Neonatal Jaundice (Neonatal Hyperbilirubinemia) — Bilirubin Levels and Pathophysiology

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Neonatal jaundice is very common in neonates and the decision to treat should be based on the levels of unconjugated bilirubin in the blood. Currently available charts allow for the plotting of serum bilirubin levels starting from the first 24 hours of life and can help the treating physician in deciding whether phototherapy, intravenous immune globulin therapy, or exchange transfusion is needed. The goal of treatment in neonatal jaundice is to prevent kernicterus.

Overview

Neonatal jaundice is a condition that is **characterized by the yellow discoloration of the skin and sclera** of the newborn due to the accumulation of unconjugated bilirubin. Unconjugated hyperbilirubinemia is usually a transient physiologic phenomenon, but if blood bilirubin rises to very high levels, kernicterus can develop. Unconjugated bilirubin is neurotoxic and is known to cross the blood-brain barrier easily. Damage to the central nervous system usually results in lifelong neurologic deficits and in some severe cases can cause death.

Epidemiology of Neonatal Jaundice

Neonatal jaundice is very common in full-term and pre-term infants. Approximately, 50% of full-term infants will develop jaundice within the first two to four days of life and 80% of pre-term infants will also develop jaundice during this period. The estimated incidence of neonatal jaundice is **based on the visual recognition of jaundice** and not on the documentation of unconjugated hyperbilirubinemia. The incidence of unconjugated hyperbilirubinemia in full-term infants is approximately 100% within the first week of life.

Neonatal jaundice is **more common in East Asian and American Indian infants** compared to white infants. African American infants very rarely develop neonatal jaundice. Clinically significant neonatal jaundice is more common in male infants. Additionally, the severity of neonatal jaundice is inversely correlated with the gestational age; therefore, the condition is usually more severe in pre-term infants.

If the infant does not develop kernicterus, the prognosis of neonatal jaundice is usually excellent if the infant receives adequate treatment. The incidence of **kernicterus in the United States is around 0.4 to 2.7 per 100,000 live births**. Death from kernicterus is very uncommon in the developed world but is more commonly reported in under-developed regions and countries such as Nigeria.

Etiology of Neonatal Jaundice

Physiologic jaundice

Physiologic jaundice is **caused by increased bilirubin production** from erythrocytes destruction, decreased the excretion of bilirubin, and **decreased the** activity of the bilirubin-conjugating enzyme uridine diphosphoglucuronyltransferase. These physiologic mechanisms are evident in almost all newborns.

Pathologic jaundice

When **the destruction of erythrocytes exceeds that of physiologic limit**, i.e. immune or non-immune hemolysis, pathologic jaundice can develop. Pathologic jaundice can also develop in infants who have polycythemia or skin bruising. Breastfeeding jaundice and breast milk jaundice appear to be caused by the decreased clearance of bilirubin in the affected infant.
The most commonly understood risk factors for neonatal jaundice are East Asian and American Indian race, infants from populations who live in high altitudes, familial predisposition, breastfeeding, and inadequate nutrition.

Inadequate nutrition

Inadequate nutrition is associated with the **increased enterohepatic circulation of bilirubin which leads to jaundice in the neonate**. Certain disorders such as glucose-6-phosphatase dehydrogenase mutations are also associated with an increased risk of jaundice in the neonatal period.

Pathophysiology of Neonatal Jaundice

Physiologic jaundice

Neonatal physiologic jaundice results from the **accelerated destruction of fetal erythrocytes, the excessive production of bilirubin from this process, and the low hepatic excretory capacity** due to the low concentrations of ligandin. These events usually happen within the first week of life, when neonatal physiology jaundice is most likely to happen.

“Physiologic Jaundice” Image created by Lecturio

Unconjugated and conjugated bilirubin

The conjugation of bilirubin is also **limited in neonates due to the decreased activity of the uridine diphosphoglucuronyltransferase** enzyme. The unconjugated bilirubin is available in the blood as an albumin-bound molecule or a free molecule. The free unconjugated bilirubin is lipid-soluble and can cross the blood-brain barrier. Free unconjugated bilirubin is neurotoxic. The conjugation of bilirubin converts the water-insoluble bilirubin molecule into a water-soluble molecule. Water-soluble conjugated bilirubin does not cross the blood-brain barrier and can be easily excreted.

The Gilbert syndrome

Infants with Gilbert syndrome have mutations in the gene encoding for the uridine diphosphoglucuronyltransferase. These infants are more likely to have severe unconjugated hyperbilirubinemia and kernicterus. Hereditary spherocytosis and glucose—phosphatase dehydrogenase deficiency can also cause severe neonatal jaundice.

Hypertrophic pyloric stenosis

Hypertrophic pyloric stenosis has been **linked to an increased risk of neonatal jaundice**. The most likely explanation for this association is the new finding that some infants with hypertrophic pyloric stenosis have a genetic variant of Gilbert syndrome which is associated with unconjugated hyperbilirubinemia.

Enteral intake

Additionally, enteral intake in neonates is usually limited compared to older infants. This is **associated with prolonged intestinal transit time and an excessive enterohepatic circulation of bilirubin**. Inadequate feeding, decreased oral intake, weight loss and jaundice are seen in breastfeeding jaundice, but not breast milk jaundice.

Breast milk jaundice

Breast milk jaundice is **caused by the increased enterohepatic circulation of bilirubin due to a reaction to breast milk contents and not due to inadequate feeding**. Infants with certain uridine diphosphoglucuronyltransferase polymorphisms are

more likely to develop breast milk jaundice.

Rh and ABO incompatibilities

Neonatal jaundice can also be observed in the case of Rh or ABO incompatibilities. **Rh isoimmunization can cause severe neonatal jaundice and kernicterus**. Rh isoimmunization has become very rare in the developed world.

Clinical Presentation of Neonatal Jaundice

Neonatal jaundice typically **presents on the second or third day of life**. If it starts within the first 24 hours of life, it is most likely nonphysiologic. Infants with prolonged and severe jaundice for more than 2 weeks of life should be screened for galactosemia and congenital hypothyroidism.

A family history of neonatal jaundice, Gilbert syndrome, anemia, or hereditary hemolytic anemia can point towards the most probable cause of jaundice in a neonate. The possibility of an acquired congenital infection should be excluded as toxoplasmosis, cytomegalovirus, rubella and other infectious etiologies have been linked to jaundice in the neonatal period. A history of birth trauma and bruising should be excluded as this can lead to blood extravasation, accelerated destruction of erythrocytes and overproduction of bilirubin and jaundice.

The postnatal history can also point towards the cause of neonatal jaundice. Specific inquiry about drug use by the mother, weight loss in the neonate, problems in breastfeeding, symptoms, and signs of hypothyroidism, such as skin mottling and hypotonia, or exposure to total parental nutrition should be carried out.

Neonatal jaundice can be identified in the face and forehead. After a while, jaundice extends to the trunk and extremities. Neonatal jaundice, therefore, is said to progress in a cephalocaudal direction. The disappearance of neonatal jaundice is also gradual, but starts from the opposite direction; therefore, jaundice in the lower limbs is indicative of severe unconjugated hyperbilirubinemia in the neonate and requires further workup.

Infants who have severe significant unconjugated hyperbilirubinemia might develop seizures, a high-pitched or weak cry, and hypotonia or hypertonia. These changes are very alarming in a neonate and they indicate impending kernicterus. Jaundiced infants with hemolysis, sepsis or congenital infections can have hepatosplenomegaly, petechia, and microcephaly.

Diagnostic Workup for Neonatal Jaundice

Tanscutaneous bilirubinometry

The laboratory studies indicated in a jaundiced neonate aim to measure the bilirubin levels, exclude the most common pathologic causes, and exclude some life-threatening conditions.
Transcutaneous bilirubinometry can be used to measure the bilirubin levels in the neonate without the need for repeated blood sampling. Transcutaneous bilirubinometry is not useful in the monitoring of response to phototherapy.

Visual assessment

Visual assessment alone for the prediction of bilirubin levels in a jaundiced neonate is not possible; however, the **exclusion of significant unconjugated hyperbilirubinemia in an infant who is completely unjaundiced can be reasonably made by visual assessment**.

Measurement of bilirubin fractions

The measurement of serum bilirubin levels **is indicated in any infant who presents with moderate to severe jaundice within the second or third day of life**. The distinction between conjugated and unconjugated bilirubin is not essential at this stage but, if jaundice persists for more than two weeks, it might be reasonable to measure bilirubin fractions. Infants with severe jaundice and pale stools should undergo fractional bilirubin measurements of conjugated and unconjugated bilirubin. Conjugated hyperbilirubinemia can be seen in infants with cholestasis.

Blood typing and Rh determination

Infants who have very high unconjugated hyperbilirubinemia might benefit from blood typing and Rh determination of the mother and infant to exclude red blood cell hemolysis due to incompatibilities, direct Coombs test to exclude immune hemolytic anemia, and serum albumin levels.

Ultrasonographic scanning

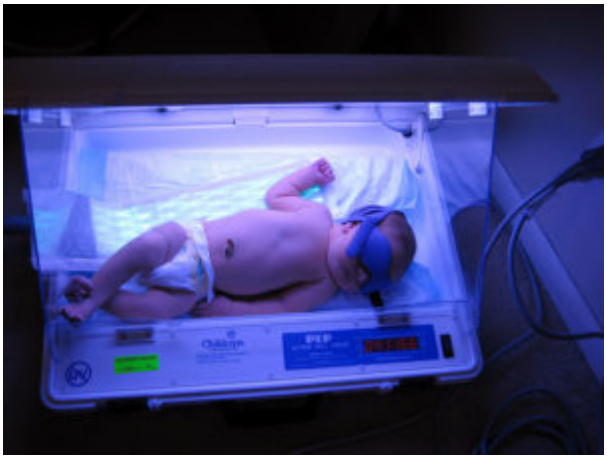
Whenever there is a possibility of congenital infection, appropriate testing should be commenced as early as possible for prognostic and treatment purposes. **Infants with suspected cholestasis should undergo ultrasonographic scanning of the liver and bile ducts**.

Treatment of Neonatal Jaundice

The management of neonatal jaundice includes phototherapy, the administration of intravenous immune globulin and exchange transfusion therapy.

Phototherapy

Overview



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Phototherapy is the first-line therapy for neonatal jaundice due to unconjugated hyperbilirubinemia. It is responsible for the conversion of the water-insoluble unconjugated bilirubin into a more water-soluble form known as lumirubin. Lumirubin can be excreted in the bile or urine of the neonate. **The most commonly used wavelengths in phototherapy are within the white, blue, or green wavelengths**. The best results are usually obtained with a blue lamp in the region of the spectrum (460 to 490 nm). This wavelength is known to have excellent absorption by bilirubin and excellent ability to penetrate the skin.

Note: The distance between the neonate and the lamp should not be greater than 50 cm and can be less than 10 cm. The irradiation level used nowadays is above 40 μW/ cm2 /nm.

Safety precautions

Infants who are going to receive phototherapy should have whole-body irradiation for optimum results. **Exposing large areas of the skin can lead to excessive heat loss or overheating and skin burns;** therefore, close monitoring of the neonate while receiving phototherapy is indicated.

During phototherapy administration, the eyes should be shielded. Fiber-optic lights have been recently introduced. These small light pads have the disadvantage of being less efficient compared to traditional blue or white lamps but have many advantages over the traditional lamps. They do not cause overheating issues, do not require eye shields, ability to be used at home, and when combined with conventional phototherapy, can increase the efficacy of phototherapy.

Serum bilirubin concentrations

Serum bilirubin concentrations, when plotted against the postnatal age in days, **can be used to decide whether phototherapy versus exchange transfusion therapy is needed**. Available charts for decision-making about the management of neonatal jaundice are available from the American Academy of Pediatrics. Infants can be classified into low-risk, intermediate-risk and high-risk. Intermediate risk and high-risk infants whose serum bilirubin levels are within the phototherapy range should receive phototherapy, whereas those whose serum bilirubin levels are high enough to be within the exchange transfusion range should receive an exchange transfusion.

Intravenous immune globulin

Infants who have jaundice due to Rh, ABO or other incompatibilities should receive intravenous immune globulin (IVIG). IVIG reduces the risk of exchange transfusion. IVIG should be avoided when the infant is severely anemic or when there is hydrops fetalis.

Exchange transfusion

When phototherapy and IVIG fail to reduce the levels of unconjugated hyperbilirubinemia, exchange transfusion therapy should be stated. Exchange transfusion therapy is also indicated in infants with jaundice due to severe anemia, hydrops or very high levels of unconjugated bilirubin. **The use of exchange transfusion therapy is limited because the efficacy of packed red blood cell transfusion has been shown to be good in preventing neurotoxicity in infants with severe anemia**. Phototherapy and the administration of IVIG are usually effective in preventing kernicterus in most cases of neonatal jaundice.

Results

Very early recognition of kernicterus, followed by aggressive phototherapy and exchange transfusion therapy, might result in a full recovery in affected infants.

References

Hansen T. Neonatal Jaundice. Background, Pathophysiology, Etiology. http://emedicine.medscape.com/article/974786. Published January 6, 2017. Accessed May 1, 2017.

Notes