids should provide 2 to 3% of energy. 2 to 3 grams of vegetable protein per kilogram per day is recommended. 1,25-dihydroxyvitamin D3 (0.05-0.2 µg/kg/day) is suggested in the presence of considerable bone changes or patients with severe cholestasis(29, 45, 46).

Specific treatment

Formulated milk and infant diets are recommended for children with special diagnoses. Nitisinone treatment, in addition to food restriction, leads to a rapid reduction of toxic metabolites in tyrosinemia. In infants with pruritus due to severe cholestasis,

ursodeoxycholic acid (UDCA) (20 mg/kg/d), rifampicin (5–10 mg/kg/d), and phenobarbitone (5–10 mg/kg/d) are drugs of choice. The kasai's procedure involves resection of atretic extrahepatic tissue and Roux-en-Y jejunal loop anastomosis to the hepatic umbilicus. If done before the end of the third month, the bilirubin of patients after Kasai portoenterostomy (KPE) will normalize(47-49).

Liver transplantation

Liver transplantation is the treatment of choice for decompensated cirrhosis of any cause and is now well established. Any infant who fails KPE is referred for transplantation(43, 50).

Conclusion

A variety of disorders can appear with cholestasis during the neonatal period. In preterm infants with cholestasis, it may be challenging to discover the exact cause of cholestasis, which is likely to be multifactorial. In all cases of neonatal jaundice lasting more than 14 days, measurement of fractionated bilirubin should be performed. BA is the most prevalent entity leading to NC. It must be differentiated from other causes of cholestasis promptly because early surgical intervention before 2 months of age results in a better patient consequence.

Conflict of interests

There is no conflict of interests.

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