



Kernicterus

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Background

Neonatal hyperbilirubinemia remains the most common cause of neonatal hospital readmissions in Canada and the United States with the risk of kernicterus and/or bilirubin-induced neurologic dysfunction (BIND) in severe cases.

Recent clinical practice guidelines on kernicterus recommend the following terminology to be used:

- acute bilirubin encephalopathy, for the early symptoms appearing within the first few weeks of life secondary to severe neonatal hyperbilirubinemia, and
- kernicterus, for the chronic clinical symptoms of bilirubin encephalopathy and pathological findings in children with neurological damage due to deposition of bilirubin in the brain.

On magnetic resonance imaging (MRI), children with kernicterus can show increased signal intensity in the basal ganglia (especially the posteromedial border of the globus pallidus) and the subthalamic nuclei. The sensitivity and specificity of this diagnostic method in newborns with bilirubin encephalopathy remains undetermined.

If a neonate survives the acute phase of bilirubin encephalopathy, the ensuing brain damage can result in an infant with clinical features such as athetoid cerebral palsy,



dystonia (hypertonia or hypotonia), and varying degrees of sensorineural hearing loss. There may also be dental enamel dysplasia, oculomotor impairments, including paralysis of the upward gaze, and less frequently, intellectual and developmental delays.

Traditionally, kernicterus was secondary to hyperbilirubinemia from hemolysis, usually due to Rh isoimmunization and ABO incompatibility. Other reported etiologies of hyperbilirubinemia include glucose-6-phosphate dehydrogenase (G6PD) deficiency, spherocytosis and pyruvate kinase deficiency. Prematurity, sepsis, acidosis and trauma also serve as additional risk factors.

From the 1950s to the 1980s, several developments resulted in a marked reduction of kernicterus, such as introduction of exchange transfusions, availability of RhoGAM for Rh negative mothers, routine testing of antibody titers during pregnancy, cord blood testing for blood group and antiglobulin antibodies (Coombs' testing) in neonates, and widespread effective use of phototherapy in treating hyperbilirubinemia of all causes.

Over the last decade, the incidence of kernicterus appears to be increasing again, even in otherwise healthy near-term and term infants. Several factors may have contributed to this disturbing trend, including:

- recommendations in 1992 for less aggressive treatment of hyperbilirubinemia,
- decreased awareness of the clinical presentation of acute bilirubin encephalopathy resulting in less aggressive management,
- early discharge of healthy newborns as soon as 24 hours after birth and before the serum bilirubin levels peak at 3 to 5 days of life,
- inadequate follow-up after discharge.

A recent surveillance study on severe hyperbilirubinemia demonstrated that ABO incompatibility followed by G6PD deficiency were the most common causes for severe hyperbilirubinemia in Canada and that almost three quarters of newborns were readmitted to hospital at a mean age of less than five days of life.

Because kernicterus is rare, there is very little national data for any country. Two papers confirmed that kernicterus remains a cause for concern in Canada, with 12 cases reported from 1990 to 2000 and seven from 1999 to 2003. Large national surveillance studies are needed to estimate the incidence and prevalence of kernicterus and to determine risk factors.

With pre-discharge screening of well newborns and the use of nomogram that accurately predicts the risk of developing severe hyperbilirubinemia based on hour-specific serum bilirubin levels, infants needing phototherapy could be identified. Treatment and follow-up could then be tailored appropriately. With early detection of severe neonatal hyperbilirubinemia, both acute bilirubin encephalopathy and kernicterus could be prevented.



Kernicterus (continued)

Method

The prevalence of kernicterus and/or bilirubin-induced neurologic dysfunction (BIND) will be ascertained through the CPSP by determining all new cases in Canada over a two-year period.

Each month, participating physicians receive an initial reporting form asking them to indicate whether they have encountered a new case of kernicterus in the preceding month. This check-off form is returned to the CPSP office even if participants see no new cases. Once a new case has been identified, a detailed questionnaire, designed by the investigators, is sent requesting case-specific data about the cause of kernicterus as well as the long-term neurological outcome. A paediatric neurologist serves as a consultant.

Objectives

1. To establish the incidence of kernicterus and/or BIND in Canada.
2. To identify epidemiological and medical risk factors, possibly useful in preventing this disease, whether it is through selective screening of newborns for serum bilirubin, G6PD and Coombs' testing, or measuring serum bilirubin in all newborns prior to discharge from hospital.

Case definition

Report any child up to six years of age with:

- a history of significant neonatal hyperbilirubinemia (peak bilirubin $>425\mu\text{mol/L}$ or exchange transfusion) **and**
- two or more of the following symptoms:
 - a) extrapyramidal disorders (e.g., dystonia, athetosis)
 - b) other movement disorder (spasticity or hypotonia)
 - c) gaze abnormalities
 - d) sensorineural hearing loss
 - e) intellectual deficits
 - f) enamel dysplasia of the deciduous teeth

OR

- abnormal MRI with bilateral lesions of basal ganglia/midbrain (globus pallidus + subthalamic nucleus) with a history of neonatal hyperbilirubinemia.

Exclusion criteria

- Born at less than 35 weeks gestational age.
- Metabolic condition with basal ganglia involvement (e.g., glutaric acidaemia type II, pyruvate dehydrogenase deficiency, Hallervorden-Spatz disease, neurofibromatosis type I, or children with carbon monoxide poisoning).



Duration

January 2007 to December 2008

Expected number of cases

Based on an annual birth rate in Canada of 330,000 (Statistics Canada, 2004 data), the expected number of cases is approximately 15 to 30 new cases per year.

Ethical approval

Toronto Academic Health Sciences Committee (TAHSC) Core Human Subjects Research

Analysis and publication

The investigators will analyze data, and annual results will be distributed to the CPSP participants. Data will be published in a peer-reviewed journal when the two-year study is completed.

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