

Rare Neonatal Case Report of Persistent Neonatal Indirect Hyperbilirubinemia – Crigler-Najjar Syndrome

A "One in a Million" in Georgia

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DOI: 10.52340/GBMN.2025.01.01.108

ABSTRACT

This case report presents the rare clinical case of a jaundiced neonate with persistent indirect hyperbilirubinemia, highlighting the diagnostic and management challenges posed by Crigler-Najjar Syndrome. Crigler-Najjar syndrome is an uncommon inherited disorder transmitted autosomal recessive, resulting in high infant bilirubin levels. The condition is mainly characterized by the absence or diminished activity of UDP-glucuronosyltransferase (UGT), an enzyme crucial for transforming unconjugated bilirubin into its conjugated form in the liver. The lack of this enzyme plays a significant role in causing jaundice in newborns that is not associated with hemolysis. The report aims to raise awareness among physicians about this infrequent but life-threatening condition, which necessitates meticulous medical management and underscores the importance of proper and timely interventions and supervision. Management of Crigler-Najjar syndrome generally requires a collaborative approach from a diverse team of healthcare specialists. The pediatrician or neonatologist is crucial for the initial diagnosis and for regularly tracking the child's progress and overall health.

Keywords: Crigler-Najjar syndrome; indirect hyperbilirubinemia; jaundice.

INTRODUCTION

Crigler-Najjar syndrome is a rare, congenital, autosomal recessive disorder characterized by nonhemolytic indirect hyperbilirubinemia, with an estimated incidence of approximately 1 in 1,000,000 live births.¹ Due to its rarity, Crigler-Najjar syndrome is infrequently encountered in clinical practice, posing challenges in timely diagnosis and effective management. The condition can affect individuals across various ethnic backgrounds, although its prevalence may vary depending on geographic and genetic factors. Given its uncommon nature, the syndrome remains a subject of ongoing medical research and investigation.

Bilirubin is a byproduct of erythrocyte degradation and represents the final product of heme metabolism. Its dual role as an antioxidant and a potential oxidizing agent at elevated serum concentrations continues to be a scientific inquiry and a topic of debate.²⁻³ While neonatal hyperbilirubinemia is generally a self-limiting physiological condition, it can also present as an acute or pathological disorder requiring clinical intervention. Before its excretion into bile, bilirubin undergoes glucuronidation, a process that renders it water-soluble through the action of bilirubin-uridine diphosphate glucuronosyltransferase (UDPGT). Deficient or altered UDPGT activity in various disorders results in unconjugated hyperbilirubinemia.⁴ Due to its lipophilic nature, unconjugated bilirubin, when present at elevated serum levels, has the potential to cross the blood-brain barrier, leading to neurotoxic effects. This neurotoxicity, known as kernicterus, is

characterized by permanent and chronic brain damage, which may result in long-term morbidity and, in severe cases, mortality.

UGT1A1 is the primary UDP-glucuronosyltransferase enzyme responsible for bilirubin glucuronidation, and either a complete absence or reduced function of UGT1A1 underlies Crigler-Najjar syndrome.⁴

The disorder is classified into two subtypes: Crigler-Najjar syndrome type 1 (CN1) and Crigler-Najjar syndrome type 2 (CN2). CN1 is associated with life-threatening jaundice, necessitating intensive phototherapy to manage bilirubin levels. Individuals with CN1 are at high risk for neurological complications.¹ Acute bilirubin encephalopathy initially manifests as drowsiness, mild to moderate hypotonia, and a high-pitched cry. If hyperbilirubinemia persists, the condition progresses, leading to additional symptoms such as fever, extreme fatigue, feeding difficulties, irritability, and hypertonia, which may cause retrocollis and opisthotonus. In severe cases, CN1 can result in seizures, respiratory distress, and altered consciousness, with potentially fatal outcomes due to respiratory failure or seizure-related complications. In contrast, CN2 is a less severe disorder, typically characterized by milder clinical manifestations and a more favorable prognosis.¹

CASE

A nine-day-old male neonate was admitted to the neonatal intensive care unit (NICU) with hyperbilirubinemia, poor



feeding, drowsiness, and signs of dehydration. The infant was born at 39 weeks and 3 days of gestation via cesarean section, with a birth weight of 3400 grams, to a 27-year-old primigravida (G1P1). The mother had multiple chronic health conditions, including hypothyroidism, obesity, cholecystitis, insulin resistance, and gastroesophageal reflux disease. Her medical history was notable for prior cholecystectomy and bariatric surgery. She received routine antenatal care, with identified prenatal concerns including pregnancy-associated anemia and polyhydramnios.

Additionally, the mother experienced a respiratory infection during pregnancy and bacteriuria one week before delivery. The father, aged 28, was in good health. The maternal blood type was A-negative, whereas the neonate's was O-positive.

The neonate was discharged at 4 days of life but continued to experience difficulties with sucking, consuming approximately 30-40 mL of breast milk every 3 hours via bottle feeding. According to the parents, jaundice was noted from the early postnatal period. However, in the 2-3 days preceding admission, the infant's jaundice worsened, accompanied by increasing lethargy. At 9 days of age, an outpatient assessment revealed a total serum bilirubin (TSB) level of 450 $\mu\text{mol/L}$. Notably, based on the neonate's gestational and chronological age, the threshold for phototherapy is a TSB level of 350 $\mu\text{mol/L}$, while the threshold for exchange transfusion is 450 $\mu\text{mol/L}$.² Given the progressive hyperbilirubinemia, the newborn was transferred to our hospital for further evaluation and management. Upon admission to the NICU, repeat laboratory analysis demonstrated a TSB level of 531 $\mu\text{mol/L}$. Given the neonate's gestational age and serum bilirubin concentration, the TSB level reached the threshold where exchange transfusion should be considered. However, before initiating this invasive intervention, intensive phototherapy and fluid resuscitation were commenced. A thorough physical examination revealed no abnormalities and instrumental investigations did not indicate any structural pathologies. No signs of hepatomegaly or intraventricular hemorrhage (IVH) were observed.

The complete blood count (CBC) and C-reactive protein (CRP) levels were within normal limits, and the reticulocyte count was also normal at 6% (reference range: 5–15%). Liver function tests showed mild elevations, with alanine aminotransferase (ALT) at 32 U/L (normal: 0–35 U/L), aspartate aminotransferase (AST) at 51 U/L (normal: 0–40 U/L), gamma-glutamyl transferase (GGT) at 214 U/L (normal:

0–122 U/L), and alkaline phosphatase (ALP) at 129 U/L (normal: 75–316 U/L).

Following two hours of intensive phototherapy, a repeat total serum bilirubin (TSB) measurement demonstrated a significant reduction to 407.1 $\mu\text{mol/L}$. According to protocol, the threshold for exchange transfusion was no longer met, and phototherapy was continued. After 24 hours, the TSB had further decreased to 288.5 $\mu\text{mol/L}$, eliminating the need for additional interventions. However, one day after discontinuing phototherapy, TSB levels began to rise again. A week after hospitalization, the bilirubin level reached the threshold, necessitating the reinitiation of phototherapy. Given the persistent hyperbilirubinemia, thyroid function tests were performed, revealing thyroid-stimulating hormone (TSH) at 0.937 mIU/L and free thyroxine (FT4) at 15.700 pmol/L, both within normal ranges. Liver function tests remained stable, and the neonate's neurological status was age-appropriate.

Despite overall clinical stability, at 16 days of age, a "blueberry muffin"-like rash appeared, primarily on the neck and abdomen, in conjunction with persistent jaundice. Shortly thereafter, the neonate exhibited early signs of feeding intolerance, including frequent diarrhea and fever (38.5°C). Further laboratory evaluation revealed an elevated CRP level of 15 mg/L, indicative of infection, prompting the initiation of empiric antibiotic therapy. As indirect hyperbilirubinemia persisted and TSB levels continued to rise following discontinuation of phototherapy, phenobarbital was introduced at 8 mg/kg/day.

Further laboratory investigations were conducted, including screening for TORCH infections. Only cytomegalovirus (CMV) IgG was detected, with a 172.5 IU/mL level. Repeat liver function tests demonstrated mild elevations, with ALT at 41 U/L, AST at 61 U/L, GGT at 135 U/L, and ALP at 369 U/L. Serum albumin was reduced to 24 g/L, while coagulation studies remained unremarkable. Renal function tests were within normal limits, with urea at 1.94 mmol/L and creatinine at 0.42 mg/dL. Bacteriological cultures of both urine and blood were negative.

Despite ongoing treatment, the neonate's clinical condition progressively deteriorated. Thirteen days after admission, he developed acute respiratory insufficiency, abdominal distension, and hematochezia, accompanied by oliguria, hypotension, hypoperfusion, and tachycardia. Additionally, neurological status declined. Given this clinical presentation, an inherited metabolic disorder and the ongoing infectious process were considered. Initial metabolic screening revealed an elevated ammonia level of 137 $\mu\text{mol/L}$, necessitating

further testing for 49 inherited metabolic disorders. Storage diseases, such as neonatal hemochromatosis, were also considered. Relevant findings included ferritin at 860 ng/mL (normal: 20–250 ng/mL), transferrin at 100.4 mg/dL, and alpha-fetoprotein at 87.7 ng/mL. The direct antiglobulin test (Coombs test) was negative.

An ophthalmologic examination showed no evidence of cataracts or chorioretinitis. An acute surgical pathology, such as ileus, was ruled out, and a lumbar puncture was performed to exclude a central nervous system (CNS) infection, with cerebrospinal fluid findings unremarkable. Tests for congenital infections yielded negative results. Whole-exome sequencing was recommended for further genetic evaluation; however, the parents declined genetic testing.

Throughout this period, the neonate continued to receive phototherapy, with only brief interruptions. Each time phototherapy was discontinued, TSB levels increased within 12–24 hours, and neurological symptoms, including head extension, opisthotonus, and occasional high-pitched crying, became apparent.

Despite intensive treatment, the neonate's condition rapidly deteriorated, necessitating mechanical ventilation and total parenteral nutrition (TPN). Broad-spectrum antibiotics, inotropes, phototherapy, and phenobarbital were continued. Periodic corrections were required for hypoalbuminemia, anemia, thrombocytopenia, and hypocoagulation. Coagulation tests showed the following abnormalities: activated partial thromboplastin time (aPTT) of 56 seconds (normal: 21–43), prothrombin time (PT) of 19.8 seconds (normal: 11–14), international normalized ratio (INR) of 1.67 (normal: 0.8–1.25), PT percentage (PT%) of 61% (normal: 70–120), thrombin time (TT) of 27 seconds (normal: 10–18), and fibrinogen (FIB) at 0.82 g/L (normal: 2–4).

With parental consent, whole-exome sequencing was performed. Metabolic screening revealed elevated 17-hydroxyprogesterone (17-OHP) at 110 ng/mL, and T-cell receptor excision circles (TREC) were less than 15 cn/mL. An abdominal ultrasound showed hepatomegaly, and a follow-up ophthalmologic examination identified cataracts in both eyes. Further hormonal testing revealed the following abnormal levels: 17-OHP at 0.88 ng/mL, DHEA-S at 99.7 µg/dL, cortisol at 0.1 µg/dL, testosterone at 12.9 ng/dL, ACTH at 9.5 pg/mL, free thyroxine (FT4) at 9.77 pmol/L, and TSH at 0.38 mIU/mL. Based on these results, the pediatric endocrinologist added hydrocortisone and euthyrox to the treatment regimen.

After 10 days of intensive care, the neonate began showing signs of spontaneous breathing, and extubation was

successfully performed. Brain MRI and EEG results were within normal limits for his age. Enteral feeding was initiated with a lactose-free formula, although phototherapy was continued based on TSB levels. Throughout hospitalization, the neonate was regularly assessed by a multidisciplinary team of neonatologists, infectious disease specialists, surgeons, pediatric nephrologists, pediatric neurologists, pediatric endocrinologists, hematologists, and gastroenterologists.

In the final 9 days of hospitalization, while TSB levels remained elevated, the neonate no longer required phototherapy. The parents purchased phototherapy blankets to continue monitoring TSB levels at home. The neonate was discharged in stable condition at 54 days of age, with improved neurological status. At discharge, TSB was 219.7 µmol/L, liver function tests showed ALT at 98 U/L, AST at 84 U/L, GGT at 805 U/L, ALP at 345 U/L, cortisol at 10 µg/dL, TSH at 1.046 mIU/mL, FT4 at 13.9 pmol/L, ferritin at 1046 ng/mL, and transferrin at 119 mg/dL. The infant was feeding well on a special lactose-free formula, and his weight at discharge was 3600 grams.

Genetic testing revealed two homozygous variants in the UGT1A1 gene: NM_000463.2:c.1133T>A, p.(Val378Asp) and NM_000463.2:c.-3275T>G. These variants are associated with Crigler-Najjar syndrome types 1 and 2. Based on the clinical presentation, the final diagnosis is pending.

The patient's condition is stable, and his liver function tests are normal. His pediatrician and pediatric neurologist are closely monitoring his development.

DISCUSSION

Crigler-Najjar syndrome (CNS) is a rare autosomal recessive disorder characterized by hyperbilirubinemia in neonates, resulting from mutations in the UGT1A1 gene, which encodes the enzyme UDP-glucuronosyltransferase (UGT).^{1,4,5} CNS is classified into two types based on UGT enzyme activity. Type 1 (CN1) is caused by homozygous or compound heterozygous mutations leading to complete or near-total loss of UGT activity.⁴ Infants with CN1 develop severe unconjugated hyperbilirubinemia within the first 3 days of life, with bilirubin levels often exceeding 25–35 mg/dL. If left untreated, this can lead to life-threatening neurological complications, such as kernicterus. Liver transplantation remains the only definitive treatment, although hepatocyte transplantation is a promising alternative. Type 2 (CN2), in contrast, is characterized by reduced enzyme activity, leading to less severe symptoms, typically presenting as intermittent jaundice that is exacerbated by stress. The unconjugated hyperbilirubinemia in CN2 is generally less pronounced and resolves with conservative management, often using oral phenobarbital

therapy. Neurological damage in CN2 is uncommon. The diagnosis of both types primarily relies on genetic testing. Treatment strategies focus on reducing unconjugated bilirubin through phototherapy, plasmapheresis, or phenobarbital. Additionally, Orlistat, when used in combination with calcium phosphate, is more effective.¹ The prognosis for CN1 is poor without timely intervention, with permanent neurological impairment occurring in up to 30% of cases, while CN2 generally has a better outcome with appropriate management.^{1,4,5}

CONCLUSIONS

This medical case is sporadic, underscoring the necessity to identify and understand persistent hyperbilirubinemia of unknown origin, especially in neonates. It highlights the importance of heightened clinical awareness and comprehensive evaluation. Although the condition is manageable, it is essential to recognize the potential high risks to neonatal outcomes.

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