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Unconjugated Hyperbilirubinemia and Early Childhood Caries in a Diverse Group of Neonates

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Abstract

We evaluated if the development of early childhood caries is associated with the severity of unconjugated hyperbilirubinemia during the first 2 weeks after birth. We performed a retrospective case-control study of children less than 6 years of age seen for comprehensive dental examination by pediatric dentists years following a hospital stay in the neonatal intensive care unit. Exclusion criteria included genetic disorders, cleft palate, direct hyperbilirubinemia, and missing information on jaundice. Children with early childhood caries were compared with those without dental caries for a panel of perinatal and neonatal clinical variables. Seventy-six children met study criteria. Of 76 children, 42 children had early childhood caries, while 34 children had healthy primary dentitions. Among clinical variables, only race and peak total serum bilirubin concentration differed significantly between the two groups on bivariate analysis. On logistic regression, peak total serum bilirubin concentration was significantly associated with early childhood caries (adjusted odds ratio 1.17, 95% confidence interval 1.04 to 1.32). Neonatal unconjugated hyperbilirubinemia may be associated with early childhood caries in children.

Keywords

Dental enamel hypoplasia; free bilirubin; total serum bilirubin; dental caries

Dental enamel defects including enamel hypoplasia and developmental opacities are extremely common in the primary and permanent dentitions of premature infants.¹⁻⁴ Several investigators have reported that dental enamel hypoplasia increases a child's susceptibility to early childhood caries (ECC).⁴⁻⁷ ECC has been defined by the American Academy of Pediatric Dentistry as the presence of one or more decayed (noncavitated or cavitated lesions), missing (due to dental caries), or filled tooth surfaces in any primary tooth in a child 71 months of age or younger.⁸ In many cases, ECC develops throughout the primary dentition causing dental pain, infection, impaired quality of life, and the need for multiple invasive dental procedures to be performed under physical restraint, sedation, or general anesthesia at very young ages.^{6,9-12}

Several neonatal clinical conditions including neonatal jaundice have been described as risk factors for dental enamel hypoplasia in children.¹³⁻¹⁵ Dental enamel hypoplasia is common among children afflicted with chronic postkernicteric encephalopathy, a late and chronic

sequela of severe unconjugated hyperbilirubinemia during the neonatal period.¹⁵⁻¹⁹ Despite knowledge about the effect of unconjugated hyperbilirubinemia on dental enamel formation and the relationship known to exist between dental enamel hypoplasia and dental caries, there is limited information available in the literature regarding the effect of neonatal unconjugated hyperbilirubinemia on ECC. Based on biological plausibility, we hypothesized that children with ECC have higher peak total serum bilirubin levels during the first 2 postnatal weeks compared with children without dental caries. Our objective was to determine if ECC is associated with the severity of unconjugated hyperbilirubinemia during the first 2 postnatal weeks of life in a diverse group of neonates admitted to the neonatal intensive care unit (NICU). The study was approved by the Institutional Research Review Board.

METHODS

Study Design

A retrospective case-control study was performed to evaluate if ECC is associated with a prior history of unconjugated hyperbilirubinemia during the first 2 weeks after birth. Our inclusion criteria included: (1) children born between January 1, 2001, and December 2005 and admitted to the NICU at the Golisano Children's Hospital at Strong in Rochester, New York, within 2 days after birth and (2) children who received at least one comprehensive dental examination in the Pediatric Dentistry clinic at the Eastman Dental Center by 71 months of age. Our exclusion criteria included genetic disorders, cleft palate, direct hyperbilirubinemia (conjugated bilirubin >20% of total serum bilirubin), and subjects with missing information on jaundice.

Subject Identification

All subjects with a date of birth between January 1, 2001, and December 2005 who had a comprehensive dental examination performed at the Eastman Dental Center were first identified through custom query of the Eastman Dental Center scheduling system. This list of subjects was then cross-referenced with Neonatal Database Systems to identify subjects who were admitted to the NICU.

Data Collection

For subjects who met study criteria, clinical information during the perinatal and neonatal period was collected using the medical charts. Data were collected on birth weight, race, gestational age, gender, small for gestational age, maternal diabetes, maternal thyroid disorders, in utero exposure to cocaine and other illicit drugs, use of antenatal magnesium sulfate, antenatal steroid exposure, mode of delivery, 5-minute Apgar score, respiratory distress syndrome (based on chest X-ray findings and clinical presentation), clinical sepsis (antibiotics for ≥ 7 days), days on mechanical ventilator (index of intubation), days on oxygen, lowest calcium concentration during the NICU stay, type of enteral feeding, and days on total parenteral nutrition. Clinical Information System, a laboratory-based database, was used to collect information on peak total serum bilirubin levels and other laboratory parameters during the first 2 weeks for each study subject.

Dental information was collected from Eastman Dental Center patient records. The presence or absence of ECC was determined through retrospective review of dental caries charting forms completed during routine patient care visits in the Pediatric Dentistry clinic. All dental caries charting forms completed on a subject up to and including 71 months of age were used to (1) assign subjects to one of two study groups and (2) record the number of decayed, extracted, and filled teeth (defect) score per study subject. Children in the case group had ECC with at least one noncavitated or cavitated tooth that required dental restoration or tooth

extraction due to dental caries. The control group consisted of subjects without dental caries amounting to a deft score of 0.

Statistical Analyses

Statistical analyses were performed using Stata 10 (Stata Corporation, College Station, TX) statistical software. The analyses were performed using chi-square test or Fisher exact test for categorical variables, *t* test for normally distributed continuous variables, and the non-parametric Wilcoxon rank sum test for nonnormally distributed continuous variables. The significance level of the data analysis was set at 0.05. Clinical risk factors associated with hyperbilirubinemia and/or ECC on bivariate analysis ($p < 0.2$) were considered as potential confounders and included in model building for regression analysis. Gestational age at birth was considered an a priori confounder based on literature. Final model buildings were performed using backward selection method. Log likelihood ratio tests were performed to evaluate the inclusion of potential confounders in the final regression model. Covariates that did not make a statistically significant contribution to the model as evaluated by the log likelihood ratio test were removed from the model. The final regression model for dental outcome was evaluated for a fitness using the Hosmer-Lemeshow test. Logistic regression analyses were performed using final regression models to control for potential confounding factors. The association between unconjugated hyperbilirubinemia and ECC was evaluated using multiple logistic regression analysis. Odds ratio (ORs) and 95% confidence intervals (CIs) were computed for significant associations.

RESULTS

One hundred children previously admitted to the NICU within 2 days after birth during the period January 2001 to December 2005 underwent at least one comprehensive dental examination at the Eastman Dental Center Pediatric Dentistry clinic by 71 months of age. Twenty-four of them (seven subjects with cleft palate and 17 subjects with missing information on jaundice during the neonatal period) were subsequently excluded. Subjects with missing information on jaundice stayed in the NICU for a short duration (mean 2 days, median 2 days) and were born at a mean gestational age of 38.5 weeks (median 39 weeks). Seventy-six subjects met the study criteria. Forty-two children had ECC (mean deft score 7.1; median deft score 6) and constituted the case group. All case subjects required invasive restorative or surgical dental procedures for management of ECC. Thirty-four children assigned to the control group were free of dental caries and received routine preventive dental services only. The perinatal characteristics of study subjects as a function of ECC are shown in Table 1. There were no significant differences in perinatal factors between children with and without ECC. Moreover, there were no significant differences in neonatal clinical risk factors with the exception of peak total serum bilirubin concentrations and race between the two groups as shown in Table 2.

Among the covariates, gestational age at birth, respiratory distress syndrome, and race were identified as potential confounders for the association between hyperbilirubinemia and ECC and included in model building. Of these potential confounders, only race was identified as a confounder using log likelihood ratio tests and was included along with gestational age in the final logistic regression model. The Hosmer-Lemeshow test suggested that there was no difference in the expected frequencies and observed frequencies and that the final model was a good fit ($p = 0.87$).

The association between unconjugated hyperbilirubinemia and ECC remained statistically significant after controlling for confounders in a regression analysis. The odds of developing ECC with each 1 mg/dL increase in peak total serum bilirubin increased by 17% (OR 1.17, 95% CI, 1.04 to 1.32) after controlling for confounding variables.

DISCUSSION

Caries is a complex chronic disease resulting from an imbalance of multiple protective factors and risk factors over time. ECC is a virulent form of dental disease that occurs in infants and young children.⁸ Although ECC is caused by decay-promoting feeding behaviors and poor oral hygiene in the setting of rampant infection with *Streptococcus mutans*, dental enamel hypoplasia has been found to increase the risk for ECC.⁴⁻⁶ It has been postulated that there is greater attachment of *S. mutans* on rough surfaces associated with dental enamel hypoplasia, promoting colonization of the cariogenic bacteria.

Enamel matrix deposition by ameloblasts commences in primary teeth before 4 months of intrauterine life.²⁰ This phase followed subsequently by tissue calcification and maturation is active at birth and continues through the eruption of the primary dentition. Metabolic disturbances and systemic insults during the process of amelogenesis result in reduced enamel quantity and quality consistent with dental enamel hypoplasia. Hyperbilirubinemia is a known metabolic insult affecting ameloblast function during early dental development.²¹ Clinically, dental enamel hypoplasia has been described in patients with chronic postkernicteric encephalopathy, a late manifestation of severe jaundice.¹⁶⁻¹⁹ Although unconjugated hyperbilirubinemia causes dental enamel hypoplasia, the association between unconjugated hyperbilirubinemia during the neonatal period and ECC has not been well studied. Our findings suggest that unconjugated hyperbilirubinemia is associated with ECC in a diverse group of neonates. We believe this is the first report describing an association between unconjugated hyperbilirubinemia in neonates and later development of dental caries in early childhood.

Despite a strong association between unconjugated hyperbilirubinemia and ECC, significant overlap in total serum bilirubin concentrations was noted between children with and without ECC. Our findings, therefore, cannot provide a threshold level of total serum bilirubin above which there may be an increased risk of dental caries. Recent literature suggests that free bilirubin (bilirubin not bound to protein) may be a more sensitive and specific biochemical indicator of chronic postkernicteric encephalopathy.²²

Several investigators have reported a high prevalence of dental enamel hypoplasia among populations of preterm infants.¹⁻³ Studies using exfoliated primary teeth have determined that the dental enamel of preterm infants is significantly thinner than term infants and displays enamel hypoplasia 52% of the time histologically even when no clinical lesion is evident to the naked eye.^{23,24} Besides hyperbilirubinemia, several other perinatal and neonatal risk factors such as neonatal hypocalcemia, maternal diabetes, and respiratory distress syndrome have been associated with a high prevalence of enamel defects.^{14,16,25-27} Similarly, local trauma from laryngoscopy and oral intubation has been implicated as a cause of enamel defects in the maxillary incisors.^{28,29} However, compared with hyperbilirubinemia, all other perinatal and neonatal clinical factors that may be associated with enamel defects were not associated with ECC in our study. This lack of association may be attributable to inadequate sample size and power to evaluate the association. There were only a few subjects with hypocalcemia (calcium <7 mEq/dL), maternal diabetes, and respiratory distress syndrome in our study population.

The retrospective design of our study is a major limitation in light of associated selection and information biases. Although the study involved a diverse population of neonates, the findings may not be generalizable to very premature infants as the mean gestational age in our study population was 34 to 35 weeks. Second, because the Eastman Dental Center serves primarily a low-income, New York State Medicaid-insured patient population, the study's findings may not be applicable to populations with private health insurance, a

marker of higher socioeconomic status and traditionally lower ECC prevalence. Furthermore, comprehensive dental examinations used for study group assignment were completed by multiple dentists as part of clinical patient care. These examinations were not calibrated or analyzed for intra- and interrater reliability. Despite these limitations, the biological plausibility for the association between jaundice and ECC strongly supports our findings.

In summary, our findings suggest that unconjugated hyperbilirubinemia may be associated with ECC. Infants and preschool children who develop ECC require invasive dental procedures using physical restraint and sedation in dental offices as well as general anesthesia in ambulatory surgical centers and hospital operating suites.¹² This treatment approach is costly and can be damaging to the developing psyche of young children.¹² If unconjugated hyperbilirubinemia predisposes neonates to ECC, neonatal interventions aimed at correcting moderate to severe hyperbilirubinemia could be a promising strategy for reducing dental caries associated morbidity and dental treatment-related expenditures in the future. A prospective well-designed longitudinal study is urgently needed to confirm our findings of significant association between severity of unconjugated hyperbilirubinemia and ECC in high-risk neonates. Future studies should also evaluate the usefulness of free bilirubin as a predictor of bilirubin-induced dental toxicity.

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Table 1

Association between Perinatal Factors and Early Childhood Caries (ECC) in Primary Teeth

	Normal (<i>n</i> = 34)	ECC (<i>n</i> = 42)	<i>p</i> Value
Gestational age (wk) *	34.1 ± 34.6	35.1 ± 34.7	0.3
Birth weight (g) *	2151 ± 3897	2447 ± 31073	0.2 [†]
Gender (male/female)	17/17	26/16	0.3
Race (% white)	41	69	0.02
Maternal drug abuse (%)	11	7	0.7
Maternal diabetes (%)	11	12	0.9
Antenatal magnesium sulfate (%)	32	21	0.3
Antenatal steroids (%)	24	21	0.5
Maternal thyroid problems (%)	2	2	0.4
Mode of delivery (% cesarean section)	38	47	0.4

* Mean ± standard deviation.

[†] Rank-sum test.

Table 2

Association between Neonatal Risk Factors and Early Childhood Caries (ECC) in Primary Teeth

	Normal (n = 34)	ECC (n = 42)	p Value
Median (mean) Apgar score at 5 min	9 (8)	9 (7.8)	0.6
Small for gestational age (%)	15	14	0.95
Peak total serum bilirubin (mg/dL) *	8.8 ± 33.9	11.5 ± 34.6	0.01 [†]
Lowest calcium (mEq/dL) *	8.6 ± 30.96	8.4 ± 30.81	0.35 [†]
Respiratory distress syndrome (%)	38	24	0.18
Median (mean) days on oxygen	0 (20.3)	2 (12.5)	0.28 [†]
Median (mean) days on ventilator	0 (9.6)	0 (4.1)	0.53 [†]
Median (mean) days on total parenteral nutrition	5 (11.1)	7 (11.6)	0.8 [†]
Type of enteral feeding (% formula)	74	81	0.44
Clinical sepsis (%)	18	26	0.37
Median (mean) days in neonatal intensive care unit	8 (31)	11 (26)	0.6 [*]

* Mean ± standard deviation.

[†] Rank-sum test.