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Review Article

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Cholestasis in Newborns and Infants

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Abstract

Cholestatic jaundice early in life is infrequent but always abnormal and must be investigated because early diagnosis is crucial to identify treatable diseases, improving the outcome and quality of life of patients. Some diagnostic tools are efficient but expensive and frequently they are not available everywhere, making difficult to reach universally applicable algorithms. In fact, criteria available in the literature often depend on the facilities of the centres where studies are performed. This explains why until today clinical assessment and frequent clinical check-ups early in life remain being main diagnostic tools for a timely diagnosis and management. This is a narrative review updates the state of the art on neonatal cholestasis and based on the evidence gathered a diagnostic approach is proposed., which considers alternatives depending on the local capacities, emphasizing the need of early recognition of altered stools and conjugated bilirubin, and opportune referral to specialized centres.

Keywords: Cholestasis, Jaundice, Biliary Atresia

Introduction

Cholestasis in infancy is a relevant problem present in 1:250 term newborns that can present serious consequences if not timely treated. Most often, neonatal jaundice is due to indirect/unconjugated bilirubin and resolves spontaneously. However, persistent jaundice is abnormal and may be the earliest sign of severe hepatobiliary or metabolic dysfunction. Among the numerous types of cholestasis, biliary atresia (BA) represents the most frequent cause of liver transplant [1]; its frequency and the number of Kasai procedures required seems to be on the rise. Delayed diagnosis is one of the most relevant factors explaining poor prognosis[1,2]. We here review the most frequent causes, diagnostic criteria, and management of cholestasis with the purpose of identifying the factors that obstruct and delay the diagnostic process and we propose an algorithm that may help improving well-timed diagnosis and treatment of affected patients.

1. Definition and Main Causes of Cholestasis

Definition

Cholestasis refers to the reduced bile production or flow secreted into the intestinal lumen. In neonates is often difficult to differentiate physiological jaundice from the other causes that produce liver injury. Jaundice becomes clinically apparent only when total serum bilirubin exceeds 2.5- 3.0. mg/dL; therefore, early measurement of total and direct serum bilirubin is relevant in jaundiced newborns. The North American Society for

Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology and the Hepatology and Nutrition (ESPGHAN, 2018)[2], currently define cholestasis at 1mg/dL direct/conjugated serum bilirubin. The definition was modified because bilirubin excretion into canaliculi may limit the general clearance speed and high non-conjugated bilirubin can retain some of the conjugated bilirubin. Diazo and van den Berg techniques are the usual methods applied[3] to measure direct bilirubin (conjugated plus delta or albumin bound bilirubin).

Causes of Cholestasis

These are diverse and numerous (Table 1); most studies focus on extrahepatic BA, a relevant condition that although infrequent (estimated incidence of 1:5,000 live births), early surgical treatment is efficacious and prevent liver failure and death. Although there are several causes of cholestasis in addition to extrahepatic BA (Table 1), their descriptions are few and relative incidence is low [4].

2. Diagnostic Approach Cholestasis

Diagnostic Approach in Newborns and Infants

Theoretical consensus seems easy, but in daily life protocols to approach the young, jaundiced patients vary considerably due to variable local difficulties to reach specialists and different local laboratory capacities to support the studies required for diagnosis. Thus, although guidelines and protocols are available, the diagnostic process is often jeopardized by local limitations [5-7]. In the next paragraphs we describe a step-by-step approach to be applied beginning at the primary health system and/or pediatric center (where first postnatal checkups occur), followed by the specialized studies in centers where diagnosis is confirmed and surgical treatment is provided, when possible. Table 2 shows the alert signs, or "red flags" revealed by the clinical history, which help directing initial diagnosis. Figure 1 proposes a diagnostic algorithm that summarizes the experiences obtained from the literature review[8,9].

Step 1: Fractionated bilirubin must be requested to all jaundiced infant at two weeks of life. This must take place during the first routine checkups performed at the primary health care level; therefore, being alert becomes critical [10, 11]. Bilirubin >1 mg/d direct/conjugated serum bilirubinmeans cholestasis and the study protocol must be initiated[2]. Stool assessment is most helpful[12, 13].Evaluation at one month of age using the stool color chart helps confirming acholic stools, which characterizes obstructive biliary conditions like BA[14]. If cholestasis is confirmed, the patient must be referred for assessment by a specialist. Referral must not be delayed since prognosis depends on early treatment. This is the fundamental step in the early diagnostic process. It depends on the clinical evaluations, and all members of the health team (including nurses, midwives, and physicians) must be involved in first suspecting jaundice and feces with altered color that deserve further study[15].

Step 2: This step characterizes by the assessment made by a specialist. The clinical history is crucial to suggest likely etiologies [16], potential anomalies and red flags (table 2). Initial laboratory tests include liver function tests (AST, ALT,INR, albumin, glycemia), which may reveal acute liver failure; and GGT, which when elevated suggests an obstructive condition and when normal or low may be secondary to progressive familial intrahepatic cholestasis (PFIC) or poor biliary acids synthesis[17]. Whole blood count and urinary tests help searching for acute or urinary infections and TSH y T4 assesses hypothyroidism. In this step is important to diagnose/reject neonatal liver insufficiency, severe bacterial infection, herpes infection, neonatal alloimmune hepatitis, galactosemia and mitochondrial diseases; all these conditions must be immediately treated, when possible[18].

Step 3: An abdominal echography must be obtained[19, 20]. Collapsed or absent gallbladder or triangular cord sign are all characteristics suggesting BA and their presence should rapidly lead to an intra operative cholangiography with liver biopsy and subsequent Kasai portoenterostomy, as needed [21-25].

If the abdominal echography shows other alterations, a cholangial resonance helps demonstrating a cyst, a biliary tract tumor, pancreatic malformations, and others. Although a normal echography does not rule out BA. Investigations searching for other diagnoses should start at this point[26].

Step 4: This phase becomes important when BA is overruled; other diagnoses must be sought, such as metabolic conditions [5, 27-33]; acyl carnitine and aminoacidic profile; urinary succinyl acetone and galactose 1PUDPG will help assessing urea cycle disorders, tyrosinemia and galactosemia among others. The infectious diseases screening is relevant when viral, bacterial, and parasitic liver infections are suspected (CMV, herpes simplex virus type 1 and 2, VHB, VHC, VEB, GBS sepsis, toxoplasmosis, rubella, Chagas disease). The immune reactive trypsinogen and sweat electrolytestests help detecting cystic fibrosis and abnormal alpha 1 antitrypsin levelwith Alpha1-antitrypsin (AAT) deficiency. Other studies include assessment of Alagille Syndrome, dysmorphic facial features, ocular assessment (posterior embryotoxon), spine radiographic evaluation (butterfly vertebrae), and cardiovascular assessment (congenital heart defects)[34].

Step 5: If the diagnosis is still unclear, the next step consists of genetic studies[35]. For many years, despite the adequate blood studies and liver biopsies performed, some cases remained undiagnosed. Today, genetic studies have revealed that there are several genetic conditions that may overlap, expressing different clinical phenotypes. Examples of these are JAG1 and NOTCH2 (Alagille syndrome), ATP8B1 (PFIC type 1), ABCB11 (PFIC type 2), ABCB4 (PFIC type 3), SERPINA1 (A1AT deficiency), ABCC2 (Dubin-Johnson syndrome) and SLC25A13 (Neonatal intrahepatic cholestasis caused by citrine deficiency (NICCD), among others[36]. The most relevant limitation at this stage is that genetic studies are expensive and not available everywhere[37, 38] (Figure 1).

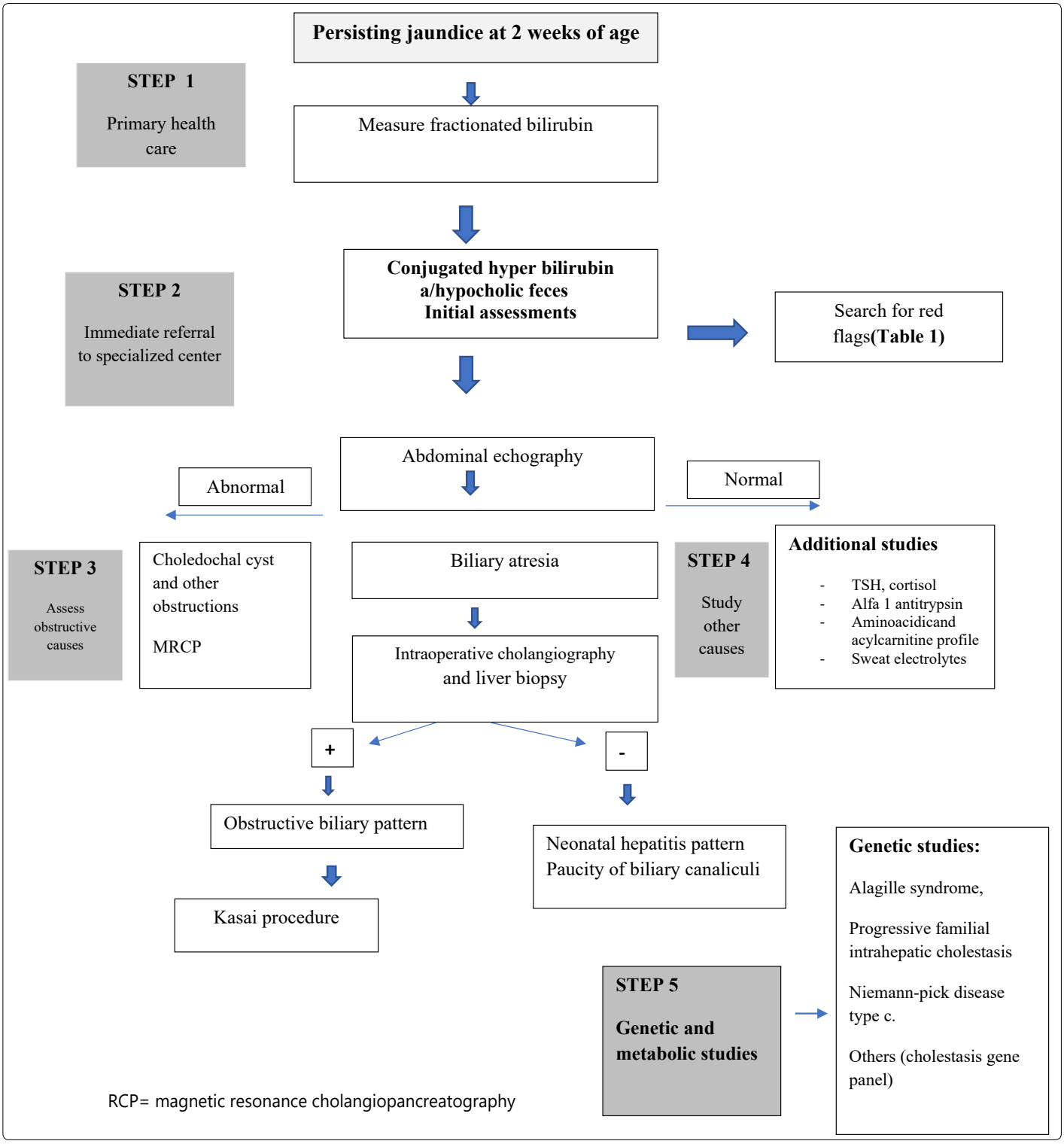

Figure 1. Algorithm guiding studies and diagnosis

Management of Cholestasis

This firstly refers to differentiate conditions that require early surgical procedures (BA, choledochal cyst) from those that have non-surgical specific treatments (infections, galactosemia, tyrosinemia, hypothyroidism, neonatal alloimmune hepatitis). In those where the primary cause cannot be modified, medical management will mainly aim at treating chronic complications (fat malabsorption, vitamin deficiencies, pruritus, hypercholesterolemia, cirrhosis, portal hypertension, liver insufficiency) and avoid nutritional deterioration. Adequate medical management maintains the best possible quality of life of patients and must start as soon as diagnosis is reached[39]. The administration of albumin and immunoglobulin can be useful in cases of neonatal alloimmune hepatitis and the use of glucocorticoids in biliary tract atresia. Nutritional support is usually necessary to minimize failure to thrive; fat-soluble vitamins, phenobarbital, ursodeoxycholic, rifampicin, cholestyramine may be helpful tools for management, but one must keep in mind that specific treatment of the different cholestatic conditions must be supervised by a specialist[40].

Discussion

The evidence reviewed confirms the diversity of protocols applied to study, diagnose and manage cholestasis in neonates and infants[41]. The algorithm proposed (Figure 1) appears as a useful tool that considers the variable capacities available in the different health systems levels in many countries. Although guidelines and recommendations are available, delayed treatment continues being the main cause of poor prognosis in cases in which surgical management is possible[42]. Difficulties in recognizing truly acholic faeces early in life, access to trained specialists and the possibility to perform expensive tests are the main limitations identified. Modification of historic cholestasis definition by NASPGHAN and ESPGHAN [2] is relevant and improves the chance of early diagnosis. Measuring fractionated bilirubin at two weeks of age must be stressed. In fully breast-fed babies, who lack risk factors or red flags this measurement could be delayed until the third week of life but, certainly the criteria to keep in mind is that fractionated bilirubin should be measured at two weeks of age.

Probably the most frequent and difficult task in daily practice is to identify significant changes in stool pigmentation (normal, hypocholic or acholic). Parents and health professionals tend to evaluate stool pigmentation subjectively, with frequent erroneous interpretations; for instance, Bakshiet al. determined that almost 40% of doctors and nurses did not recognize altered stools as abnormal[12]. A stool pigment chart is available to help evaluation and using this chart in Taiwan, Shan-Ming Chen et al. obtained 95.2% sensitivity[4]. Yan-Hong Gu et al. conducted a 19-year study using the same chart and found that BA was diagnosed earlier and long-term survival of the native liver was greater[13]; however, this kind of charts in most countries are ignored and not utilized.

Studies assessing the criteria applied for decision making differ in their results, probably influenced by the conditions of the different studies performed, but also, recommendations available somewhat disagree with the evidence reported. The epidemiology and diagnostic results reported in two cohorts, assessed before and after year 2000 described that age of detection diminished from a median of 43 days to 22 days and this resulted in better survival rates[5]. These results are significant and show that it is possible to do better, but unfortunately early diagnosis at 22 days of life is not representative of the typical mean time to reach diagnosis everywhere. Assessment of attitudes and behaviour of 116 participants that provided medical care in primary paediatric systems[41] showed that 94.8% felt confident to correctly diagnose hyperbilirubinemia, though only 10.3% knew the biochemistry of direct bilirubin; of 56% participants that stated to know the "current criteria in use", only 18.5% answered that the criteria to define cholestasis recently changed. Studies often emphasize the use of certain tests that are expensive and not always available[31]; in contrast, in most studies reviewed the relevance of clinical history and the benefits of using standardized protocols are ignored[43]. In a recent survey applied to paediatricians, most of them answered that they would order measuring fractionated bilirubin at 4 weeks of life, but many did not program the visits needed to perform such measurement and 25% did not see the baby between week 1 and 8 of life[44].

The relevance of early diagnose when surgery is possible is shown by a French study that assessed 695 BA patients and found that the native liver had better survival when the Kasai procedure took place during the first 30 days of life[22]. To improve the situation, predictive models for initial assessment were developed based on hierarchic classification and regression tree (CART) or by logistic regression[21]. Both methodologies failed; 12% of BA babies were erroneously classified as non-BA and 17% of non-BA patients classified as BA. Thus, clinicalhistory and physical examination remain being relevant tools when first assessing the patients and his/her stool characteristics[45]. Fractionated bilirubin, blood screening and imaging assessment are crucial in the next steps.

Table 1. Causes of neonatal cholestasis

Infectious
Viruses, bacteria, spirochaetes and parasitess
Toxins
Drugs, endotoxins, total parenteral nutrition-associated cholestasis and herbal products
Endocrine
Hypothyroidism and panhypopituitarism
Immune
Gestational alloimmune liver disease
Anatomic obstruction
Biliary atresia, choledochal cyst, cholelithiasis, biliary sludge, inspissated bile,spontaneous perforation of common bile duct and tumor
Other
Idiopathic neonatal hepatitis (transient neonatal cholestasis), cardiovascular andcirculatory disorders,
hemophagocytic lymph histiocytosis, malignancy andcongenital lupus
Genetic and metabolic conditions
α1-Antitrypsin deficiency (SERPINA1)
Alagille syndrome (JAG1 and NOTCH2)
Arthrogryposis–renal dysfunction–cholestasis syndrome (VPS33B and VIPAR)
Caroli disease and congenital hepatic fibrosis (PKHD1)
Chromosomal (trisomy 21; Turner syndrome)
Citrine deficiency (SLC25A13)
Cystic fibrosis (CFTR)
Disorders of bile acid synthesis (AKR1D1, AMACR, CYP7B1, HSD3B7, CYP7A1 and
CYP27A1)
Disorders of bile acid conjugation (BAAT and SLC27A5)
Fatty acid oxidation defects (SCAD and LCAD)
Galactosemia (GALT)
Glycogen storage disease type IV (GBE1)
Hereditary fructose intolerance (ALDOB)
Mitochondrial respiratory chain disorders (DGUOK, MPV17 and POLG)
Neonatal ichthyosis–sclerosing cholangitis syndrome (CLDN1)
Neonatal sclerosing cholangitis (DCDC2)
Niemann–Pick disease type C (NPC1 and NPC2)
Peroxisomaldisorders (PEX1, PEX6, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16,
PEX19, PEX2, PEX26, PEX3, PEX5 and PEX7)
Progressive familial intrahepatic cholestasis (ATP8B1, ABCB11, ABCB4, TJP2, NR1H4,
MYO5B and UNC45)
Lipid storage diseases (SCP2)
Tyrosinemia (FAH)
Urea cycle defects

Table 2. Clinical history suggesting likely etiologies and red flags

Inquiring	Information suggests
Family and clinical history	
Consanguinity	Increased risk of autosomal recessive disorders
Neonatal cholestasis in parents or siblings	Cystic fibrosis, alpha 1 antitrypsin deficiency, familial intrahepatic cholestasis, Alagille syndrome
History of repeated foetal loss or early death	Alloimmune liver disease
Spherocytosis and other haemolytic diseases	Conjugated hyperbilirubinemia worsens
Prenatal history	
Findings on prenatal ultrasound	Choledochal cyst, cholelithiasis
Cholestasis in pregnancy	Seen in heterozygotes for mutations of the PFIC gene, mitochondrial disorders.
Acute liver failure in pregnancy	Neonatal long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency
Maternal infections	TORCH infections
Child's history	
Gestational age	Prematurity as a risk factor for neonatal hepatitis
Neonatal infection	Urinary tract infection, sepsis-related cholestasis, CMV, HIV, syphilis, etc.
Nutrition source: breast milk, formula, PN	Galactosemia, hereditary fructose intolerance, PN-associated liver disease
Failure to thrive	Metabolic and genetic disease
Ophthalmological disturbances	Septo-optic dysplasia
Vomiting	Metabolic disease, intestinal obstruction, pyloric stenosis
Physical examination	
General aspect	Poor appearance may indicate infection or metabolic disease, babies with biliary atresia typically look good.
Specific facial features	Dysmorphic features: Alagille syndrome rarely has facial features in the newborn. Typical facial features may appear around 6 months of age, but are often nonspecific (broad nasal bridge, triangular facies, and sunken eyes).
Vision test/slit lamp	Congenital infection, storage disease, septo-optic dysplasia, posterior embryotoxon
Cardiac examination: murmur, signs of heart failure	Congenital heart disease: Alagille syndrome, splenic malformation syndrome of biliary atresia
Abdominal examination	Ascites; veins of the abdominal wall, size, and consistency of the liver and of the spleen (or lack thereof) should be assessed, abdominal masses, umbilical hernia.

Conclusion

Cholestatic jaundice that lasts more than the first two weeks of life must be studied because it may be the first sign of severe liver disease. Early detection and confirmation of jaundice and altered colored fecesat the primary health care level and subsequent diagnostic assessment by a specialist are essential for early diagnosis and treatment that result in better prognosis. Specialists are necessary to guide the studies, imaging, liver biopsy and the genetic studies (Figure 1); these guide subsequent studies searching for treatable underlying causes like infections (sepsis), various metabolic and genetic diseases, etc. All studies reviewed agree on that ultrasound is one of the useful initial tests to be performed. Independent of causes, a precise and predetermined approach is the fundamental piece in the process of diagnosis and treatment, and nutritional support is relevant to maintain the best condition possible in the patient.Up to date, variability on how to conduct diagnostic studies adjusted to local limitations remains being the main challenge to obtain better outcomes. The algorithm proposed (Figure 1) considers the potential restrictions locally present, describing the steps to follow at the different health service levels. We emphasize the importance of the primary health level in early detection and timely referral.

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