

CASE REPORT

Alagille Syndrome: Case Report and Approach to Neonatal Hyperbilirubinemia

Abhishek Raut, B.H.Sc.

Ritika Goel, B.Sc.

ABSTRACT

Hyperbilirubinemia is a common condition encountered during the first week of life. The majority of cases involve unconjugated hyperbilirubinemia and can be categorized as physiologic or pathologic. Other classification systems such as hemolytic or non-hemolytic can also be used. All types of unconjugated jaundice can lead to kernicterus if not managed correctly. It is therefore essential to closely monitor infants with hyperbilirubinemia. If jaundice persists or clinical suspicion exists, both conjugated and unconjugated bilirubin should be measured. If the unconjugated component is greater than 20% of the total, various etiologies must be considered. We present a case of a full term infant with an unconjugated hyperbilirubinemia soon after birth that progressed to a conjugated hyperbilirubinemia. Through his presentation, we discuss an approach to hyperbilirubinemia in the neonatal population and include useful clinical pearls. We further explore the uncommonly encountered Alagille Syndrome as the etiology of our patient's presentation.

INTRODUCTION

Neonatal jaundice is the most commonly encountered problem in the newborn period, affecting 60% of full term and 80% of preterm infants within the first three days of life.¹ For this reason alone, it is essential for caregivers to have a thorough understanding of and approach to the diagnosis of the variety of cases leading to this condition. It can unfortunately often incorrectly be dismissed as benign or physiologic jaundice, leading to kernicterus.^{1,2} The complications of neonatal jaundice are easily preventable but require close monitoring and prompt action.^{2,3}

In the following case, we will present a general approach to neonatal jaundice, and an overview of the less common conjugated hyperbilirubinemia. Additionally, we provide a brief summary of Alagille syndrome, a rare cause of conjugated hyperbilirubinemia.

HYPERBILIRUBINEMIA

The definition of hyperbilirubinemia is dynamic and dependent on a patient's gestational age, age in hours and clinical status. The most recent CPS statement (June 2007)

states that all babies should be screened for hyperbilirubinemia either by serum bilirubin or transcutaneous bilirubin before being discharged from hospital.¹¹

Hyperbilirubinemia is caused by an increased bilirubin load, decreased bilirubin conjugation, or impaired bilirubin excretion.^{1,4} Increased bilirubin load can be a result of a hemolytic process. In order to help distinguish between the different etiologies of hyperbilirubinemia, several classification systems have been developed. One common system classifies etiologies according to whether the hyperbilirubinemia is a result of elevated conjugated or unconjugated bilirubin, the latter of which is the most common and can be further subdivided according to whether there is a hemolytic component (see table 1).⁷

Another useful classification system distinguishes between physiologic and pathological causes of hyperbilirubinemia. It is important to make this distinction because it markedly changes the natural history and clinical course of the condition.

Physiologic jaundice is primarily caused by the hepatic immaturity of the neonate, relative polycythemia, and the decreased life span of neonatal red blood cells (80 versus

Table 1. Causes of Hyperbiliruninemia⁷

	Unconjugated with Hemolysis	Unconjugated without Hemolysis	Conjugated
Common	Blood group incompatibility, ABO, Rh, Kell, Duffy	Physiologic, breast milk, cephalohematoma, bruising, sepsis, polycythemia, Infant of Diabetic Mother	Hyperalimentation cholestasis, TORCH infection, neonatal hepatitis, sepsis, biliary atresia, choledochal cyst
Rare	Glucose 6 Phosphate Dehydrogenase deficiency, pyruvate kinase defect, spherocytosis, elliptocytosis, thalassemia	Crigler-Najjar or Gilbert's syndromes, pyloric stenosis, hypothyroidism, immune thrombocytopenia	Hepatic infarct, galactosemia, tyrosinosis, cystic fibrosis, alpha1antitrypsin deficiency, neonatal iron storage disease, Alagille syndrome, Byler Disease

120 days).^{5,6,7} A common etiology relates to breastfeeding, which can cause physiological jaundice by two different mechanisms. Physiological breastfeeding jaundice is due to dehydration and caloric deprivation caused by initial latching and gastrointestinal changes of initial feeding.⁷ Breast milk jaundice is caused by the inhibition of bilirubin metabolism by β -glucuronidase and nonesterified fatty acids contained in the milk.⁷

Pathologic jaundice is associated with an earlier presentation, persistence of jaundice, higher bilirubin level and an increased rate in the rise of bilirubin.^{5,6}

The consequence of hyperbilirubinemia is kernicterus, which quite literally refers to the yellowing of the kern, or the basal ganglia and brain stem nuclei, leading to profound neurological complications.^{2,5,6} Kernicterus initially presents as lethargy, hypotonia, and high-pitched cries which can progress to irritability, opisthotonos, seizures, apnea, and hypertonia.^{2,5,6} The long term consequences of kernicterus include athetoid cerebral palsy, high-frequency hearing loss, paralysis of upward gaze, dental dysplasia, and mental retardation.⁶

In the following, we will present a case in order to illustrate and discuss an approach to neonatal jaundice, addressing different elements of history, physical exam, and investigations. This will be followed by a brief discussion of a rare condition that affected our patient, Alagille Syndrome.

HISTORY

Patient A presented with jaundice at birth, as well as hypoglycemia and hypothermia. This patient was born at approximately 37 weeks' gestation to a 17-year-old primigravida mother. The pregnancy was complicated by a urinary tract infection and potential maternal drug use, but was otherwise uneventful. Delivery records indicated a spontaneous vaginal delivery with good Apgar scores. However, the child was born with symmetrical intrauterine growth retardation, with a birth weight of 2097g. No relevant family history was noted.

ANALYSING THE HISTORY

The timing of the initial presentation of jaundice is a vital

factor in differentiating between a physiologic or pathologic entity. Jaundice that is visible during the first 24 hours is always considered pathologic in nature.^{1,3,4} It is important to take note of any family history of neonatal jaundice, Gilbert syndrome, congenital hepatic disease, bile stones and hemolytic disorders.^{1,3,4} A pregnancy and delivery history can reveal vital risk factors for jaundice if there is a history of infection, trauma, or maternal drug use.^{7,8} The risk of developing jaundice is highest in males.^{3,4}

PHYSICAL EXAMINATION

The patient's vital signs were within normal limits and stable, and the patient's skin had a greenish-hue. His entire body was jaundiced. He was small for gestational age, but active and responding appropriately. He was noted to have a broad forehead and pointed chin. The patient was found to have a Grade 2, soft systolic murmur heard best at the left lower sternal border radiating to the back and axilla. The remainder of the examination was normal.

ANALYSING THE PHYSICAL EXAMINATION

Visible jaundice first becomes apparent on the forehead, eyes and face before it progresses inferiorly.⁴ Gentle blanching of the skin is necessary to provide visualization of unconjugated bilirubin deposition in the skin. The infant's state of alertness can reassure the clinician that the early stages of kernicterus are not present.⁴ For most neonates, jaundice is the only physical examination finding.¹ A green tone may point to a conjugated cause.⁷ Although not evident in our patient, a finding of bruising warrants investigation for hemolytic causes of jaundice.^{7,8} Always take note of any dysmorphic features.

INVESTIGATIONS

The patient's first total bilirubin was 220 $\mu\text{mol/L}$ at 17 hours, which increased to a peak of 251 $\mu\text{mol/L}$ at 54 hours, at which point the patient required triple phototherapy. The Coombs' test, which was done to determine the presence of any immune-mediated hemolysis, was negative. A complete blood count (CBC) revealed normal hemoglobin concentration, platelets, and leukocytes. Peripheral smears were nor-



Figure. A neonate with hyperbilirubinemia that is undergoing phototherapy. Photographer: S. Tanzil Rahman 2008.

mal and blood cultures were negative. As part of a septic workup, a screen for TORCH infections – a group of vertically-transmitted infections acquired in utero (such as toxoplasmosis, cytomegalovirus, rubella and herpes simplex virus) that can lead to various fetal anomalies – was performed and found to be normal. Liver function tests were initially normal. The TSH and metabolic screen were within normal limits. An abdominal ultrasound revealed a small liver, arteriovenous malformation and bilateral hydronephroses. Ecocardiography revealed branch pulmonic stenosis.

On day of life 14, a total and direct bilirubin was ordered due to persistent jaundice. Total bilirubin was 200 $\mu\text{mol/L}$ with a direct component of 47 (23% conjugated). There was also evidence of a mild transaminitis. Given the child's conjugated hyperbilirubinemia, branch pulmonic stenosis and bilateral hydronephrosis, Alagille Syndrome was suspected. A spinal x-ray did not show the butterfly vertebrae often associated with this syndrome, and a renal ultrasound revealed that the bilateral hydronephrosis had resolved. On initial examination, an ophthalmologist visualized no poste-

rior embryotoxon (a congenital abnormality of the eye that can be found in Alagille syndrome) and a slit lamp exam was arranged to be done as an outpatient. The consultant geneticist felt that the patient had the characteristic facial features of the syndrome, and believed that the father shared these facial features. The father had a Tetralogy of Fallot that was corrected at birth, and had been given the presumptive diagnosis of Alagille syndrome, but no genetic testing had been done. The father did not have any of the gastrointestinal problems usually associated with Alagille Syndrome. The fact that the patient's father showed some features of Alagille Syndrome suggests that, if this is the appropriate diagnosis, the father likely has a minor sporadic mutation that showed full effect in the child.

While the genetics service arranged confirmatory testing of the neonate's DNA for the JAG 1 mutation, his parents left the hospital with a fairly certain diagnosis. He was started on a high dose of ursodeoxycholic therapy to replace bile acids in order to control pruritus, decrease cholesterol and clear xanthomas.

ANALYSING THE INVESTIGATIONS

The first investigation that should be performed in any visibly jaundiced neonate is measurement of serum bilirubin concentrations. The majority of the time, only a total bilirubin is needed in the first week of life. However, if jaundice persists or there is clinical suspicion, a total and direct bilirubin should be ordered. Comparing levels of conjugated to unconjugated bilirubin help broadly differentiate between causes of the neonate's condition.⁸ Typically, a conjugated bilirubin above 20% of the total bilirubin level points to a pathological cause of hyperbilirubinemia.⁸ Since this patient was jaundiced at birth, it was essential to rule out causes such as hemolysis and sepsis, which require urgent treatment.^{1,7} The CBC helps identify hemolysis or infection as the cause. Elevated leukocytes with increased immature-to-total neutrophil band ratios point to an infectious etiology.⁸ As part of the septic workup, a TORCH screen is routinely performed.^{1,4,8} Additionally, peripheral blood smears might reveal spherocytes or elliptocytes.^{7,8}

If bilirubin levels reveal unconjugated hyperbilirubinemia, the blood type and Rh comparisons of mother and child and direct Coombs' testing should be done.^{4,8} If conjugated hyperbilirubinemia is identified, liver enzymes must be ordered to detect hepatitis, as well as an abdominal ultrasound.^{4,8}

If the patient has an unconjugated hyperbilirubinemia, regardless of the cause, prompt treatment is initiated based on the particular institution's guidelines for phototherapy and exchange transfusion.^{1,3,4,5} If there is a significant conjugated component to the hyperbilirubinemia, the risk of kernicterus is reduced and the decision regarding phototherapy should be made on a case-by-case basis.

ALAGILLE SYNDROME

Alagille syndrome is a rare autosomal dominant disorder which causes conjugated hyperbilirubinemia in the neonatal period.⁹ It is associated with various abnormalities affecting multiple organ systems, as shown in Table 2.

Table 2. Features of Alagille Syndrome⁹

Head and Neck	Broad forehead, pointed chin, elongated nose, posterior embryotoxon
Cardiovascular	Peripheral pulmonic stenosis, atrial septal defect, ventricular septal defect, Tetralogy of Fallot, patent ductus arteriosus, pulmonary atresia
Hepatic	Organomegaly, hyperbilirubinemia, ↑bile
Skeletal	Butterfly vertebrae
Neurologic	Mild developmental delay

Alagille syndrome is caused by a mutation to the JAG1 gene located at c20p12 which encodes for a fetal development signaling cascade.¹⁰ Due to the large number of organ systems affected, and the massive potential for resulting complications, only 50% of those afflicted survive into adulthood.¹⁰ Treatment is symptomatic and is geared towards the correction of vitamin deficiencies, particularly fat soluble vitamins.^{9,10} In adulthood, there is a strong association with hepatocellular carcinoma, and routine liver function tests are warranted.^{9,10}

CONCLUSION

The purpose of this case presentation was to work through a systematic approach to a particular patient with neonatal jaundice from initial presentation to diagnosis. It is essential to definitively differentiate between pathological and physiological jaundice to avoid the long-term sequelae of kernicterus and any undiagnosed conditions or diseases. Key investigations are essential in order to isolate the etiology of the hyperbilirubinemia as conjugated or unconjugated and hemolytic or nonhemolytic jaundice. In addition to this, our case demonstrates how the knowledge of a condition can lead to the appropriate suspicion, investigation and eventual diagnosis of that disease. †

REFERENCES

1. Petrova A, Mehta R, Birchwood G, et al. (2006). Management of neonatal hyperbilirubinemia: pediatricians' practices and educational needs. *BioMed Central Pediatrics*. 2006 Mar 6;6:6.
2. Dixon KT. (2004). Newborn jaundice and kernicterus. Greater awareness and action needed. *Advance Nurse Practitioners*. Dec;12(12):43-6, 63.
3. Worsley JB. (2004). Hyperbilirubinemia guidelines and unintended harms. *Pediatrics*. Oct;114(4):1134-5; author reply 1135-7.
4. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. (2004). Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. Jul;114(1):297-316.
5. Melton K, Akinbi HT. (1999). Neonatal jaundice: Strategies to reduce bilirubin-induced complications. *Postgraduate Medicine*. Nov;106(6):167-8, 171-4, 177-8.
6. Wennberg RP, Ahlfors CE, Bhutani VK, et al. (2006). Toward understanding kernicterus: a challenge to improve the management of jaundiced newborns. *Pediatrics*. Feb;117(2):474-85.
7. Kliegman R, Jenson H, Marecdante K, Behrman R. (2006). *Essentials of Pediatrics: Fifth Edition*. Elsevier Incorporated: Philadelphia.
8. Hay W, Sondheimer J, Levin M, Deterding R, et al. (2007). *Current Pediatric Diagnosis & Treatment: Eighteenth Edition*. The McGraw-Hill Companies.
9. Scheimann A. (2006). Alagille Syndrome. Retrieved May 15, 2007 from the World Wide Web: <http://www.emedicine.com/ped/topic60.htm>
10. Krantz ID, Piccoli DA, Spinner NB. (1999). Clinical and molecular genetics of Alagille syndrome. *Current Opinion in Pediatrics*. Dec;11(6):558-64.
11. Fetus and Newborn Committee. Canadian Pediatric Society. (2007). Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants (35 or more weeks' gestation). *Pediatrics & Child Health* 2007;12(5): 1B-12B.

Author Biographies

Abhishek Raut is a third-year medical student who will be pursuing his residency training in family medicine at the University of Toronto. Prior to medical school, he obtained a Bachelor's degree in Health Sciences at McMaster University.

Ritika Goel is also a third-year medical student who will be pursuing her residency training in family medicine at the University of Toronto. Prior to medical school, she was studying to obtain a Bachelor of Medical Sciences at McMaster University.