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Review Article

Narrative Review of Hyperbilirubinemia

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Abstract: Hyperbilirubinemia refers to an elevated level of bilirubin in the blood. Bilirubin is a yellow pigment produced during the normal breakdown of red blood cells. It is processed by the liver and excreted in bile. When bilirubin levels rise above normal, it can cause jaundice, a condition characterized by yellowing of the skin, eyes, and mucous membranes. Hyperbilirubinemia is common in newborns due to immature liver function and is usually transient. However, untreated severe cases can lead to complications like kernicterus (brain damage).there are three types of Hyperbilirubinemia: Physological jaundice due to hemolysis of blood cell, pathological jaundice due to pathological disorders such as rubella, and bacterial septicemia, Breast Milk Jaundice resulting from a combination of genetic and environmental factors such as the components of breast milk , Hemolytic Jaundice due to many reasons : Rhesus hemolytic disease, Blood group incompatibility, Glucose-6 phosphate dehydrogenase deficiency and minor blood group incompatibility.

Keywords: Hyperbilirubinemia, Jaundice, Hepatobiliary.

INTRODUCTION

Neonatal Jaundice: It is a condition characterised by the excessive accumulation of bile in the gallbladder, resulting in elevated concentration and secretion within the body. It frequently impacts neonates, namely those born prior to the 36th week of gestation, and arises from the degradation of haemoglobin molecules, resulting in the liberation of iron and the formation of a yellow compound known as bilirubin, which has a molecular weight of (584 - 65) Dalton [1]. It often manifests between the second and fifth days postnatally and is a natural occurrence observed in over 50% of neonates within their initial week, enabling parents and physicians to identify it during examinations [2]. This leads to yellowing of the skin, sclera, and mucous membranes due to an increase in bodily fluids [3]. The colouration typically arises from the buildup of unconjugated and non-polar bilirubin in the dermis, which is fat-soluble and exhibits an indirect reaction. This bilirubin variant is not readily eliminated from the child's body, since the liver transforms it from the unconjugated form to the conjugated form by the activity of the liver enzyme uridine diphosphate glucuronic acid, thereby aiding in its excretion, but it may induce a deficit. The liver function in infants is compromised, resulting in an inability to work properly, which causes elevated bilirubin levels in the blood [4]. Bilirubin-induced neurodegenerative syndrome (BNDS) is a constellation of symptoms and indications indicative of a particular disease in neonates susceptible to elevated bilirubin levels. Timely identification of this illness can safeguard against enduring and permanent cerebral harm. Numerous factors significantly influence hyperbilirubinemia in neonates, including physical determinants such as birth weight, gestational age, and maternal exposure to specific diseases during gestation [5].

Bilirubin Metabolism

Bilirubin production and metabolism are the final outcome of heme synthesis. Approximately 80% of bilirubin is generated by the degradation of haemoglobin in red blood cells inside the reticuloendothelial system, while the other 20% is derived from senescent red blood cells produced in the bone marrow and the catabolism of other proteins [6, 7]. The process commences with the enzymatic conversion of heme into biliverdin by haemoxygenase. Biliverdin synthesis constitutes the initial significant phase in the route. The subsequent step involves the enzyme biliverdin reductase, which

turns biliverdin into unconjugated bilirubin. Bilirubin is conjugated in the liver by the enzyme Glucuronyl transferase, rendering it water-soluble. The conjugated form is the primary variant of bilirubin, classified as direct bilirubin, the majority of which is transported to the gallbladder before being released into the proximal segment of the small intestine. While the majority of bile acids are absorbed at the distal ileum to engage in enterohepatic circulation, conjugated bilirubin is not absorbed and proceeds to the colon, where colonic bacteria act upon it. It is decomposed and metabolised producing colourless bilirubin, which can be oxidised to produce urobilin and stercobilin. Urobilin is eliminated by the kidneys through urine, imparting its characteristic yellow hue. Stercobilin is expelled in faeces, imparting a characteristic yellow hue to them. Approximately 1% of urobilinogen is reabsorbed in the enterohepatic cycle for excretion in the bile (Figure 1) [8, 9]. Conditions leading to hyperbilirubinemia can be categorised into those characterised by excessive bilirubin due to haemolysis and those where bilirubin clearance is impaired by the liver, gut, or both. Newborns are especially vulnerable to hyperbilirubinemia due to elevated bilirubin production (high haemoglobin levels and reduced red blood cell lifespan) and diminished hepatic absorption, conjugation, and elimination of bilirubin [10].

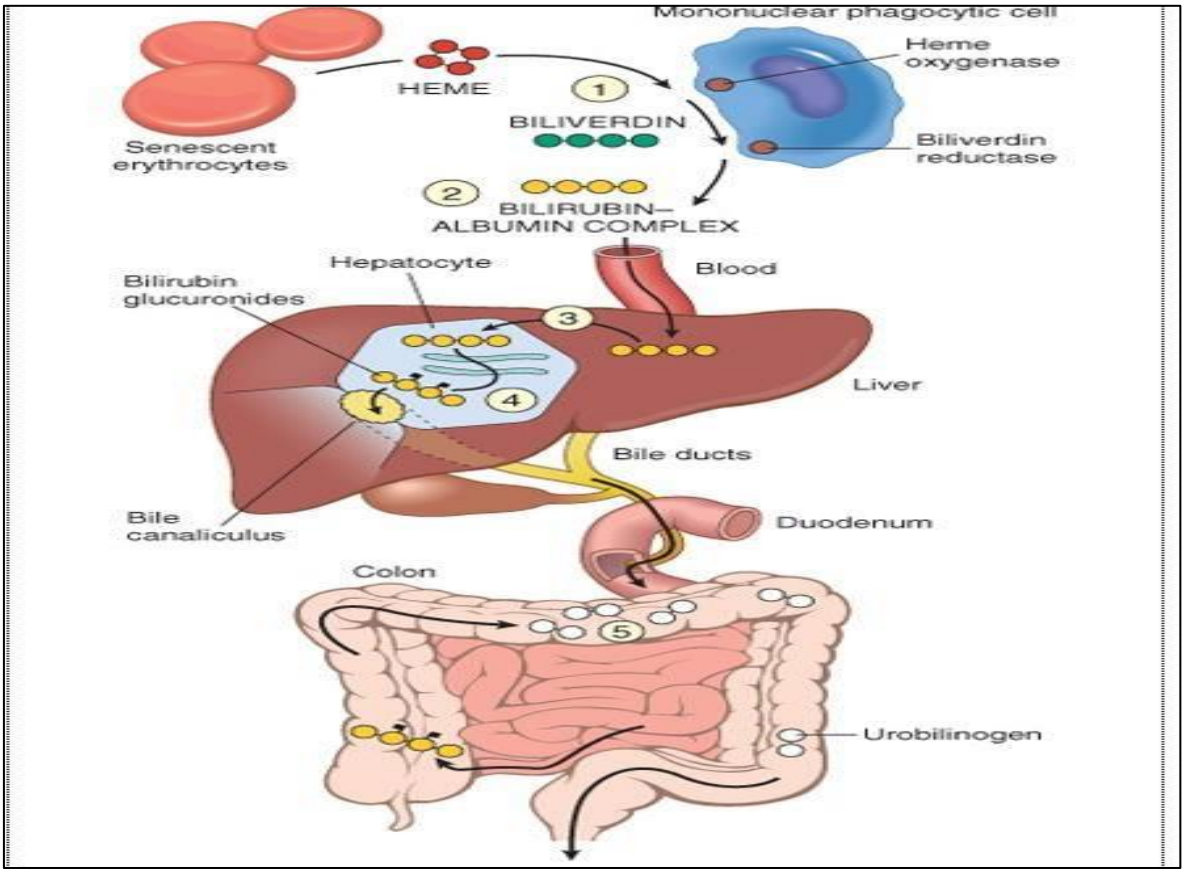

Figure 1: Production and metabolism of bilirubin

Types of hyperbilirubinemia

Newborn hyperbilirubinemia encompasses various forms, including physiological jaundice, pathological jaundice, breastfeeding-related jaundice, and haemolytic jaundice, the latter of which comprises three subtypes: Rh incompatibility, ABO blood group incompatibility, and jaundice related to Glucose-6-phosphate dehydrogenase (G6PD) deficiency [11].

1- Physological jaundice

Jaundice in healthy, full-term neonates is termed physiological jaundice, as hyperbilirubinemia is universally present in both parents. TSB It reaches a maximum of 5 to 15 mg/dL on the second or third day postnatally [12]. Physiological jaundice manifests in two forms: Firstly, it arises from elevated bilirubin levels due to the rapid degradation of erythrocytes (elevated haemoglobin content and reduced erythrocyte lifespan), inadequate hepatic absorption, and diminished capacity to eliminate bilirubin. Humans possess two varieties of haemoglobin, determined by the individual's stage of puberty: foetal haemoglobin is synthesised prenatally, while adult haemoglobin is created postnatally. The synthesis of foetal haemoglobin ceases shortly after birth. Haemoglobin consists of two alpha chains and two non-alpha chains. Foetal haemoglobin has a molecular configuration of two alpha chains and two gamma chains ($\alpha 2\gamma 2$), with variations in amino acid composition, specifically glycine or alanine. In contrast, adult haemoglobin (HbA1), which predominates in adults, comprises approximately 96-98% HbAA with a structure of two alpha chains and two beta chains

(α2β2), 3.5% HbA2 with a structure of α2δ2, and less than 1% HbF [13]. The substitution of glutamic acid with valine at the sixth position in the beta chain results in sickle cell disease. This alteration is referred to as haemoglobin HbS, an aberrant form of haemoglobin resulting from a genetic disorder that disrupts oxygen delivery. When individuals are subjected to low oxygen levels, their haemoglobin S (HbS) precipitates into elongated crystals that assume a sickle form instead of a disc shape. Sickle cell disease is marked by vascular obstructions, organ dysfunction, and even mortality [14].

Secondly, there is a diminished concentration of ligandin in hepatic cells, together with reduced activity of the conjugated bilirubin enzyme UDP-glucuronyl transferase [10]. This form is the most prevalent among newborns, and its problems are minimal [15]. They may encompass neurodevelopmental problems, such as muscle spasms and auditory impairment. In exceptional instances, intellectual disability may arise, all linked to elevated bilirubin toxicity. Physiological jaundice peaks between 24-72 hours and again between the fourth and fifth days postnatally, however in premature children, it peaks on the seventh day and resolves between the 10th and 14th days following birth [16]. Multiple factors contribute to the onset of physiological jaundice in neonates, including inadequate hepatic metabolism of indirect bilirubin, the brief lifespan of easily soluble erythrocytes, and underdeveloped intestinal flora responsible for bilirubin degradation, resulting in heightened absorption of indirect bilirubin [17].

2- Pathological Jaundice

Pathological jaundice refers to bilirubin levels that depart from the normal range and may necessitate medical intervention [18]. This form of jaundice manifests within the initial 24 hours as a result of a bilirubin elevation in the blood above 5 mg/dl daily. Prolonged clinical jaundice lasting over two weeks, accompanied by conjugated bilirubin, would be categorised under this form of jaundice [11]. The aetiologies of this condition encompass pathological illnesses like toxoplasmosis, rubella, and bacterial septicaemia [5].

3-Breast Milk Jaundice

Research suggests that breast milk jaundice results from an interplay of hereditary and environmental variables [10]. Elevated bilirubin levels have been identified in these breastfed newborns [19]. Mild jaundice may persist for 10-14 days postnatally or may reoccur during lactation due to insufficient milk consumption and certain instances of dehydration [20]. Mild clinical jaundice has been noted in one-third of breastfed newborns during the third week of life, potentially persisting for two to three months postnatally in a minority of cases [21]. Encouraging moms to nurse their infants a minimum of 10-12 times daily is a crucial approach for managing jaundice in healthy infants [22]. Hyperbilirubinemia is linked to breast milk [23]. indicating that approximately 2-4% of exclusively breastfed newborns exhibit jaundice that surpasses 10 feedings per week of age. These infants should be checked for bilirubin levels throughout the third week postnatally. Serum values exceeding 10 mg/dL resulting from chronic jaundice [24]. Maisels Mothers should be counselled against discontinuing breastfeeding unless levels surpass 20 mg/dL; nevertheless [25]. Herschel and Gartner [26] indicated that breast milk should be substituted with artificial feeding, as it reemerges when the infant resumes breastfeeding. The aetiology of this jaundice is attributed to an enzyme in breast milk and unbound fatty acids that impede the normal metabolism of bilirubin.

4-Hemolytic Jaundice

The most common causes of hemolytic jaundice include: 1- Rhesus hemolytic disease [27], 2- Blood group incompatibility [28], 3- Glucose-6-phosphate dehydrogenase deficiency [29] and minor blood group incompatibility.

Causes of jaundice

Causes of jaundice [30] mentioned that there are several reasons that lead to jaundice, which are:

1. Children born before the natural date of birth (premature)
2. Incompatibility of blood types between the mother and the child
3. Cutaneous or cranial haemorrhage during parturition (congenital injury).
4. The rate of red blood cell degradation in neonates is elevated relative to adults, perhaps attributable to the brief lifespan of red blood cells in infants, approximately 70 days, resulting in an increased concentration of bilirubin in the bloodstream.
5. Liver immaturity. The concentration of ligandin protein, which facilitates bilirubin coupling, is minimal in the body, alongside the diminished activity of the enzyme that catalyses the conjugation of bilirubin with glucuronic acid, resulting in an inability to eliminate excess bilirubin from the bloodstream.
6. Elevated bilirubin levels can adversely affect the brain, resulting in hazardous jaundice. The accumulation of this material in a child's brain may lead to a severe disease known as jaundice, potentially resulting in cognitive impairment and muscular paralysis.
7. Dehydration in neonates and insufficient caloric intake.
8. Administering water and glucose or fluid substitutes to newborns prior to breastfeeding, based on misconceptions aimed at reducing jaundice, may actually exacerbate the condition.
9. Family medical history if the newborn has a sibling who previously experienced jaundice.

10. Pregnancy diseases (gestational diabetes).
11. The utilisation of certain drugs, including Diazepam and Oxytocin, by the pregnant woman.

Symptoms of Jaundice

Jaundice is accompanied by a set of symptoms, which are:

1. The child's body turns yellow.
2. Constant drowsiness and lethargy.
3. Crying in a high tone.
4. The child's urine is dark in color.
5. The whites of the eyes turn yellow.
6. The child's stool is light in color.
7. Swelling in the legs and swelling in the abdomen due to fluid accumulation.
8. Fever and weight loss [31].

Complications of jaundice

Elevated bilirubin levels can result in jaundice and, if addressed, may lead to subsequent consequences [32].

Initial: Cerebral trauma: Bilirubin is a neurotoxic chemical. An elevation in its blood levels results in its infiltration into brain cells, manifesting various symptoms, including:

1. Ambulatory challenges.
2. The child's appearance is thin.
3. Loud crying.
4. Weakness in the ability to swallow food.
5. High temperature.

Second: Kernicterus

It is cerebral impairment resulting from elevated bilirubin levels in the bloodstream. The likelihood of this disorder is elevated in premature infants, individuals with severe illnesses, or those undergoing specific pharmacological treatments. This kind of jaundice is infrequent; nevertheless, it may typically be prevented with early detection and treatment of hyperbilirubinemia. Once brain damage transpires, no medication exists to reverse it. This condition can be identified by the following symptoms:

1. Involuntary and uncontrollable movements.
2. Hearing loss.
3. The cornea is fixed upward.
4. Weak mental ability.
5. Improper growth of tooth enamel [33, 34].

Disease Prevention

The American Academy of Paediatrics advises the following for all near-term neonates: Medical practitioners should counsel moms to breastfeed their infants a minimum of 8 to 12 times daily during the initial days. Insufficient caloric intake or dehydration linked to poor nursing may lead to the onset of hyperbilirubinemia. Augmenting the frequency of breastfeeding diminishes the probability of future hyperbilirubinemia in breastfed infants. Offering suitable assistance and counselling to breastfeeding mothers enhances the probability of successful breastfeeding. Physicians must perform continuous systematic evaluations during the neonatal period to assess the infant's risk of developing severe hyperbilirubinemia [35].

CONCLUSION

Jaundice is very common disease. Yellowing of skin, sclera and mucous membranes are common manifestations of jaundice due to defect in production, metabolism and excretion of bilirubin. The causes of jaundice are either congenital or acquired. Serum bilirubin level and ultrasonography are used for differential diagnosis. High water intake and low fat diet are best proper managements of jaundice. The treatment of jaundice varies with the type of jaundice.

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