



# A case of classic galactosemia manifesting as neonatal early and profound indirect hyperbilirubinemia

Erken ve şiddetli indirekt hiperbilirübinemi ile belirti veren bir klasik galaktozemi vakası

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## The known about this topic

Galactosemia is a carbohydrate metabolic disorder with a hereditary deficient galactose metabolizing enzyme. Neonatal cholestasis is a major and known major manifestation of the disease.

## Contribution of the study

Severe indirect hyperbilirubinemia also could be an initial symptom of the disease, and should be kept in mind and added to differential diagnoses.

## Abstract

Galactosemia is a rare autosomal recessive metabolic disorder that has three major types. The most common type is classic galactosemia. These patients have deficient galactose-1-phosphate-uridylyltransferase. The enzyme deficiency often results in symptomatic disease if breastfeeding or lactose-containing formulas continue. Neonatal jaundice is among the most prevalent symptoms. Although patients with classic galactosemia mostly demonstrate direct neonatal hyperbilirubinemia (cholestasis), seldom they may initially have indirect hyperbilirubinemia. Herein, we present a newborn with initial neonatal profound indirect hyperbilirubinemia who responded well to intensive phototherapy, then presented with cholestasis and was finally diagnosed as having classic galactosemia. Unfortunately, major textbooks of neonatology and pediatrics are still missing galactosemia as one of the differential diagnoses of neonatal indirect hyperbilirubinemia. It is just mentioned as prolonged or direct neonatal hyperbilirubinemia. We recommend that galactosemia be included in the differential diagnosis of neonatal early indirect hyperbilirubinemia because neonatal screening results may be delayed or missed completely.

**Keywords:** Cholestasis, galactosemia, indirect hyperbilirubinemia, neonatal jaundice

## Öz

Galaktozemi nadir görülen otozomal resessif metabolik bir hastalıktır ve üç ana tipi vardır. En sık görülen tip klasik galaktozemi'dir. Bu hastalarda, galaktoz-1-fosfat-üridiltransferaz eksikliği vardır. Emzirmeye veya laktoz içeren formül mamalara devam edilirse, enzim eksikliği sıklıkla semptomatik hastalıkla sonuçlanır. Yenidoğan döneminde sarılık en sık görülen belirtiler arasındadır. Klasik galaktozemili hastalar çoğunlukla direkt yenidoğan hiperbilirübinemisi (kolestaz) göstermelerine rağmen, nadiren başlangıçta indirekt hiperbilirübinemi bulunabilir. Burada, başlangıçta şiddetli indirekt hiperbilirübinemisi olan, yoğun fototerapiye iyi yanıt veren, daha sonra kolestaz ile başvurmuş ve sonuçta klasik galaktozemi tanısı konulan bir yenidoğan olguyu sunuyoruz. Ne yazık ki, neonatoloji ve pediatri ile ilgili temel ders kitaplarında, yenidoğan döneminde indirekt hiperbilirübineminin ayırıcı tanılarından biri olarak galaktozemiye halen yer verilmemektedir. Sadece uzamış veya direkt yenidoğan hiperbilirübinemisi varlığında galaktozemi söz edilmektedir. Galaktozeminin yenidoğanın erken indirekt hiperbilirübinemisinin ayırıcı tanısına dahil edilmesini öneriyoruz, çünkü yenidoğan tarama sonuçları gecikebilir veya tanı tamamen atlanabilir.

**Anahtar sözcükler:** Galaktozemi, indirekt hiperbilirübinemi, kolestaz, yenidoğan sarılığı

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## Introduction

Galactosemia is a metabolic disease with three major types, and classic galactosemia is the most common (1). Poor feeding, poor weight gain, and jaundice are among the most common symptoms. The infant's condition worsens if untreated. Lethargy, hypotonia, hypoglycemia, hemolysis, vomiting, abdominal distension, and ecchymosis will develop. Galactosemia has been a known cause of neonatal jaundice for a long time (2), which is often described as direct or prolonged hyperbilirubinemia (2, 3).

## Case

Here, we report a female newborn with severe indirect-hyperbilirubinemia who was eventually diagnosed as having classic galactosemia. She was born at 38 gestational weeks to a 34-year-old mother with an unremarkable prenatal history. The baby was delivered by cesarean section with normal Apgar score, 2920 g birthweight, and normal growth parameters/examinations except for right-hand polydactyly.

Her parents were healthy first-cousin adults with O+ blood-group. The father had a neonatal history of jaundice and blood-exchange-transfusion. Her sibling was a normal 4-year-old female, who also had a history of neonatal jaundice that recovered with home phototherapy. The parents denied having any liver/hemolytic or other disorders in the family. She was discharged after 36-hr in a good condition without icterus from the nursery.

She was first icteric on the 4<sup>th</sup> day with total (T) bilirubin (Bil): 18 mg/dL and direct (D) Bil: 0.6 mg/dL. The parents chose home phototherapy although they were advised for hospital admission. They rechecked bilirubin on the 7<sup>th</sup> day of life because they felt the jaundice was getting worse. The mother mentioned some poor feeding in her baby. She was hospitalized with TBil: 34 mg/dL and DBil: 2.7 mg/dL, so intensive phototherapy, sepsis tests, and antibiotic therapy were performed. She was prepared for exchange transfusion. The infant responded very well to intensive phototherapy; therefore, the exchange transfusion was withheld. The mother was satisfied with her breastfeeding soon after. Six-hours of intensive phototherapy resulted in TBil: 22 mg/dL and DBil: 1.2 mg/dL. The baby had bronze skin and dark urine, but her stool had a greenish color. In laboratory tests, white blood cells (WBC) were 12,700, hemoglobin (Hb): 16.9 mg/dL, platelet (Plt): 223,000, glucose (Glu): 122 mg/dl, erythrocyte sedimentation rate (ESR): 1 mm/h, C-reactive protein (CRP): 5.3 mg/L, sodium (Na): 147 mmol/L, potassium (K): 5.5 mmol/L, creatinine (Cr): 0.4 mg/dl, reticulocytes (retic): 0.3%, blood group and

Rh: O+, glucose-6-phosphate dehydrogenase (G6PD): normal. Urinalysis first showed blood (+1), protein (2+), and bilirubin (2+). The second urine sample was normal. Blood/urine cultures were negative, alanine aminotransferase (ALT) as 91 IU/L, aspartate aminotransferase (AST): 100 IU/L, and thyroid-stimulating hormone (TSH): 1.8 mIU/L. Abdominal ultrasonography was normal, showing normal sized liver/spleen. Cardiac consultation and echocardiography showed normal results. The infant's yellowish and bronze-skin color improved significantly, with normalization of urine color. Stool color was still normal. T/Dbilirubin and hemoglobin levels gradually decreased. She was discharged after 7 days of antibiotic-therapy and advised to be followed as an outpatient with ALT: 61 IU/L, AST: 69 IU/L, gamma-glutamyl transpeptidase (GGT): 25 IU/L, TBil: 9.2 mg/dl, DBil: 1.2 md/dl, Hb: 10.3 mg/dL. The baby still looked icteric and mildly bronzed a week later; she had an acceptable weight gain while on breastfeeding with normal urine/stool color, and neither hepatosplenomegaly nor abdominal distension. At the second outpatient visit, laboratory values were TBil: 5.2 mg/dl and DBil: 2.4 mg/dl, Hb: 9.7 mg/dL, WBC: 7600/mm<sup>3</sup>, Glu: 169 mg/dl, retic: 0.4%, ALT: 61IU/L, AST: 69 IU/L, and she was still icteric and producing greasy stool. Metabolic screen tests were ordered. A week later, abdominal distension with dark urine and acholic stool developed. She was readmitted. Her feeding was good and she was lively. Hepatosplenomegaly could not be detected because of severe ascites, but abdominal ultrasonography revealed enlarged liver/spleen with a large amount of fluid in the abdominal cavity. Blood tests revealed the following: WBC: 6500/mm<sup>3</sup>, Plt: 266,000/mm<sup>3</sup>, Hb: 8.7 mg/dL, mean corpuscular volume (MCV): 110 fl, and retic: 16.7%. A blood-smear showed a large amount of acanthocytes (spur cells). Glu: 169 mg/dl, TBil: 6.3 mg/dl, DBil: 4 mg/dl, ALT: 84 IU/L, AST: 304 IU/L, albumin (Alb): 2.8 mg/dl, ESR: 6 mm/hr, CRP: 5 mg/L, prothrombin time (PT): 21 sec, partial thromboplastin time (PTT): 65 sec, Na: 134 mmol/L, K: 5 mmol/L, ferritin: 2827 ng/ml. Ascitic fluid had Glu: 95 mg/dl, protein: 0.8 mg/dl, WBC: 0–1 mm<sup>3</sup>, and RBC: 3200 mm<sup>3</sup> and a negative culture. Urinalysis showed 12–15 leukocytes unit.

Broad-spectrum antibiotics, vitamin K, packed-cell, and albumin were administered. In this hospital admission, the mother informed us that three of the paternal second cousins had icterus and abdominal distension requiring exchange-transfusion and one with kernicterus; one of which is still alive. She added no more information. As the patients' records were reviewed, we noticed that their living relative had known galactosemia. The infant's soy-based formula was substituted thereafter.

All fluid cultures were negative except for urine culture which revealed *Klebsiella* (25,000 colony count). The infant's condition, icterus, and abdominal distention gradually improved. Urine sugar chromatography then also showed a dense galactose band. All tests significantly improved after the lactose-free formula substitution. The baby did well and had normal growth and feeding without icterus in subsequent follow-up visits. Galactose-1-phosphate-uridylyl-transferase deficiency (<5%) also confirmed the diagnosis. An ophthalmic examination was also normal. Written informed consent was obtained from the patient's family.

### Discussion

The newborn patient described here had severe indirect hyperbilirubinemia in the first week of life that even fulfilled indication criteria for blood exchange transfusion. In this patient, jaundice responded to intensive phototherapy very well and quickly, so the physician decided to withhold exchange transfusion.

The first diagnostic suspicion in this baby was sepsis that responded well to antibiotic therapy. Hemolytic diseases were excluded because of a normal reticulocyte count and blood smear. Liver diseases were also under consideration, but the improvement of clinical status with antibiotics was assumed as liver involvement in the septic process.

We could find just three case reports of galactosemia and indirect hyperbilirubinemia described in the literature (4–6). Woo et al. (4) described a newborn with early severe indirect hyperbilirubinemia requiring exchange-transfusion very early in life. The patient's sibling died in early infancy because of indirect hyperbilirubinemia despite performing exchange-transfusion (presumably of galactosemia). Takci et al. (5) reported a neonate with vitreous hemorrhage and galactosemia who first was admitted because of indirect hyperbilirubinemia on the 7<sup>th</sup> day of life and received intensive phototherapy for two days. She was then sent to another hospital because of poor feeding, cholestatic jaundice, and hepatomegaly. Her parents (first cousins) described two abortions and a female neonate with indirect hyperbilirubinemia requiring exchange-transfusion who died after 7 days. Karadag et al. (6) also presented a newborn who was admitted on his 3<sup>rd</sup> day of life for indirect hyperbilirubinemia and long QT-syndrome with galactosemia. Although some experts accept galactosemia as an etiology of early indirect hyperbilirubinemia, it is still missing among the etiologic causes in popular pediatric/neonatal textbooks (3, 7).

Mass neonatal screening including galactosemia is performed in the United States (8), and some European

countries (9), but many countries such as Iran have minor neonatal screening tests, among which galactosemia is not yet included (10).

**Informed Consent:** Written informed consent was obtained from the patient's family.

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### References

- Berry GT. Classic Galactosemia and Clinical Variant Galactosemia. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews. Seattle,WA: University of Washington;1993.
- Millis SC. Jaundice associated with galactosemia in the newborn. J Indiana State Med Assoc 1958; 51: 1656–7.
- Kaplan M, Wong RJ, Sibley E, Stevenson DK. Neonatal jaundice and liver diseases. In: Martin R, Fanaroff A, Walsh M, editors. Fanaroff and Martin's Neonatal-Perinatal Medicine. 10<sup>th</sup> edition. Philadelphia,PA: Elsevier, Saunders; 2015.p.1643–5.
- Woo HC, Phornphutkul C, Lupton AR. Early and severe indirect hyperbilirubinemia as a manifestation of galactosemia. J Perinatol 2010; 30: 295–7.
- Takci S, Kadayırcılar S, Coskun T, Yigit S, Hismi B. A rare galactosemia complication: vitreous hemorrhage. JIMD Rep 2012; 5: 89–93.

6. Karadag N, Zenciroglu A, Eminoglu FT, et al. Literature review and outcome of classic galactosemia diagnosed in the neonatal period. *Clin Lab* 2013; 59: 1139–46.
7. Squires JE. Manifestations of liver diseases. In: Kliegman RM, Stanton B, St. Geme J, Schor NF, editors. *Nelson Textbook of Pediatrics*. 2 volume Set. 20 edition. Philadelphia, PA: Saunders, Elsevier; 2016. p.1923–5.
8. Pyhtila BM, Shaw KA, Neumann SE, Fridovich-Keil JL. Erratum to: Newborn screening for galactosemia in the United States: Looking Back, Looking Around, and Looking Ahead. *JIMD Rep* 2015; 15: 133.
9. Ohlsson A, Guthenberg C, von Döbeln U. Galactosemia screening with low false-positive recall rate: the Swedish experience. *JIMD Rep* 2012; 2: 113–7.
10. Senemar S, Ganjekarimi A, Senemar S, Tarami B, Bazrgar M. The prevalence and clinical study of galactosemia disease in a pilot screening program of neonates, southern Iran. *Iran J Public Health* 2011; 40: 99–104.