Hyperbilirubinemia in a Neonatal Intensive Care Unit: Incidence and Etiology

Thesis

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Abstract

Although most newborns develop some degree of jaundice, bilirubin levels high enough to put a newborn at risk of bilirubin encephalopathy and kernicterus are rare but still occur in Egypt.

The aim of current study was to assess the magnitude of neonatal jaundice and detect possible etiologies. This study included retrospective analysis of the data of all jaundiced cases admitted to NICU of Cairo University Pediatric Hospital during the period from the first January to the end of December 2007 and the data of the referred neonatal cholestatic cases in hepatology unit at the same hospital.

In the study period, there were 808 patients having neonatal jaundice who were admitted to neonatal intensive care unit with a mean age of 5.74±4 days and a mean weight of 2658.6±710 grams. They represented 72.9% of all cases admitted in the year 2007. Neonatal jaundice alone as a cause of admission represented 54.1% of all cases admitted. The mean total bilirubin level at day of presentation was 23.1±9.87 mg/dl. It was found that ABO incompatibility, Rh incompatibility and sepsis (18.7%, 5.8% and 12.5% respectively) are the main causes of indirect hyperbilirubinaemia. In 56% of cases the cause was unknown. It was found that 325 (40%) studied cases had extreme hyperbilirubinemia with peak of total bilirubin ≥25 mg/dl. Phototherapy was the only therapy in 68.4% of cases while 29.9% required exchange transfusion. Eleven (1.4%) cases were discharged with frank kernicterus. Among 23 referred cholestatic cases, it was found that inspissated bile syndrome then neonatal sepsis and extrahepatic biliary atresia are the main causes of neonatal cholestasis.

From this study, we concluded that, neonatal jaundice is still a major problem in our community. The main causes are ABO incompatibility, Rh incompatibility and sepsis especially in extreme hyperbilirubinemia which shows high prevalent in the NICU population. Any infant with direct hyperbilirubinemia should be diagnosed to rule out cholestatic liver disease.

Key words: Neonatal jaundice, hyperbilirubinemia, kernicterus, cholestasis, neonates.

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List of Abbreviations

AAP	American Academy of Pediatrics
AAT	Alpha-1-antitrypsin
ABC	ATP-binding cassette
ABE	Acute bilirubin encephalopathy
ABR	Auditory brainstem responses
AGS	Alagille syndrome.
ALT	Alanine transferase
AN/AD	Auditory neuropathy/auditory dys-synchrony
AST	Aspartate transferase
ATP	Adenosine triphosphate
B/A ratio	Bilirubin/albumin ratio
BA	Biliary atresia
BASD	Bile acid synthetic defect
BBI	Blood–brain interface
Bf	Free bilirubin
BIND	Bilirubin-induced neurologic dysfunction.
BSA	Body surface area
BSEP	Bile salt export pump
CBC	Complete blood count.
cMOAT	Canalicular multispecific organic anion transporter
CMV	Cytomegalovirus
CN-1	Crigler-Najjar syndrome type 1
CN-2	Crigler-Najjar syndrome type 2
CNS	Central nervous system
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CP	Cerebral palsy
CRP	C-Reactive protein
CSF	Cerebrospinal fluid
CUPH	Cairo University Pediatrics Hospital

DAT	Direct antiglobulin test
DCT	Direct Coombs' test
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
ET	Exchange transfusion
ETCOc	End- tidal concentration of CO corrected for the ambient CO
G-6-PD	Glucose-6-phosphate dehydrogenase.
GGT	Gamma glutamyl transpeptidase
HCT	Hematocrit
IBS	Inspissated bile syndrome
IDM	Infant of diabetic mother
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INH	Idiopathic neonatal hepatitis
ISBT	Ileal Na+-dependent bile salt transporter
IVIG	Intravenous immune globulin
LBW	Low birth weight.
LPS	Lipopolysaccharide
MDR1	Multidrug resistance-1 P-glycoprotein
MDR3	Multidrug resistance-3 P-glycoprotein
MRI	Magnetic Resonance Imaging
mRNA	Messenger ribonucleic acid
MRP1	Multidrug resistance-associated protein-1
MRP2	Multidrug resistance-associated protein-2
MRP3	Multidrug resistance-associated protein-3
NADPH	Reduced form of nicotinamide adenine dinucleotide phosphate
NCS	Neonatal Cholestasis Syndrome
NICU	Neonatal intensive care unit
NISD	Neonatal iron storage disease
NTCP	Na+-taurocholate transporter
OATP	Organic anion transporting polypeptide

OATP1B1	Organic anion transporter polypeptide 1B1
OH	Heme oxygenase
PBC	Primary biliary cirrhosis
PCV	Packed cell volume
PFIC	Progressive familial intrahepatic cholestasis
PH	Concentration of hydrogen ion.
PSC	Primary sclerosing cholangitis
RBCs	Red blood cells
T4	Thyroid hormone, Thyroxine
TC	Triangular cord
TcB	Transcutaneous bilirubin
Torch	Toxoplasmosis, other viruses, rubella, cytomegalovirus, herpes (simplex) viruses
TPN	Total Parenteral Nutrition
TSB	Total serum bilirubin.
TSH	Thyroid stimulating hormone
UCB	Unconjugated bilirubin
UDCA	Ursodeoxycholic acid
UGT (UDPGT)	Uridine diphosphoglucuronate glucuronosyltransferase
UGT1A1(UDP-GT1A1)	Uridine diphosphate glucuronosyl transferase 1A1
US	Ultrasonographic
USA	United States of America
UTI	Urinary tract infection
UV	Ultraviolet
VDRL	Venereal Disease Research Laboratory
VeCO	Pulmonary excretion rate of CO
VLBW	Very low birth weight

Introduction

Jaundice is the most common condition that requires medical attention in newborns. The yellow coloration of the skin and sclera in newborns with jaundice is the result of accumulation of unconjugated bilirubin **(Hansen, 2009)**. Alterations in the equilibrium between bilirubin production, conjugation, and excretion cause this transitional elevation during the neonatal period. The pathophysiology of this condition may vary according to the etiology. Different clinical entities presenting with neonatal jaundice include physiological jaundice, blood group iso-immunization, immaturity, or genetic deficiency of enzyme systems among others. Common clinical risk factors associated with neonatal jaundice include prematurity, low birth weight, neonatal sepsis, Asian race, bruising, previous sibling with a history of jaundice, breast feeding, epidural anesthesia, instrumental delivery and oxytocin use during labor **(Tioseco et al, 2005)**.

Early discharge of the healthy newborn infant, particularly those in whom breastfeeding may not be fully established, may be associated with delayed diagnosis of significant hyperbilirubinemia **(Canadian Paediatric Society, 2007)**.

Discriminating between benign and serious causes of jaundice is a common task faced by most pediatricians and neonatologists in their daily practice **(Karpen, 2002)**.

In many cases, a causal etiology for hyperbilirubinemia will not be found and performing a battery of laboratory tests will in most cases not shed further light on the cause of the jaundice. Save for TSB monitoring, only a few laboratory tests, summarized in CBC, reticulocyte count, red-cell morphology, blood group, DAT (Direct antiglobulin test) and G-6-PD test are actually indicated for the average hyperbilirubinemic neonate. Liver function tests and direct bilirubin fractionation add little information in the first days of life and should be performed only in cases of persistent or unexplained prolonged jaundice, or in the presence of evidence of disease **(Kaplan et al, 2008)**.

The principal issue facing the clinician is the ability to distinguish between hyperbilirubinemia resulting from a variety of causes and those with underlying liver disease. This is critical because the earlier an infant is recognized as having serious cholestatic liver disease, the more likely a correct diagnosis can be made, and institution of appropriate therapy begun. In general, if a patient is developing progressive jaundice soon after birth, is still jaundiced at 2 weeks of life, or develops jaundice within the first month of life, a work-up for neonatal cholestasis should begin **(Karpen, 2002)**.

Regardless of the cause of indirect hyperbilirubinemia, the goal of therapy is to prevent indirect-reacting bilirubin related neurotoxicity while not causing undo harm.

Phototherapy and, if unsuccessful, exchange transfusion remain the primary treatment modalities used to keep the maximal total serum bilirubin below the pathologic levels **(Piazza and Stoll, 2007)**.

Although neonatal jaundice is usually a self limiting condition, in exceptional circumstances, extreme hyperbilirubinaemia, with its devastating potential of irreversible brain damage due to bilirubin encephalopathy or kernicterus, may occur **(Kaplan and Hammerman, 2005)**.

Cholestatic jaundice in early infancy is an important clinical condition that results from diminished bile flow and/or excretion, and can be caused by a number of disorders. Idiopathic neonatal hepatitis (INH) and biliary atresia (BA) are two main causes **(Dehghani et al, 2006)**.

Aim of the study

The aim of this study is to assess, retrospectively, the magnitude of jaundice and its possible etiologies in-patients attending the Neonatal Intensive Care Unit (NICU) of Cairo University Pediatrics Hospital (CUPH).

Chapter 1

Bilirubin Metabolism

Neonatal jaundice refers to the accumulation of the yellow-orange pigment, bilirubin, in the skin and sclerae of the newborn, some degree of hyperbilirubinemia invariably occurs in the human newborn after birth. The syndrome of neonatal jaundice can be best understood by analogy to a temporarily and partially clogged sink. In this example, the spigot represents the processes of bilirubin production and the drain represents the processes of bilirubin elimination. When the rate at which bilirubin is produced exceeds (spigot ‘‘on’’) the rate at which bilirubin can be eliminated (drain ‘‘clogged’’) , the level of bilirubin in the circulation and body (sink) increases as a result. Therefore, the relative imbalance of these processes determines the pattern and degree of neonatal hyperbilirubinemia, which vary for a variety of reasons and represent the known risk factors **(Stevenson et al, 2001)**.

Bilirubin formation: (Figure 1)

Eighty to ninety percent of bilirubin is derived from the breakdown of hemoglobin from senescent or hemolyzed red blood cells. The proportion of bilirubin arising from hemoglobin varies with the pathologic condition, and may increase greatly in the circumstance of hemolysis or ineffective erythropoiesis. A smaller proportion of total bilirubin formation comes from the degradation of the heme from other heme-containing proteins, such as myoglobin, cytochromes, guanylyl cyclase, nitric oxide synthase, and others. **(Stevenson et al, 2001)**.

- ***The first step:***

Heme from erythropoietic and other origins is degraded by heme oxygenase enzyme complex to equimolar amounts of carbon monoxide (CO) and biliverdin **(Stevenson et al, 1994)**.

Heme oxygenase (HO), the rate - limiting enzyme in bilirubin production, has been identified from the late 1960s. This enzyme allows for the degradation of heme from hemoglobin or other heme- containing proteins to form biliverdin. This process is energy requiring because NADPH donates electrons through the cytochrome cP450 system and molecular oxygen is consumed for the liberation of iron from the porphyrin ring of heme, the release of carbon monoxide (CO), as well as the formation of biliverdin **(Dennery et al, 2001 b)**.

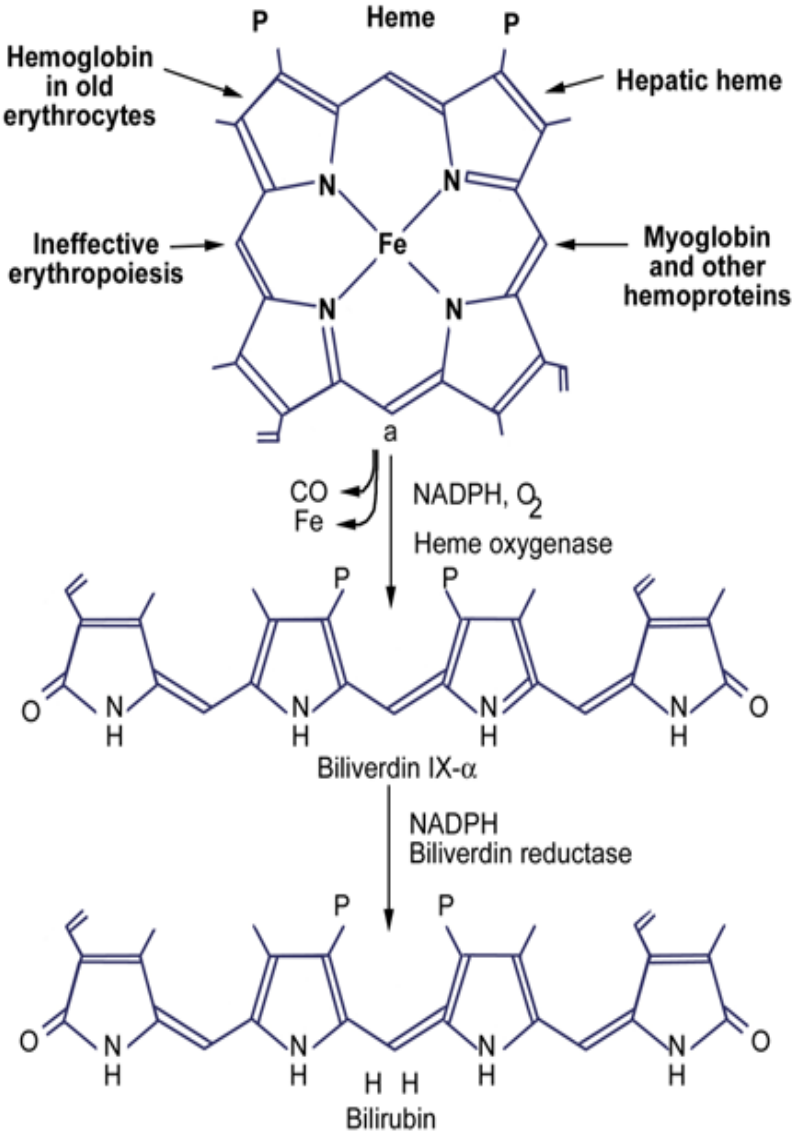

Figure 1: Production of Bilirubin. (**Mukherjee, 2008)**

Heme oxygenase is found in several tissues, with significant activity levels in the liver, spleen, and erythropoeitic tissue. HO activity is inducible by heme and other metalloporphyrins ,hormones , starvation, stress, toxins, and xenobiotics. Heme oxygenase induction is generally considered to be the result of an increased protein synthesis and gene transcription. This hypothesis is supported by studies of the heme oxygenase gene. In the developing fetus and neonate, hepatic HO activity and mRNA levels are elevated above that of the adult. This suggests that the elevated heme catabolism observed in neonates may be associated with an increased transcription of the heme oxygenase gene. The apparent induction of hepatic HO during the neonatal period is probably the result of tissue-specific and time-dependent transcriptional