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ORIGINAL ARTICLE

Severe hyperbilirubinemia in newborns, risk factors and neurological outcomes

Hiperbilirrubinemia severa en Recién Nacidos, factores de riesgo y secuelas neurológicas

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Abstract

Introduction: Hyperbilirubinemia is highly prevalent in newborns, with risk of neurological involvement with bilirubinemia higher than 20 to 25 mg/dl. This progression is preventable with early detection and treatment. **Objective**. To describe the incidence and associated factors in hospitalized patients with hyperbilirubinemia higher than 20 mg/dl, and the follow-up of symptomatic cases during hospitalization. **Patients and Method**: Retrospective study of patients with severe hyperbilirubinemia, between 2013 and 2016. Risk factors were evaluated, stratifying by bilirubin level, admission age, and gestational age. The data were compared with Fisher's exact test, chi-square test, and relative risk (RR) in an Excel database, with an alpha error of $p < 0.05$. The data were obtained from the electronic discharge summary and the medical record of secondary level follow-up. **Results:** During the studied period, out of 25,288 live newborns (NB), 593 were hospitalized due to hyperbilirubinemia higher than 20 mg/dl, one per each 42 live NB; and 59 with bilirubinemia higher than 25 mg/dl, one per each 428 live NB. Hyperbilirubinemia was more frequent in males, with RR 1.22 (95% CI 1.04-1.44), and in late preterm newborns, with RR 2.39 (95% CI 1.96-2.93) compared with term NB. In those admitted with more than four days, the main associated factor was excessive weight loss, whereas in the first three days was classic group incompatibility. Three of ten cases with acute encephalopathy persisted with neurological involvement, which means 11.8 per 100,000 live births. **Conclusions**: The main risk factors for developing severe hyperbilirubinemia were prematurity, excessive weight loss, classic group incompatibility, and male sex. These findings allow to focus attention on risk groups and decrease the probability of neurological damage.

Keywords:
Severe hyperbilirubinemia; prematurity; bilirubin encephalopathy; classic group incompatibility

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Introduction

Jaundice is highly prevalent in the newborn (NB), affecting up to 60-80% of newborns[1-3]. It is considered hyperbilirubinemia (HBR) when serum bilirubin level is higher than the 95th percentile for age, and it is generally considered severe when levels exceed 20 or 25 mg/dl[4,5].

Bilirubin is an important antioxidant, which has a fine regulatory system that maintains stable levels, but it can be affected by different causes, leading to a bilirubin increase[6]. As bilirubin levels increase, there is a risk of developing neurological toxicity or bilirubin encephalopathy. This spectrum includes acute and chronic bilirubin encephalopathy and isolated neurologic dysfunction[7]. Acute encephalopathy can range from weak suction to severe neurological involvement with deep stupor and opisthotonos. Chronic encephalopathy or kernicterus is a devastating neurological entity characterized by athetoid cerebral palsy, with oculomotor paresis, dental enamel dysplasia, and auditory neuropathy[8-11]. The auditory system is particularly sensitive to the bilirubin effects, ranging from speech processing disturbances to profound deafness. Hearing damage due to bilirubin requires a time window, occurring when cells are developing the formation of the neuronal circuits, thus premature infants are at greater risk. In addition, sensory pathways are myelinated before motor pathways, leading to a more common observation of kernicterus with predominant hearing damage in children under 34 weeks, in contrast to the classic motor type which is more frequent in term NBs[7,12,27]. This may occur at levels that were not previously considered harmful, but in general, with bilirubin levels higher than 20 mg/dl, long-term hearing follow-up is necessary[6,7,12] . It has been described that more than half of NBs with bilirubin higher than 30 mg/dl develop neurological sequelae[26].

Phototherapy and exchange transfusion have led to a reduction in acute and chronic bilirubin encephalopathy[6,9]. With the Rh isoimmunization prevention, the use of immunoglobulin and the phototherapy effectiveness, the need for exchange transfusion, which is an invasive procedure, not risk-free, has been markedly reduced[4,9].

Despite the existence of efficient treatment, the severe HBR risk and its consequences are observed with a wide range of incidence worldwide, depending on the used control strategies[4,9,13,14].

The objective of this study is to describe the incidence and risk factors associated with bilirubinemia equal to or higher than 20 mg/dl, and the evolution of patients with signs of bilirubin encephalopathy during hospitalization, compared with data in the literature.

Patients and Method

Descriptive, retrospective study. Based on information from the electronic discharge database, we included newborns hospitalized in the Neonatology service of the Dr. Sótero del Río Asistencial Complex (SRAC) between January 1, 2013 and December 31, 2016, with a discharge diagnosis of hyperbilirubinemia and a maximum value of total serum bilirubin higher than or equal to 20 mg/dl. With this information, we reviewed the discharge summary of the newborns. NBs whose electronic discharge summary could not be accessed were excluded.

During the study period, bilirubin levels were analyzed using the same method, Total Bilirubin: endpoint/Diazonium salt.

NBs were stratified by bilirubin values in two levels, higher than or equal to 20 mg/dl, and higher than or equal to 25 mg/dl; by age of admission, as less than or equal to three days, between 4 and 7 days, and higher than or equal to 8 days; and by gestational age. Table 1 shows the risk factors for severe hyperbilirubinemia that were evaluated, such as sex, gestational age, birth weight adequacy, excessive weight loss, group and Rh incompatibility, cephalhematoma, polycythemia, sepsis, perinatal asphyxia, urinary tract infection, and hypothyroidism.

Presence of neurological symptoms during hospitalization, compatible with acute bilirubin encephalopathy was recorded, and the outpatient child neurology care data in the SRH of these patients were reviewed.

Data were compared with Fisher's exact test, chi-square, and relative risk (RR) in an Excel database, with a $p<0.05$ alpha error.

The study was reviewed and approved by the Ethics and Research Committee of the South-East Metropolitan Health Service.

Results

In the studied period, there were 25,288 live newborns (LNB), 48.3% female and 51.6% male. 599 NBs were hospitalized with bilirubin levels higher than or equal to 20 mg/dl, of which six cases were excluded, as there was no access to electronic discharge summary. In the 593 cases left, 2.3% of incidence (1 in 42 LNB) was observed. 59 NBs had bilirubin levels higher than or equal to 25 mg/dl, with 0.23% of incidence (1 in 428 LNB). 53 NBs (9% of cases) were rehospitalized due to severe HBR, six of them had bilirubin levels higher than 20 mg/dl in both hospitalizations.

Out of the total of patients, 80.6% were term newborns, 18.7% were late preterm newborns, and 0.7% were moderate ones. There were no cases of severe hy-

perbilirubinemia in NBs under 32 weeks of gestational age.

Figure 1 describes the bilirubinemia risk between 20 and 24.9 mg/dl and higher than 25 mg/dl, depending on the gestational age at birth. The highest bilirubinemia risk between 20 and 25 mg/dl was seen at 35 weeks (1 in 16 NBs of that gestational age), and higher than 25 mg/dl at 36 weeks (1 in 85 NBs). Compared with term NBs, preterm infants are at higher risk of severe HBR, with RR 1.78 (95% CI 1.45-2.17), especially late preterm infants, between 34 and 36 weeks, with RR 2.39 (95% CI 1.96-2.93).

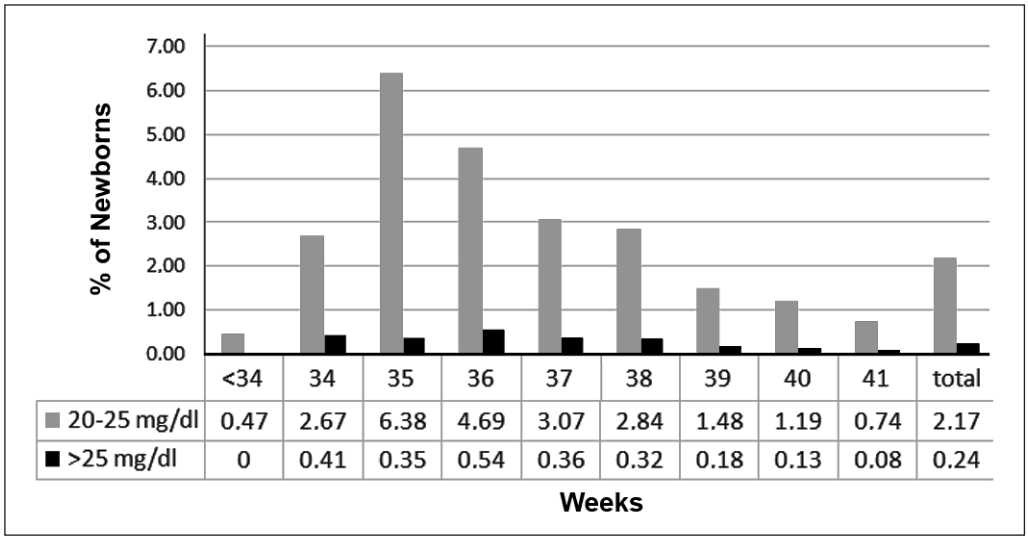
Table 2 shows the characteristics of the group according to age at hospitalization and associated causes. 19.4% of the cases were under 37 weeks. Globally, the male sex presents a higher risk than the female sex, with a RR of 1.22 (95% CI 1.04-1.44) and it also increases with days of presentation. Cases of hyperbilirubinemia higher than 25 mg/dl were mostly observed in children under 8 days of life.

In NBs hospitalized before 4 days of age, the main risk factor was classical group incompatibility, with a RR of 3.78 (95% CI 1.84-7.78). In NBs hospitalized from 4 days of life, the most important risk fac-

Table 1. Definitions

Term	Definition
Extremely preterm NB	Born before 32 gestational weeks
Moderate preterm NB	Born between 32 to 33 gestational weeks
Late preterm NB	Born between 34 to 36 gestational weeks
Term NB	Born between 37 to 41 gestational weeks
Small for gestational age[19]	Birth weight less than percentile 10 for gestational age
Adequate for gestational age[19]	Birth weight between percentile 10-90 for gestational age
Large for gestational age[19]	Birth weight more than percentile 90 for gestational age
Excesive weight loss	Loss between 8 to 12% of birth weight or don't recover weight after a week of life
Severely weight loss	Loss more than 12% of birth weight
Classic group incompatibility	Blood group between newborn and mother suggestive, direct Coombs test positive or reticulocytes count more than 6% in the hemogram of newborn
Rh incompatibility	Negative Rh mother sensitized and her NB Rh positive with direct Coombs test positive
Polycythemia	Hematocrit equal or more than 65%
Sepsis	Positive blood culture or antibiotic treatment for 5 days or more, with clinic and laboratory suggestive despite negative blood cultures
Urinary tract infection	Positive urine culture by sounding for a pathogenic microorganism, with more than 10.000 colony forming unit

NB: newborn.



	<34	34	35	36	37	38	39	40	41	total
20-25 mg/dl	0.47	2.67	6.38	4.69	3.07	2.84	1.48	1.19	0.74	2.17
>25 mg/dl	0	0.41	0.35	0.54	0.36	0.32	0.18	0.13	0.08	0.24

Figure 1. Risk of severe hyperbilirubinemia (%) between 20-25 mg/dl and more than 25 mg/dl according to gestational age

Table 2. Main characteristics of NBs hospitalized by severe hyperbilirubinemia, according to age of admission

Characteristics	≤ 3 days	4-7 days	≥ 8 days
Total NB	186	288	119
Male sex (%)	51.1%	59.0%	59.7%
Averange gestacional age, weeks (SD)	37.9 (1.6)	37.7 (1.6)	37.8 (1.6)
Preterm NB, number (%)	37 (19.9%)	58 (20.1%)	20 (16.8%)
Averange age at admission, days (SD)	2.5 (0.65)	5.31 (1.1)	9.89 (2.8)
Small for gestational age (%)	14 (7.5%)	16 (5.6%)	9 (7.6%)
Large for gestational age (%)	23 (12.4%)	21 (7.3%)	10 (8.4%)
Weight loss 8-12% (%)	34.4%	24%	23.5%
Weight loss > 12% (%)	3.2%	10.8%	12.6%
Classic group incompatibility	19 (10.2%)	6 (2.1%)	5 (4.2%)
Rh incompatibility	3 (1.6%)	3 (1%)	3 (2.5%)
Urinary tract infection, number/total ex	1/4	4/17	8/27
Hypothyroidism, number / total ex	0/3	0/7	1/22
Exchange transfusion, number (%)	6 (3.2%)	5 (1.6%)	1
IV immunoglobulin use, number	13	(1)	(2)

NB: newborn; ex: exams.

Table 3. Main characteristics of NBs hospitalized by hyperbilirubinemia ≥ 25 mg/dl, according to age of admission

Characteristics	≤ 3 days	4-7 days	≥ 8 days
Total NB	11	32	16
Male sex (%)	63.6%	56.3%	62.5%
Averange gestacional age, weeks (SD)	38.09 (1.7)	37.91 (1.4)	37.68 (1.6)
Preterm NB, number (%)	2 (18.2%)	4 (12.5%)	3 (18.8%)
Averange age at admission, days (SD)	2.4 (0.7)	5.6 (1.2)	9.2 (0.9)
Small for gestational age (%)	0	1 (3.1%)	0
Large for gestational age (%)	2 (18.2%)	2 (6.3%)	2 (12.5%)
Weight loss 8-12% (%)	45.5%	21.9%	50%
Weight loss > 12% (%)	0%	18.8%	12.5%
Classic group incompatibility	3 (27.3%)	4 (12.5%)	2 (12.5%)
Rh incompatibility	0	4 (12.5%)	1 (6.3%)
Urinary tract infection, number/total ex	0/1	3/9	0/3
Hypothyroidism, number / total ex	0/1	0/6	0/3
Exchange transfusion, number (%)	3 (27.3%)	5 (15.6%)	1 (6.3%)
IV immunoglobulin use, number	2/11	0/16	0/16

NB: newborn; ex: exams.

tor was excessive weight loss, with RR 2.61 (95% CI 1.74-3.92) in NBs between 4 and 7 days, and RR 6.71 (95% CI 4.59-9.81) in those older than or equal to 8 days of age.

44 cases were analyzed for urinary tract infection and 27% of them had positive urine culture. A case of hypothyroidism stands out for its importance. In 75 NBs (12.6%) more than one risk factor was associated, with prematurity and excessive weight loss more frequently observed.

Other risk factors, such as birth weight adequacy, cephalohematoma , polycythemia, sepsis, or asphyxia were not associated with increased risk of severe HBR.

All hospitalized NBs due to severe HBR received phototherapy, 16 NBs received immunoglobulin, and 12 exchange transfusion. Out of the NBs who received immunoglobulin, three cases corresponded to rehospitalizations, who received this drug during the first hospitalization.

Table 3 describes the subgroup with HBR higher

Table 4. Cases of acute bilirubin encephalopathy and neurological evolution

BW (grs)	GE (weeks)	Age (days)	% BW	Inc	Uro	Bili (mg/dl)	ExT	Neurological signs	Neurological Evolution
3155	37	7	10.0		(-)	30		Hypotonia	¿?
3400	38	5	2.9		(+)	27.6		Hypertonia	Normal
2310	35	9	3.0			28.5		Hypertonia	Normal
2545	37	4	5.5		(+)	29	(+)	Hypertonia	Dystonic syndrome, N BAEP
3720	38	6	6.5	0-A		30.8	(+)	Hypertonia	Language delay, N BAEP, N motor
3530	39	9	15.2		(-)	28.9		Hypertonia	¿?
3615	40	1	11.3	0-B		25.4	(+)	Hypertonia	Normal
3580	38	6	14.9	0-B		32.4	(+)	Hipertonía	Normal, N BAEP
3390	40	6	8.6			26.6		Hypertonia, acute crying, opisthotonos	Psychomotor delay
3180	38	6	11.0	Rh		29.1	(+)	Hypotonia, weak suction	Normal

BW: birth weigth; GE: gestational age; % BW: percentage of loss of birth weigth at admission; Inc: blood incompatibility; Uro: urocultive; Bili: maximun bilirubin mg/dl; ExT: Exchange transfusion; BAEP: brainstem auditory evoked potentials; N: normal; ¿? Without information.

than 25mg/dl in the same admission periods, with higher predominance of male sex and incompatibility.

Ten of 59 NBs with bilirubin levels equal to or higher than 25 mg/dl had an abnormal neurological exam. Mild hypotonia was described in two cases, mild hypertonia in six cases, and encephalopathy in two cases, which determines a 0.04% acute bilirubin encephalopathy incidence in the total NBs. Table 4 describes the cases and their associated factors. Two patients have normal MRI results. In five cases exchange transfusion was performed, in the other cases, bilirubin levels decreased significantly with the first hours of phototherapy and hydration. There is no follow-up in two cases, and in three cases there is a clinical picture compatible with chronic bilirubin encephalopathy, with an incidence of 11.8/100,000 newborns.

Discussion

Severe hyperbilirubinemia, defined as levels of total bilirubin higher than 25 mg/dl in a term newborn or higher than 20 mg/dl in a premature infant older than or equal to 34 weeks of gestation, represents a risk factor for the appearance of neurotoxicity and sequelae secondary to the nerve tissue impregnation by bilirubin, in which visual and hearing disorders, and signs of extrapyramidal cerebral palsy stand out[4,6,8,9,21,22]. It's a permanent concern in neonatology.

The severe HBR incidence was surprisingly high, from almost double to 40 times that described in the literature in developed countries[5,10,21]. In the global analysis, 1 case in 47 NBs with HBR between 20-25 mg/dl was observed; and 1 in 428 NBs with HBR higher than 25 mg/dl. California data show bilirubinemia higher than 20 mg/dl in 1 of 72 LNBs, and higher than 25 mg/dl in 1 of 1430 LNB[29]. In developed countries, between 1/2,000 - 1/10,000 cases of NBs with HBR higher than 25 mg/dl have been observed, and 1/18,000 NBs have even been reported in Israel, which has fluid coordination with primary care and a detailed protocol for prevention and detection[28]. In low-income countries, such as countries from Africa and Asia, the reported HBR incidence higher than 25 mg/dl varies between 4 and 46%[23]. We did not find information on its incidence in Latin America.

The main risk factors for developing severe HBR were male sex, prematurity, excessive weight loss, and classic group incompatibility. The highest risk group is late preterm infants, between 34-36 weeks of gestational age, who have a RR of 2.39 (95% CI 1.96- 2.93) regarding term infants, similar to that described in the literature[9,10,15-17,23,24].

The maximum bilirubin increase in term NBs occurs between 3 to 5 days of age when the NB has already been discharged, thus follow-up in at-risk children is important. In addition, the maximum loss of normal weight occurs on the third day, with an average loss between 6 and 8% of birth weight. In newborns who have lost more than 10% of weight, evaluation is necessary to eventually supplement breastfeeding and evaluate the presence of HBR[3,9].

The relationship between HBR and urinary tract infection is not yet fully understood. It has been described that about 8% of HBR in which no cause can be found, present urinary tract infection, especially due to *Escherichia coli*[25]. Due to the retrospective nature of the work, urine culture was not found in all patients, the-

refore, it is not possible to determine the urinary tract infection incidence in this group. Urine culture was positive in 27% of the evaluated cases and constitutes an important morbidity to rule out in late hyperbilirubinemia that has suggestive symptoms such as fever, weight loss, and procalcitonin alteration.

The evaluation of hypothyroidism should be reserved for the case without elements that explain hyperbilirubinemia and especially if there are elements of a primary defect, which is not detectable with screening.

Twelve cases required exchange transfusion, 47/100,000 LNB, compared to 1.9 to 3.6/100,000 LNB in California[22]. Of the ten symptomatic cases, only five were treated with exchange transfusion, since while it was being prepared, a significant decrease in bilirubin was observed, or the neurological alteration was later, but when facing a symptomatic case, the recommended therapy is the exchange transfusion[15].

Although acute neonatal bilirubin encephalopathy has decreased dramatically due to adequate control and treatment of the mother with Rh-negative blood type to prevent sensitization, there is some risk increase with the early discharges rise, lack of warning to parents about the risk of hyperbilirubinemia, and lack of timely control at the outpatient level, especially of patients at risk, such as late premature infants and early term NBs[7,9,26]. In addition, neurological and hearing alterations may be transitory or late onset, so short and long term follow-up of NBs exposed to high bilirubin levels is very important[7].

Acute and chronic encephalopathy incidence has decreased significantly. An incidence of 0.3 to 1 in 10,000 LNB has been estimated for acute encephalopathy and around 1 in 100,000 for chronic type [4.9,13,14]. In this review, 4 cases in 10,000 of acute encephalopathy and 11.8 cases in 100,000 of chronic encephalopathy were observed. There are no national data on chronic bilirubin encephalopathy, but a national publication shows that it has not disappeared[30].

The limitations of this study are that it is retrospective and data were obtained from discharge summaries, where information could have been omitted, such as searching for other diagnoses if the cause of hyperbilirubinemia was unclear. The admission date was not necessarily due to hyperbilirubinemia, and weight loss corresponds to the minimum observed weight. Interesting data such as the feeding type before hospitalization and the mother's perception of jaundice were not available. All cases of hyperbilirubinemia higher than 25 mg/dl are referred to child neurology and a healthcare center to follow up encephalopathy, but short-term non-attendance and lack of a rescue system has prevented complete patient information. Out of the 10 identified patients with signs of acute encephalopathy, follow-up information was obtained of eight of them, and among them, there is one case identified with chronic encephalopathy and two probable cases.

The strength of this study is to show that the risk of neurological damage due to bilirubin is still occurring, therefore, an early HBR detection and treatment is important. Severe hyperbilirubinemia is a sentinel event that must be avoided. Therefore, it is necessary to establish regulations to follow according to gestational age, hours of life, and the pertinent follow-up, different from those previously used, broadening the control ranges. Late preterm newborns must be monitored for bilirubin levels at discharge, regardless of jaundice and follow-up.

The determination of transcutaneous bilirubin in serial form using known nomograms would alert especially when there are important changes in levels[31]. For late risk, it is necessary greater coordination with the primary level and early follow-up after discharge, especially of late premature infants, whose follow-up should be before 72 hours of the discharge, as has been pointed out in the new childcare program of the Ministry of Health[32]. With the installation of a surveillance and intervention system, the risk of severe hyperbilirubinemia and its potential sequelae could be reduced[28,29].

In conclusion, the severe HBR incidence in this period was unacceptably high. The main risk factors for developing severe HBR were male sex, prematurity, excessive weight loss, and classic group incompatibility. Clinical practices to control bilirubinemia should be modified, especially for late preterm infants, high criteria for phototherapy and establish a prospective protocol for surveillance of severe HBR, which due to its consequences, should be considered as a sentinel event watched nationally.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors state that the information has been obtained anonymously from previous data, therefore, Research Ethics Committee, in its discretion, has exempted from obtaining an informed consent, which is recorded in the respective form

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Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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