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Method of identifying newborns at risk of severe hyperbilirubinemia

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Abstract:

Jaundice in the neonatal period is an extremely common condition. This condition is usually benign and resolved spontaneously. However, in case of intense jaundice, the newborn may be exposed to dangerous neurological complications responsible for permanent damage, due to the neurotoxicity of free bilirubine.

Aims: Describe the clinical characteristics of full-term and near-term newborns with severe hyperbilirubinemia

Materials and methods: This is a cohort, analytic, and single-center prospective study conducted between January 2014 and December 2016 in newborns with severe neonatal jaundice with a total blood bilirubin (TSB) level> 200 mg / l or a BST level indicating exchange transfusion and / or a disturbed neurological examination.

Results: during the 3-year study period, 32,439 term and pre-term newborns were born and 133 newborns met the inclusion criteria with an incidence of severe jaundice of 4.1 per 1000 live births. Severe jaundice constituted 7.8% of all neonatal jaundice. Neurological signs on admission were present in 18.8% of the newborns. Jaundice started within the first 24 hours of life in 19% of newborns and resulted in a mean hyperbilirubinemia of 261.7 ± 35 mg / l. Etiologies were dominated by ABO incompatibility which represented 30% etiologies. The need for exchange transfusion was in 9% of newborns. 8 children had abnormal psychomotor development ranging from simple delay in psychomotor acquisition to overall and severe developmental delay.

Conclusion: The evolution towards the more and more early exits of maternity leads to a resurgence of neurological risk. This neurological risk prompts us to pay more 3 attention to this pathology. Thus, we can only insist on a rigorous evaluation of risk factors, an early detection of newborns at risk of developing severe jaundice.

Index Terms **- Severe hyperbilirubinemia; Acute bilirubin encephalopathy; kernictus; Direct Coombs test.**

I. INTRODUCTION

Jaundice in the neonatal period is a pathology that is usually benign and resolves spontaneously. However, in the event of severe jaundice, the newborn may be exposed to many neurological complications responsible for permanent sequelae, due to the neurotoxicity of free bilirubin.

in 1950 the management of Rhesus incompatibilities by exchange transfusions, the development of Rhesus immunoprophylaxis , then the introduction of phototherapy as well as its technical improvements, considerably reduced the incidence of these severe hyperbilirubinemias, suggesting that this pathology had disappeared.

The National Academy of Medicine has been reporting for several years a resurgence of cases of severe hyperbilirubinemia after returning home following alerts from numerous European countries and across the Atlantic.

In Algeria, in the absence of comprehensive and reliable data, the incidence of severe jaundice remains unknown, as does the incidence of neurosensory after-effects attributable to it. Faced with this observation, we sought for studying it by carrying out a prospective study.

II. RESEARCH METHODOLOGY

This is an analytical and single-center cohort study with prospective data collection, carried out between January 2014 and December 2016 in newborns with severe neonatal jaundice with a TSB level >200 mg/l (1 mg/l =1.71 µmol/l) or a total blood bilirubin indicating exchange transfusion and/or disturbed neurological examination on admission, hospitalized in the neonatology department and pediatric department B at Hussein Dey University Hospital.

III. RESULTS

During the 3-year study period, 32,439 term and pre-term newborns were born and 133 newborns met the inclusion criteria with an incidence of severe jaundice of 4.1 per 1000. live births and 7.8% of all newborns treated for neonatal jaundice.

The demographic and clinical characteristics of the 133 newborns are presented in **Table 1**.

We note a predominance of the male gender in our study, which represented 58% (78 boys) with a sex ratio of 1.4. The average age of admission in our series was 82 ± 35 hours, 53.4% of newborns had an age > 72 hours, with extremes ranging from 0 to 10 days, jaundice was early in 19%. cases. Only 70% of cases of newborns were exclusively breastfed due to early discharge of newborns and the lack of postnatal monitoring which would have identified the difficulties encountered by mothers in maintaining exclusive breastfeeding.

In fact, 25 newborns (18.8%) presented with drowsiness, a weak cry, hypotonia or hypertonia with head throwing back and incomplete primary reactions.

The average level of total bilirubinemia was 261.7 ± 35 mg/l with a minimum of 170 mg/l and a maximum of 500 mg/l. 19 newborns (14.3%) had a TSB level ≥300 mg/l

The total bilirubin level was higher in newborns whose gestational age was between 37 and 38 weeks.

88% of newborns (117 cases) who presented with severe neonatal jaundice were readmitted after leaving the hospital early, for which the average age of leaving the maternity ward was 20 hours (age range 8-48 hours). 52% of these newborns had left the maternity ward before 24 hours of life.

The diagnosis of severe jaundice was made and treated before leaving the maternity ward in only 16 newborns, or 12% of the cases included.

Readmission of newborns for management of severe jaundice was at an average age of 100 hours after birth (age range: 28-240 hours), while the average age of onset of jaundice was 55 hours with extremes ranging from 14 to 120 hours. The mean maximum TBB level of the 117 newborns readmitted for severe jaundice was 279 mg/l (215-500 mg/l). Concerning newborns whose diagnosis of severe jaundice was made before leaving the maternity ward, the average maximum TBB level was 224 (170-325) mg/l, this difference was statistically significant ($p<0.001$) between both groups. 38 newborns (28.5%) had a weight loss ≥ 8% among them 31 (23.3%) were newborns readmitted for treatment of severe jaundice.

Weight loss was found in 7 newborns among the 16 whose diagnosis of severe jaundice was made before leaving the maternity ward. This difference was not statistically significant ($p=0.7$) between the two groups. .

Treatment was started on average after 100 hours of life with extremes ranging from 2 to 240 hours in newborns readmitted for severe jaundice versus 20 hours of life on average (2-28 hours) in newborns for whom the diagnosis of severe jaundice was made during the stay in the maternity ward. This difference was statistically significant ($p<0.001$) between the two groups. Among the 12 newborns who received EST, 9 were among the newborns readmitted for severe jaundice. This difference was not statistically significant ($p=0.19$) between the two groups.

A multivalent immunoglobulin infusion was administered to 28 newborns readmitted for severe jaundice out of the 38 children who received this therapy vs. 10 newborns whose diagnosis was made before leaving the maternity ward. This difference was statistically significant ($p=0.003$) between the two groups.

Acute neurological damage was observed in 22 newborns among the 117 (15.5%) compared to 3 among the 16 newborns (i.e. 2.25%) not carried leaving the maternity ward. This difference was statistically significant. ($p=0.01$) between the two groups. Among the 8 newborns (9%) who developed neurosensory aftereffects, 7 (6.7%) were among the newborns who were readmitted for treatment of severe jaundice compared to 1 case among the children taken in charge before leaving the maternity ward. This difference was statistically significant ($p=0.03$) between the two groups.

The etiologies or possible etiologies of severe hyperbilirubinemia are shown in Table 2. ABO blood group incompatibility (maternal blood group O, newborn blood group A or B) was present in 43 neonates. born (32.5%). Thirteen of them (10%) had a positive Coombs test, but the maximum TBB did not differ significantly from the negative Coombs test group. 6 newborns had glucose-6-phosphate dehydrogenase (G6PD) deficiency and two newborns had Rh incompatibility hemolytic disease c. Incompatibility in the Rh D system was found in 08 newborns, 3 of whom had bilirubin induced encephalopathy on admission.
For 54 newborns (40.6%), no underlying etiology, except breastfeeding, was found.

IV. DISCUSSION

In Algeria, due to lack of global data, the incidence of neonatal jaundice and severe jaundice remains poorly known.
Severe jaundice affected 1.4% of all newborns admitted to the two neonatology units during the period of our study (n=9320).which represented 4.1 per 1000 births.
The incidence rate in the United Kingdom in 2001 was 5.5 per 1000 live births (TBB>200 mg/l) [1]. In Denmark, in 2000-2001, an incidence of 25 per 100,000 births was noted for severe jaundice above 226 mg/l [2].
In the USA, in 1995-1996, rates of 20 per 1000 births were reported for TBB > 200 mg/l, 1.5 per 1000 births for TBB > 250 mg/l and 10 per 100,000 births for TBB > 300 mg/l [3].
Under-evaluation is very likely in our context and the recruitment bias resulting of non-exhaustive collection of cases is also to blame.
Postnatal stays in maternity wards have become increasingly shorter over the last two decades [4]. Throughout the world, the children most severely affected by jaundice are those readmitted after leaving the maternity ward [5].
In our study, 88% of newborns who had severe neonatal jaundice were readmitted after leaving the maternity ward; the average age of discharge of these newborns was 20 hours, 44.4% were released within 24 hours of birth. These early exits from maternity wards in our study are explained by a significant flow of parturients in maternity wards.

Early discharge may also contribute to the higher frequency among readmitted newborns. The average time to discharge from the maternity ward for apparently healthy full-term newborns has been reduced in recent years. Thirty-four percent of Danish mothers were discharged from hospital before the age of 72 h in 2001, compared to 45% in 2005 (Steen Rasmussen, personal communication from the Danish National Board of Health). We also noted a reduction in the time spent in the hospital before discharge compared to the past (34 h of life compared to 49 h of life) [6].

The Danish study by Bjerre et al, showed that of 69% of newborns with severe neonatal jaundice who were readmitted after discharge from the maternity ward, 38% were discharged within 24 hours of birth and 87 % before 72 hours. [7],
Another Danish study by Ebbesen et al. [8] found that 59% of cases occurred before their discharge from the maternity ward and only a minority of cases after their readmission; the median age of discharge from the maternity ward was 49 hours.
In our study the average age of readmission was 4 days with an average total serum bilirubin level of 279 mg/l in the readmitted group versus 224 mg/l in the group diagnosed in the maternity ward and the age of diagnosis was 20 hours versus 100 hours if the newborns were readmitted. ($p<0.001$)
The British and Irish study [9] showed that the average hospital discharge time for newborns readmitted with severe jaundice was 48 hours. The Canadian group led by Sgro et al [10] found that 65% of cases were readmitted within 5 days of birth, with higher serum total bilirubin levels. The Danish study by Bjerre et al showed that many newborns were diagnosed on day 5 of life, in fact the TBB measurement was done at the same time as the screening procedure [7].

In the readmitted group; the serum bilirubin level was 280 mg/l versus a level of 250 mg/l in the group diagnosed in the maternity ward and the age of diagnosis was 2.6 days versus 5.4 days if the newborns were readmitted. ($p<0.001$)

Jaundice alone may not alert parents until neurological symptoms appear. As was the case for the 8 out of 22 readmitted newborns who were not taken to the hospital until these symptoms became evident. Incidence may also be influenced by healthcare personnel awareness of jaundice neonates due to the resurgence of acute bilirubin encephalopathy in the Western world [11,12,13].Ebbesen et al. [6] found that newborns readmitted after discharge from the maternity ward were more often neurologically affected.

This was not the case in the study Danish de Bjerre et al[7] where increased vigilance could therefore have attracted the medical attention of a larger number of unaffected newborns than before.

Treatment and diagnosis of hyperbilirubinemia were delayed in readmitted neonates. They more often had a weight loss ≥ 8% and all were breastfed. Among the 12 newborns who received EST, 9 were among the newborns readmitted for severe jaundice.

In a Danish study by Bjerre et al, only four newborns underwent exchange transfusion. The main reason for not transferring neonates or performing exchange transfusions was a rapid decrease in TBB levels during intensive phototherapy. This could not only be explained by different causes of jaundice, but also by different doses of phototherapy due to the lack of a standardized method to deliver phototherapy [11].

In accordance with the guidelines of the American Academy of Pediatrics (AAP) on hyperbilirubinemia and the European Society for Pediatric Research with

AAP consensus statement on neonatal jaundice [11-14], we recommend systematic evaluation of all newborns at risk of severe hyperbilirubinemia. This should include: (1) generalization of transcutaneous bilirubin measurements [15,16] (2) special attention to G6PD deficiency [17] (3) written and oral information on jaundice to all parents, (4) information on the benefits of breastfeeding and (5) appropriate and early follow-up of newborns discharged at ≤72 h of life [11].

V. *Conclusion:*

here we present a study with a method for identifying term or near-term newborns with severe hyperbilirubinemia. It is an accurate and sensitive method for obtaining reliable epidemiological data for use in monitoring the clinical characteristics of newborns with severe hyperbilirubinemia

VI. *FiguresandTables*

Table 1: Characteristics of newborns with severe HB according to readmission after early discharge versus no early discharge

	All newborns (n=133.100%)	**Severe HB diagnosed before leaving the maternity ward (n=16, 12%)**	**Severe HB diagnosed after leaving the maternity ward(n=117.88 %)**	**P**
Gestational age< 38 weeks (n, %)	35 (25.6)	7 (5.2)	28 (21.5)	0.20
BW (g), mean (range)	3383(1500-4700)	2920(1500-4700)	3469(2300-4400)	0.4
Primiparity ; number (n, %)	29(21.8)	5(3)	24(18.5)	0.5
ATCD of severe jaundice in siblings (n, %)	38(28.5)	7(3,7)	31(26.5)	0.17
Gender (M/F)	78 /55	10/7	68/49	0.9
Time of discharge from the hospital (hour of life), Median (range)			20(8-48)	
Time of readmission (Hour of life) Median (range)			100(28-240)	

Jaundice onset time (life time), median (range)	51(2-120)	15 (2-48)	55 (14-120)	**<0.001**
Time of maximum TSB (hour of life), median (range)	91(2-240)	20 (2-28)	100 (28-240)	**<0.001**
Maximum TSB (mg/l), median (range)	261 (170-500)	224 (170-325)	279 (215-500)	**<0.001**
Early phase of acute bilirubin encephalopathy, number of infants (n,%)	25(18.8)	3(2.25)	22(16.5)	**0.01**
Advanced phase of acute bilirubin encephalopathy, number of infants (n,%)	8(9.02)	1(0.3)	7(8.27)	**0.03**
Weight loss ≥8% (n, %)	38(28.5)	7(5,2)	31(23.3)	0.7
Start of treatment (Time of life)	92(2-240)	20(2-96)	100(28-240)	**<0.001**
Exchange transfusion (n, %)	12(9)	3(2,3)	9(6,7)	0.19
Intravenous Ig (n, %)	38(28)	10(7.5)	28(21.5)	**0.003**

H.B.: Hyperbilirubinemia; **BW**: Birth weight; **TSB**: Total serum bilirubin;**Ig** : Immunoglobulins

Table 2: Etiologies of severe hyperbilirubinemia in 133 newborns term and near term

	All newborns (n=133,100%)	**Severe HB diagnosed before leaving the maternity ward (n=16,12%)**	**Severe HB diagnosed after leaving the maternity ward (n=117.88%)**
Probable ABO incompatibility	13(10)	5	9
Possible ABO incompatibility	30(22.5)	4	26
Rh D incompatibility	8(6)	5	3
Rh c incompatibility	2(1.25)	1	0
G6PD deficiency	6(4.5)	1	2
Congenital hypothyroidism	1(0.75)	0	1
Hemorrhagic syndrome	14(10.5)	0	14
Polycythemia	4(3)	0	4
Undetermined	54(40.6)	0	54

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