
WHAT'S KNOWN ABOUT THIS SUBJECT: Severe neonatal hyperbilirubinemia can lead to acute bilirubin encephalopathy and, subsequently, chronic bilirubin encephalopathy (CBE). This condition is preventable through routine identification and proper treatment; therefore, it is rare for permanent neurologic complications to occur.

WHAT THIS STUDY ADDS: This article describes the incidence of CBE in Canada, which is higher than previously reported in the literature. Furthermore, it describes the underlying causes of CBE and the spectrum of neurologic disease.

abstract

BACKGROUND AND OBJECTIVES: Despite the implementation of screening guidelines to identify infants at risk for hyperbilirubinemia, chronic bilirubin encephalopathy (CBE) continues to be reported worldwide in otherwise healthy infants. The incidence of CBE in Canada is unknown. The objectives of this study were to establish the incidence of CBE in Canada and identify epidemiological and medical risk factors associated with its occurrence.

METHODS: Data on infants were collected prospectively through the Canadian Pediatric Surveillance Program. Infants born between January 1, 2007 and December 31, 2008 were included if they either had symptoms of CBE and a history of hyperbilirubinemia, or if they presented in the newborn period with severe hyperbilirubinemia and an abnormal MRI finding as per the reporting physician.

RESULTS: During the study period, 20 cases were identified; follow-up data were available for 14 of these. The causes for the hyperbilirubinemia included glucose-6-phosphate dehydrogenase deficiency (n = 5), sepsis (n = 2), ABO incompatibility and other red blood cell antibodies (n = 7). Fifteen infants had abnormal brain MRI findings during the neonatal period. At follow-up, 5 infants developed classic choreoathetoid cerebral palsy, 6 had spectrum of neurologic dysfunction and developmental delay (as described by the reporting physician), and 3 were healthy.

CONCLUSIONS: CBE continues to occur in Canada at an incidence that appears to be higher than previously reported. Pediatrics 2012;130:e886–e890

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KEY WORDS chronic bilirubin encephalopathy, neonatal hyperbilirubinemia, incidence, neurologic outcomes

ABBREVIATIONS ABER—abnormal auditory brainstem–evoked responses CBE—chronic bilirubin encephalopathy CPSP—Canadian Paediatric Society Surveillance Program

The authors completed all aspects of the study (design, conduct, data collection, management, analysis, interpretation, manuscript preparation, and approval); Drs Sgro and Campbell were responsible for study concept and design; Drs Sgro, Campbell, Kandasamy, and Shah were responsible for acquisition of data; Drs Sgro, Campbell, Kandasamy, and Shah were responsible for analysis and interpretation of data; Drs Sgro, Campbell, and Kandasamy were responsible for drafting of the manuscript; Dr Shah was responsible for critical revision of the manuscript for important intellectual content; Drs Sgro and Campbell were responsible for statistical analysis; and Dr Sgro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.


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With the availability of treatment modalities for hyperbilirubinemia, including phototherapy and exchange transfusion, most infants with severe hyperbilirubinemia survive and recover from the acute phase of bilirubin encephalopathy. Despite early recovery, these infants may develop permanent sequelae within the clinical spectrum of chronic bilirubin encephalopathy (CBE), including: choreoathetoid cerebral palsy, degrees of dystonia (hypertonia or hypotonia), and/or sensorineural hearing loss. Most, but not all children with CBE have previously displayed symptoms of acute bilirubin encephalopathy in the neonatal period. In addition, recent studies have suggested that CBE has a much broader spectrum of chronic neurologic symptoms than previously thought (bilirubin-induced neurologic dysfunction) and may include extended neurologic disease, such as speech delay, global developmental delay, and autism. The incidence of CBE has been difficult to measure, with estimates ranging from 1:50,000 to 1:100,000 in Europe and North America. Although rare, this condition can be severe, placing an enormous burden on the family and costing the health system significant money.

With proper identification of at-risk infants through routine bilirubin testing and key timely treatment including Rhogam to the mother, phototherapy, and exchange transfusion, CBE is preventable. Several factors may have contributed to the continued incidence of CBE, including less aggressive management of neonatal hyperbilirubinemia based on the recommendations published by the American Academy of Pediatrics in the 1990s, early discharge of the at-risk newborn, and inadequate follow-up of these neonates after discharge. All of these factors warrant ongoing surveillance of this condition. Recent surveillance reports in the United Kingdom and Canada have noted relatively high incidences of severe hyperbilirubinemia and acute bilirubin encephalopathy. However, the incidence of CBE in similar surveillance data has not been reported. The objective of our study was therefore to assess the incidence of CBE in Canada.

METHODS
To estimate the incidence of CBE, we identified cases reported by the Canadian Pediatric Society Surveillance Program (CPSP) from January 1, 2007 to December 31, 2008, because we expected that all infants and children who have chronic sequelae from severe hyperbilirubinemia would be followed up by a pediatrician. The CPSP surveys >2500 Canadian pediatricians and other pediatric subspecialists on a monthly basis. This is an ongoing national surveillance program involved in tracking a number of pediatric illnesses. Research ethics board approval for this study was obtained through St. Michael’s Hospital and Mount Sinai Hospital, Toronto, Ontario.

A 2-tiered voluntary reporting process was used to identify and verify cases. Potential cases were identified by using an initial “check-form” that is returned monthly to the CPSP office even if the pediatrician/health care provider identifies no new cases. Quarterly reminders were mailed to respondents who had not replied for all months of the year. Each physician that identified a case (meeting our case definition indicated below) was then asked to complete a detailed questionnaire developed for this study to gather more patient information about the cause of the hyperbilirubinemia and long-term neurologic outcome (see Supplemental Information). During 2007 and 2008, the mean reporting rate was 80% for the initial survey (lowest reporting by a province was 68% in Saskatchewan), and detailed reporting rates in response to our questionnaire were 94% and 88%, respectively, for the 2 years. Follow-up questionnaires were mailed and phone calls made to reporting physicians 12 to 18 months after initial reporting of the case to assess long-term developmental outcome.

Case Definition
Infants were considered eligible for inclusion if they met either of 2 definitions for CBE: symptoms of kernicterus and a history of hyperbilirubinemia (definition 1), or if they presented in the newborn period with severe hyperbilirubinemia and specific abnormalities on MRI as per the reporting physician (definition 2).

Definition 1
History of significant neonatal hyperbilirubinemia (highest recorded bilirubin >425 µmol/L [24.8 mg/L] or exchange transfusion) and 2 or more of the following chronic neurologic symptoms: (a) extrapyramidal disorders (eg, dystonia, athetosis); (b) other movement disorders (spasticity or hypotonia); (c) gaze abnormalities; (d) sensorineural hearing loss; (e) intellectual deficits; and/or (f) enamel dysplasia of the deciduous teeth.

Definition 2
History of significant neonatal hyperbilirubinemia (highest recorded bilirubin >425 µmol/L or 24.8 mg/L), and an abnormal MRI finding, defined as bilateral lesions of the basal ganglia/midbrain (globus pallidus and subthalamic nucleus).

Exclusion Criteria
Infants who were born at <35 weeks gestational age or had received other diagnoses that could have basal ganglia involvement, such as glutaric acidemia type II, pyruvate dehydrogenase deficiency, Hallervorden Spatz disease, neurofibromatosis type I, or carbon monoxide poisoning, were excluded.
RESULTS

Over the 2-year study period, 29 cases of suspected CBE were reported to the CPSP, of which 20 were confirmed as per our definition following the second questionnaire. Of these, 18 were confirmed based on definition 2, and 2 were confirmed based on definition 1. The remaining 9 were excluded for the following reasons: duplicate reporting (n = 5), did not fulfill our case definition (n = 2), and insufficient information to confirm a case diagnosis (n = 2). The characteristics of the 20 confirmed cases and the etiology of hyperbilirubinemia in these infants are presented in Table 1.

Follow-up data were available for 14 of the confirmed neonatal cases (65%; Table 2), with CBE evident in 11 cases. Of the 4 cases that did not show signs of abnormal neurologic findings during the neonatal period, 2 nonetheless went on to develop abnormal findings at follow-up. Abnormal auditory brainstem–evoked responses (ABERs) that were reported in 14 infants at the neonatal diagnosis were associated with subsequent development of persistent hearing loss and/or speech delay in 7 cases.

Abnormal MRI findings reported by pediatricians included bilateral basal ganglia enhancement or enhancement of the globus pallidus and subthalamic nuclei consistent with kernicterus. Of the cases that had abnormal neonatal MRI findings (as per case definition) at initial presentation, 3 subsequently had normal development reported at the time of follow-up. However, an absence of identified abnormalities at neonatal MRI was not found to be indicative of prognosis, because the 2 cases in which the initial MRI findings were reported as normal later presented with abnormal developmental outcomes at follow-up.

There were no differences in the infants with follow-up data (n = 14) in comparison with the infants lost to follow-up (n = 6) with respect to highest recorded serum bilirubin (P = .41) and abnormal MRI findings at presentation (P = .53). However, all 6 infants lost to follow-up exhibited abnormal neurologic findings at presentation in the neonatal period compared with only 4 of 14 infants with follow-up data (risk difference, 0.71; 95% confidence interval, 0.42–0.92).

DISCUSSION

Over the 2-year study period, we found that CBE continues to occur among infants born in Canada. We identified 20 cases in children <1 year of age during the study period based on our case definition. Etiologies of severe hyperbilirubinemia were similar to previously reported case series. If we excluded 3 of these children who were later found to have normal development in follow-up, this would correspond to an incidence of 1 in 44 000 live births (Canadian birth rate,

<table>
<thead>
<tr>
<th>Table 1 Characteristics of Neonates With CBE</th>
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<tr>
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G6PD, glucose-6-phosphate dehydrogenase; VEP, visual-evoked potentials; SEP, sensory-evoked potentials; N/A, not available.
370,000 per year \(^{24}\). Of these cases, 11 (1 in 67,000) showed signs of chronic neurologic abnormalities at follow-up, and 6 were lost to follow-up. The rate we have reported is higher than that been reported in other industrialized countries \(^{12-15}\); however, the majority of these previous studies relied on voluntary reporting that was not part of an active surveillance system. A study conducted in Denmark from January 2000 to December 2001 found the incidence of CBE to be 1.4 per 100,000 live births \(^{13}\) based on informal case findings. Similar estimates of 1 per 100,000 were obtained in the United States based on the kernicterus registry, to which physicians, nurses, parents, and other caregivers report cases on a voluntary basis. \(^{14}\) By contrast, the current study took a systematic approach by using an active national surveillance program (CPSP), with a successful track record of ongoing surveillance studies since its inception in 1996. This, in turn, reduces the chances of underreporting errors, and strengthens the reliability of our estimated incidence.

In a study of acute bilirubin encephalopathy, Manning et al.\(^{15}\) reported an incidence of \(\sim 1\) in 95,000 live births in Ireland and the United Kingdom based on surveillance from May 2003 to May 2005. The likely reason for the lower incidence in this study in comparison with ours is the inclusion criteria used, because Manning et al. only included infants with serum bilirubin levels \(>515\ \mu mol/L\). In our cohort, 5 infants had serum bilirubin levels \(<515\ \mu mol/L\), all of whom would not have been included in the British study. One of these infants had developed CBE in follow-up, whereas the other 4 were lost to follow-up. It is likely that our estimated incidence of CBE would be even higher had we been able to obtain data on those infants that were lost to follow-up, because they all had abnormal neurologic symptoms at the time of presentation.

In our cohort, physicians established a diagnosis of CBE based on a combination of confirmed severe hyperbilirubinemia and abnormal neurologic findings and/or abnormal MRI findings of the brain (performed in the majority of the infants). The combination of persistent neurologic abnormalities, an abnormal MRI finding, consisting of bilateral lesions of the basal ganglia/midbrain and abnormal ABERs, clearly points to an infant that is at high risk for permanent sequelae secondary to their hyperbilirubinemia. An abnormal MRI finding did not always point to long-term disability, because 2 children with abnormal MRI findings presented with no concerns in developmental follow-up. Further investigation in this area is needed, because MRI may or may not provide predictive information regarding CBE.

Not all the children in our cohort with CBE had choreoathetoid cerebral palsy. Other authors have reported other developmental delays, including global developmental delay, speech delay, and autism,\(^{9-11}\) in children without cerebral palsy who had severe neonatal hyperbilirubinemia.

This study has a number of limitations. Our estimated incidence of CBE is conservative in that serum bilirubin levels \(<425\ \mu mol/L\) have been associated with bilirubin encephalopathy. The inclusion definitions used in this study might have caused a small number of eligible cases to be missed. Also, almost all the cases were reported at 3 months of age or less, and subsequent long-term follow-up was not available for some of these infants. Furthermore, although mechanisms are in place to improve the level of systematic reporting, the surveillance program

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**TABLE 2** Follow-up Data on Infants With Severe Hyperbilirubinemia

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Follow-up, mo</th>
<th>Abnormal Findings at Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>Mild sensorineural hearing loss, speech delay</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>Choreoathetoid cerebral palsy, gait abnormality, cochlear implants, language delay, mental retardation</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>Choreoathetoid cerebral palsy, walks using hand-held device, gait abnormality, severe sensorineural hearing loss, G-tube feeds</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>No concerns</td>
</tr>
<tr>
<td>5</td>
<td>Unknown</td>
<td>Choreoathetoid cerebral palsy</td>
</tr>
<tr>
<td>6</td>
<td>Unknown</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>7</td>
<td>22</td>
<td>Generalized hypotonia with abnormal wide based gait, fine motor delay, speech and language delay</td>
</tr>
<tr>
<td>8</td>
<td>N/A</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>9</td>
<td>Unknown</td>
<td>Choreoathetoid cerebral palsy, G-tube feeds</td>
</tr>
<tr>
<td>10</td>
<td>N/A</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>Cerebral palsy spastic, dental enamel dysplasia, speech delay</td>
</tr>
<tr>
<td>12</td>
<td>N/A</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>13</td>
<td>N/A</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>14</td>
<td>N/A</td>
<td>Lost to follow-up</td>
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<tr>
<td>15</td>
<td>20</td>
<td>No concerns</td>
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<tr>
<td>16</td>
<td>13</td>
<td>Generalized hypotonia, visual impairment, severe global developmental delay</td>
</tr>
<tr>
<td>17</td>
<td>12</td>
<td>No concerns</td>
</tr>
<tr>
<td>18</td>
<td>14</td>
<td>Mild postural asymmetry, right hand preference</td>
</tr>
<tr>
<td>19</td>
<td>23</td>
<td>Hypotonic, cerebral palsy, global developmental delay, G-tube feed, bilateral hearing loss requiring cochlear implants</td>
</tr>
<tr>
<td>20</td>
<td>12</td>
<td>Choreoathetoid cerebral palsy, gait abnormal, truncal hypotonia, hearing loss (central)</td>
</tr>
</tbody>
</table>

\(N/A\) not available.
used still requires physicians to voluntarily report to the network; nonetheless, the response rate was high. In addition, the reporting system used in this study relies on the physician caring for the child or infant to accurately report all the relevant data on a detailed questionnaire, because it was not feasible for the study group to review each hospital or patient chart to corroborate the data. It is clear, however, that the diagnosis in our cases would be CBE given the extremely high neonatal bilirubin levels and the combination of abnormal clinical neurologic findings and corroborating MRI findings and/or abnormal ABERs.

This study highlights that CBE continues to occur in a well-developed health care system that has attempted to design programs to prevent CBE. Six months before (June 2007) the commencement of our study, the Canadian Paediatric Society published a position statement on the detection, management, and prevention of hyperbilirubinemia in term and late-term infants ≥35 weeks’ gestation. Despite the introduction of the guidelines, cases of CBE continued to be reported as part of the CPSP study, possibly because of limited penetration of these guidelines during the study period. In addition, there is evidence suggesting that there were a number of delays within Canada in the implementation of the new guidelines. Ongoing surveillance will help demonstrate a trend to reduction in CBE following the implementation of the guidelines.

CONCLUSIONS

Despite being a preventable disease with serious and debilitating sequelae, CBE continues to occur in Canada. Further efforts are required to identify the underlying reasons for this continuing incidence and to further develop and/or adapt existing guidelines in clinical practice.

REFERENCES

Michael Sgro, Douglas M. Campbell, Sharmilaa Kandasamy and Vibhuti Shah
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