PORTUGUESE JOURNAL OF PEDIATRICS

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CASE REPORT

Breast milk jaundice: when to cease investigation in the jaundiced neonate?

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Abstract

Introduction: Breast milk jaundice is a benign condition in breastfed newborns, characterized by an increase in indirect bilirubin levels, resulting in yellowish discoloration of the skin and sclerae. It usually appears in the first week of life, with a peak incidence in the second week, and can persist for up to twelve weeks. This physiological condition is a diagnosis of exclusion and is not associated with any underlying pathology. **Case report:** A full-term previously healthy newborn presented with jaundice in the first week of life, which persisted beyond 14 days, requiring several cycles of phototherapy. After pathological conditions were excluded, the diagnosis of breast milk jaundice was confirmed, with complete resolution by two months of age. **Discussion:** This case highlights the importance of recognizing and properly managing this condition, emphasizing the need to educate parents about its benign nature and encouraging the continuation of breastfeeding.

Keywords: Neonatal jaundice. Breastfeeding. Neonatal hyperbilirubinemia. Phototherapy. Bilirubin. Infants.

Icterícia do leite materno: quando interromper a investigação no recém-nascido com icterícia?

Resumo

Introdução: A icterícia do leite materno é uma condição benigna em recém-nascidos amamentados; caracteriza-se pelo aumento dos níveis de bilirrubina indireta, resultando na coloração amarelada da pele e escleróticas. Geralmente surge na primeira semana de vida, com um pico de incidência na segunda semana, podendo persistir até às doze semanas. Esta condição fisiológica é um diagnóstico de exclusão, não estando associada a nenhumapatologia subjacente. **Relato de caso:** Recém-nascido de termo, previamente saudável, com icterícia na primeira semana de vida, que persistiu além dos 14 dias, com necessidade de vários ciclos de fototerapia. Após exclusão de causas patológicas,assumiu-se o diagnostico de icterícia do leite materno, com resolução da icterícia aos dois meses de vida. **Discussão:** O caso sublinha a importância de reconhecer e orientar corretamente esta condição e destaca a necessidade de educar os pais sobre a sua natureza benigna, incentivando a continuação da amamentação.

Palavras-chave: Icterícia neonatal. Aleitamento materno. Hiperbilirrubinemia neonatal. Fototerapia. Bilirrubina. Recém-nascido.

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Received: 29-10-2024
Accepted: 12-06-2025
https://pjp.spp.pt

Available online: 16-07-2025
Port J Pediatr. 2026;57(2):111-115
DOI: 10.24875/PJP.24000085

Keypoints

What is known
- Breast milk jaundice is a benign condition that occurs in breastfed newborns.
- It appears in the first week of life and can persist for up to 12 weeks.
- It is a diagnosis of exclusion that rarely requires treatment.

What is added
- An atypical presentation, with extremely high bilirubin levels and multiple cycles of phototherapy with a small initial response to treatment.
- Description of a practical management approach to breastfeeding jaundice.
- Systematic review of the diagnostic assessment required to rule out pathological conditions of neonatal jaundice.

Introduction

Jaundice is characterized by yellow pigmentation of the skin and eyes caused by increased bilirubin levels in the blood. Almost all newborns have circulating bilirubin levels above 1 mg/dL and changes in the skin and sclerae are visible when levels are above 5 mg/dL. This makes jaundice one of the most prevalent conditions of the neonatal period, arising from elevated bilirubin production due to the short lifespan of fetal erythrocytes and immature hepatic enzymes.

Breast milk jaundice is a benign condition identified in healthy newborns who are being breastfed, and is marked by an increase in unconjugated bilirubin. This usually emerges after the first week of life, reaching its peak between the second and third weeks, and can persist – albeit with gradual improvement – for up to twelve weeks. Considered a diagnosis of exclusion, other potential causes must be ruled out, such as hemolytic disease, infections, or liver abnormalities. Despite its duration, this condition does not reflect any underlying illness, nor does it require the cessation of breastfeeding.[1,2]

This case is reported due to its atypical course of severe hyperbilirubinemia, responding to phototherapy but with repeated rebounds, requiring multiple treatment cycles. Despite extensive diagnostic evaluation, the final diagnosis was breast milk jaundice. This case demonstrates the difficulty of diagnosing neonatal jaundice and outlines a practical approach managing breastfeeding-associated hyperbilirubinemia.

Case report

A four-day-old newborn was seen at the pediatric emergency department with jaundice and excessive sleepiness. The pregnancy progressed without complications, and a fetal ultrasound at 22 weeks and six days detected an aberrant right subclavian artery. Group B *Streptococcus* screening was negative.

According to the obstetric history, this was the first infant of an O, Rh-negative mother, who received Rho (D) immune globulin at 32 weeks and had hypothyroidism managed with levothyroxine. The newborn was delivered via vacuum extraction at 38 weeks and five days, with a birth weight of 3130 grams, Apgar score of 10/10/10, and a small occipital cephalohematoma. The infant's blood type was A, Rh-positive, and the direct Coombs test was negative. The newborn remained hospitalized with her mother and was discharged on day three, exclusively breastfed, with a maximum weight loss of 8.5%. Jaundice was noted at discharge and a transcutaneous bilirubin assessment registered 11.8 mg/dL – below the threshold for phototherapy according to the 2022 American Academy of Pediatrics guidelines.

At the emergency department, blood testing revealed hemoglobin 18.3 g/dL, leukocytes 11,800/µL (Neutrophils 5,020/µL, Lymphocytes 5,060/µL), no reticulocytosis (67 G/L), platelets 279,000/µL, total bilirubin 26.8 mg/dL, direct bilirubin 0.5 mg/dL, lactate dehydrogenase 531 U/L, aspartate transaminase 53 U/L, alanine transaminase 29 U/L, gamma-glutamyl transferase 111 U/L, total proteins 5.2 g/dL, albumin 3.5 g/dL, C-reactive protein 0.37 mg/dL, and procalcitonin 0.09 ng/mL. The blood culture was negative. The urine sample obtained via bladder puncture showed normal urinalysis and a negative culture. Respiratory secretions tested negative for respiratory viruses.

According to the guidelines applied, the threshold for phototherapy at that time was 20.8 mg/dL, so treatment was initiated. After 24 hours, bilirubin levels declined, allowing for safe discontinuation.

Despite initial improvement, serial evaluations after cessation showed slight bilirubin rebounds, with values of 13.8 mg/dL at 12 hours and 16.3 mg/dL at 36 hours. These levels did not meet treatment criteria.

By day seven, total bilirubin increased to 21.4 mg/dL, crossing the threshold of 21.1 mg/dL, prompting phototherapy. After 24 hours, phototherapy was discontinued as total bilirubin decreased to 12.7 mg/dL. A cerebral ultrasound was performed with no abnormal findings.

On day eight, further lab investigations showed a decrease in lactate dehydrogenase from 531 to 432 U/L, no increase in transaminases, gamma-glutamyl transferase, or liver function abnormalities, no thyroid abnormalities, and no signs of hemolysis or anemia. The newborn screening test performed on day four was negative. Elevated lactate dehydrogenase prompted an evaluation for hemoglobinopathies. A hemoglobin electrophoresis showed 78.6% fetal hemoglobin and the remainder was hemoglobin A, which was consistent with the patient's age.

Approximately 48 hours after phototherapy cessation, on day 10, bilirubin rebounded to 21.7 mg/dL, just above the threshold of 21.5 mg/dL, leading to the resumption of phototherapy. A subsequent liver profile and cholestatic enzyme study showed no abnormalities. Another blood typing and direct Coombs test retrieved the same results as before.

The case was discussed with specialists in Medical Genetics and Hepatology, leading to an investigation to rule out Crigler-Najjar and Gilbert syndromes, which were both negative. DNA sequencing of the UGTA1 gene excluded Lucey-Driscoll syndrome and its variants.

On day 12, after 36 hours of therapy, double phototherapy was discontinued as bilirubin levels normalized. A follow-up re-evaluation on day 15 showed total bilirubin at 14.1 mg/dL. Urinary *cytomegalovirus* DNA was not detected; alpha 1 antitrypsin levels, cryotest, and eosin-5-maleimide test results were normal.

Throughout hospitalization, the newborn was breastfed exclusively, maintained good sucking reflexes, normal urination and defecation, adequate weight gain, and remained clinically stable with a normal physical examination. After three cycles of phototherapy, bilirubin levels stabilized, and multiple secondary causes were ruled out. The newborn was discharged on day 17. Outpatient follow-up showed a downward bilirubin trend and the patient became anicteric by two months, with no recurrence of jaundice.

Discussion

Bilirubin is a product of heme protein breakdown from erythrocytes. In the bloodstream, bilirubin is primarily bound to albumin and transported to the liver, where it binds to ligandins (Y proteins), which are in lower concentrations at birth. It is transported to the smooth endoplasmic reticulum, where it undergoes conjugation. This process attaches glucuronic acid to bilirubin under the action of the enzyme uridine diphosphoglucuronate glucuronosyltransferase (UDPGT), making it water-soluble and allowing excretion in the bile. However, UDPGT activity is significantly reduced in newborns, leading to less efficient conjugation.[2]

A genetic mutation in the *UGT1A1* gene, which encodes UDPGT, can further impair bilirubin conjugation. After conjugation, bilirubin is excreted into the duodenum via the bile ducts and metabolized by intestinal bacteria into urobilinogen. A portion is reabsorbed into the enterohepatic circulation, while the rest is excreted as stercobilin in feces or filtered by the kidneys as urobilin in urine. Unconjugated bilirubin, being lipophilic, can cross the blood-brain barrier and cause central nervous system damage. In severe hyperbilirubinemia (levels above 25-30 mg/dL), there is a significant risk of kernicterus, a form of neurological dysfunction.[3,4]

The exact cause remains unclear; there is scientific evidence that genetic and environmental factors have a role in breast milk jaundice. Certain components of breast milk, such as pregnane-3α,20β-diol, might inhibit UDPGT activity, reducing bilirubin conjugation and excretion. Additionally, ß-glucuronidase in the intestinal mucosa hydrolyzes conjugated bilirubin back into its unconjugated form, increasing enterohepatic circulation. This is aggravated by lower intestinal bacterial enzyme levels in newborns, which limit bilirubin degradation into stercobilin.[1,3]

Inflammatory cytokines, particularly interleukin-1β (IL-1β), can suppress *UGT1A1* gene expression and increase intestinal permeability, promoting bilirubin reabsorption. IL-1β also modifies the intestinal microbiome, intensifying the enterohepatic cycle of bilirubin.[2,3]

Epidermal growth factor (EGF), another breast milk component, enhances gastrointestinal tract development but slows intestinal transit, favoring bilirubin reabsorption. EGF also interferes with bilirubin transport in hepatocytes, impairing its excretion into bile.[1,2]

Elevated alpha-fetoprotein (AFP) levels are often found in newborns with breast milk jaundice. AFP inhibits *UGT1A1* activity, interferes with bilirubin transporters like MRP2, and influences genes responsible for bilirubin metabolism and excretion.[1,2,4,5]

Breast milk jaundice is a multifactorial condition involving enzymatic inhibition, increased enterohepatic circulation, and altered bilirubin metabolism.

Treatment depends on the infant's total serum bilirubin level but the prognosis is favorable. First-line treatment is phototherapy, initiated if bilirubin levels exceed the thresholds recommended by the 2022 American Academy of Pediatrics' guidelines, except in cases requiring immediate exchange transfusion.

Table 1. Differential diagnosis of breast milk jaundice

Pathological causes of indirect hyperbilirubinemia	Laboratory exams/tests in the newborn
Increased production	
Immune-mediated hemolysis	
ABO incompatibility Rh incompatibility	Blood type and Rh factor typing Positive direct coombs test Decreased hematocrit and hemoglobin Reticulocytosis Peripheral blood smear with microspherocytes
Non-immune-mediated hemolysis	
Congenital defects of the erythrocyte membrane (e.g., spherocytosis, elliptocytosis)	Decreased hematocrit and hemoglobin Reticulocytosis Peripheral blood smear with spherocytes, elliptocytes EMA binding test, cryotest, erythrocyte osmotic fragility test
Erythrocyte enzymatic defects (e.g., G6PD, pyruvate kinase deficiency, and congenital porphyria)	Decreased hematocrit and hemoglobin Reticulocytosis Peripheral blood smear with bite cells, "prickle" cells Blood G6PD level measurement (outside the acute phase)
Hemoglobinopathies	Decreased hematocrit and hemoglobin Reticulocytosis Peripheral blood smear with target cells Hemoglobin electrophoresis
Infection/sepsis	Leukocytosis, neutrophilia Increased C-reactive protein/procalcitonin Positive blood culture/urine culture
Polycythemia (children of diabetic mothers, LGA, IUGR, high altitudes)	Increased hematocrit and hemoglobin
Blood sequestration in closed areas (e.g., cephalohematoma)	Decreased hematocrit and hemoglobin CT/MRI of the Head
Decreased clearance	
Crigler-Najjar syndrome Type I and II Gilbert's syndrome	Genetic test (sequencing of the UGTA1 gene)
Congenital hypothyroidism	Newborn screening Thyroid function
Inborn errors of metabolism (galactosemia, tyrosinemia)	Newborn screening Extended analytical assessment with uric acid, ammonia, lactate Capillary glucose and ketone levels Arterial blood gas Urine sample collection Genetic tests (for confirmation)
Breastfeeding jaundice	Hypovolemia and hypernatremia

EMA: eosin-5-maleimide; G6PD: glucose-6-phosphate dehydrogenase; CT: computed tomography; MRI: magnetic resonance imaging.

The gravest complication of neonatal jaundice, although rare in breast milk jaundice, is acute bilirubin encephalopathy and kernicterus (chronic bilirubin encephalopathy) due to its potential for severe neurological damage.[6]

Parents should be informed about the nature of breast milk jaundice and its likely clinical progression. Additionally, breastfeeding should be continued unless contraindicated.

In cases of elevated and recurrent jaundice after phototherapy, as described in this case, further investigation must exclude pathological conditions. It is key to rule out secondary causes of unconjugated hyperbilirubinemia, such as hemolysis due to isoimmunization (e.g., ABO or Rh incompatibility), erythrocyte membrane/enzyme defects, hereditary hemolytic diseases (e.g., hemoglobinopathies), infections, polycythemia, thyroid disorders

(e.g., hypothyroidism), metabolic diseases related or unrelated to bilirubin metabolism, blood sequestration in closed areas (e.g., cephalohematoma), or breastfeeding-associated jaundice (by assessing breastfeeding techniques and weight gain).[1-3]

In neonatal jaundice, investigations should be guided by the clinical presentation, the progression of hyperbilirubinemia, and the exclusion of key pathological conditions, as outlined in table 1. In the absence of significant family history and other clinical manifestations such as anemia, lethargy, anorexia, or neurological changes, it is considered jaundice with no alarming signs. Furthermore, an adequate clinical and laboratory response to treatment, along with the exclusion of risk factors (e.g., blood incompatibilities, hemolytic diseases, infections, and genetic disorders) and a normal neonatal screening test, supports the diagnosis of breast milk jaundice.[1,6]

Nonetheless, clinical follow-up is essential to monitor the emergence of warning signs.

In this case, given the infant's excellent clinical condition, adequate weight gain, clinical evolution consistent with breast milk jaundice and exclusion of pathological conditions of neonatal jaundice due to unconjugated bilirubin, a diagnosis of breast milk jaundice was established. After discharge, clinical monitoring was chosen, with further investigation reserved if warning signs were identified.

In summary, breast milk jaundice is a benign condition that can persist for several weeks in breastfed newborns. Accurate diagnosis and identification are essential, as is the exclusion of serious pathological conditions, to reach the final diagnosis. Distinguishing it from other forms of jaundice is crucial for properly managing the newborn and ensuring the safe continuation of breastfeeding.

Author contributions

C. Gomes: planning; resources; writing; F. Curinha: planning; writing; R. Castelo: planning; supervision; validation; writing.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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