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Editorial

Unconjugated Bilirubin the Double the Edged Weapon

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Jaundice comes from the French word jaune, which means yellow. When it is said that a baby is jaundiced, it simply means that the color of his skin appears yellow. The serum bilirubin level required to cause jaundice varies with skin tone and body region, but jaundice usually becomes visible on the sclera at a level of 2 to 3 mg/dL (34 to 51 μmol/L) and on the face at about 4 to 5 mg/dL (68 to 86 μmol/L). With increasing bilirubin levels, jaundice seems to advance in a head-to-foot direction, appearing at the level of umbilicus at about 15 mg/dL (258 μmol/L) and at the feet at about 20 mg/dL (340 μmol/L). The explanation for this phenomenon is not well understood, but both changes in bilirubin-albumin binding related to pH and differences in skin temperature and blood flow have been proposed [1,2]. Premature infants are more likely to develop jaundice than full-term babies.

Neonatal hyperbilirubinemia or neonatal jaundice most of the time is a normal physiological event and is not serious. Slightly more than half of all neonates become visibly jaundiced in the first week of life Majority of newborns are jaundiced by adult standards i.e. unconjugated serum bilirubin level of more than 30 μmol/L (1.8 mg/dL) during the first week of life and an estimated 50% of term and 80% of preterm infants develop visible jaundice, typically 2 - 4 days after birth [3]. In most of the cases, this jaundice will disappear after a few days, often without any special treatment and once this type of physiological jaundice disappears, there is no evidence that it will appear again or that it has any lasting effects on the baby. Bilirubin is produced in the reticuloendothelial system as the end product of heme catabolism and is formed through oxidation-reduction reactions. Approximately 75% of bilirubin is derived from hemoglobin, but degradation of myoglobin, cytochromes, and catalase also contributes. In the first oxidation step, biliverdin is formed from heme through the action of heme oxygenase, the rate-limiting step in the process, releasing iron and carbon monoxide. Carbon monoxide is excreted through the lungs and can be measured in the patient's breath to quantify bilirubin production whereas the iron is conserved for reuse,. In next step water-soluble biliverdin is reduced to bilirubin, due to the intramolecular hydrogen bonds being insoluble in water in its most common isomeric form (bilirubin IXα Z,Z). Because of its hydrophobic nature, unconjugated bilirubin is transported in the plasma tightly bound to albumin. Binding to other proteins and erythrocytes also occurs, but the physiologic role is limited. Binding of bilirubin to albumin increases postnatally with age and is reduced in infants who are ill.

The presence of endogenous and exogenous binding competitors, such as certain drugs, also decreases the binding affinity of albumin for bilirubin. A minute fraction of unconjugated bilirubin in serum is not bound to albumin. This free bilirubin is able to cross lipid-containing membranes, including the blood-brain barrier, leading to neurotoxicity [4]. In fetal life, free bilirubin crosses the placenta, apparently by passive diffusion, and excretion of bilirubin from the fetus occurs primarily through the maternal liver [4].

Neonatal Jaundice or Neonatal hyperbilirubinemia is the most common clinical entity that needs medical attention in newborns. which reflects a normal transitional phenomenon. Incidence varies with ethnicity and geography. Incidence is higher in East Asians, American Indians and in populations living at high altitudes but is lower in blacks. In 1984, Moore et al reported 32.7% of infants with serum bilirubin levels of more than 205 μmol/L (12 mg/dL) at 3100 m of altitude [5]. In Denmark, 24 in 100.000 infants met exchange transfusion criteria, while 9 in 100.000 developed acute bilirubin encephalopathy [6].

Bilirubin has a potent antioxidant activity and has got a physiologic role as a cellular antioxidant [7] but in newborns our main concern is to identify and treat the pathological jaundice due to excess serum levels of unconjugated or indirect bilirubin which happens to be the

most common reason for hospital readmission in the first two weeks of life. Clinical jaundice appearing in the first 24 hours, rise in the level of total bilirubin by more than 0.5 mg/dL per hour or 5 mg/dL per 24 hours, total bilirubin more than 19.5 mg/dL and direct bilirubin more than 2.0 mg/dL are suggestive of pathological jaundice. Approximately 5-10% of all the newborns have clinically significant hyperbilirubinemia i.e. serum bilirubin levels may rise excessively due to mutations/polymorphisms in the genes that code for enzymes and proteins involved in bilirubin metabolism, infants with homozygous or heterozygous glucose-6-phosphatase dehydrogenase (G-6-PD) deficiency, polycythemia or bruising and extravasation, hereditary hemolytic anemias and combinations of multiple genetic variants which mandate the use of different treatment modalities like phototherapy or exchange transfusion [8-12]. Bilirubin level greater than 20 mg/dL in term appropriate for date baby is correlated with kernicterus i.e. an abnormal accumulation of bile pigment in the brain and other nerve tissue that causes yellow staining and tissue damage. The mildest form of bilirubin encephalopathy can lead to sensorineural hearing loss whereas severe form of neonatal jaundice can cause death in newborns and lifelong neurologic sequelae of kernicterus in infants who survive. Though it is very difficult to assess the exact mortality due to kernicterus, but mortality and morbidity are commonly seen in clinical settings in country with less developed medical care systems.

It is very important to differentiate between normal physiological jaundice and harmful pathological jaundice as it is the later which requires immediate medical attention. Neonates on exclusive breastfeeding have a different pattern and degree of jaundice as compared to artificially fed babies. American Academy of Pediatrics (AAP) has given separate guidelines for the management of jaundice in sick term babies, preterm and low birth weight babies, for hemolytic jaundice and prolonged hyperbilirubinemia [13].

Depending upon serum levels of bilirubin, phototherapy, intravenous immune globulin (IVIG), and exchange transfusion are the most widely used therapeutic modalities in infants with neonatal jaundice. Although medications that impact bilirubin metabolism have been used in studies, drugs are not ordinarily used in unconjugated neonatal hyperbilirubinemia [14-18]. The complications of neonatal hyperbilirubinemia are preventable if health care personnel follow the recommendations and guidelines in the management of the same. The importance of universal, systematic assessment for the risk of severe hyperbilirubinemia, close follow-up, and prompt intervention needs be adhered to [13].

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