Cardiovascular Changes in Neonates with Unconjugated Hyperbilirubinemia

Thesis

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List of Abbreviations

AAP	=	American Academy of Pediatrics
ABE	=	Acute bilirubin encephalopathy
AO	=	Aortic outflow
Azg. v	=	Azygos vein
B/A	=	Bilirubin / Albumin ratio
BMG	=	Bilirubin monoglucuronide
BDG	=	Bilirubin dinoglucuronide
CW	=	Continuous wave
DAT-test	=	Direct anti globulin test
EF	=	Ejection fraction
EGF	=	Epidermal growth factor
ET	=	Ejection time
FH	=	Family history
FS	=	Fractional shortening
G6PD	=	Glucose 6-phosphate dehydrogenase
LA	=	Left atrium
LV	=	Left ventricle
LVEDD	=	Left ventricular enddiastolic diameter
LVESD	=	Left ventricular endsystolic diameter
IVIG	=	Intravenous immune globulin
LVPW	=	Left ventricular posterior wall
IVS	=	Interventricular septum
MV	=	Mitral valve
NICU	=	Neonatal intensive care unit
OATP	=	Organic anion transporter
PA	=	Pulmonary artery
PAP	=	Pulmonary artery pressure
PPHN	=	Persistent pulmonary hypertension
PW	=	Posterior wall
RA	=	Right atrium
ROS	=	Reactive oxygen species
RPV	=	Right pulmonary vein
RV	=	Right ventricle
RVOT	=	Right ventricular outflow tract
SV	=	Stroke volume
SVC	=	Superior vena cava

List of Abbreviations continue ……

TcB	=	Transcutaneous bilirubin
TSB	=	Total serum bilirubin
TV	=	Tricuspid valve
UCB	=	Unconjugated bilirubin
UDPGT	=	Uridine diphosphate-glucuronyl transferase

Abstract

Introduction: Jaundice affects nearly 60% of term and 80% of preterm neonates during the first week of life. Unconjugated hyperbilirubinemia may result in severe medical conditions when left untreated. The most serious of them is encephalopathy. Cardiac affection was also reported in many studies.

The aim of this work: was to study prospectively the effects of unconjugated hyperbilirubinemia on the cardiovascular status and myocardial function in jaundiced neonates admitted to Cairo University NICU over a period of 3 consecutive months (May to July 2009).

Patients and methods: The study included 135 neonates. We studied the impact of different clinical parameters (e.g. mode of delivery, gestational age, admission weight, etc.) and laboratory parameters (e.g. level of total and unconjugated bilirubin on admission and after 48 hours, hemoglobin, etc.) on the cardiac functions measured by echocardiography.

Results: The studied patients represented 46.1% of all admissions in these 3 months. Males were more prevalent than females (54.8% versus 45.2%). The gestational ages ranged from 35 weeks to 40 weeks, and their admission's weights varied from 1.5 to 4.5 kg. The jaundice was noticed from day 1 to as late as day 7, while the admission ages ranged from 1 day to 27 days. On admission, total serum bilirubin ranged from 6.7 to 45.8 mg/dl and unconjugated bilirubin ranges were from 6.4 to 42.9 mg/dl. Other parameters also were measured e.g. hemoglobin, albumin, B/A ratio, potassium etc. Nineteen percent of the studied cases had fractional shortening below 30% as documented by echocardiography, indicating affection of left ventricular systolic function. Cases with cardiac affection had significantly higher bilirubin levels and B/A ratio on admission than cases without cardiac affection. They also showed increased left ventricular enddiastolic, left

ventricular endsystolic, aortic outlet and left atrial measurements. On follow up after 1 month for reevaluation of their echocardiographic findings, only 10 cases came. Three out of the ten cases had still an affection of cardiac contractility and were referred to cardiology clinic.

Conclusion: Neonatal unconjugated hyperbilirubinemia is still a main cause of admission to the NICU. The public and professional awareness of the problems associated with neonatal jaundice should be highlighted and affection of cardiac contractility should also be considered. Patients with severe hyperbilirubinemia (> 25 mg/dl) are more susceptible to cardiac affection. Early detection and follow up of cases with high unconjugated hyperbilirubinemia are recommended.

KEY WORD: NEONTES-UNCONJUGATED-ECHOCARDIOGRAPHY-SVC

Introduction

Neonatal hyperbilirubinemia is extremely common, because almost every newborn develops an unconjugated serum bilirubin level more than 30μmol/l (1.8 mg/dl) during the first week of life. Jaundice in neonates is common affecting nearly 60% of term and 80% of preterm neonates during the first week of life ***(Agarwal and Deorari, 2002).*** Almost all newborn infants develop a total serum bilirubin (TSB) level greater than 1 mg/dl (17 micromol/l), which is the upper limit of healthy adults. As the TSB increases, it produces a yellowish discoloration of the skin and/or sclerae caused by bilirubin deposition, and this is called jaundice ***(Dennery et al., 2001).***

Incidence figures are difficult to compare because authors of different studies do not use the same definitions for significant neonatal jaundice. Also, incidence, extent and duration of elevation of total serum bilirubin vary among populations of different racial and geographic distributions ***(Madan et al., 2005).***

Hyperbilirubinemia may be conjugated or unconjugated. Conjugated hyperbilirubinemia is due to hepatic and post hepatic causes. The unconjugated hyperbilirubinemia may be physiological or non physiological. In most infants, unconjugated hyperbilirubinemia reflects a normal transitional phenomenon (physiologic jaundice). This jaundice is caused by a combination of increased bilirubin production secondary to accelerated destruction of erythrocytes, decreased excretory capacity secondary to low levels of ligandin in hepatocytes, and low activity of the bilirubin-conjugating enzyme UDPGT ***(Hansen, 2011).***

Pathologic neonatal jaundice with unconjugated hyperbilirubinemia occurs when additional factors accompany the basic mechanisms described above. These factors may lead to hemolysis (hemolytic jaundice) or nonhemolytic jaundice. Hemolytic factors include intrinsic causes e.g. G6PD deficiency and spherocytosis. Extrinsic factors include: alloimmunity due to ABO and RH incompatibility (hemolytic disease of the newborn). Nonhemolytic causes include cephalhematoma and polycythemia ***(Piazza and Stoll, 2007).***

Hyperbilirubinemia may require therapy, which is mainly in the form of phototherapy or exchange transfusion. The values for this in infants of 35 weeks gestation follow specific curves ***(AAP, 2004)*** and in preterms less than 35 weeks of gestation the choice of therapy depends on the weight ***(Cloherty et al., 2008).***

Unconjugated hyperbilirubinemia may result in severe medical conditions when left untreated. The most serious of them is encephalopathy. Cardiac affection due to unconjugated hyperbilirubinemia was reported in many studies. In 1990, a study reported a significant, but previously unrecognized cardiac hypertrophy with disproportionate septal hypertrophy in patients with erythroblastosis fetalis ***(Carter et al., 1990).*** Left ventricle (LV) systolic dysfunction was detected in full-term neonatal with unconjugated hyperbilirubinemia caused by decreased conjugating activity and hemolytic disease of the newborn. This finding was documented by echocardiography ***(Prakhov and Girshovich, 2004).***

Aim Of Work

The main objectives of this work are:

- To prospectively study neonates with unconjugated hyperbilirubinemia admitted to Cairo University Neonatal Intensive Care Unit (NICU) for therapy over a period of 3 consecutive months.

- To assess the cardiovascular status of the patient and myocardial function by echocardiography.

- Obtained data analysis may shed some light on the effect of unconjugated hyperbilirubinemia on the cardiovascular affection in neonates.

Neonatal Hyperbilirubinemia

Definition

Neonatal hyperbilirubinemia is defined as a total serum bilirubin level above 5 mg per dL (86 μmol per L). Deposition of unconjugated bilirubin pigment in the skin and mucus membranes results in neonatal jaundice, which is manifested as some degree of yellowness of the skin or sclera, occurring when the total serum bilirubin level exceeds 5-6 mg/dl. Neonatal jaundice is a very common condition worldwide occurring in up to 60% of term and 80% of preterm newborns in the first week of life, where few have significant underlying disease ***(Slusher et al., 2004)***. In most cases, the total serum bilirubin concentrations (TSB) do not exceed the normal range, the upper limit for which may be defined as the 95th percentile for hour of life ***(Haque and Rahman, 2000).*** However, hyperbilirubinemia in the newborn period can be associated with severe illnesses such as hemolytic disease, metabolic and endocrine disorders, anatomic abnormalities of the liver, and infections. Depending on the patient group under consideration, TSB values peak on the 3rd to 4th day of life. The 95th percentile at this age corresponds to TSB concentrations of 15.0 mg/dl to 17.0 mg/dl ***(Maisels, 2001)***. Even though extreme hyperbilirubinemia is rare in developed countries it is still quite high in developing countries often resulting in kernicterus with its attendant medical, economic and social burden on the patient, family and society at large ***(Wang et al., 2005; Ho, 2002).***