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An Incident Case-control Study of Nonphysiologic Neonatal Hyperbilirubinemia: Evaluation of Pre and Perinatal Risk Factors

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Abstract

Introduction: Neonatal jaundice is a well-known phenomenon which can be potential cause of permanent brain damage.

Methods: There were 621 infants included in the retrospective case-control study: 590 were a control group (physiological jaundice), 31 were study group (nonphysiologic hyperbilirubinemia.

Results: There were significantly more cases of usage pregnancy sustaining drugs and forceps delivery in neonates who developed hyperbilirubinemia. Mean values of Apgar score, weight, height and head circumference statistically correlated with hyperbilirubinemia occurrence.

Conclusions: The study indicates that pregnancy sustaining drugs and using forceps during delivery increase risk of hyperbilirubinemia incidents. The study underlines that severe hyperbilirubinemia is often connected with prematurity and unfavorable general health state.

Keywords: Hyperbilirubinemia; Infants

Introduction

Although physiologic neonatal jaundice is a well-known phenomenon which may not be essential to the future developmental outcome, severe hyperbilirubinemia is a serious potential cause of permanent brain damage. There are only few population-based studies characterizing risk factors for later hyperbilirubinemia occurrence. For this reason, the present study was performed to determine how far mode of delivery, maternal and fetal conditions increase risk of neonatal jaundice in order to improve health care of expectant mothers and prevent from potential brain damage, significant for future neurological and mental development.

Physiological jaundice refers to over a half of full-term newborns as a result of accumulation of unconjugated bilirubin. This is a consequence of immaturity of the UDP-glucuronylotransferase [1,2]. In term and near-term infants peak bilirubin levels commonly occur in the second half of the first week and disappear before the end of the second week of life [2]. Firstly it is manifested by yellowing visible in the face and forehead. Identification is supported by pressing gently baby's skin for several seconds. When the finger is removed, the skin will show a pale white circle. Jaundice starts at the top of the body and moves down, so the level of yellow skin roughly corroborates to the total serum bilirubin level [3].

However, in some infants serum bilirubin level may rise excessively, considerably exceeding correct range 12 mg/dl. In this group more intense jaundice is associated with changes in muscle tone, seizures, altered crying characteristics, petochiae, which are danger signs and require immediate attention to avoid kernicterus. Prospective studies indicate that especially premature infants are more liable to reveal future developmental retardation at bilirubin levels just after 12 mg/dl. That explains, why screening and early diagnosis supported by clear-sighted observation of skin and sclera, serum investigation and efficient assessment of risk factors enable early application of phototherapy and other interventions in order to prevent from potential adverse consequences [3] (Table 1).

1	Jaundice appearing in the first 24 hours after birth and persisting >7 days in term or >14 days in pre-term infants.
2	Male gender
3	Low gestational age ≤37 weeks of gestation
4	Birthweight <2500 g (Incidence is higher in premature infants and/or in infants with low birth weight)
5	Apgar score
6	Evidence of asphyxia

7	Abnormal deliveries
8	Birth trauma, bruising and cephalohematomas (which increase the production of bilirubin)
9	Hospital discharge before 48 hours of life, with no early follow-up
10	Maternal age of 25 years or more
11	Past obstetric history, especially spontaneous and induced abortions
12	Maternal drug intake
13	Use of oxitocin to induce labour
14	Hemolysis due to maternal isoimmunisation

Table 1: Common risk factors for hyperbilirubinemia mentioned in the literature.

Methods

This retrospective case-control study was performed at Medical University Hospital in Gdańsk in Poland. There were 621 infants included in the study. The control group consisted of 590 (95.01%) newborns with physiological jaundice in differentiation to the study group, which consisted of 31 (4.99%) newborns affected by nonphysiologic hyperbilirubinemia. All of the deliveries were conducted in hospital in a period of one year.

An infant was classed as jaundiced if plasma bilirubin level exceeded 1, 4-5 mg/dl on the 1st, 9 mg/dl on the 2nd and 12 mg/dl from 3rd day of life. Infants with hemolytic jaundice due to maternal rhesus isoimmunisation or ABO incompatibility were classified as a result of known patomechanism and excluded from the study.

Every infant with hyperbilirubinemia had a complete history of neonatal period. First screening method was precise clinical observation of the skin and sclera (jaundice was usually visible when total serum bilirubin level reached 6 mg/dl). Second screening test was a total serum bilirubin level (TSB), which is the current standard for diagnosing neonatal jaundice. There was no case of hospital discharge before 48 hours of age.

Both control and study group of infants were compared for a wide range of obstetric and pediatric factors. Some of them had little obvious direct revalescence to the jaundice occurrence, and only those associated with relevant findings are discussed here.

"Preterm" was defined as delivery before 37 completed weeks of gestation.

"Term" was defined as delivery after 37 completed weeks of gestation.

"Bruising and cephalohematoma" was observed and analyzed because of accumulation of blood in extravascular compartments, which may increase bilirubin production as the blood is absorbed and degraded.

Statistical analysis of data was performed with Statistica® 6.0 for Windows® and Microsoft Excel®. Chi-square analyses were used for discrete data and Fisher exact test for analysis of 2 x 2 tables with small frequencies. For continuous variables, comparisons of two independent groups were performed using the Student t test, when distributions were normal or approximately normal, and the Mann-Whitney test, the nonparametric counterpart of the t test, when distributions were skewed. For multivariate analysis logistic regression was performed. $P < .05$ was considered statistically significant.

Results

From the total 621 infants, 31 (4, 99%) developed hyperbilirubinemia with markedly elevated bilirubin levels. None of the infant had serum bilirubin level over 20 mg/dl (Table 2 and Figure 1).

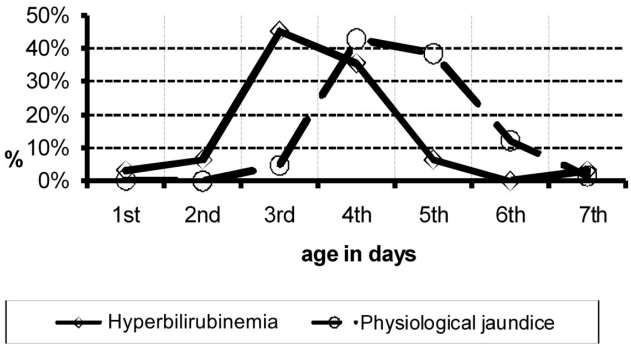

Figure 1: Correlation of age in days and percentage of infants in both compared groups.

Age in days	1st	2nd	3rd	4th	5th	6th	≥7th
Number of infants	1	2	14	11	2	0	1

% of infants	3.23	6.45	45.16	35.48	6.45	0.00	3.3

Table 2: Age in days of 31 infants with hyperbilirubinemia at which peak of TSB level was obtained.

Previous pregnancy complications

The present study evaluated that complications affecting previous pregnancies occurred more often among mothers of newborns with hyperbilirubinemia. This was referred to the higher rate of neonatal mortality, prematurity extrauterine pregnancy and spontaneous abortion. Induced abortions were not statistically significant (Table 3).

	Study group	**Control group**	**P**
Neonatal death No (%)	4 (12.90)	26 (4.41)	0.03
Extrauterine pregnancy No (%)	1 (3.23)	3 (0.51)	0.06
Premature delivery No (%)	3 (9.68)	30 (5.08)	0.48
Spontaneous abortion No (%)	11 (35.48)	113 (19.15)	0.11
Induced abortion No (%)	1 (3.23)	58 (9.83)	0.16
Caesarian section No (%)	4 (12.90)	37 (6.27)	0.21

Table 3: Previous pregnancy complications in mothers of two compared groups.

Present pregnancy history

Maternal age: Age of the mothers in two analysed groups yielded no considerable difference and was estimated on average: 29 in the study group and 30 in the control group (P= 0.01).

Drugs: There were significantly more mothers in the study group (n=3; 9.68%) that needed to receive pregnancy sustaining drugs, such as Fenoteroli hydrobromidum. It referred only to 60 (3.22%) mothers of the control group. Statistical analysis showed a certain icterogenic effect of received progestational agents.

A list of drugs given during pregnancy because of particular internal diseases was assembled and compared between two groups, but none of them was given more often in one group than in the other.

Use of oxytocin: Of the 31 infants from study group 10 were born after oxitocin administration and it was not statistically significant.

Gestational age: Although 61.3% of the study group infants were born between 37 and 41 week of gestation, prematurity in the same group was statistically significant. There were almost 39% infants with low gestational age affected by hyperbilirubinemia, whereas control group consisted of only 8% (p<0.001).

Mode of delivery: In the study group forceps delivery was much commoner (P=0.01) among mothers of severe jaundiced infants (n=2; 6.54%), compared to the newborns with correct serum bilirubin level (n=6; 1.04%).

Infant conditions: It has appeared that the mean Apgar score in a group of nonphysiologic jaundice achieved 7, 5 and was significantly lower than in the second group (P= 0.004). Also general measurements after birth, including: weight, height, head and chest circumference were considerably lower than in the study group (Table 4).

In spite of the correlation between severe jaundice and neonatal anemia incidents (n=1; 3.23%), the difference was only probably significant (P= 0.06).

Moreover, it should be emphasized that infants affected by hyperbilirubinemia, prematurity, lower Apgar score and birth weight needed to be incubated almost three times as often as control group newborns.

There was not found a higher frequency of asphyxia, gender of the baby, bruising or cephalohematoma.

	Study group	**Control Group**	**P**
Apgar score (mean)	7.5	7.8	0.004
Weight [g] (mean)	2939	3371	0.001
Height [cm] (mean)	51.7	54.6	0.004
Head circumference [cm] (mean)	33.3	35.1	<0.001
Chest circumference [cm] (mean)	32.5	34.5	0.003
Anemia No (%)	1 (3.23)	3 (0.51)	0.05

Incubator No (%)	6 (19.35)	46 (7.80)	0.01

Table 4: Infant conditions in two compared groups of children.

Discussion

Nonphysiologic hyperbilirubinemia is a condition requiring medical attention because of the potential consequences, which may occur in case of remissness or mistake. This usually happens, when jaundice is not apparent or after hospital discharge [4]. Therefore risk factors for severe hyperbilirubinemia should be discussed and observed very closely both during hospitalization and also after discharge. In order to reach this, it may be important to prepare parents to inform pediatricians about distressing symptoms and premises from the past obstetric history [5-8]. The present study indicates that pregnancy sustaining drugs and using forceps during delivery considerably increase risk of hyperbilirubinemia incidents. Besides, the study underlines that that severe hyperbilirubinemia is often connected with prematurity and unfavorable general health state, including lowered proportions of the body, Apgar score less than 8, placing in the incubator and always requires special precautions [9-11].

Conclusion

What is already known?

Hyperbilirubinemia may lead to the permanent brain damage, which is a reason of severe neurological and mental disabilities.

What this study adds?

Pregnancy sustaining drugs and using forceps during delivery considerably increase risk of hyperbilirubinemia incidents. Hyperbilirubinemia is often connected with and unfavorable general health state of infant.

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