Extreme Neonatal Hyperbilirubinemia and a Specific Genotype: A Population-Based Case-Control Study

WHAT’S KNOWN ON THIS SUBJECT: For newborn infants, extreme hyperbilirubinemia (≥24.5 mg/dL) is associated with risk for severe bilirubin encephalopathy. The causal factor of extreme hyperbilirubinemia is often not established. The genotype of Gilbert syndrome, the UGT1A1*28 allele, is considered a potential risk factor.

WHAT THIS STUDY ADDS: The UGT1A1*28 allele was not associated with risk for developing extreme hyperbilirubinemia.

abstract

OBJECTIVES: Extreme hyperbilirubinemia (plasma bilirubin ≥24.5 mg/dL) is an important risk factor for severe bilirubin encephalopathy. Several risk factors for hyperbilirubinemia are known, but in a large number of patients, a causal factor is never established. UGT1A1 is the rate-limiting enzyme in bilirubin’s metabolism. The genotype of Gilbert syndrome, the UGT1A1*28 allele, causes markedly reduced activity of this enzyme, but its association with neonatal hyperbilirubinemia is uncertain and its relationship with extreme hyperbilirubinemia has not been studied. We examined whether the UGT1A1*28 allele is associated with extreme hyperbilirubinemia.

METHODS: The UGT1A1*28 allele was assessed in a case-control study of 231 white infants who had extreme hyperbilirubinemia in Denmark from 2000 to 2007 and 432 white controls. Cases were identified in the Danish Extreme Hyperbilirubinemia Database that covers the entire population. Genotypes were obtained through the Danish Neonatal Screening Biobank. Subgroup analysis was done for AB0 incompatible cases.

RESULTS: No association was found between the UGT1A1*28 allele and extreme hyperbilirubinemia. With the common genotype as reference, the odds ratio of extreme hyperbilirubinemia was 0.87 (range, 0.68–1.13) for UGT1A1*28 heterozygotes and 0.77 (range, 0.46–1.27) for homozygotes. Also, no association was found for AB0 incompatible cases.

CONCLUSIONS: The UGT1A1*28 allele was not associated with risk for extreme hyperbilirubinemia in this study. Pediatrics 2014;134:510–515

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KEY WORDS
bilirubin, kernicterus, UGT1A1*28, Gilbert syndrome, neonates, encephalopathy

ABBREVIATIONS
OR—odds ratio
UGT1A1—uridine diphosphate glucuronosyltransferase 1A1

Dr Petersen conceptualized and designed the study, carried out the initial analyses, and drafted the initial manuscript; Professor Henriksen assisted in the design of the study, supervised the analyses, and critically reviewed and revised the manuscript; Mr Hollegaard and Dr Hougaard coordinated and supervised the DNA extraction and genotyping, identified the control population, and critically reviewed the manuscript; Dr Vandborg identified the case population, collected the clinical data in the Danish Extreme Hyperbilirubinemia Database, and critically reviewed the manuscript; Professor Thorlacius-Ussing assisted in the design of the study and critically reviewed and revised the manuscript; Dr Ebbesen assisted in the conceptualization and design of the study, coordinated and supervised the data collection for Danish Extreme Hyperbilirubinemia Database, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Hyperbilirubinemia arises from an imbalance between production and elimination of bilirubin. Among newborn infants, it is almost universal and generally benign, but may in rare instances cause severe bilirubin encephalopathy. This condition is primarily seen with extreme hyperbilirubinemia (ie, plasma bilirubin values \( \geq 24.5 \text{ mg/dL} \)).

In Denmark, extreme hyperbilirubinemia and chronic bilirubin encephalopathy (kernicterus) occur in 1 in 2000 live births and 1 in 95,000 live births, respectively.5-6 These rates correspond well with reports from other parts of the privileged world,7 but in the developing world, bilirubin encephalopathy persists as a frequent cause of neonatal morbidity.8

Several risk factors for hyperbilirubinemia are known, among these are blood type iso-immunization, congenital hemolytic diseases, gender, prematurity, race, starvation, and early discharge from hospital, but in a large number of patients, a causal factor is never established.1,2,5,6,9,10 Thus, despite neonatal hyperbilirubinemia being 1 of the most frequent hospital-treated conditions in the developed world with 2% to 7% of a population receiving phototherapy in the first days of life, much is still not understood about its development.

Bilirubin is an end-product of the catabolism of heme. It is created in the reticuloendothelial system of the liver and glucuronidated in the hepatocytes by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) and can be excreted into the bile.11 UGT1A1 is the rate-limiting enzyme in this process, with activity presumed low at birth.12,13

A possible contributor to the development of hyperbilirubinemia is the genotype behind Gilbert-Meulengracht syndrome known as the UGT1A1*28 allele. This polymorphism affects the UGT1A1 gene located on chromosome 2q37, where a thymine-adenine base pair is inserted into the TATA box of the promoter region, resulting in 7 thymine-adenine base pairs instead of the normal 6. The promoter region controls expression of the UGT1A1 gene, and for UGT1A1*28 alleles, UGT1A1 enzyme activity is reduced to 30% of common allele levels.14-17

The contribution of UGT1A1*28 alleles to the development of hyperbilirubinemia among newborn infants is not yet settled, but it has been proposed that additional icterogenic factors are necessary for the allele to influence the incidence of hyperbilirubinemia, and that 1 such factor could be AB0 blood type incompatibility.13,18

The association between the UGT1A1*28 allele and the development of extreme hyperbilirubinemia has not been studied, and a call for such studies has been made in recent international reviews.13,19,20 Hence, we investigated the relationship between UGT1A1*28 genotypes and extreme hyperbilirubinemia in a case-control design, encompassing all incident cases in Denmark from 2000 to 2007.

METHODS

Setting

The study base was all live newborn infants in Denmark from 2000 to 2007. Denmark has a public health care system that grants universal access to both primary and secondary care. The population is 5.5 million, and the median number of live births per year in the study period was 64,600.

Materials

Our study combined clinical information from The Danish Extreme Hyperbilirubinemia Database, with genotypes estimated from dried blood spot samples stored in the Danish Neonatal Screening Biobank.

The aim of the Danish Extreme Hyperbilirubinemia Database is to encompass all newborn infants who have extreme hyperbilirubinemia born \( \geq 35 \) gestational weeks in the current century in Denmark. For the period 2000 to 2003, the inclusion criterion was a serum bilirubin \( \geq 26.3 \text{ mg/dL} \). From 2004, the inclusion criterion has been a serum bilirubin \( \geq 24.5 \text{ mg/dL} \). At inclusion, several clinical and paraclinical variables are obtained from the patient’s medical files, among these are race, Rhesus hemolytic disease, AB0 incompatibility (blood type: mother O, infant A or B), direct antiglobulin test, any diagnosis of congenital hemolytic disease, weight loss, and early discharge.4

At birth, all Danish citizens are assigned a unique 10-digit civil registration number, which gives data on date of birth and gender and allows unambiguous individual-level identification and data linkage across nationwide public health registers.21 We used the civil registration number to identify cases in the Danish Neonatal Screening Biobank.

As part of the Danish national neonatal screening for metabolic diseases, a dried blood spot sample is collected from all newborn infants shortly after birth. Since 1982, the excess dried blood spots have been stored in the Danish Neonatal Screening Biobank that covers \( \sim 99\% \) of all children born after 1982.22

The study was restricted to infants of white ancestry. For cases, this information was registered in the Extreme Hyperbilirubinemia Database, and controls were found by computerized, randomly selected dried blood spot samples from term infants born in the study period in the Biobank’s database of mothers who had a northwestern European last name.

Genotypes

From each of the dried blood spot samples, 2.32-mm disks were punched, DNA extracted, and subsequently whole-genome amplified (wgaDNA) in triplicates, as previously described.23 Genotyping of wgaDNA made from dried blood spot samples has been shown to be feasible and valid.24 Genotyping was performed at Statens Serum Institute (Copenhagen, Denmark).
Denmark), on a Pyrosequencer (Qiagen, Hilden, Germany), using a previously published approach.25

Statistical Methods

All statistical analysis was done with the Stata statistical software package version 12.1 (StataCorp, College Station, TX). The genotype Hardy Weinberg equilibrium was explored for controls with the hwsnp command. Associations between genotype and outcome were expressed as odds ratios (OR) using logistic regression, with participants who had the common genotype as the reference group. Genotypes were in primary analysis treated as a continuous variable and secondarily tested as a categorical variable. Confidence intervals are reported as 95%.

A priori we decided to control for gender. Potential effect modulation of gender was tested by fitting an interaction term and inspecting the P values, and further by stratifying the analysis on gender and inspecting results.

Ethics

The study was approved by the regional Ethics Committees on Human Studies [J.nr. 2012-145596], the Danish Data Protection Agency, and the Danish Neonatal Biobank Steering Committee and was conducted according to the principles of the Declaration of Helsinki.

RESULTS

Between 2000 and 2007, 257 cases of extreme hyperbilirubinemia among white infants were present in the database. For 238 of these, a dried blood spot sample suitable for further analysis was present in the Danish Neonatal Screening Biobank. For 7 cases, genotyping or DNA amplification failed, making 231 cases available for the study. Dried blood spot samples of 432 controls were randomly picked in the Danish Neonatal Screening Biobank, as described above. For 6 controls, genotyping or DNA amplification failed, making 426 controls available for the study.

Demographic and clinical characteristics of cases and controls are shown in Table 1.

Genotype distribution among controls did not deviate from Hardy-Weinberg equilibrium (P = .46).

No association was found between extreme hyperbilirubinemia and UGT1A1*28 genotypes. With participants who had the common genotype as reference group, the OR per UGT1A1*28 allele was 0.87 (range, 0.68–1.13), making the OR for heterozygotes 0.87 (range, 0.68–1.13) and 0.77 (range, 0.46–1.27) for homozygotes. Treating genotype as a categorical variable gave similar estimates (data not shown). There was no evidence of effect modulation for gender, and adding gender to the logistic regression model did not change estimates. Genotype frequencies and gender-adjusted estimates are shown in Table 2.

The ABO subtype

For the ABO incompatible case subgroup, no association was found between extreme hyperbilirubinemia and UGT1A1*28 genotype. With participants who had the common genotype as reference, the OR per UGT1A1*28 allele was 1.01 (range, 0.67–1.53), making the OR for heterozygotes 1.01 (range, 0.67–1.53) and 1.02 (range, 0.45–2.32) for homozygotes. Treating genotype as a categorical variable gave similar estimates (data not shown). There was no evidence of effect modulation for gender, and adding gender to the logistic model did not change estimates. Genotype frequencies and gender-adjusted estimates are shown in Table 3.

DISCUSSION

In this study the UGT1A1*28 allele was not associated with risk for extreme hyperbilirubinemia.

### TABLE 1 Baseline Characteristic of Cases and Controlsa

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases, N (100%)</th>
<th>Median (Range)</th>
<th>Controls, N (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>140 (60.6)</td>
<td>—</td>
<td>215 (50.5)</td>
</tr>
<tr>
<td>Girls</td>
<td>91 (39.4)</td>
<td>—</td>
<td>211 (49.5)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>—</td>
<td>3500 (2178–4870)</td>
<td>—</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>—</td>
<td>36 (35–42)</td>
<td>—</td>
</tr>
<tr>
<td>Maximum serum bilirubin (mg/dL)</td>
<td>—</td>
<td>26.8 (24.5–38.9)</td>
<td>—</td>
</tr>
<tr>
<td>Weight loss &gt;10%</td>
<td>41 (22.5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Born in hospital</td>
<td>226 (98.3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Exclusively breastfed</td>
<td>195 (92.4)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ABO incompatibility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>65 (40.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No</td>
<td>91 (58.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rhesus immunization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (1.9)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No</td>
<td>153 (88.1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Congenital hemolytic disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (spherocytosis)</td>
<td>2 (1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No</td>
<td>223 (99)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Early discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>155 (69.8)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No</td>
<td>67 (30.2)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>DAT test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>25 (15.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Negative</td>
<td>134 (84.3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>DAT test for ABO incompatibles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>20 (34.5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Negative</td>
<td>38 (65.5)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

DAT, direct antiglobulin test; —, no value

*a If the total number of cases is <251, it is because of missing values in the Extreme Hyperbilirubinaemia Database.
TABLE 2 Genotypes for Cases and Controls, and Gender-Adjusted Odds Ratios of Extreme Hyperbilirubinemia

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Cases N (%)</th>
<th>Controls N (%)</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/6</td>
<td>123 (53.3)</td>
<td>200 (47.0)</td>
<td>Reference</td>
</tr>
<tr>
<td>7/6</td>
<td>87 (37.7)</td>
<td>190 (44.6)</td>
<td>0.88 (0.68–1.13)</td>
</tr>
<tr>
<td>7/7</td>
<td>21 (9.1)</td>
<td>36 (8.5)</td>
<td>0.77 (0.46–1.27)</td>
</tr>
<tr>
<td>N</td>
<td>231</td>
<td>426</td>
<td>—</td>
</tr>
</tbody>
</table>

The common genotype is 6; UGT1A1*28 is 7.

TABLE 3 Genotype Frequencies for Controls and AB0 Incompatible Cases, and Gender-Adjusted Odds Ratios of Extreme Hyperbilirubinemia

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Cases N (%)</th>
<th>Controls N (%)</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/6</td>
<td>30 (47.6)</td>
<td>200 (47.0)</td>
<td>Reference</td>
</tr>
<tr>
<td>7/6</td>
<td>27 (42.9)</td>
<td>190 (44.6)</td>
<td>1.01 (0.87–1.52)</td>
</tr>
<tr>
<td>7/7</td>
<td>6 (9.5)</td>
<td>36 (8.8)</td>
<td>1.02 (0.45–2.33)</td>
</tr>
<tr>
<td>N</td>
<td>63</td>
<td>426</td>
<td>—</td>
</tr>
</tbody>
</table>

The common genotype is 6; UGT1A1*28 is 7.

* Gender-adjusted odds ratios.

**Strengths and Limitations**

A main strength of our study is the completeness and nationwide coverage. The Danish Extreme Hyperbilirubinemia Database has been meticulously validated and is nationally complete for the investigated timespan. Therefore we consider the risk for misclassification for cases and controls negligible. Furthermore, the existence of a unique biological resource, the Danish Neonatal Screening Biobank, gave us the opportunity to test the association between UGT1A1*28 genotypes and extreme hyperbilirubinemia for cases compiled over 8 years. This has led to a reasonably large sample size and a correspondingly high statistical power reflected in narrow confidence intervals for the primary outcome. For the AB0 incompatible subgroup, the number of cases, and thus statistic power, was more limited, which is reflected in wider confidence intervals. Because of the dose-response relationship between UGT1A1*28 genotypes and UGT1A1 enzyme activity, in the primary analysis the genotypes were treated as a continuous variable and as a categorical variable in the secondary analysis. Effect estimates were similar for the 2 analytic strategies, but the primary analysis had a higher statistical power and a better precision of estimates.

The frequency of the UGT1A1*28 allele varies greatly with race. Therefore we restricted the study to infants of white descent to limit confounding from other genetic and sociodemographic factors affecting bilirubin metabolism. The UGT1A1*28 genotype frequencies in our data correspond well with those expected for a white north European population.

**Interpretation**

Our study diverges from previous studies by being population-based, by containing multiple causes of hyperbilirubinemia (eg, AB0 incompatibility, early discharge, starvation), by its case-control design, and by being to our knowledge the first to directly explore the association between UGT1A1*28 genotypes and extreme hyperbilirubinemia. Most studies find that the UGT1A1*28 allele is unrelated to neonatal hyperbilirubinemia, but some studies have shown that UGT1A1*28 allele status is associated with increased levels of plasma bilirubin in conjunction with hemolytic factors (AB0 serum incompatibility, spherocytosis, and some variants of glucose-6-phosphate dehydrogenase deficiency). Two studies have found that UGT1A1*28 contributed to prolonged neonatal jaundice. Thus, our primary outcome is consistent with most of the previous findings.

Contrary to the neonatal population, for the adult population the association between UGT1A1*28 genotypes and plasma bilirubin is well established. In adult North-European white populations, the UGT1A1*28 genotype is the major known genetic determinant of plasma bilirubin and accounts for 18% of all variations.

We suggest that the difference between adult and neonatal findings is in concordance with evidence pointing toward UGT1A1 enzyme expression as being modulated in a developmental manner such that its activity at term birth is ~1% of adult values, and that it first reaches mature levels by 14 weeks of postnatal life, a process that is believed to be primarily induced by unconjugated bilirubin itself. Accordingly, it could stand to reason that variations in UGT1A1 activity have no great impact on bilirubin metabolism in the first days of life, but that it could influence the duration of neonatal hyperbilirubinemia. Also, it seems plausible that the effect of genetically downgraded enzyme activity could be stronger in the face of overt hemolysis, as suggested by Kaplan et al.18

Our data do not support this later theory, as we find no association between UGT1A1*28 genotype and extreme hyperbilirubinemia for AB0 incompatible cases. However, the precision of the effect estimate for the AB0 incompatible cases in our data is limited and strong assumptions should not be based on it. Furthermore, a limitation in our study lies in the biological generalizability and external validity of results. In Denmark, most infants at risk for extreme hyperbilirubinemia are identified and treated before the condition develops. Association between biological risk factors for extreme hyperbilirubinemia and actual
development is thus modulated by clinical intervention. Our data should be interpreted with this in mind. Although we think our results provide a precise estimate of the association between UGT1A1*28 and clinical risk for extreme hyperbilirubinemia, they do not necessarily precisely reflect the underlying biological association between UGT1A1*28 genotypes and plasma bilirubin in the first days of life. Our data do not exclude an association between UGT1A1*28 and development of neonatal hyperbilirubinemia, especially not at lower bilirubin plasma levels. This association could more accurately be explored in prospective cohort studies. Also, we suggest that the association between the UGT1A1*28 allele and extreme hyperbilirubinemia could be different in populations with restricted access to health care and/or a higher incidence of hemolysis owing to factors like glucose-6-phosphate dehydrogenase deficiency, and further studies in such populations would be relevant.

CONCLUSIONS

Our study explored whether the UGT1A1*28 allele is a clinical risk factor for development of extreme hyperbilirubinemia. This is not the case among white infants born in Denmark.

REFERENCES


**SHIFT OR NO SHIFT?:** I was at a T-ball game this past weekend watching one of my nephews play. When in the field he played first base. He (as well as second baseman, shortstop, and third baseman) were all in the usual spots that I knew from when I played baseball. A father, an excited observer, gushed that T-ball helped prepare children for the game of baseball. I am not sure if T-ball truly helps prepare children to play our national pastime, but certainly how professional baseball players are stationed in the field is now quite different from when I played baseball or how children are arranged during T-ball.

As reported in The New York Times (Baseball: May 12, 2014), professional baseball teams are commonly using the infield shift to position players according to where the batter has a natural tendency to hit the ball. With powerful computer programs charting every pitch, swing, and hit coaches know the propensity of hitters. So, if a left handed hitter with a tendency to pull the ball to the right side of the field is at bat, the second baseman may play between first and second base and the shortstop in shallow right field or behind second base instead of the usual position between second and third base. The reason teams are so often using the shift is because it works. Teams routinely employing infield shifts drop the batting average of the opponents by 30-40 points on ground balls. Anyway, I was just as happy that the coaches were not busy moving the children around the field and allowing them just to have fun chasing the ball.

*Noted by WVR, MD*
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