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Emergencies in neonatal management: jaundice and biliary atresia

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Rapid progress in recent years has brought significant advances in our understanding of neonatal hepatobiliary pathophysiology and of the phenomenon of neonatal transitory cholestasis caused by the immaturity in the mechanisms of hepatic bile secretion.

During the newborn period, cholestatic liver diseases characteristically present with the clinical sign of jaundice, due to elevated levels of bilirubin in the blood, namely the indirect or unconjugated bilirubin and the direct or conjugated bilirubin.

The presence of even trace levels of conjugated bilirubin should always trigger an evaluation for neonatal cholestasis, which has an estimated incidence of 1:2.500.

Depending on the underlying cause and of the severity of the cholestatic liver disease, isolated jaundice is often the initial and only clinical sign on physical exam, while signs of liver failure and portal hypertension are indicative of the most advanced stages of cholestatic liver diseases also in the newborns.[1]

When jaundice is the only clinical sign of neonatal cholestasis, delays in making the correct diagnosis are still, unfortunately, quite common especially if only the total bilirubin level is measured. A delay of weeks or months might have significant impact on the outcome, with both short and longer term consequences.[2]

A common reason for a delay in performing the necessary testing and making the correct diagnosis is neonatal age, which is a period in life commonly characterized by the presence of jaundice due to normal physiologic causes and breast feeding, resulting in transiently elevated unconjugated bilirubin levels which are typically self-limited and benign.[1,2] More rarely, neonatal jaundice is simply due to immaturity in the hepatic mechanisms of bile secretion, a transitory and benign condition characterized by a mixed hyperbilirubinemia with mildly elevated serum hepatic transaminases that spontaneously resolve within a few weeks of life.

Unfortunately, these common and benign conditions contributing to jaundices in the neonatal period can mask and delay the proper diagnosis of hyperbilirubinemia due to more rare, but severe and often dramatically progressive cholestasis due to other liver diseases.

Another key aspect to consider in the differential diagnosis of jaundice is the timing of appearance and duration of physical findings. Physiologic jaundice typically begins after the 2nd day of life and lasts no more than 2weeks in full term newborns and 3weeks in preterm infants. Any jaundice that continues beyond the expected physiologic time, must be quickly investigated by examining blood levels of both bilirubin fractions, unconjugated and conjugated.

Maternal "breast milk jaundice" probably represents the most common diagnosis beyond the time of physiologic jaundice.[1–3] It is due to elevated indirect or unconjugated bilirubinemia as the only abnormal blood test and it can last through the 4thmonth of life. For this reason, maternal breast milk jaundice often causes delayed or missed diagnosis of the rarer conditions of hepatic cholestasis in these few affected infants.[2]

Progressive and gradual reduction of total bilirubin serum levels due to resolving maternal breast milk jaundice, might easily give false reassurance of improvement while potentially masking a subtly slow, but progressive increment of direct bilirubin elevation, seen due to hepatic cholestatic jaundice.[2] As such, it is always important to be sure to rule out other possible underlying causes for neonatal jaundice, keeping in mind that early recognition allows prompt and adequate intervention, assuring a much better prognosis for the affected infants.

Prolonged neonatal jaundice affects upwards to 15% of all newborns. Only 0.2 -0.4% of those with prolonged jaundice are due to neonatal cholestasis. These few new borns need to be identified as early as possible, and immediately referred to a pediatric gastroenterology and hepatology center for further investigation. Delays in diagnosis significantly affect the short and long-term prognosis of these infants.

The underlying causes might vary from the transitory neonatal cholestasis due to immaturity of the mechanisms of bile transport and secretion to more severe conditions due to a variety of genetic or malformative hepatopathy, which can also significantly benefit from early medical or surgical interventions, among which biliary atresia deserves particular attention.

Advances in molecular genetics have helped to better characterize and identify the majority of disorders underlying neonatal cholestasis, which historically had been treated as "idiopathic".[1,2] As a result, the diagnosis of idiopathic neonatal hepatitis is currently made in no more than 15% of neonatal cholestasis.[1] Currently, biliary atresia accounts for 25% of all cases while infectious disease are < 5%. More than half of the diagnosis today are due to genetic defects of hepatobiliary transport and secretion of bile acid salts, as well as inborn genetic disorders affecting the metabolic pathways.[1,2] These include disorders of intracellular organelles, such as lysosomes, mitochondria and peroxisomes.

Most of these disorders benefit from medical therapy and from specific changes in dietary formula, including prompt discontinuance of breast-feeding or the addition of specific dietary supplements to the diet.

From a practical point of view, the genetic disorders at the base of neonatal cholestasis can be further subdivided into two groups: 1) genetic defects in which the macroscopic architecture of the hepatobiliary structure is preserved, as the defects of synthesis and transport of bile acids; 2) genetic defects which interfere with the embryogenesis resulting in macroscopic anomalies of the biliary tree (i.e., biliary atresia, Alagille syndrome, Caroli's disease).[4–6]

This distinction is an important diagnostic framework and tool to consider when planning for diagnostic imaging investigations. However, lack of universally accepted guidelines for the diagnosis of biliary atresia is certainly another reason for delay in making a correct diagnosis.

Biliary atresia is a severe and progressive inflammatory process of unknown cause, which initially involves the extrahepatic bile ducts but which quickly proceeds towards the intrahepatic bile tree leading rapidly to biliary cirrhosis.[6] Biliary atresia is the major reason for liver transplantation during childhood. The extrahepatic bile ducts in biliary atresia become connective fibrotic cords which is irreversibly damaged.

Etiology

The disorder refers to "atresia" but this is incorrectly used because beyond a structural malformation it is the result of an inflammatory and fibrotic process whose etiology is largely unknown.[7–11] Among the possible pathogenic factors are the following:

i. **Genetic factors:** Demonstrated only in the embryonic BA associated with polysplenia which accounts for 10-20% of all the cases of BA;

ii. **Malformative factors:** Causing a developmental arrest of the ductal plate during the embryo genesis of the bile duct system;

iii. **Ischemic factors:** Resulting from morphologically abnormal hepatic arteries.

iv. **Infective viral factors:** several viruses have been implicated such as rotavirus, cytomegalovirus, Epstein-barr virus, papilloma virus and especially reovirus III, with extensive animal model studies on triggering BA- like cholangiopathy.

v. **Immunomediated inflammatory factors:** causing progressive inflammation and fibrosis; a hypothesis supported by elevated expression of intracellular adhesion molecules (ICAM-1, CD80, CD86 e CD40) and cytokines (IL-6) in bile duct epithelial cells.

vi. However, none of these hypotheses has reached sufficient clinical value; it is quite possible that BA results from a combination of multiple factors. In this hypothesis, the acquired form of BA is thought to be a multifactorial disease, where an environmental factor such as a viral infection or a toxin could initiate the process which is then protracted and worsens, depending on the host genetic background.[7–11]

Incidence

Biliary Atresia is the most common extra-hepatic cause of neonatal cholestasis with an estimated global incidence of 1:10-20.000 live born infants.

Pathology

The disease involves both the extra- and the intra-hepatic biliary tree, in variable ways, totally or partially, leading to the traditional classification of BA into 3 main groups.

a. Type I and II BA known in the past as correctible BA types because of the presence of part of the proximal biliary duct connected to the intact intrahepatic biliary tree, and therefore susceptible of surgical treatment by standard biliary-digestive tract anastomoses.

b. Type III BA in the past classified as not correctible, characterized by a deep fibrotic plate, obliterating the common biliary duct and both left and right biliary hepatic ducts.

c. Type III BA are, unfortunately, the overwhelming majority (80%) of all diagnoses of BA. Depending on the presence or absence of associated malformations, this form of BA is further classified into "embryonic" BA (with associated malformations, 25%) versus "acquired" BA (without associated malformations, 75%). There is the belief that BA begins earlier in life in the embryonic than in the acquired BA.

Clinical presentation

Newborns affected by BA are usually healthy babies at birth, often only exhibiting prolonged neonatal jaundice. The second event is the appearance at the 2nd or 3rdweek of life of discoloration of previously normally colored stools, namely ipo- or acholic stools. This is not always present and sometimes it is not noted because of the additional presence of urine, that is hyperchromic during cholestasis. In the majority of BA infants, stools appear intermittently ipo-acholic, and gradually become persistently acholic. In 20% of all embryonic BA cases, the stools are persistently acholic from birth. Acholic stools represent an important early diagnostic tool in BA infants. When it is not evident from birth, parents are critical in making this observation and addressing it with the child's doctors. It is therefore necessary to educate parents in recognizing the different normal stool colors, whose variability also in healthy babies is often a source of anxiety for parents. Several centers, such as the Johns Hopkins Children Center in Baltimore, Maryland, USA, have created an infant stool color guide, to be given to parents at discharge from the nursery (http://hopkinschildrens.org/stool-color-card/).[12]

Physical exam

Both scleral and skin jaundice can be observed, whose shades of yellow can progressively become greener when conjugated bilirubin blood levels become particularly elevated. Hepatomegaly is always present, while splenomegaly appears late when cirrhosis produces secondary portal hypertension. In BA neonates, ascites is rarely observed.

Diagnosis

Laboratory blood testing shows elevated conjugated hyperbilirubinemia constantly associated with high levels of the γ-glutamyl transferases due to severe cholestasis, and usually mildly elevated transaminases levels caused by the hepatic inflammation.

Diagnostic imaging is fundamental. A low cost, noninvasive ultrasound of the liver can be highly informative in presence of the so called "triangular cord" sign.[13] This so-called "triangular cord" is a hyperechogenic area at the hepatic hilum due to the fibrotic mass in the advanced stage of BA. With 100% specificity for BA, the

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triangular cord sign is an indication to immediate laparotomy which allows to perform the liver biopsy and the cholangiography, whose pictures and images confirm BA diagnosis.[14]

An indirect and less specific ultrasound sign is the absence of gallbladder or an irregular shaped small gallbladder.

In several centers, a HIDA scan or hepatobiliary scintigraphy is performed when stools are not clearly ipo-acholic.[15] The presence of biliary to bowel transit times within 24hours allows one to rule out the diagnosis of BA with 100% negative predictive value. Less powerful is its positive predictive value (75%) because diseases other than BA can also cause high grades of biliary obstruction.[15]

Surgical treatment

When BA diagnosis is confirmed within the first 45 days of life, the surgical intervention of "Hepatic-Portoenterostomy according to Kasai" allows avoiding or postponing the need of liver transplantation, later in life, in about half of cases. Kasai's procedure consists in creating anastomoses between the microstructures of bile ducts newly formed within the fibrotic mass at the hepatic hilum by a Roux-Y hepato-jejunostomy reconstruction.[16]

The age at operation had significant impacts on the 5-year survival rates without LTx.[17] However, the preoperative value of serum direct bilirubin had no influence on it (Table 1).

Table 1 Biliary atresia: the impact of age on the 5-year survival rate without LTx.

	Five-Year Survival, mean (SD)		
	YES	**NO**	**P Value**
Age at operation (day)	65 (27.7)	72.7 (33)	0.008
Direct bilirubin at operation (mg/dL)	7.2 (2.8)	7.15 (2.8)	0.8161

Modified from: Nio M, et al.,[17]

In conclusion, the main reasons for a missed or delayed BA diagnosis are the following:

A. BA is a rare diagnosis. Pediatricians will only see 1 or 2 BA infants during their entire career, while the more commonplace physiologic and maternal breast milk jaundice will be a much more common observation and diagnosis.

B. Lack of valid screening methods for early diagnosis**.** Preliminary stool color screening studies are giving promising results, as well as screening studies performed by measuring conjugated bilirubin levels.

C. Neonates with prolonged jaundice might not come to medical attention in time to be seen by the child's pediatrician.

D. Unfortunately, there is still limited awareness regarding the need for medical concern when witnessing prolonged neonatal jaundice. It is indeed a neonatal emergency. It is therefore recommended that healthcare professionals make the diagnosis of maternal breast milk jaundice only after having excluding the rarer but more severe causes of neonatal jaundice for which an early diagnosis can serve to prevent a potentially devastating or fatal outcome, that would significantly compromise the future quality of life of the affected infants.

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Conflicts of interest

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