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Risk Factors of Severe Neonatal Hyperbilirubinemiain Mosul City

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ABSTRACT

Hyperbilirubinemia is a common disorder during the neonatal period. Severe neonatal hyperbilirubinemia carries a potential for permanent neurological impairment .To identify risk factors of severe hyperbilirubinemia among neonates admitted to the neonatal intensive care units in Al-Khansaa and Ibn Al-Atheer Teaching Hospital in Mosul city.A case-control study was conducted in six months period from Feb 2015 to the end of July 2015 on neonates who had admitted to the neonate care unit due to neonatal jaundice and divided into two groups according to level of serum bilirubin (≥ 20 mg/dL and < 20 mg/dL) each group of 100 neonate, all subjects were chosen randomly. One hundred neonates who admitted to NICU due to neonatal jaundice with age of ≤ 28 days old and TSB level ≥ 20.0 mg/dL.And One hundred neonates admitted to NICU due to neonatal jaundice with age of ≤ 28 days old and TSB level < 20.0 mg/dL. This study revealed that Male gender show a higher mean bilirubin level (64%) than females (36%) . ABO incompatibility was more frequent among all neonatesin (24%) .Followed by babies of mothers with urinary tract infections (18.5%); Rh sensitization (16.5%) ;babies of diabetic mothers (11.5%). In conclusion ABO incompatibility was the most common risk factor for sever jaundice.

Key Words: sever hyperbilirubinemia, risk factor, neonate.

INTRODUCTION

Jaundice is one of the most frequent problems of the neonatal period and corresponds to the clinical expression of hyperbilirubinemia, defined as a serum Unconjugated Bilirubin concentration of greater than 1.3 to 1.5 mg/dL or conjugated Bilirubin concentration of higher than 1.5 mg/dL , or as total serum bilirubin (TSB) levels greater than 5 mg/dL.(1)

Jaundice is observed in approximately 60% of term infants and 80% of preterm neonate during the first week of life.(2) Hyperbilirubinemia defined as a total serum or plasma bilirubin >95 percentile on the hour-specific Bhutani nomogram (3), can be caused by certain pathologic conditions or by exaggeration of the mechanisms responsible for neonatal jaundice (NNJ), Neonatal hyperbilirubinemiais the most common reason of readmission after early hospital discharge .(4)

Identification of the cause of neonatal hyperbilirubinemia is useful in determining whether therapeutic interventions can prevent severe hyperbilirubinemia .(5)

The estimated occurrence of hyperbilirubinemia based on peak TSB severity has been reported as :

- more than 17 mg/dL, defined as significant, at (1 in 10)
- more than 20 mg/dL, defined as severe, at (1:70)
- more than 25 mg/dL, defined as extreme, at (1:700); and
- more than 30 mg/dL, defined as hazardous, at (1:10,000) live births.(5)

Classifications of Jaundice:

It is essential to distinguish whether the jaundice is physiologic or pathologic. Jaundice noted within the first 24 hours is pathologic and a TSB should be drawn. Early jaundice is usually related to hemolysis, infection, drug effect, neonatal hepatitis or liver enzyme defects (e.g., Crigler-Najjar-deficiency of UDPGT).(5)

Physiological jaundice: in newborns is caused as a result of increased bilirubin production, increased red blood cell mass and short-lived red blood cells. Physiologic jaundice becomes visible on the second or third day, usually peaking between the second and fourth days at 5-6 mg/dL and decreasing to less than 2 mg/dL between the fifth and seventh days of life .[4]

Physiological jaundice is very common and usually harmless and is not associated with any disease. Jaundice is more likely in the first week of life in infants who are breastfed. This may be caused due to receiving fewer calories and increase the entero-hepatic circulation of bilirubin. Non-conjugated jaundice is defined as prolonged jaundice remains beyond the second week of life. The jaundice is seen in infants fed breast milk. The mechanism of breast milk jaundice syndrome is still not completely understood .[6]

The purpose of diagnosis and treatment of NNJ, is remove the pathologic causes of hyperbilirubinemia and early treatment to prevent neurological toxicity. The diagnosis of physiologic jaundice in term or preterm infants can be established only by excluding known causes of jaundice on the basis of the history, clinical findings, and laboratory data .[4]

Pathological jaundice: Any TSB elevation exceeding 17 mg/dL is considered pathologic and warrants investigations for a cause and possible therapeutic intervention[7,8]. Jaundice that persists beyond 2 weeks should be evaluated beginning with a fractionated bilirubin .[9]

In general, a search to determine the cause of jaundice should be made if :

1. it appears in the first 24-36 hr of life,
2. serum bilirubin is rising at a rate faster than 5 mg/dL/24 hr,
3. serum bilirubin is >12 mg/dL in a full-term infant (especially in the absence of risk factors) or 10-14 mg/dL in a preterm infant,
4. jaundice persists after 10-14 days of life ,
5. direct bilirubin fraction is >2 mg/dL at any time. [4]

Marked hyperbilirubinemia can lead to acute bilirubin encephalopathy (ABE) and evolve into chronic bilirubin encephalopathy (CBE), a devastating, permanently disabling neurologic disorder, synonymous with kernicterus. [9, 10]

PATIENTS AND METHODS

Administrative agreements:
Before the start of study, an official agreement was abstained from the health directorate.

Study setting:
The present study was conducted at Al-Khansaa and Ibn Al-Atheer Teaching Hospitals/NICU in Mosul city.

Study design:
This study was a case-control study which is a type of observational study, where the subject is selected on basis of whether they have the disease (case), or do not have disease (control) under study. The groups are then compared for the proportion of having a history of previous exposure or not. In this study, all subjects having neonatal jaundice then divided according to severity of hyperbilirubinemia and TSB level (≥ 20.0 mg/dL and < 20.0 mg/dL)

Severe neonatal hyperbilirubinemia was diagnosed when a newborn had a TSB level ≥ 20.0 mg/dL in serum .[5] Sample size was 100 cases (Sever Hyperbilirubinemia) and 100 as control.

Case Definition: One hundred neonates who admitted to NICU due to neonatal jaundice with age of ≤ 28 days old and TSB level ≥ 20.0 mg/dL.

Control Definition: One hundred neonates (50 boys and 50 girls) who admitted to NICU due to neonatal jaundice with age of ≤ 28 days old and TSB level < 20.0 mg/dL.

Inclusion Criteria:
Newborns ≤ 28 days old.Newborns whose gestational age were ≥ 35 weeks and ≤ 42 weeks divided into infants with 35 to 37 weeks of gestation were defined as near-term and constituted, whereas those with 38 to 42 weeks of gestation were defined as term.Newborns weighting above 2000 grams

Exclusion Criteria:
Newborns above 28 days old**.** Newborns whose gestational age were < 35 weeks (preterm) and > 42 weeks (post term).Newborns who presented with twin, respiratory distress, G6PD deficiency, and congenital major malformations**.** Newborns weighting below 2000 grams or diagnosed as small for gestational age and large for gestational age.

Statistical analysis:

Data analysis was carried out by using computer facility Through the use of two by two tables and compare groups then use the following equation:

odd ratio (OR) = a X d / b X c

Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for severe hyperbilirubinemia of various risk factors by JAVA stat software program.

$P < 0.05$ and a 95% CI for OR ≥ 1.0 was defined as statistically significant.

RESULTS

Table 1: Distribution of studied groups according to the gender

Gender	*Case*	*Control*	*OR*	*(95% CI)*	*p**
Male	64	50	**1.778**	1.011 – 3.125	**0.032**
Female	36	50	0.563	0.320 – 0.989	0.984

* (chi- square test was used)

Table 2: Distribution of studied groups according to the presence of ABO incompatibility

ABO incompatibility	*Case*	*Control*	**OR**	**(95% CI)**	*p**
present	30	18	**1.952**	1.009 – 3.775	**0.034**
absent	70	82			

* (chi- square test was used)

Table 3: Distribution of studied groups according to the presence of Rh sensitization

Rh sensitization	*Case*	*Control*	**OR**	**(95% CI)**	*p**
present	21	12	**1.949**	0.911 – 4.165	0.063
absent	79	88			

* (chi- square test was used

Table 4: The presence of diabetes among mothers of studied neonates

Baby of diabetic mothers	*Case*	*Control*	*OR*	*(95% CI)*	*p**
present	16	7	**2.531**	1.016 – 6.285	**0.037**
absent	84	93			

* (chi- square test was used)

Table 5: The presence of polycythemia among the studied neonates

Polycythemia	*Case*	*Control*	*OR*	*(95% CI)*	*p**
present	9	5	**1.879**	0.634 – 5.551	0.203
absent	91	95			

* (chi- square test was used)

Table 6: Comparison of the neonatal gestational age in both groups

Gestational age, wks	*Case*	*Control*	*OR*	*(95% CI)*	*p**
Near term (35 – 37 wk)	33	21	**1.853**	0.985 – 3.485	**0.04**
Term (38 – 42 wk)	67	79	0.540	0.287 – 1.016	0.981

* (chi- square test was used)

Table 7: Maternal age for the studied neonates

Age, yrs	*Case*	*Control*	*OR*	*(95% CI)*	*p**
< 25	28	34	0.755	0.415 – 1.373	0.858
≥ 25	72	66	**1.325**	0.728 – 2.409	0.222

* (chi- square test was used)

Table 8: Postnatal age when jaundice noticed first

Time when jaundice notice first	*Case*	*Control*	**OR**	**(95% CI)**	*p**
First 24 hr of life	57	26	**3.773**	2.082 – 6.835	**0.00**
24 – 48 hrs	19	42	0.324	0.172 – 0.611	1.00
> 48 hrs	24	32	0.671	0.362 – 1.245	0.922

Table 9: Differences between the mean of postnatal age when jaundice notice first and the mean of age at admission.

Postnatal Age	*Case*	*Control*
Time jaundice noticed , days	1-8 (mean = 1.93)	1-9 (mean = 2.45)
Time of admission, days	2-20 (mean = 7.46)	1-21 (mean = 5.65)

Table 10: Distribution of studied groups according to the presence of sepsis that proven by clinical and laboratory evaluations

Proven sepsis	*Case*	*Control*	*OR*	*(95% CI)*	*p**
present	11	7	**1.642**	0.627 – 4.291	0.230
absent	89	93			

* (chi- square test was used)

Table 11: Distribution of studied groups according to the presence of urinary tract infection that proven by urine culture

Urinary tract infection	*Case*	*Control*	*OR*	*(95% CI)*	*p**
present	15	22	0.626	0.306 – 1.281	0.928
absent	85	78			

* (chi- square test was used)

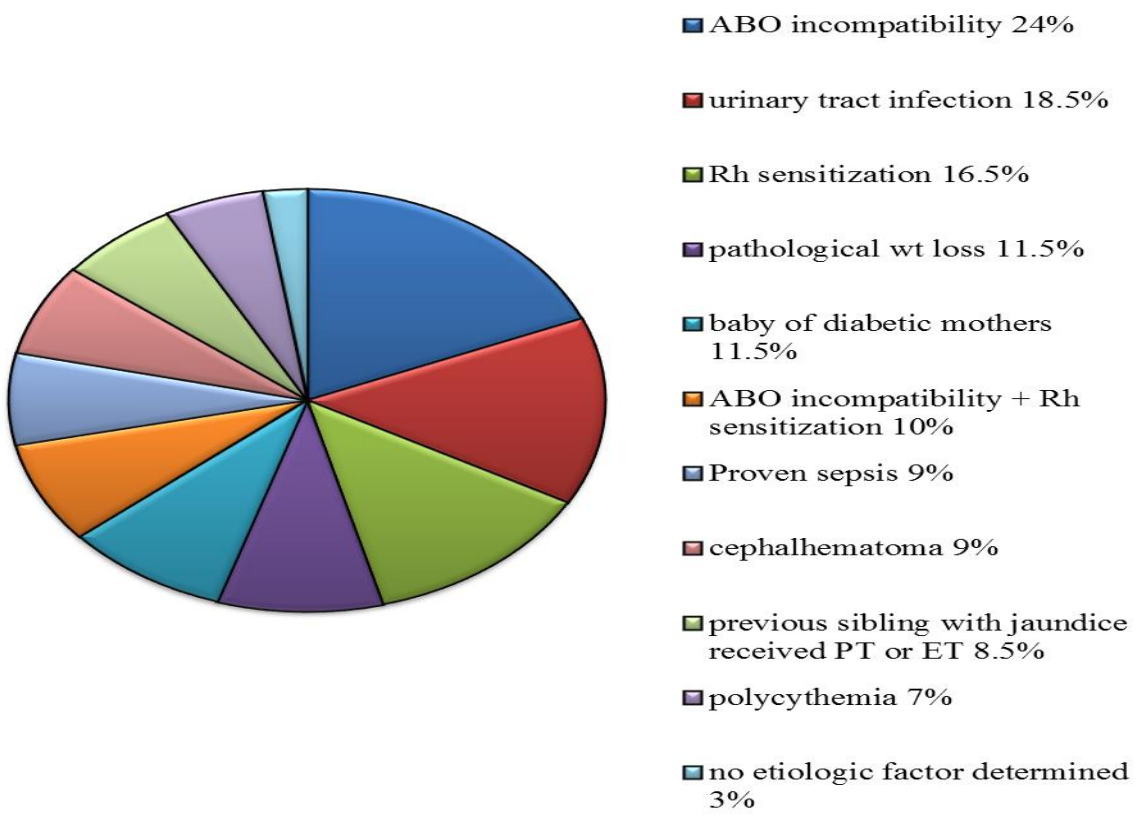

Fig 1: pie diagram showing the frequency of risk factors of hyperbilirubinemia in all studied neonates

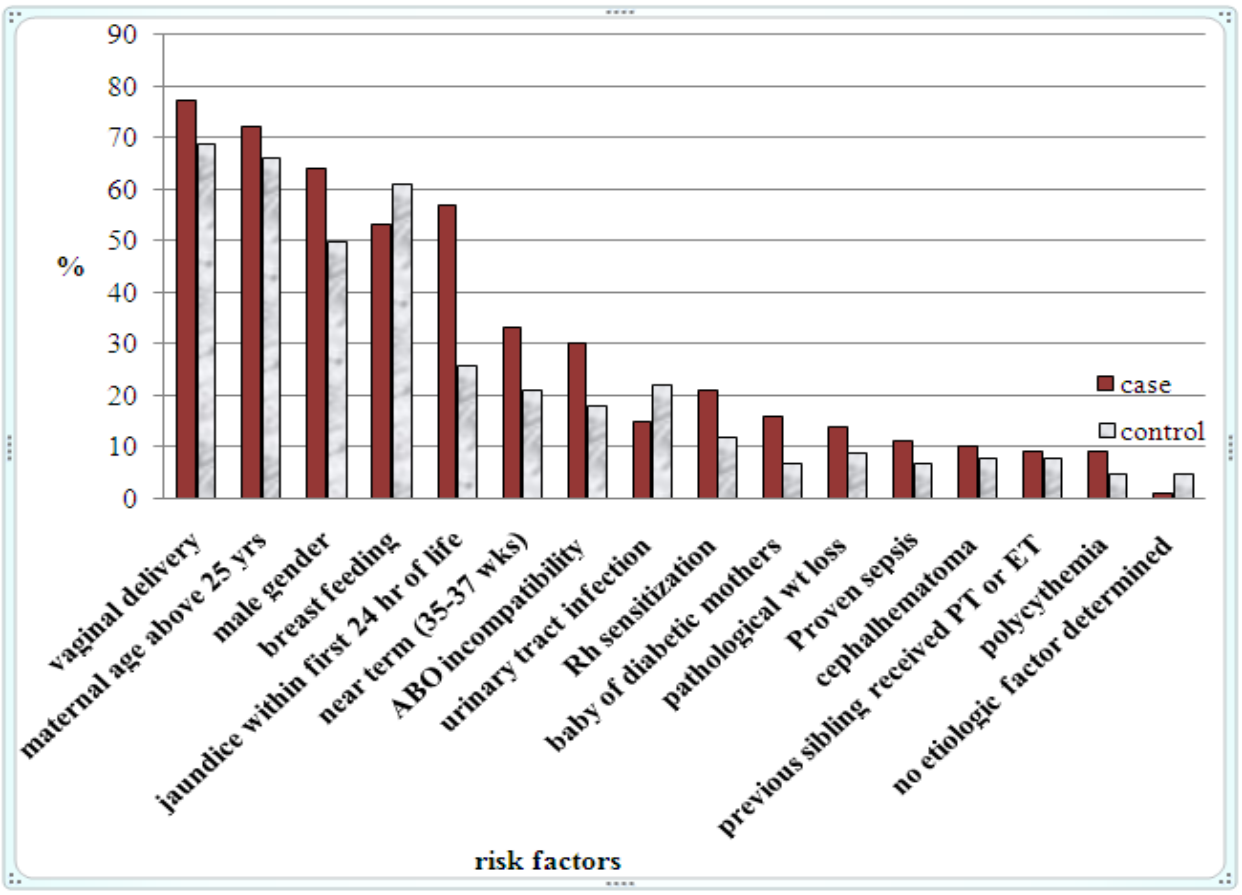

Figure 2: The distribution of the studied groups according to the exposure to risk factors of severe hyperbilirubinemia

DISCUSSION

Jaundice is usually benign. However, because of the potential toxicity of bilirubin, newborns must be monitored to identify those who might develop severe hyperbilirubinemia and, in rare cases, acute bilirubin encephalopathy or kernicterus. [9, 11]

Male gender found to be a risk factor for the higher bilirubin levels statistically (OR = 1.778 and P value = 0.032), and the mean bilirubin levels were higher in males than females.

Newman et al.[12] and Chou and et al.[13] reported that male gender was a risk factor for sever hyperbilirubinemia. In cross-sectional study conducted at 2009 in Nigeria [14] and in retrospective Cohort study conducted at 2013 in Nepal [15] showing that male gender is risk factor for sever hyperbilirubinemia statistically.

In this study, ABO incompatibility was found to be the most common risk factor in newborns with hyperbilirubinemia about 24% of all studied neonate which is less than a result of a study conducted at 2011 in Baghdad city 31% . [16] The present study show that ABO incompatibility was statistically significant risk factor for the development of sever jaundice (OR= 1.952 and P value = 0.03), which is consistent with other studies like that cross sectional studies done in Canada 2006 [17] and in Iran 2010 [18] was identify that ABO incompatibility as most common factor for development of sever jaundice.

There are two case-control studies from Nepal 2009[19]and India 2014[20]that examined ABO incompatibility showed a statistically significant risk factorfor severe hyperbilirubinemia. While a case-control study conducted in Turkey2014 [21]showed that ABO incompatibility was not specific risk factor for sever jaundice. But a case-control study conducted in Taiwan 2004 [22], show only arelationship between this factor and the development of sever type of jaundice(OR= 1.5 and P value =0.4).

This difference may be in some extent due to some difficulties in diagnosing ABO incompatibility (diagnosis done with evidences of hemolysisincluding, positive direct and/or indirect coombs tests, hemoglobin decrementand reticulocytosis), or due to the small sample size and community differences[20].

In this study, There was a relationship with the development of sever jaundice and the presence of Rh sensitization (OR= 1.949 and P value = 0.06). The frequency of this risk factor among all neonates was 16.5% and it was agree with a cross sectional study done in Iran 2010[18] and another in Baghdad 2011 [16] where it was 16.1, 17.0 % respectively. In a cross sectional study done in Egypt 2011 on cases with TSB ≥ 25mg/dL[23], show that Rh sensitization were at increased risk of severe hyperbilirubinemia .

In a study conducted in KSA 2014 [24], Rh sensitization subjects showed higher susceptibility to develop hyperbilirubinemia but still no significant relation seen, this goes with the study of Gatea [2]

Infants of Insulin dependent diabetes mellitus mothers was 2.5 time risky to have sever hyperbilirubinemia than other group (OR = 2.5 and P value = 0.03), In a study in Bangladesh [25] reveal that there is a positive relation between gestational diabetes of mother and a higher Bilirubin level of the neonate.

Polycythemia and cephal hematoma which can be associated with IDM showed a relationship with occurrence of sever hyperbilirubinemia. (OR = 1.8, P value = 0.2 and OR= 1.2 with P value =0.4 respectively).

Infants of diabetic mothers have an increased risk of NNJ. Neonates born to diabetic mothers who have macrosomia tend to have bruising at birth, and resorption of subcutaneous blood can contribute to NNJ [26]. Polycythemia is present in 20% to 30% of infants born to poorly-controlled diabetic mother [27]. Indirect hyperbilirubinemia is a common finding in IDMs as they have an increased red cell mass, ineffective erythropoiesis, and relative immaturity of hepatic bilirubin conjugation and excretion [27] .

Infants of 35 to 37 weeks' gestation were 1.4 times more likely to develop significant hyperbilirubinemia than those of 38 to 42 weeks' gestation, and thus they should be considered a high-risk group. (OR = 1.8 and P value = 0.04). Infants with low gestational age (< 37 weeks) had significant risk factor for severe jaundice in two Cohort studies from India at 2009 and 2010.[28,29]

In a case control study done in India 2009 [30] on neonates with sever jaundice show no specific relation between low gestational age and sever hyperbilirubinemia, these results again found in two cohort studies done at Nepal 2013 [15] and 2009 [19]. These differences may be due to small sample size used in these studies.

Mothers with age of 25 years and more regarded as a risk factor for sever hyperbilirubinemia.[9] This study was not found maternal age ≥ 25 as a risk factor for the higher bilirubin levels statistically and only there was a relation between them (OR= 1.3 and P = 0.22).

The result of a cross sectional study in Nigeria [31] show that maternal age above 25 years had an increase risk for development of sever hyperbilirubinemia. The differences may be due the small sample size and community differences.

First day jaundice was more in sever hyperbilirubinemia group than the other group, and it was statistically significant as a risk factor for sever hyperbilirubinemia (OR = 3.773 and P value = 0.00). Which was similar to the result of a study in Turkey [21] (p value = 0.006).

In both groups although the families noticed the jaundice of the newborns on the second or third day of life or even first day, they stayed at home for two days and brought the newborns to the hospital on the fifth day of life. In a study conducted in Canada 2006, Sgro et al.[17] reported that age of the 66 % of the newborns with severe hyperbilirubinemia when the first admission was 111 hours (5 days). In this study, the mean age at first admission to be seven days in the severe hyperbilirubinemia group. This age was higher than other group. This means that newborns with severe hyperbilirubinemia were brought to hospital later. For this reason the families must be informed about jaundice and its complications before discharge from the hospital and must be told the importance of early admission to hospital as soon as jaundice is noticed .

Most cases (76%) of severe hyperbilirubinemia in this study started within 48 hours from birth. This corresponds with views of AAP and Canadian Pediatric Society, which recommend clinical assessment of infants for jaundice within the first 48 hours of birth [9] .

The present study show that the frequency of urinary tract infection and neonatal sepsis among all studied neonate were 18.5% and 9% respectively, the presence of sepsis had a relationship with severe jaundice (OR = 1.6 and P value = 0.2) and not a statistically significant.

Three studies from Turkey [21], Egypt [23], and India [20], studied the role of sepsis on the risk of severe hyperbilirubinemia and indicated that neonates diagnosed with sepsis were at increased risk of severe hyperbilirubinemia (both had p< 0.001).

In this study, the presence of urinary tract infection was 37 cases among all subjects but our result showedno relation with the development of sever jaundice. In a cross sectional study in Turkey 2006 [32] show a relation in between.

CONCLUSIONS

ABO incompatibility; male gender of neonate; Baby of diabetic mothers birth weight, pathological weight loss and age of the mother have a relation with the severity of the disease.

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