Neonatal hyperbilirubinaemia

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Abstract

Neonatal hyperbilirubinaemia is an extremely common condition which continues to be a significant cause of readmission of neonates to hospitals. The aim of early recognition and appropriate treatment is to prevent bilirubin encephalopathy which can cause severe neurodisability. This article reviews the national guidelines issued by various organizations like American Academy of Paediatrics in USA and National Institute of Clinical Excellence in the UK which have attempted to standardize approaches to diagnosis and management. This review highlights how early detection with measurement of bilirubin as opposed to visual estimation and appropriate use of high intensity phototherapy based on recommended treatment threshold charts reduces the incidence of severe jaundice requiring exchange transfusion and how evaluation and support of new mothers and their babies in the community by trained nurses with access to transcutaneous bilirubinometers can reduce hospital referrals while providing safe care at home.

Keywords exchange transfusion; hyperbilirubinaemia; intravenous immunoglobulin; kernicterus; neonatal jaundice; phototherapy; transcutaneous bilirubinometer

Incidence

Neonatal jaundice affects 60% of term babies and 80% of preterm infants. Only a small proportion of these need treatment. Estimation during a quality improvement project undertaken by the ABMU Health Board in Wales in 2014 over a 6 month period looking at all births in the area showed 1046 (19%) of babies reviewed by community midwives required testing with transcutaneous bilirubinometers for visible neonatal jaundice. 63 babies (1%) required referral to hospital. 69% of babies referred needed admission and 54% received phototherapy.

Incidences of bilirubin encephalopathy (kernicterus) appear to have increased within the last decade. A "kinder gentler approach" to treatment, early post-natal discharges and inadequate monitoring in the community could be contributing to this. The British Paediatric Surveillance Unit (BPSU) surveyed babies in the first month of life born in United Kingdom or Republic of Ireland between May 2003 and May 2005. They found an incidence of 0.9/100,000 live births (95% CI 0.46 to 1.5) for bilirubin encephalopathy in the UK. The survey estimated that the incidence of severe jaundice with bilirubin levels more than 510 μmol/litre was 7.1/100,000 live births (95% CI 5.8 to 8.6). Incidence in the USA was considered to be around 1.5/100,000 live births since 1994. A pilot USA Kernicterus Registry with voluntary reporting of kernicterus between 1992 and 2004 identified 125 infants ≥35 weeks gestation with this preventable but severely disabling condition. Six of these died in the first year. Unfortunately the precise incidence of other conditions that are associated with bilirubin toxicity like dental dysplasia, high frequency hearing loss and visual abnormalities remain unknown. Common definitions associated with neonatal jaundice are summarized in Box 1.

Pathophysiology of jaundice

Bilirubin metabolism

Bilirubin is produced by the catabolism of haem in the reticuloendothelial system. Haem is mainly produced from breakdown of red blood corpuscles (RBC). Myoglobin and cytochrome also release haem when broken down. Haem in presence of haem oxygenase and biliverdin reductase is converted to bilirubin. Carbon monoxide and iron is released during this process. Bilirubin is transported to liver bound to albumin. It is then conjugated in liver with glucuronic acid in the presence of the enzyme

Definitions

Neonatal jaundice is defined as elevated levels of total serum bilirubin. Thresholds for treatment vary based on parameters such as gestation and age of the baby.

Prolonged jaundice is defined as elevated levels of bilirubin in blood seen beyond 2 weeks of life in term babies and 3 weeks of life in preterm babies. The National Institute of Clinical Excellence (NICE) in the United Kingdom recommends that levels of conjugated bilirubin more than 25 μmol/litre warrants further investigation.

Physiological jaundice: Cord blood bilirubin levels are usually 20—35 μmol/litre. Serum bilirubin rises in all babies and peaks at around 3—4 days in term babies and 5—7 days in preterm babies. Jaundice is clinically visible usually when bilirubin levels are more than 80 μmol/litre. This jaundice which usually occurs after 24 hours and is generally benign is called physiological jaundice.

Pathological jaundice: This term signifies that the jaundice is likely to be due to an underlying pathology. Jaundice appears earlier, usually less than 24 hours. A rapid rise of bilirubin more than 8.5 μmol/litre/hour (0.5 mg/dL/hour) and a serum bilirubin level of more than 340 μmol/litre increases the risk of kernicterus.

Kernicterus: Yellow discolouration of susceptible parts of the brain due to deposition of bilirubin leading to choreoathetoid cerebral palsy and/or other neurodisabilities like visual and hearing disabilities.

Box 1

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Conflict of interest: the author was provided with few JM 103 TcB devices free of cost for undertaking a pilot quality improvement project in ABM University Health Board by the manufacturer Draeger. The company did not have any influence on the design of the study or evaluation or reporting of results. The author was provided a lecture fee for delivering a lecture at a trade conference in Germany by Draeger.

uridine diphospho glucuronosyl transferase (UGT). Conjugated bilirubin is excreted in the bile into the small intestine. β glucuronidase present in the villi of the intestinal wall will convert some of the conjugated bilirubin back to unconjugated bilirubin. This could get reabsorbed leading to the enterohepatic circulation of bilirubin. Colonic bacteria will act on most of the conjugated bilirubin and convert it into urobilinogen and stercobilinogen which is then excreted in urine and stools respectively.

Neonates are prone to developing jaundice because:

1. At birth there is a greater RBC load which leads to higher bilirubin turnover.
2. Hepatic enzymes, especially UGT are less well developed in neonates than in older children.
3. Suboptimal feeding in the first few days of life can lead to dehydration and increase the enterohepatic circulation. Presence of β glucuronidase in breast milk can also increase the breakdown of conjugated to unconjugated bilirubin in the gut in breastfed babies.
4. Blood supply to the liver is reduced during the first week of life due to time needed to establish the hepatic arterial supply and open patent ductus arteriosus.
5. Colonic bacterial flora may not be well established.

Bilirubin encephalopathy or kernicterus

Unconjugated bilirubin is lipid soluble and therefore can cross blood–brain barrier. Here it can deposit in areas of the brain. There is a predilection for deposition to occur in the basal ganglia, auditory pathways, and oculomotor nucleus. This deposition and accompanying damage result in the classical symptoms associated with kernicterus. Hypoxia, acidosis, prematurity, and genetic predispositions all increase the risk for kernicterus. Some medicines e.g. ceftriaxone and high dose lipid preparations of parenteral nutrition (PN) will displace bilirubin from albumin and increase toxicity. An exact threshold at which kernicterus occurs is not possible to define. In well term babies risk for kernicterus increases after bilirubin levels cross 340 μmol/litre (20 mg/dL) and it is very high above 510 μmol/litre (30 mg/dL). In preterm babies the threshold for damage from bilirubin could be as low as 240 μmol/litre. The risk increases with increasing serum levels of unconjugated bilirubin. The kernicterus registry in the USA identified haemolysis and glucose-6-phosphate dehydrogeranse (G6PD) deficiency as two major risk factors for kernicterus.

Acute bilirubin encephalopathy presents as lethargy, high pitched cry, poor feeding, abnormal tone, opisthotonus, upgaze palsy and seizures. Aggressive treatment at this stage can reduce the damage caused. Chronic bilirubin encephalopathy leads to conditions like choreoathetoid cerebral palsy, high frequency hearing loss, dental dysplasias including greenish discolouration of enamel and oculomotor palsies. There could also be processing defects with auditory and visual stimuli and cognitive defects.

Diagnosis and management of hyperbilirubinaemia

The best approaches to diagnosis for neonatal hyperbilirubinaemia facilitate early detection and management of treatable conditions. Most cases of unconjugated hyperbilirubinaemia are due to haemolysis, immaturity of liver, or infection. The majority of these respond to treatment with appropriate hydration and phototherapy. Occasionally riskier interventions including intravenous immunoglobulin and exchange transfusions are required (see below). Antibiotics are indicated for infections and blood transfusions might be required for managing the anaemia. Common causes of unconjugated hyperbilirubinaemia are outlined in Table 1.

Conjugated hyperbilirubinaemia is less common and the common causes and suggested second line investigations are

Causes of unconjugated hyperbilirubinaemia

Increased bilirubin production

Haemolysis
Increased RBC turnover e.g. polycythaemia.
RBC membrane defects e.g. spherocytosis, elliptocytosis.
RBC enzyme defects e.g. G6PD deficiency, pyruvate kinase defect.
Haemoglobinopathies e.g. α thalassaemia
Immune haemolysis e.g. ABO incompatibility, Rh incompatibility, minor blood group incompatibilities.

Extravasated blood
e.g. cephalhaematoma, birth trauma.

Infection
e.g. Group B streptococcus, *Escherichia coli*

Reduced bilirubin excretion

Prematurity

Disorder of bilirubin uptake and conjugation
e.g. Crigler–Najjar syndrome, Gilberts syndrome Types 1 and 2, Rotor syndrome (*SLCO 1B* mutation)

Endocrine causes
e.g. hypothyroidism, hypopituitarism.

Breast milk jaundice

Genetic
e.g. Down's syndrome, gene polymorphism like *G211A* mutation affecting the UGT activity.

Increased enterohepatic circulation
e.g. intestinal obstruction, dehydration, meconium plug.

Table 1