

## RESEARCH ARTICLES

# PROLONGED JAUNDICE IN NEWBORNS: WHAT IS IT ACTUALLY DUE TO?

## YENİDOĞANDA UZAMIŞ SARILIK: GERÇEKTE NEYE BAĞLI?

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### ABSTRACT

**Purpose:** Hyperbilirubinemia is a frequently observed medical condition in the neonatal period. Hyperbilirubinemia that persists beyond 2 weeks in term neonates is named "prolonged jaundice". Investigations directed towards an etiological explanation of prolonged jaundice involve multiple and expensive laboratory tests. Furthermore, no consensus has been achieved about the priority and the necessity of the laboratory tests performed during the investigation of prolonged jaundice. In this study, we assessed neonates followed in our division with a diagnosis of prolonged jaundice. **Patients and Methods:** Term neonates with prolonged jaundice who had been previously hospitalized in Gazi University Hospital Neonatal Intensive Care Unit (NICU) with a diagnosis of hyperbilirubinemia, between January 1999 and December 2001 were evaluated with respect to their etiology. **Results:** Among 381 neonates admitted to the NICU for hyperbilirubinemia, 31 were diagnosed with prolonged jaundice (8.1%). Of these 31 infants 26 were evaluated with respect to etiology and prognosis. Direct hyperbilirubinemia was documented in 1 infant. Fourteen infants were thought to have breast milk jaundice, while 5 infants had hemolysis to account for prolongation of their jaundice. Four infants with inadequate weight gain who had been breastfed and 2 more breastfed infants with inadequate weight gain and additional hemolysis were identified. **Conclusion:** Jaundice observed beyond the first 2 weeks of life in term or near term infants is mostly due to breast milk, inadequate caloric intake or hemolysis. Nevertheless, it is important to keep in mind conditions such as hypothyroidism or biliary anomalies in which early diagnosis is of vital importance.

**Key Words:** Prolonged Jaundice, Neonate, Breast Milk.

### INTRODUCTION

Jaundice is a common clinical finding in

### ÖZET

**Amaç:** Hiperbilirubinemi yenidoğan döneminde sık olarak izlenen bir tıbbi durumdur. Term yenidoğanlarda ikinci haftanın sonrasında devam eden hiperbilirubinemi "uzamış sarılık" olarak isimlendirilir. Uzamış sarılığın etiyolojik izahına yönelik araştırmalar, çok sayıdaki pahalı laboratuvar testlerini içermektedir. Bunun da ötesinde, uzamış sarılığın araştırılması sırasında kullanılan laboratuvar testlerinin öncelikleri ve önemleri konusunda bir fikir birliğine ulaşılamamıştır. Bu çalışmada, bölümümüzde uzamış sarılık tanısı ile izlenen yenidoğanları değerlendirdik. **Gereç ve Yöntem:** Ocak 1999 ile Aralık 2001 tarihleri arasında, daha önce hiperbilirubinemi tanısı ile Gazi Üniversitesi Hastanesi Yenidoğan Yoğun Bakım Ünitesi'nde (YDYBÜ) izlenmiş olan ve takiben uzamış sarılık tanısı alan term infantlar, etiyolojilerine yönelik olarak değerlendirildiler. **Bulgular:** YDYBÜ'ye hiperbilirubinemi sebebi ile yatırılan 381 yenidoğandan 31 tanesinde uzamış sarılık belirlendi (%8,1). Bu 31 yenidoğandan 26 tanesi etiyolojilerine ve prognozlarına göre değerlendirildi. Bir infantta direkt hiperbilirubinemi belirlendi. On dört infantta anne sütü sarılığı düşünülürken, 5 infantta sarılıklarının uzama sebebi olarak hemoliz gösterildi. Anne sütü alırken yetersiz kilo alımı olan dört infant varken, benzer şekilde anne sütüne devam ederken yetersiz kilo alan ve ek olarak hemoliz bulguları gösterilen iki infant belirlendi. **Sonuç:** Term ya da terme yakın infantlarda hayatın ilk iki haftasından sonra izlenen sarılık sıklıkla anne sütüne, yetersiz kalori alımına ya da hemolize bağlıdır. Bununla birlikte, erken tanının büyük bir önem taşıdığı hipotiroidi ya da bilier atrezi gibi sorunların da akılda tutulması önem taşımaktadır.

**Anahtar Kelimeler:** Uzamış Sarılık, Yenidoğan, Anne Sütü.

most newborn infants and is usually called physiologic jaundice of the newborn. Physiologic

jaundice is observed in 60% of term infants and 80% of preterm infants in the first week of life (1, 2). Physiologic jaundice is characterized by a progressive rise in serum unconjugated bilirubin concentration and is generally first observed during the third to fifth days of life (1, 3, 4). Hyperbilirubinemia is a generally benign condition in the newborn; however, it does create some anxiety amongst health care professionals due to the neurotoxic effects of bilirubin. Hyperbilirubinemia evident in the first 24 hours of life or a rapid rise in total bilirubin levels (>5 mg/dl/day) is called pathological jaundice (1). Hyperbilirubinemia persisting beyond 2 weeks of age in term infants and beyond 3 weeks of age in preterm infants is called prolonged jaundice (2). According to the literature this condition is observed in 15-40% of breast-fed infants (5, 6). Prolonged jaundice could occur due to several factors, such as breast-feeding, hemolysis, inadequate caloric intake, metabolic diseases, pyloric stenosis, hypothyroidism, different mutations in glucuronyl transferase enzyme like in Crigler Najar syndrome or Gilbert syndrome, and liver diseases. The etiological investigation of prolonged jaundice includes numerous tests, some of which are quite expensive and therefore it is difficult to establish guidelines for the management of prolonged jaundice. The objective of this study is to evaluate our cases of prolonged jaundice with respect to their etiology and appropriateness of clinical approach.

#### **PATIENTS AND METHODS**

Term (gestational age  $\geq$  37 weeks) or near term (gestational age = 36 weeks) newborns who had been treated for hyperbilirubinemia in Gazi University Hospital Neonatal Intensive Care Unit (NICU) during January 1999-December 2001 were included in the study. Infants who were still visibly jaundiced by 14 days of postnatal age were considered to have prolonged jaundice and were included in the investigation of the etiology of the condition. During the initial work-up of hyperbilirubinemia, all patients had undergone total bilirubin level measurements, complete blood counts (CBC) and blood type determination, together with mother's, direct coombs test, neonatal thyroid stimulating hormone (nTSH) screening, and blood and urine aminoacid screening. When being evaluated for prolonged jaundice, total and direct bilirubin levels together with liver enzymes, urine

analysis, urine cultures, glucose-6-phosphate dehydrogenase (G6PD) enzyme levels, T3, T4, and TSH levels, feeding regimens, and current weights together with birth weights were recorded. Following the diagnosis of prolonged jaundice, the infants were examined weekly with regards to bilirubin levels, feeding regimen and increments in weight, until jaundice was no longer visible. Weight gain was considered adequate if it was above 14-15 g/kg/day in infants of 36 weeks' gestational age and above 7-9 g/kg/day in infants of gestational age 37 weeks or above (7).

Infants who had been small for dates or who had had abnormal liver functions were also evaluated for TORCH infections.

Hemolysis was considered in infants who had had low hemoglobin values for the neonatal period, increased reticulocyte counts, and findings of hemolysis on peripheral smears. Infants who had had intermediate or high risk bilirubin levels according to Bhutani (8) within the first 72 hours of life were also considered at risk for hemolysis.

Liver functions were evaluated by measuring total and direct bilirubin levels, and aspartate aminotransferase and alanine aminotransferase enzyme levels.

When no additional etiological factors apart from breast-feeding had been identified as the possible cause of hyperbilirubinemia, a diagnosis of breast milk jaundice was considered.

#### **RESULTS**

Three hundred eighty-one newborns were admitted to the newborn nursery for hyperbilirubinemia during the study period. Amongst these newborns, 31 had been diagnosed with prolonged jaundice (8.1%), and 26 of these were evaluated for etiology and prognosis.

Of these 26 infants, 11 were female and 15 were male. Mean gestational age was 38 weeks (range: 36-41 weeks), mean birth weight was 3,164 g (range: 2,220-3,900 g). Mean age at which the diagnosis of prolonged jaundice had been made was 19 days (range: 15-35 days), and mean bilirubin level at the time of diagnosis was 14.4 mg/dl (range: 9.8-26.1 mg/dl). Direct hyperbilirubinemia had been found in only 1 patient, who was referred to the department of pediatric gastroenterology for a possible

diagnosis of biliary atresia. Thyroid functions were normal in all infants. Fourteen infants were diagnosed with breast milk jaundice, while 5 infants had hemolysis to account for prolongation of their jaundice (2 with ABO incompatibility, 2 with Rh incompatibility, and 1 with both). Four newborns had inadequate caloric intake and were being exclusively breast fed at the time of diagnosis. Finally, 2 newborns had prolonged jaundice probably due to a combination of hemolysis (1 with ABO and 1 with Rh incompatibility), breast milk jaundice and inadequate caloric intake. Table 1 summarizes the probable etiologies of prolonged jaundice in the group, while the infants who had prolonged jaundice due to breast milk and due to both breast milk and inadequate caloric intake are summarized in Table 2. Breast milk was

newborns who are exclusively breast fed, although there is not a definite value for the whole population of newborns (5, 6). The conditions that need urgent recognition and treatment in these infants are hypothyroidism, metabolic diseases, and hepatic diseases such as biliary atresia. Urinary tract infections or TORCH infections must also be considered so as to avoid important complications. Therefore, when evaluating newborns who are still jaundiced beyond 2-3 weeks of life, thyroid functions, direct bilirubin measurements, urinary and blood aminoacid and reducing substance screenings, and examination of urine and feces by the physicians are to be performed initially. However, breast milk jaundice, hemolysis and infections are identified more frequently in newborns with prolonged jaundice. Although

Table-1: The etiology of prolonged jaundice in newborns.

Etiology	No. of patients	%	Mean age at which jaundice resolved (days)
Breast milk	14	53.8%	53 (29-129)
Hemolysis	5	19.3%	70 (48-117)
Breast milk + Inadequate caloric intake	4	15.4%	24 (18-28)
Breast milk + Inadequate caloric intake + Hemolysis	2	7.7%	45 (30-60)
Other (direct hyperbilirubinemia)	1	3.8%	-

Table-2: Details of the patients with prolonged jaundice due to breast milk or breast milk and inadequate caloric intake.

		BREAST MILK (N=14)	BREAST MILK + INADEQUATE CALORIC INTAKE (N=6)
Weight gain	Before diagnosis	24 g/kg/d	1.75 g/kg/d
	After diagnosis	18 g/kg/d	15.4 g/kg/d
Feeding regimen	Before diagnosis	Breast milk	Breast milk
	After diagnosis	Breast milk	Breast milk + Formula
Mean bilirubin level (mg/dl)		14.5	15.6
Mean age at diagnosis (days)		19.3	15

#### ABBREVIATIONS

CBC: Complete blood count  
 G6PD: Glucose-6-phosphate dehydrogenase  
 IVIG: Intravenous immunoglobulin  
 NICU: Neonatal intensive care unit  
 nTSH: Neonatal thyroid stimulating hormone  
 UDPGT: Uridine-diphosphate glucuronyltransferase

supplemented with formula feeding in infants who had had inadequate weight gain.

#### DISCUSSION

Prolonged jaundice is reported in 15-40% of

TORCH infections and urinary tract infections are well-known causes, we did not diagnose either of these conditions in our group.

Although there are no compatible data in the literature, the use of intravenous immunoglobulin (IVIG) in place of exchange transfusions in infants with hemolytic jaundice due to ABO or Rh incompatibility may result in prolongation of jaundice because of the persistence of antibodies in the circulation, instead of their removal by

exchange transfusions. In our group, none of the patients with hemolysis due to ABO or Rh incompatibility had received exchange transfusions, but instead they were treated with IVIG, which, as hypothesized above, might be responsible for prolonging the jaundice due to ongoing hemolysis.

Jaundice related to breast milk is defined as 2 different entities. The first is called breast feeding jaundice and is observed in the early days of life and is considered to be mostly due to inadequate caloric intake. These babies are noted to have more weight loss than formula-fed infants of the same age (4, 9-11). The second is called breast milk jaundice and is observed after the first week of life (4, 10). Although not clear, the etiology is considered multifactorial, including factors such as breast milk pregnane-3(a),20(b)-diol, non-esterified fatty acids, and beta glucuronidase enzyme, all of which have been shown to be associated with unconjugated hyperbilirubinemia (4,11). Recently, Gilbert syndrome was also considered to play a role in breast milk jaundice. Mauro et al. (12) have shown uridine-diphosphate glucuronyltransferase (UDPGT) gene mutations in 17 newborns with breast milk jaundice. In particular, the breast milk following the colostrum is held responsible for this type of association. In our group, 53.8% of the infants, who had had a mean bilirubin level of 14.5 mg/dl, were suspected of having breast milk jaundice. Similarly, Tekinalp et al. (13), in their study investigating prolonged jaundice in the neonatal period, were not able to demonstrate any etiologies in 76.8% of their patients, and considered breast-feeding the possible cause of hyperbilirubinemia in these infants.

In our group of infants with prolonged jaundice, 6 (23.1%) demonstrated inadequate weight gain while being fed exclusively with breast milk. Although jaundice due to inadequate caloric intake is reported to occur during the early days of life in breast-fed infants, Ishihara et al. (14) reported fasting hyperbilirubinemia in adults. Therefore this group of infants was considered jaundiced due to both breast milk and inadequate nutrition. The rapid decline observed in bilirubin levels following formula supplementation and associated weight gain support this consideration.

Mutations related to Gilbert syndrome were

not investigated in our patients; these also might have played a contributory role. Jaundice due to G6PD deficiency involving novel mechanisms other than hemolysis is being reported with increasing frequency in the literature. A genetic interaction between Gilbert syndrome and G6PD deficiency has also been shown to cause prolonged jaundice (15). In patients with G6PD deficiency, the rapid rise in bilirubin levels in the first 72 hours of life is considered suggestive of this condition. Nevertheless, when the ethnic and geographical characteristics of Turkey are considered, G6PD enzyme level measurements may be regarded as an important factor in the investigation of prolonged jaundice.

In conclusion, jaundice observed or still continuing after 14 days of life in term or near term infants is mostly due to breast milk, inadequate caloric intake, hemolysis or any combination of these conditions. G6PD deficiency or UDPGT gene mutations are other conditions deserving attention. As prolonged jaundice in the neonatal period is mostly related to breast-feeding, early intensive and expensive investigations are not mandatory in most cases. As the concept of feeding of newborns with breast milk only is strongly supported in our country, as it is throughout the world, an increase is observed in the number of newborns with prolonged jaundice in whom no apparent causes were detected. However, this observation does not necessitate stopping or interrupting breast-feeding in any way. On the contrary, it has been suggested that this prolongation of physiologic jaundice in breast-fed infants may provide protective effects in newborns due to the antioxidant effects of bilirubin (4).

In newborns with prolonged jaundice, diseases such as hypothyroidism and biliary atresia should be eliminated for an early diagnosis, and treatment reduces morbidity and mortality. A careful history for the evaluation of urinary and stool color is very important and it is also suggested that the physician personally see the stools and obtain a direct bilirubin level to avoid further unnecessary tests for the evaluation.

According to the results of our study, prolonged jaundice in newborns is mostly related to breast-feeding and is benign in course. Therefore we think that intensive early etiological investigations may not be mandatory

in the absence of clear clinical clues related to hyperbilirubinemia disorders.

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#### REFERENCES

1. MacMahon JR, Stevenson DK, Oski FA. Bilirubin. In: Taesusch HW, Ballard RA (eds). *Avery's Diseases of the newborn*. Philadelphia, W.B. Saunders Press, 1998: 995-1045.
2. Maisles MJ. Neonatal hyperbilirubinemia. In: Marshall HK, Avroy AF (eds). *Care of the high-risk neonate*. Philadelphia, W.B. Saunders Press, 2001: 324-363.
3. Frank CG, Cooper SC, Merenstein GB. Jaundice. In: Merenstein GB, Gardner SL (eds). *Handbook of neonatal intensive care*. St Louis, Mosby Press, 1998: 393-413.
4. Gartner LM, Herschel M. Jaundice and breastfeeding. *Pediatric Clin North Am* 2001; 48: 389-401.
5. Hall RT, Barun WJ, Callenbach JC, Metzl K, Sheehan NB, Karth CG. Hyperbilirubinemia in breastfed vs formula-fed infants in the first six weeks of life: Relationship to weight gain. *Am J Perinatol* 1983; 1: 47-51.
6. Kelly DA, Stanton A. Jaundice in babies: Implications for community screening for biliary atresia. *Br Med J* 1995; 310: 1172-1173.
7. Kalhan CSC, Price PT. Nutrition and selected disorders of the gastrointestinal tract. In: Marshall HK, Avroy AF (eds). *Care of the high-risk neonate*. Philadelphia, W.B. Saunders Press, 2001: 147-194.
8. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a precharge hour-specific bilirubin for subsequent hyperbilirubinemia in healthy term and near-term newborns. *Pediatr* 1999; 103: 493-498.
9. Arias IM, Gartner LM, Seifter S, Furman M. Prolonged neonatal unconjugated hyperbilirubinemia associated with breast feeding and a steroid, pregnane-3(a),20(b)-diol in maternal milk that inhibits glucuronide formation in vitro. *J Clin Invest* 1964; 43: 2037-2047.
10. Gourley GR. Breastfeeding, diet, and neonatal hyperbilirubinemia. *Neo Rev* 2000; 1: 25-30.
11. Gourley GR, Arend RA. b-glucuronidase and hyperbilirubinemia in breastfed and formula-fed babies. *Lancet* 1986; 1: 644-646.
12. Maruo Y, Nishizawa K, Sato H, Sawa H, Shimada M. Prolonged unconjugated hyperbilirubinemia associated with breast milk and mutations of bilirubin uridine-diphosphate glucuronosyltransferase gene. *Pediatr* 2000; 106: 1-4.
13. Tekinalp G, Ergin H, Erdem G, Yurdak k M, Yiđit Ő. Yenidođan d neminde uzamıř sarılıklar: 82 vakanın deđerlendirilmesi. *Çocuk Sađlıđı ve Hastalıkları Dergisi* 1996; 39: 441-448.
14. Ishihara T, Gabazza EC, Adachi Y, Sato H, Maruo Y. Genetic basis of fasting hyperbilirubinemia. *Gastroenterology* 1999; 116: 1272-1278.
15. Kaplan M. Genetic interactions in the pathogenesis of hyperbilirubinemia: Gilbert's syndrome and glucose-6-phosphate dehydrogenase deficiency. *J Perinatol* 2001; 21: 30-34.