Incidence and causes of neonatal hyperbilirubinemia in a center of Catania

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Aim and scope: We conducted this study to estimate the incidence of hyperbilirubinemia in a small neonatal care unit in Catania, Italy, and to determine the underlying causes, which would be of value in identifying and implementing strategies to prevent morbidity from this condition.

Background: Management of hyperbilirubinemia remains a challenge for neonatal medicine because of the risk for serious neurological complications related to the toxicity of bilirubin.

Methods: From January 2006 to January 2007, we screened 525 newborns born at the Neonatal Care Unit of Valsalva Hospital in Catania, Italy. Infants aged 3–5 days and with unconjugated hyperbilirubinemia were included for assessment if they had a peak serum total bilirubin level exceeding 6 mg/dl (102 μmol/L). Sex, birth weight, gestational age, breast feeding, type of birth, presence of facial bruising (including cephalohematoma) and ABO group were noted. Patients with Toxoplasma or Cytomegalovirus infection, hepatic insufficiency, or suspected drug-induced hyperbilirubinemia were excluded from more detailed analysis.

Results: Our year-long nursery sample examined otherwise healthy-appearing term infants for the prevalence of hyperbilirubinemia (defined as bilirubin levels exceeding 6 mg/dL [11mol/L]). We found hyperbilirubinemia in 19% (100/525). Among the patients with hyperbilirubinemia, almost all (99%) had peak levels of bilirubin >20 mg/dL, levels which are generally considered to be potentially neurotoxic.

Conclusions: In our clinic experience, hyperbilirubinemia was generally a serious medical issue and one whose etiology can usually be well defined.

Keywords: hyperbilirubinemia, newborns, incidence, breastfeeding

Introduction

Severe hyperbilirubinemia continues to be the most common cause of neonatal readmission for hospitals in North America.1–5 This pattern continues despite attempts to identify newborns at risk of clinically important hyperbilirubinemia before they are discharged from hospital.6–9 Long-term results of severe hyperbilirubinemia, including bilirubin encephalopathy and kernicterus, were thought to be rare since the advent of exchange transfusion, maternal Rh immunoglobulin prophylaxis, and phototherapy.10–12 However, cases of kernicterus have been reported recently in healthy near-term and term infants without evidence of hemolytic disease or other risk factors.13,14

We begin our study of this problem with a survey of a single clinic experience over a year with respective to severity and probable causes of hyperbilirubinemia.

Background

Management of hyperbilirubinemia remains a challenge for neonatal medicine because of the risk for serious neurological complications related to the toxicity of bilirubin. The neonatal hyperbilirubinemia practice guidelines published in 2004 by the American Academy of Pediatrics (AAP) expresses the pediatric community’s concern regarding bilirubin-induced neurological pathology. Risk factors recognized...
to be associated with severe hyperbilirubinemia in newborns
have included jaundice in the first 24 hours of life, jaundice
noted before discharge from hospital, a sibling who had
jaundice treated with phototherapy, near-term gestational age
of 35–36 weeks, and the presence of infant with bruising or
cephalohematoma.

Materials and methods
From January 2006 to January 2007, we screened 525 newborns
born at the Neonatal Care Unit of Valsalva Hospital in Catania,
Italy. Infants aged 3–5 days and with unconjugated hyper-
bilirubinemia were included for assessment if they had a peak
serum total bilirubin level exceeding 6 mg/dl (102 μmol/L).
Sex, birth weight, gestational age, breast feeding, type of birth,
presence of facial bruising (including cephalohematoma),
and ABO group were noted. Patients with Toxoplasma or
Cytomegalovirus infection, hepatic insufficiency, or suspected
drug-induced hyperbilirubinemia were excluded from more
detailed analysis.

We focused on healthy term infants without risk factors.
Infants who had known Rh iso-immunization were excluded
since antenatal and postnatal strategies already exist to
prevent the occurrence of severe neonatal hyperbilirubinemia
from this cause. Infants who were born at less than 36 weeks’
gestational age were also excluded as well as newborn
with severe facial bruising or cephalohematoma from more
detailed analysis.

Data were summarized using descriptive statistics.
Continuous variables were analyzed using the independent
Student’s t-test and Fisher’s exact test. A chi square test was used
to test associations between all other categorical variables.

Results
We found 100 children with unconjugated hyperbilirubinemia.
Causes identified by laboratory investigations include Rh
and ABO incompatibility, as well as glucose-6-phosphate
dehydrogenase (G6PD) deficiency. We found potentially
neurotoxic levels of hyperbilirubinemia in only one case,
with value of peak bilirubin of 20 mg/dL (342 mmol/L),
treated with phototherapy. The other 99 cases had milder
hyperbilirubinemia and did not receive any treatment.

In our series, we found breastfeeding in 65 cases, cesarean
section in 61, and mild facial bruising in 16. Medicaments
during the pregnancy were used in 39 cases and post-pregnancy
in 35 (Table 1). A single case showed evidence of liver
disease (Gilbert disease). Cytomegalovirus and toxoplasmosis
infection were found in 2% and 6% of the cases, respectively
(Table 1). Maternal microcytosis was found in two cases.

We also evaluated the ABO group in the mothers and
in the newborns (Table 2). No significant differences were
found in the examined group. No other risk factors were
found in those patients.

We tried to analyze the characteristics of neonatal
jaundice. We took in consideration over 525 children,
100 infants with a value of bilirubin level of more than
6 mg/dl (102 μmol/L) (Table 3).

Discussion
Hyperbilirubinemia is felt to be a benign condition for
infants born at term or near-term gestation. In around 5%
of healthy term infants, however, serum bilirubin values
exceed 17 mg/dL (291 mmol/L), a value which the AAP
deems significant. Levels exceeding 20 mg/dL (342 mmol/L)
occur in 1.2% of healthy newborn infants. The vast majority
of infants with serum bilirubin values of 20 mg/dL remain
well; mostly need minimal care other the occasional use of
phototherapy and careful monitoring of serum levels. Before
1990, kernicterus in the previously healthy-term infant was
extraordinarily rare and for most pediatricians, it was a
disease they were unlikely to see in their practice lifetimes. Since 1990, there has been an increase in the number of reported cases of kernicterus in the United States. Thirty-one cases have been reported in term infants who were well at the time of hospital discharge, and several additional cases have occurred in near-term infants. Although it is unknown whether there is an actual increase in the incidence of kernicterus in the United States or simply better detection, reported cases are thought to be attributable to a variety of events including: shortened hospital stays with inconsistent follow-up beyond discharge; an increase in the frequency of breastfeeding; and a lack of concern about high bilirubin levels among pediatric care providers.

Although the relationship between hyperbilirubinemia and brain injury in healthy term infants has been recently questioned, in a reevaluation of the data from the Collaborative Perinatal Project, Newman and Klebanoff could not demonstrate a relationship between bilirubin levels 26 mg/dL (342 uM/L) and an abnormal neurologic examination.

Breastfeeding is still debated as probably an important variable in the incidence of kernicterus. In the present series, almost 65% of hyperbilirubememic patients were breastfed, as it has been for the other cases of kernicterus reported in the literature. In our series, no significance statistical difference in bilirubin levels were found according to whether or not the infant was breastfed.

In a case-controlled study Maisels found that hyperbilirubinemia was the major reason for hospital readmission during the first two weeks of life. Moreover, the majority of the jaundiced infants in their study were breastfed and had a greater mean weight loss since birth than nonjaundiced controls, suggesting that even mild degrees of dehydration in conjunction with breastfeeding impacts on the severity of hyperbilirubinemia.

Our series comes from a small center in Catania, Italy. Catania is one of the sunniest spots on Earth, with approximately 225 sunny days per year (which does not include partly cloudy days). It is possible that this plays some role in the relatively low incidence of hyperbilirubinemia in our studies as compared to previous studies. Furthermore future studies should investigate the presence of individual susceptibility, environmental factors, especially environmental climate (daylight), and genetic factors to explain the different incidences of the disease, and the frequency of such findings in infants with moderate degrees of hyperbilirubinemia and possible modes of prevention and new therapeutic strategies.

### Disclosure

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### References


### Table 3 Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No (%) of infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 100</td>
<td></td>
</tr>
<tr>
<td>Gestational age: wk, mean (SD)</td>
<td>38.5 (1.4)</td>
</tr>
<tr>
<td>Sex: male 42 and female 68</td>
<td></td>
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<tr>
<td>Birth weight: g, mean (SD)</td>
<td>3250 (+/− 489)</td>
</tr>
<tr>
<td>Age at presentation of jaundice, h, mean (SD)</td>
<td>78.5</td>
</tr>
<tr>
<td>Breast-feeding 65</td>
<td></td>
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<tr>
<td>Peak total bilirubin level, µmol/L, mean (SD)</td>
<td>186 (+76)</td>
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