Underlying Etiologies of Prolonged Icterus in Neonates

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Abstract: The purpose of this study was to determine underlying causes of prolonged neonatal icterus. Icterus or jaundice is an important common problem in neonatology. When this condition persists beyond 14 days, it is called prolonged or protracted neonatal icterus. Determining underlying causes of this problem is a pivotal step for management, because a delay in treatment may lead to serious complications or even death. In a prospective study, newborns with diagnosis of prolonged icterus were evaluated during a six-month period in Tabriz Children Teaching Hospital. Data regarding the past medical history, physical examination and appropriate laboratory and paraclinical investigations were gathered and accordingly, the underlying cause of jaundice was documented. One hundred newborns, 67 males and 33 females with a mean age of 21.5±4.5 days were enrolled. Breastfeeding, urinary tract infection, glucose 6-phosphate dehydrogenase deficiency and hypothyroidism were found as the main underlying causes in 75, 7, 7 and 4% of the cases. The exact etiology was unknown in 4% of newborns. ABO incompatibility, sepsis and Down syndrome were underlying etiologies in remaining three patients. Present study showed that the underlying causes of prolonged neonatal jaundice could be determined in majority of cases and breastfeeding is the most common one in this regard.

Key words: Newborn, protracted jaundice, cause, breastfeeding, infection

INTRODUCTION

Hyperbilirubinemia is a common problem during the neonatal period. It is usually benign in nature; however, severe indirect hyperbilirubinemia may induce irreversible toxic consequences mainly in the nervous system if left untreated. Furthermore, direct (conjugated) hyperbilirubinemia may be along with serious underlying causes (Kliegman et al., 2007; Martin et al., 2005). The etiological factors may be affected by the population characteristics, gestational age, sex, maternal medication, feeding status and the geographical variations. However, in some cases even the most sophisticated investigations fail to reveal any etiological factors and these cases are then labeled as idiopathic. Some of the most common causes of neonatal jaundice include physiologic hyperbilirubinemia, breastfeeding jaundice, breast milk jaundice and pathologic hyperbilirubinemia due to hemolytic disease. Liver dysfunction (e.g., caused by parenteral alimentation causing cholestasis, neonatal sepsis, neonatal hepatitis) may cause a conjugated or mixed hyperbilirubinemia (Beers and Berkow, 2000). Prolonged neonatal icterus which is defined as the jaundice persisting beyond 14 days can also be a sign of an occult pathology (Mc-Kiernan, 2002). Like in the neonatal jaundice, etiologies of prolonged neonatal icterus could be categorized as follows: structural, infection (viral, bacterial, parasitic), metabolic, genetic, neoplastic, toxic, endocrine, immune, vascular and idiopathic (Gilmour, 2004; Roberts, 2003; Karpen, 2002). In this regard, the most common causes are: hemolysis, congenital deficiency of glucuronyl transferase enzyme, jaundice due to breastfeeding, hyperthyroidism, intestinal obstruction, pyloric stenosis, rare conditions such as Gilbert’s syndrome, etc. (Taeusch et al., 2004; Laforgia et al., 2002). Considering all these possible etiologies is essential in evaluating infants with protracted jaundice, because missing a case may result in drastic morbidity and even mortality. Family history of medical conditions, method of feeding, quality and quantity of growth and development, results of complete physical examination and findings in general or especial laboratory and paraclinical investigations are all key points in this investigation (Mishra et al., 2008). This study aims at determining the underlying etiologic causes of prolonged neonatal jaundice in a group of Iranian newborns.

MATERIALS AND METHODS

In this prospective study, outpatient or hospitalized neonates with prolonged icterus (100 cases) were enrolled in Tabriz Children Teaching Hospital, Northwest of Iran, during a six-month period between April 2009 and October 2009. Jaundice persisting beyond 14 days was considered...
as prolonged (Hussein et al., 1991). Patients’ characteristics and general data were documented including age, sex, birthweight, age at onset, type of delivery, type of feeding, previous history of jaundice therapy and previous history of jaundice in siblings. All the cases were thoroughly examined on admission. The following investigations were undertaken: serum bilirubin (total and conjugated), liver function tests including aspartate aminotransferase (AST), gamma glutaryl transferase (gamma GT) and alkaline phosphatase (ALP) levels, blood group and Coomb’s test, full blood count, thyroid function tests (TSH and T4), glucose-6-phosphate dehydrogenase (G6PD) level (qualitative measurement) and urine for culture. A conjugated bilirubin of greater than 20 mmol L\(^-1\) and consisting of more than 20% of the total bilirubin was considered to be abnormal. The normal ranges of serum TSH and T4 were 0.5-6.5 and 8.2-17.2 mU L\(^-1\), respectively. Urine samples were obtained using urine bags and sent for microscopy and culture. With no white cells or organisms, the urine was considered normal. If a pure growth of greater than 105 organisms was found, the sample was repeated and if there was still a pure growth a suprapubic aspirate was performed. Statistical evaluation was made using SPSS for Windows V 15.0 (SPSS Inc., IL, USA). Data are shown as mean±standard deviation or frequency (percentage).

**RESULTS**

One hundred newborn with prolonged icterus were enrolled. The mean age of these patients was 21.5 days and the mean age of jaundice onset was 4.7 days. Sixty seven patients were male and 33 patients were female with a male to female ratio of about 2/1. Breastfeeding was the main route of feeding in majority of patients (75%). Previous therapy for icterus was documented in 77 patients with phototherapy as the major treatment in 73 newborns. Characteristics and general data of the studied group are summarized in Table 1. In physical examination, there was a case with cephalhematoma and another with hepatomegaly. Paleness, petechiae, purpura, ecchymosis, splenomegaly or caput succedaneum were not detected in any newborn on initial examination. Laboratory results are summarized in Table 2. Accordingly, hypothyroidism, G6PD deficiency and urinary tract infection (UTI) were diagnosed in 4 (4), 7 (7) and 7 (7) newborns, respectively. In cases with the UTI, urine cultures were positive for *E. coli* in 6 cases and *Klebsiella pneumoniae* in one case. Finally, the main underlying causes of prolonged neonatal icterus were as follows: breastfeeding in 75 cases, G6PD deficiency in 7 cases, UTI in 7 cases, hypothyroidism in 4 cases, septicemia in 1 case, Down syndrome in 1 cases and ABO incompatibility in 1 case. The underlying etiology was unknown in 4 cases. Percentages of underlying causes of prolonged icterus are shown in Fig. 1, according to this figure, breastfeeding was the major underlying cause in 75% of the cases. The etiological cause was unknown in 4% of the cases.

![Fig. 1: Percentage of underlying causes of prolonged icterus in 100 neonates](image-url)
DISCUSSION

In current study, the most common etiologic causes of prolonged neonatal jaundice were breast feeding, G6PD deficiency, UTI and hypothyroidism, respectively. Hannam et al. (2000) assessed 154 term infants with prolonged jaundice (persisting beyond 14 days of age) in England. They also showed that the majority of infants (almost 92%) had an unconjugated hyperbilirubinaemia probably due to breastfeeding. Other uncommon causes were giant cell hepatitis (one patient), hepatoblastoma (one patient), trisomy 9p (one patient), urinary tract infections (two patients), G6PD deficiency (three patients) and failure to regain birthweight (one patient). They concluded that a large number of infants with prolonged jaundice have detectable underlying problems. The results of this study also support ours, first regarding the breastfeeding as the main etiological cause of neonatal jaundice and second about the frequency of undetermined etiologies. In another series by Maruo et al. (2000) in Japan, 17 breastfed infants with apparent prolonged jaundice were analyzed. Except for jaundice, the infants were healthy and did not show evidence of hemolytic anemia, liver dysfunction, or hypothyroidism. They concluded that breastfeeding was the main cause of prolonged icterus in these infants. This is also in line with our main result. Ince et al. (1993) concluded that breast milk beta-glucuronidase activity may play a role in inducing prolonged jaundice in breastfed neonates; however, this is not definite. Maruo et al. (2000) showed that defects of uridine diphosphate-glucuronosyltransferase gene (UGT1A1) are an underlying cause of the prolonged unconjugated hyperbilirubinemia associated with breast milk. They concluded that one or more components in the milk may trigger the jaundice in infants who have such mutations. Whatever the underlying mechanism is, pediatricians usually recommend that breastfeeding should not be accepted as the sole cause of jaundice beyond 2 week of age and that jaundice should be investigated even if the infant is otherwise well (Mackinlay, 1993; Crofts et al., 1999). However, the result of this study shows that in majority of cases, breastfeeding would be the main and sole underlying cause of jaundice in these patients. It should be born in mind that it has been shown mothers who are breastfeeding are more likely to stop if their baby is jaundiced and they are likely to be further discouraged by repeat visits to the hospital for blood or urine tests (Hannam et al., 2000). Jaundice associated with a UTA is also well recognized (Hannam et al., 2000). Pashapour et al. (2007) evaluated 100 Iranian newborns with prolonged jaundice. All the patients were breastfed and UTI was diagnosed in 6 cases. They concluded that in Iran, with a high rate of breastfeeding, UTI remains as an important cause of prolonged jaundice. They proposed that performing urine cultures should be considered as a routine procedure in the evaluation of every infant with prolonged jaundice. Bilgen et al. (2006) evaluated 102 Turkish infants and UTI was diagnosed in 8% of the cases. They also concluded that urine culture should be considered in the bilirubin work-up of infants older than three days of age with an unknown etiology. In a study by Ghaemi et al. (2007) in Iran, 400 neonates with late onset jaundice were evaluated. Of the 400 icteric neonates, 23 (5.8) were diagnosed to have UTI, 5 cases (1.3) had G6PD deficiency, 19 (4.8) had dysmorphic red blood cell and 3 (0.75) had ABO or RH incompatibility. They suggested that evaluation for urinary tract infection should be considered as a screening test in all cases of neonatal late onset jaundice. The UTI was the third common cause in present study; so the mentioned recommendations by other studies are also supported by our series. Abdel-Fattah et al. (2010) evaluated 69 Egyptian neonates with jaundice. The G6PD deficiency was detected in 14.4% of the patients. They concluded that G6PD deficiency is an important cause for neonatal jaundice in Egyptians. Neonatal screening for its deficiency was recommended. In a similar study by Abolghasemi et al. (2004) in Iran, they showed that the incidence of G6PD deficiency in newborns of Tehran was 2.1%, which was relatively high and also hyperbilirubinemia and jaundice were approximately 3-fold higher in G6PD-deficient group than in the G6PD-normal group (51 vs. 16%). They emphasized the necessity of neonatal screening on cord blood samples for G6PD deficiency and the need to watch closely for development of hyperbilirubinemia. In another study by Ahmadi and Ghazizadeh (2008) in Iran, the prevalence of G6PD deficiency in icteric newborns was considerably high and most of them were non hemolytic, so they recommend G6PD test as a screening program for every newborn at the time of delivery. As mentioned earlier, G6PD deficiency was also one of the most common causes of prolonged neonatal jaundice in present study. Hypothyroidism has also been proposed as an important etiology for prolonged jaundice during neonatal period in a study by Scott et al. (2004). In accordance with previous reports, in present study hypothyroidism was also a common underlying cause of prolonged jaundice in neonates and should be considered in the list of differential diagnosis. Conclusively, the common underlying etiologies of prolonged neonatal jaundice are very similar in different studies, with varying rates probably due to different sample sizes, different methods
employed for evaluating patients, different socioeconomic status of societies and perhaps, due to racial specifications. Conducting similar studies in different societies may contribute to better understanding of the role of ethnicity in this regard.

**CONCLUSION**

Current study showed that underlying etiology of prolonged neonatal jaundice is determinable in majority of cases (96%). These causes were breast feeding (75%), G6PD deficiency (7%), UTI (7%), hypothyroidism (4%) and miscellaneous (3%).

**REFERENCES**


