Pattern of Neonatal Liver Disease in Egyptian Neonates Admitted To NICU's A Single Center - One Year Study

By

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بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

وَلَقَدْ خَلَقْنَا الْإِنسَانَ مِن سُلَالَةٍ مِّن طِينٍ {12} ثُمَّ جَعَلْنَاهُ نُطْفَةً فِي قَرَارٍ مَّكِينٍ {13} ثُمَّ خَلَقْنَا النُّطْفَةَ عَلَقَةً فَخَلَقْنَا الْعَلَقَةَ مُضْغَةً فَخَلَقْنَا الْمُضْغَةَ عِظَامًا فَكَسَوْنَا الْعِظَامَ لَحْمًا ثُمَّ أَنشَأْنَاهُ خَلْقًا آخَرَ فَتَبَارَكَ اللَّهُ أَحْسَنُ الْخَالِقِينَ {14}

صدق الله العظيم

سورة المؤمنون (12 – 14)

Conclusions

- Although hepatic insult in babies admitted to NICU had a low prevalence (9.4%), yet - with this group - it contributed to the mortality of 44.4% of these cases.
- Cholestatic jaundice is a typical presenting feature of neonatal liver disease rather than a late manifestation, as often observed in the older child. It is crucial to identify the cause of neonatal cholestasis because many of these infants need prompt medical or surgical intervention.
- Primary liver diseases as extrahepatic biliary atresia and congenital infection in neonates are uncommon; much of the liver dysfunction seen in the neonatal period is secondary to systemic illness such as sepsis or hypoxic injury.
- Sepsis - whether community acquired or hospital acquired – was the major contributing factor for hepatic insult among our neonates.
- Severe neonatal hyperbilirubinemia (SNH) is still a major prevalent in our NICU population and the incidence seems to be increasing. SNH is missed in our community and kernicteric babies still present to our neonatal units.
- Delayed diagnosis of EHBA is still a major problem in our country.

Dedication

To my Father and my Mother whom taught me the principles and patience

To my children Hussein, Mustafa and Farida who gave me the smile during hard time

To all who sacrificed for me

Mohammed Farouk

Discussion

Neonatal liver diseases could be presented in many aspects; the most important is cholestasis or conjugated hyperbilirubinemia which is the cornerstone manifestation of neonatal hepatitis syndrome. This neonatal hepatitis syndrome has numerous possible causes, classified as infective, anatomic/structural, metabolic, genetic, neoplastic, vascular, toxic, immune and idiopathic ***(Roberts, 2003).***

The number of distinct disorders presenting with cholestasis may be greater in the neonatal period than any other time of life, this is because of the immaturity of hepatic excretory function, the susceptibility to infection during the perinatal period, the initial effects of congenital malformations particularly of the biliary tree, and the presentation of genetic and metabolic disorders. In the United States, neonatal liver disease may occur in as many as 1 in 2500 newborn infants ***(Suchy, 2004).***

An abnormal direct bilirubin has been designated as greater than 1 mg/dL if the total bilirubin is less than 5 mg/dL, or a value of direct bilirubin that represents more than 20% of the total bilirubin level when total bilirubin is greater than 5 mg/dL ***(Moyer et al., 2004).***

Establishing a rapid and accurate diagnosis of the cause of neonatal liver disease is an urgent matter. The initial detection of this condition relies on the sensitivity of the primary care provider or

pediatrician to the signs and symptoms of jaundice and abnormal stool and urine color ***(Emerick and Whitington, 2006).***

This prospective study was carried out through 12 months to high light the occurrence of hepatic problems among neonates admitted to the neonatal and surgical neonatal intensive care units of the Children's Hospital, Cairo University.

It included 153 neonates who were admitted to NICU and SNICU with different patterns of liver affection with a mean age of 7.4 ±9.15 days having a range 1-72days. This represents (9.4%) of the total admissions (1622 cases) during this period. Liver problems were either present initially in these neonates or developed later during the period of their hospital stay.

In our study, cholestasis was the most common form of liver affection during the neonatal period, it constituted (73.9%) of cases presented with liver problems with mean age of onset 6.7± 9.2 days ranging from 1-72 days. Among these, inspissated bile plug syndrome, secondary to hemolytic anemia, and bacterial infection, in particular gram negative sepsis, were the main causes of acute cholestasis of the studied neonates. In a previous retrospective study done in Sweden that investigated etiologic factors in neonatal cholestasis on 85 infants with mean age 61 days, Fischler et al found that the most common cause of neonatal cholestasis was due to extrahepatic biliary atresia (35% of cases) ***(Fischler et al., 2001)***. Whereas another study in

Bangladesh done by Bazlul-Karim and Kamal who examined 62 infants with a mean age 3.5 months, reported that neonatal hepatitis (congenital infection and urosepsis) was the most common cause of cholestasis (35.5% of cases) ***(Bazlul-Karim and Kamal, 2005)***. The babies in both these series were older than the infants in our study, indicating that these previous reports were focused on chronic cholestasis. Other research group in Turkey found that, in most neonates with early onset conjugated hyperbilirubinemia, cholestasis was caused by several associated factors, including culture-proven sepsis, immaturity of bile secretion and perinatal disease leading to hepatic hypoxia or ischemia ***(Tiker et al., 2006).*** The previous report and our study findings revealed that the causes of early, acute cholestasis are different from those of chronic forms.

In our study it was noted that, during the period of the study, 565 neonates were admitted to NICU because of neonatal jaundice, this represented 61.5% of the total admissions in NICU (919 cases). This is in comparison to a study done in our unit from April 2003 to October 2004 which reported that neonatal hyperbilirubinemia was a cause of 35.8% of total admissions ***(Seoud et al., 2005).*** Also in another study in the same unit done from October 2004 to October 2005 jaundiced newborns accounted for 38.2% of NICU admissions ***(Seoud et al., 2007a).*** This was also much higher than that obtained by a multicenter study conducted in several governmental hospitals all

over Egypt which reported an incidence of jaundice of 36.4% of 10563 admissions ***(Helal, 2006).*** These results revealed an increase in cases of neonatal jaundice in our unit in the last year which comes in agreement with a prospective Canadian study that conducted to estimate the incidence of severe neonatal hyperbilirubinemia on term infants (60 days of age and younger) with unconjugated hyperbilirubinemia from 2002 to 2004 and revealed that the problem of jaundice is increasing in the last years ***(Sgro et al., 2006).*** However in most countries although the magnitude of the problem is increasing yet jaundiced patients accounted for a less percent of total admissions. In a study from Turkey, the incidence of severe neonatal hyperbilirubinemia requiring phototherapy was 10.5% in term infants and 25.3% in near term infants ***(Sarici et al., 2004)*** and in another study from Nepal, jaundiced patients accounted for only 14.3% of admissions to the NICU ***(Kaini et al., 2006).***

Generally, hemolytic anemia produces increased unconjugated bilirubin which could cause jaundice. However, it can also result in severe, early onset conjugated hyperbilirubinemia. The suggested mechanisms of conjugated hyperbilirubinemia in severe hemolytic anemia are excessive bilirubin load causing inspissated bile syndrome and rarely functional and/or anatomical liver cell damage secondary to heart failure or anemia. Cholestasis due to hemolytic anemia has been

reported to resolve within a month, but in some cases it persists for over 3 months ***(Allgood and Bolisetty, 2006).***

During the period of our study, cases presented with severe unconjugated hyperbilirubinemia that necessitated exchange transfusion constituted 22.1% of the totally admitted cases with neonatal jaundice (125 out of 565 cases), out of them 40% of cases developed cholestasis (n=50). Inspissated bile syndrome following severe hemolytic anemia, was the most common cause of cholestasis, accounted for 44.3% of cholestatic cases. In a previous study done in Thailand, Aanpreung et al reported that hemolytic anemia was a common cause of neonatal cholestasis during the first week of life, accounted for 4 out of 17 cases (23.5%) ***(Aanpreung et al., 2005).***

In our study, ABO incompatibility accounted for 56% of cases presented with severe hemolytic anemia, Rh incompatibility for 14%, combined ABO and Rh incompatibility for 4% and glucose 6 phosphate dehydrogenase deficiency (G6PD) for 4% of cases. Cephalhematoma and extravasated blood were the cause in 12% of cases. **Seoud et al (2007a)** reported that the incidence of ABO incompatibility was 23% of admitted jaundiced cases, Rh incompatibility for 10.9%, and G6PD deficiency for 3.2% of cases. This reveals the higher incidence of ABO incompatibility in cases of neonatal hyperbilirubinemia as suggested by other studies ***(Kaini et al., 2006 and Seoud et al., 2007b).***

Neurological manifestations of acute Bilirubin Induced Encephalopathy (BIND) were present in 54% of our cases who presented with inspissated bile syndrome (27 out of 50 cases). These cases presented initially with severe indirect hyperbilirubinemia with mean serum total bilirubin level 39.9 $\pm$ 7.9 mg/dL. However 13 cases improved clinically and 14 cases remained with frank kernicterus (3 cases died and 11 cases were discharged). This is an alarmingly high percent condition and knowing that it is a handicapping disorder. However it strongly correlates with highly hazardous levels of TSB in neonates admitted to our unit.

Long term follow up of infants with extremely high TSB levels is required to exclude minor neurological dysfunction that may not be currently apparent. The collaborative perinatal project ***(Newman et al., 2002)*** suggested that infants with a bilirubin level > 20 mg% were at higher risk for subtle neurological abnormalities but **Newman et al** in **2006** compared 140 infants recruited from Kaiser Permanent Hospital in California, USA with bilirubin levels > 25 mg with 419 random controls and demonstrated that infants admitted with non hemolytic jaundice of 25-30 mg% bilirubin levels did not differ in outcome from their control group regarding major or minor BIND till the age of 5 years. Their results are reassuring in that prompt treatment of even very elevated levels of bilirubin can prevent long term adverse effects

and that a trial of effective phototherapy with reassessment in 4 hours may save babies from the risk of undue exchange.

In our study, blood culture proven sepsis was the second most common cause of cholestasis among the studied neonates, constituted 37.2% (40 out of 113) of the cholestatic cases. Out of them, gram negative organisms were isolated in 78.6% of cases (33 out 0f 40), *Klebsiella pneumoniae* was the most common agent isolated (42.8%).

Sepsis is a well documented cause of cholestasis. Not all cases of cholestasis associated with sepsis feature direct infection of the liver. In sepsis without direct hepatic infection, bile flow becomes markedly reduced, leading to conjugated hyperbilirubinemia but no significant transaminase elevation. The mechanism of cholestasis in such cases is not clear, but some have been postulated, including changes in hepatic microcirculation, direct effects from bacterial products, and effects caused by endotoxin-induced mediators ***(Karpen, 2002).***

The incidence of neonatal sepsis in developed countries is 1-4/1,000 live births. Early onset disease can manifest as asymptomatic bacteremia, generalized sepsis, pneumonia, and/or meningitis. Other less specific signs of sepsis include irritability, temperature instability, poor perfusion, and hypotension. Disseminated intravascular coagulation (DIC) can occur in severe septic shock ***(Puopolo, 2008).*** Several studies have evaluated relationships between infection and hyperbilirubinemia, In Turkey, one study reported that bacterial

infection and gram negative sepsis in particular, was the main cause of acute cholestasis in 42 infants in which onset of jaundice occurred at a mean age of 10 days (35.7% of cases). E. coli was the most common gram negative agent isolated (46.6%) ***(Tiker et al., 2006).*** In a thesis that investigated etiological factors of cholestasis in 100 neonates admitted to our unit from April 1999 to October 1999, gram negative septicemia was dignosed in 7 out of 9 cases with an incidence 77.7%. Enterobacter was the most common isolated organism. ***(Mohey El-Dein, 2002).*** In another American prospective study, Garcia and Nager documented urinary tract infection in 7.5% of 160 asymptomatic infants with jaundice who were younger than 8 weeks old. Two of the 12 infants who had urine culture positive for *Klebsiella pneumoniae* and *E. coli* had higher than normal conjugated bilirubin fraction ***(Garcia and Nager, 2002).*** In Israel, one report on premature infants with gram negative bacteremia noted that liver enzyme abnormalities were more frequent than elevated conjugated blilirubin levels ***(Shamir et al., 2000).*** However, in our study, only 28% of these septic neonates had significantly elevated enzymes. This is compatible to the results obtained by Tiker et al. who noted that only 20% of their septic neonates had elevated liver enzymes ***(Tiker et al, 2006).***

In our study, EHBA was identified in 2.7% of cholestatic cases (3 out of 113 cases) with mean γ glutamyl transpeptidase level (GGT)

844.4±262 U/L. Diagnosis of EHBA was primarily based on the inability to visualize the gallbladder and the presence of the triangular or band like periportal echogenic density >3 mm in thickness (TC sign) by ultrasonography, and the histological findings obtained from percutaneus liver biopsy. It was observed that one of them had also choledochal cyst in addition to EHBA. Two out of these three cases are diagnosed after the age of 8 weeks denoting that delayed diagnosis of EHBA is still a major problem in our country.

Extrahepatic biliary atresia (EHBA) is an idiopathic inflammatory process resulting in obstruction of the biliary tract, chronic cholestasis, and progressive fibrosis and eventually progress to biliary cirrhosis ***(Suchy, 2001)***. In the United States, the incidence of EHBA has been estimated to be about 1: 15000 live births. It is the most common cause of end-stage liver disease in the infant and is the leading pediatric indication for liver transplantation ***(Venigalla and Gourley, 2004).*** Earlier diagnosis (<30-45 days of life) is associated with improved outcomes following the Kasai portoenterostomy and longer survival with the native liver. However, establishing this diagnosis is problematic because of its rarity and the much more common indirect hyperbilirubinemia that occurs in the newborn period ***(Sokol et al., 2007).***

Tiker et al (2006) found that, among the 42 newborn infants with early onset conjugated hyperbilirubinemia, EHBA was diagnosed in

only 2.4% of cases. In a tertiary-care hospital in Bangladesh, Bazlul-Karim and Kamal reported that the incidence of EHBA - among cholestatic infants before the age of 3 months - reached up to 25% of cases ***(Bazlul-Karim and Kamal, 2005).***

In our study, perinatal hypoxia-ischemia, was a cause of elevated liver transaminases in 7.8% (12 out of 153) of the totally included cases of the study, with mean ALT level (195±147 U/L). Also perinatal hypoxia was identified as a cause of cholestasis in 2.7% (3 out of 113) of the cholestatic neonates.

In Turkey, **Tiker et al (2006)** reported perinatal asphyxia as a cause of cholestasis in as high as 7/42 neonates (16.7%). Six out of these 7 asphyxiated neonates died. However, **Mishra and Arora (2007)** recommended that perinatal asphyxia should not be labeled as the sole etiology of cholestasis in these infants without ruling out inborn errors of metabolism that could lead to neonatal encephalopathy at birth and cholestasis. **Tarcan et al (2007)** did also a retrospective study on 56 newborns with perinatal asphyxia and found that 39% of them had hepatocyte injury.

Previously, several studies also identified hypoxia as an important causal factor in transient neonatal cholestasis. One of these studies, reported that hypoxia constituted 17% of cases presented with cholestasis in the first week of life ***(Aanpreung et al., 2005).*** Another research group assessed 181 asphyxiated newborn infants born with

appropriate birth weight for gestational age (AGA) or small weight for gestational age (SGA) at Sainte-Justine Hospital, Montreal, Quebec between 1989 and 1993. They found that transient neonatal cholestasis was developed in 8.5% of asphyxiated AGA and 33% of SGA newborn infants, compared with 3.94% cholestasis of any etiology in nonasphyxiated SGA infants. Asphyxiated neonates born before the age of 35 weeks had an increased risk for transient neonatal cholestasis ***(Herzog et al., 2003).***

In our study, two cases with trisomy 21 presented with neonatal hepatitis syndrome, constituted 1.8% of the cholestatic cases. **Aanpreung et al (2005)** reported that Down syndrome represented 4.4% of the etiological causes of neonatal cholestasis. Both neonatal hepatitis syndrome and EHBA have been reported in association with trisomy 17-18 syndrome (trisomy E), and trisomy 21 (Down's syndrome). The mechanism is unknown ***(Jonas and Perez-Atayde, 2007).***

In our study, congenital toxoplasmosis was the proven etiology in a cholestatic neonate with positive serum specific immunoglobulin M, represented 0.9% of the cholestatic neonates (1 out of 113). The clinical data included low birth weight, jaundice that appeared on first day, abnormal facial features and high imperforate anus. Ophthalmologic examination revealed bilateral corneal opacities.