Prolonged jaundice in an apparently healthy baby: A review

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ABSTRACT

Jaundice persisting beyond 14 days of life is a commonly encountered problem in the neonatal follow-up clinic. Although by far the most common underlying etiology is breast milk jaundice, clinician should not miss out an important surgical condition the extrahepatic biliary atresia (an incidence of about 1 in 10000 live births) whose outcome without a surgical intervention before 8 weeks is dismal. Eminently treatable entities such as hypothyroidism and urinary tract infection also can present as prolonged jaundice. This article will synthesize the available literature on this topic and present an algorithm for evaluation of neonates presenting with prolonged jaundice useful to pediatricians in outpatient practice.

Key words: *Breast milk, Extra hepatic biliary atresia, Neonate, Prolonged jaundice*

Jaundice persisting for more than 14 days after birth is termed as prolonged jaundice [1]. Although jaundice in a preterm baby is termed as prolonged after 21 days, it is advisable that all babies jaundiced at 14 days undergo a pediatrician's evaluation irrespective of gestation. By the term apparently healthy baby, we would assume that it refers to babies presenting to pediatrician's outpatient clinic with jaundice or incidental detection of jaundice in babies presenting for another reason that is not sick enough for inpatient admission.

Jaundice presenting in the first 10 days of life need urgent attention from a therapeutic point of view to assess the level of jaundice and to determine the need for intervention with phototherapy or exchange transfusion. On the other hand, babies with prolonged jaundice need an etiological evaluation to identify those with liver disease (neonatal hepatitis and extrahepatic biliary atresia) and potentially treatable causes such as hypothyroidism and urinary tract infection (UTI), which are summarized in Tables 1 and 2 [2].

DIFFERENTIAL DIAGNOSIS OF PROLONGED JAUNDICE

About 15-40% of exclusively breastfed neonates are still jaundiced at 14 days thus making breast milk jaundice the most common cause of prolonged jaundice [3,4]. About 80-90% of neonates with prolonged jaundice suffer from breast milk jaundice. But breast milk jaundice is a diagnosis of exclusion. Prolonged jaundice can be classified into prolonged unconjugated hyperbilirubinemia and prolonged conjugated hyperbilirubinemia based on the level of conjugated (direct) bilirubin in split bilirubin test. If the conjugated fraction is <20% of the total bilirubin, then it is unconjugated hyperbilirubinemia and if it is more than 20% of the total, it is conjugated hyperbilirubinemia. In a prospective study of neonates with prolonged jaundice, conjugated hyperbilirubinemia was diagnosed in only one neonate out of 154 with prolonged jaundice or 0.14/1000 live births [1]. The causes of unconjugated hyperbilirubinemia and conjugated hyperbilirubinemia are tabulated. It has to be remembered that breast milk jaundice is unconjugated hyperbilirubinemia.

EXTRA HEPATIC BILIARY ATRESIA

Biliary atresia has an incidence of 1 in 15000 live births [5]. The diagnosis has to be suspected in all neonates with prolonged jaundice and pale or clay colored stools. The diagnosis is confirmed by a HIDA scan (following 5 days pretreatment with phenobarbitone 5 mg/kg/day) showing failed or reduced excretion into intestine at 24 h despite a good hepatic uptake and operative cholangiogram showing atretic extrahepatic biliary tract. An early Kasai's procedure before 2 months of age gives the affected child 80% chance of good quality survival without liver transplantation up to adolescence. Although early diagnosis is emphasized, even in the USA, a trend toward an increased age at diagnosis was observed in a recent study (Median age at diagnosis 69 days in 2000-2004 vs. 48.5 days in 1990-1994) [6]. This means that it is necessary to pick up the diagnosis early when the neonate will be apparently normal.

BREAST MILK JAUNDICE

Although breast milk jaundice is the most common cause of prolonged jaundice and can past up to 3 months, it is a diagnosis of exclusion. The putative factors causing breast milk jaundice are

Table 1: Causes of unconjugated hyperbilirubinemia

Breast milk jaundice
Hemolysis
Blood group incompatibilities (ABO and G-6PD)
Polycythemia
Extravasated blood
Increased enterohepatic circulation
Pyloric stenosis
Bowel obstruction
Endocrine/metabolic (also cause conjugated hyperbilirubinemia)
Hypothyroidism
Hypopituitarism
Hypoadrenalism
Galactosemia
Sepsis
Urinary tract infection

Table 2: Causes of conjugated hyperbilirubinemia

A. Extrahepatic biliary duct disorders
Biliary atresia
Choledochal cyst
Gallstone
B. Bile duct hypoplasia syndromes (alagilles)
C. Neonatal hepatitis syndrome
Idiopathic neonatal hepatitis syndrome
Intrauterine infections
Metabolic
Hypothyroidism
Hypopituitarism
α-1 antitrypsin deficiency
Galactosemia
Tyrosinemia type 1
Hereditary fructose intolerance
Niemann pick type C
Zellweger's
Cystic fibrosis
D. Sepsis
Urinary tract infection

1. Pregnane-3-alpha 20 beta-diol, an unusual metabolite of progesterone present in human milk which inhibits UDP-Glucuronyl transferase enzyme
2. Increased concentration of free fatty acids inhibiting glucuronyltransferase enzyme
3. Increased enterohepatic circulation of bilirubin due to beta-glucuronidase enzyme in breast milk and delayed establishment of enteric flora in breastfed infants
4. Homozygosity or heterozygosity for Gilbert's syndrome (found in up to 5 % of the population) and other genetic factors like mutations in UDPG genes [3,4].

The infant should be thriving and well established on breast feeds. No treatment is warranted if bilirubin is <17 mg but monitor the bilirubin levels. Between 17 and 25 mg, we consider phototherapy mainly to relieve parental anxiety although literature is silent on bilirubin thresholds for phototherapy beyond 14 days of age in a term baby [7]. Although temporary interruption of breastfeeding (usually 2 days) promptly brings down the bilirubin levels that do not raise again even with reinitiation of exclusive breastfeeding, it is rarely needed unless the levels are approaching exchange level. There has not been a single occasion where this was warranted in an India's premier medical institution [8].

UTI

About 6% of neonates with prolonged jaundice were found to be suffering from (UTI) in an Iranian study of 100 neonates with prolonged jaundice, and all of them had unconjugated hyperbilirubinemia [9]. The jaundice in babies with UTI is unconjugated in the early stages but becomes conjugated in the later stages [10].

CONGENITAL HYPOTHYROIDISM

About 6 out of 110 infants evaluated for prolonged jaundice had overt primary hypothyroidism giving an incidence of 5.5% in a Turkish study [11]. A further seven neonates in the same study were found to have borderline hypothyroidism by thyrotropin releasing hormone stimulation test. As thyroxine therapy brings about a prompt resolution of clinical symptoms, it is important to carry out thyroid function tests in all neonates with prolonged jaundice [12].

APPROACH TO A NEONATE WITH PROLONGED JAUNDICE

A detailed clinical history is undertaken including delivery details, birth weight, gestation, early jaundice, blood group incompatibilities, jaundice in sibs, feeding history, and the most important of all stool color. Pale or clay colored stools warrant urgent investigations to rule out extrahepatic biliary atresia as surgical intervention has to be carried out before 2 months of age to save the liver from permanent damage.

Thorough clinical examination paying special attention to infant's weight, grade of dermal icterus, hepatosplenomegaly, activity level, stigmata of TORCH infections, etc., is the next step. It has to be borne in mind in the early stages of the illnesses tabulated the infant is apparently normal except those with stigmata of TORCH. Our endeavor is to diagnose these illnesses in their early stages, and this is, in particular, true with respect to biliary atresia and hypothyroidism where early diagnosis significantly influences the final outcome.

ALGORITHM FOR EVALUATION OF NEONATES WITH PROLONGED JAUNDICE

The algorithm for neonates presenting with prolonged jaundice should be able to identify all neonates with biliary atresia, hypothyroidism and UTI while avoiding many blood tests in

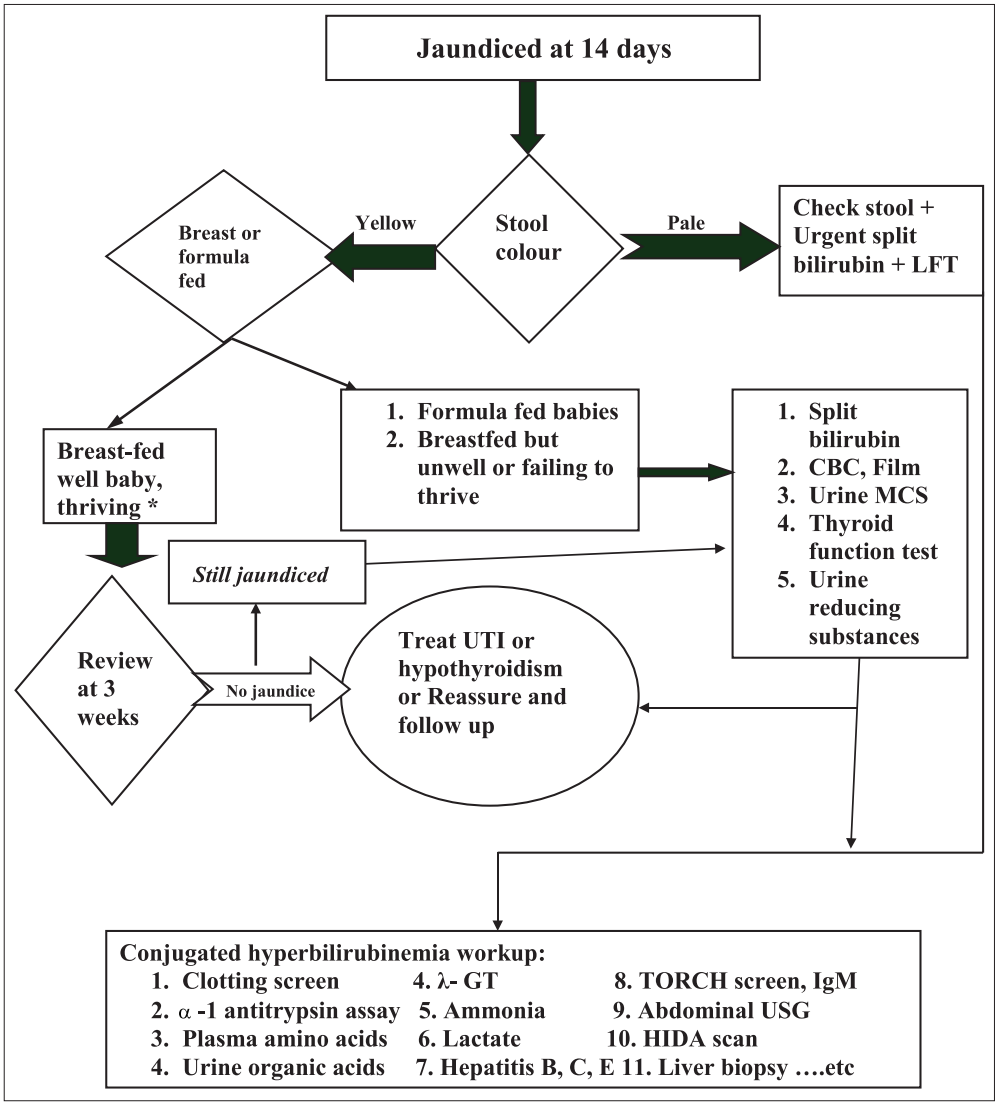

Figure 1: Algorithm for evaluation of neonates with prolonged jaundice, *serum bilirubin if deeply, jaundiced as some may require phototherapy

babies with breast milk jaundice which is by far the commonest cause of prolonged jaundice.

1. Well breastfed neonates with normal colored stools can be safely sent home and a split bilirubin checked if still jaundiced at 3 weeks along with urine microscopy, routine and culture and thyroid function test
2. Breastfed babies who are not thriving or are unwell and all formula fed babies need split bilirubin + urine microscopy, routine, and culture + thyroid function test done before sending home
3. Hypothyroidism, UTI and galactosemia can present with prolonged unconjugated jaundice and hence need to be looked at in all babies with prolonged jaundice
4. More extensive tests are warranted only if the jaundice is conjugated, i.e., investigations for neonatal hepatitis/ extrahepatic biliary atresia
5. All babies with prolonged jaundice need follow-up visits to the hospital until the jaundice is resolved or an etiological diagnosis is established and appropriate treatment is initiated.

We have evolved the following algorithm for the evaluation babies jaundiced at 14 days presenting in an outpatient setting based on literature search and common clinical diagnostic probabilities (Fig. 1).

SUMMARY AND RECOMMENDATIONS

1. It is essential to examine babies jaundiced earlier on at 15 days of age to confirm resolution of jaundice. Always ask and confirm the stool color as pale stools need urgent intervention
2. Prolonged Jaundice in a thriving exclusively breastfed baby is due to breast milk jaundice but do confirm that the jaundice is unconjugated hyperbilirubinemia as conjugated jaundice is against a diagnosis of breast milk jaundice
3. It is also important to rule out two treatable medical entities, UTI and hypothyroidism in all babies with prolonged jaundice
4. Prolonged conjugated hyperbilirubinemia needs further evaluation to identify cases of extrahepatic biliary atresia that require surgical intervention before 8 weeks of age and in cases where this entity is ruled out specialist metabolic tests (neonatal hepatitis syndrome) are indicated

5. All neonates with prolonged jaundice need follow-up visits until jaundice resolves or an etiological diagnosis is established and appropriate treatment initiated.

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